Application de la chimie radicalaire par Xanthates: Synthèse des composés hétéroaromatiques

Zhibo Liu

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THESIS

submitted for the award of the degree of

DOCTOR OF PHILOSOPHY

In the field of

ORGANIC CHEMISTRY

by

Zhibo LIU

Application of the Radical Chemistry of Xanthates to the Synthesis of Novel Heteroaromatic Compounds

Presented on 20 January 2014 to a committee composed of:

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Abbreviations

Ac	**acetyl**
AIBN	**2,2'-azo-*bis*-isobutyronitrile**
Ar	**aryl**
Bn	**benzyl**
Boc	***tert*-butoxycarbonyl**
CSA	**camphorsulfonic acid**
DBP	**dibenzoyl peroxide**
DBU	**1,8-diazabicyclo[5.4.0]undec-7-ene**
DCE	**1,2-dichloroethane**
DCM	**dichloromethane**
DDQ	**2,3-dichloro-5,6-dicyano-1,4-benzoquinone**
DIPEA	***N*,*N*-diisopropylethylamine**
DLP	**dilauroyl peroxide**
DMAP	**4-dimethylaminopyridine**
DMC	**dimethylcarbonate**
DMF	***N*,*N*-dimethylformamide**
DTBP	**di-*tert*-butyl peroxide**
EDG	**electron donating group**
EP	**petroleum ether**
Et	**ethyl**
EWG	**electron withdrawing group**
***i*-Pr**	**isopropyl**
LDA	**lithium diisopropylamide**
***m*-CPBA**	***meta*-chloroperoxybenzoic acid**
Me	**methyl**
Ms	**mesyl**
Ph	**phenyl**
PhCl	**chlorobenzene**
Pht	**phtalimide**

Piv	**pivalate**
***t*-Bu**	***tert*-butyl**
TEA	**triethylamine**
TFA	**trifluoroacetic acid**
THF	**tetrahydrofuran**
TMS	**trimethylsilyl**
Ts	**tosyl**
Xa	***O*-ethyl xanthate**

cat.	**catalytic quantity**
°C	**degree Celsius**
eq.	**eq.alents**
Δ	**heating**
Hz	**hertz**
h	**hour**
IR	**infrared**
In	**initiator**
min	**minute**
M	**mole per litre**
NMR	**nuclear magnetic resonance**
Nu	**nucleophile**
Ox.	**oxidation**
ppm	**parts per million**
hν	**photochemical irradiation**
Red.	**reduction**
TLC	**thin layer chromatography**

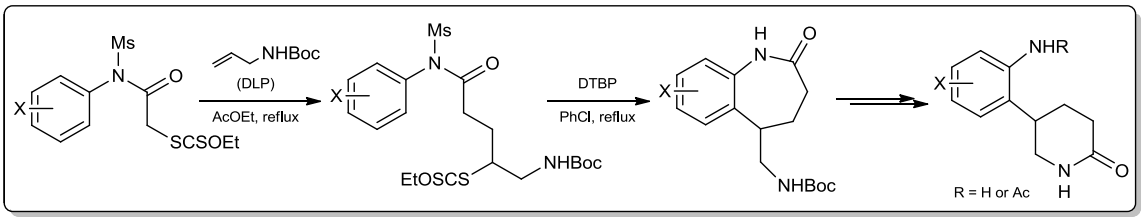
Avant-propos

Avant-propos

Au cours de cette thèse nous nous sommes intéressés à la synthèse d'hétérocycles azotés dérivés de benzazépinones et de composés pyridiniques et pyrimidiniques. Ces travaux ont été menés sous la direction du Pr. Samir Z. Zard au Laboratoire de Synthèse Organique à l'Ecole Polytechnique. Ce manuscrit est composé de cinq chapitres.

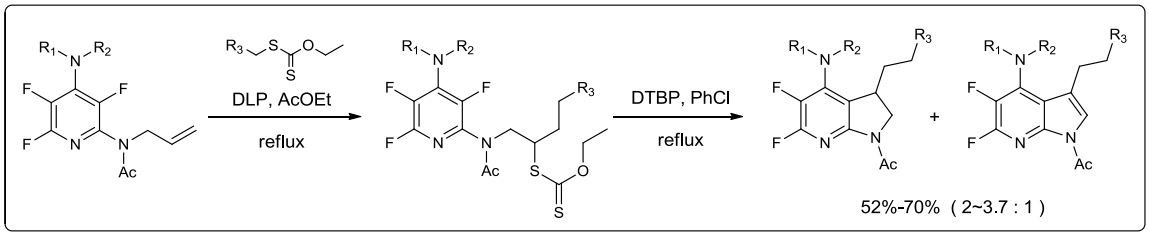
Dans un premier temps, nous presentons brièvement les grands principes de la chimie radicalaire (Chapitre 1), et puis plus particulièrement la chimie radicalaire des xanthates qui a été développée au laboratoire (Chapitre 2), afin de familiariser le lecteur à la chimie radicalaire par transfert de xanthate.

Le Chapitre 3 concerne une nouvelle synthèse de benzazépin-2-ones et 5-arylpipéridin-2-ones par voie radicalaire à partir de matières premières simples, via une cyclisation radicalaire sur noyau aromatique de type 7-endo-trig.



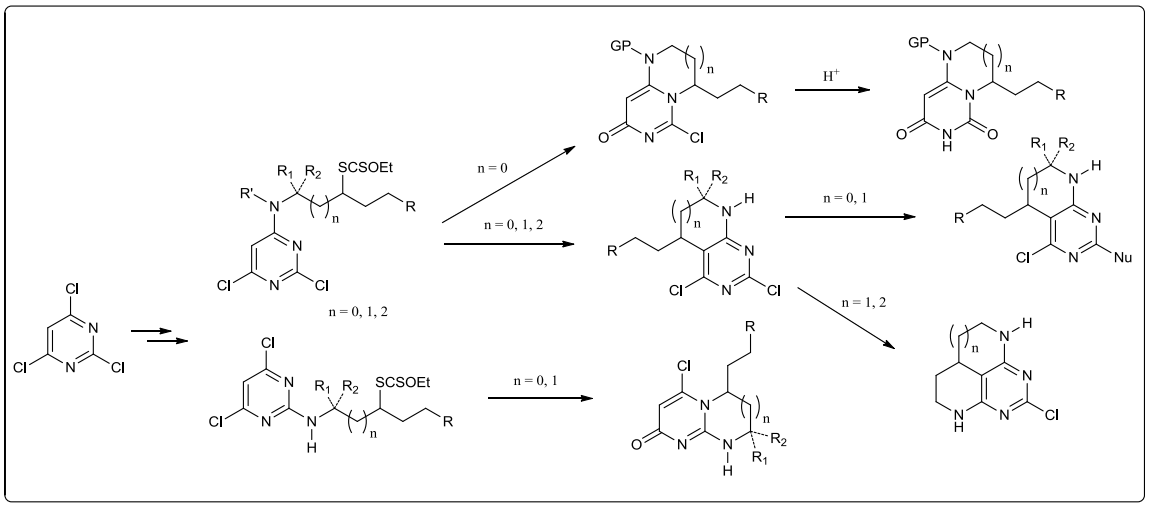
L'optimisation de l'étape de cyclisation a permis d'obtenir des rendements modérés à excellents. De plus, grâce à la présence de substituents halogènes sur le noyau aromatique, il est possible de combiner ce processus radicalaire avec d'autres réactions importantes, ce qui pourrait avoir des applications intéressantes.

Le Chapitre 4 traite de la préparation de nouveaux 3,4-disubstitués-5,6-difluoro-7-azaindoles et 7-azaindolines avec de bons rendements par voie radicalaire à partir de la pentafluoropyridine.



La formation de ces deux composés comprend la rupture homolytique d'une très forte liaison C-F, ce qui est très rare dans de telles conditions douces. L'efficacité de cette cyclisation radicalaire se trouve être très sensible à la propriété électronique de la substitution en C-4. Sur la base de ce travail, une mini-librairie de composés divers de 7-azaindoles et 7-azaindolines pourrait être créée.

Enfin, le dernier chapitre a été réalisé en collaboration avec M. Ling QIN, que j'ai été amené à encadrer au cours de ma thèse. Dans cette partie, nous nous sommes interessés à de nouvelles cyclisations radicalaires de xanthates sur des noyaux hétéroaromatiques bis-azotés.



L'un des développements de ce travail est la possibilité d'utiliser des substrats où l'azote non aromatique n'est pas protégé. La méthode pourrait être partiellement étendue à des pyridines. En outre, la première cyclisation radicalaire à l'azote hétéro-aromatique de type 6-endo-trig a également été réalisé. Les développements de ces voies de synthèse a permis de mieux comprendre certains mécanismes réactionnels ainsi que d'en découvrir de nouveaux.

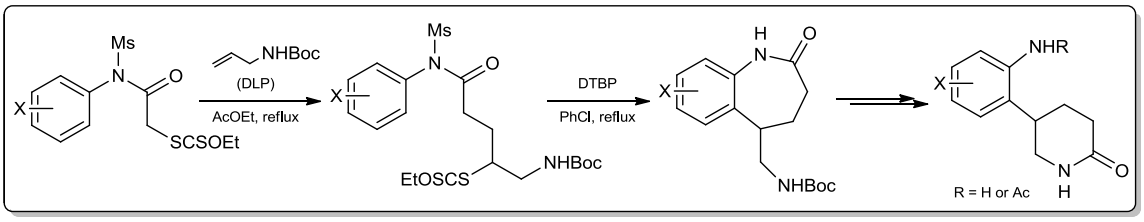
General Introduction

General Introduction

In this thesis we are interested in the synthesis of nitrogen-containing heterocyclic derivatives, which are based on benzazepinones, pyridines and pyrimidines. These works are carried out under the supervision of Prof. Samir Z. Zard in Laboratory of Organic Synthesis in Ecole Polytechnique. This manuscript consists of five chapters.

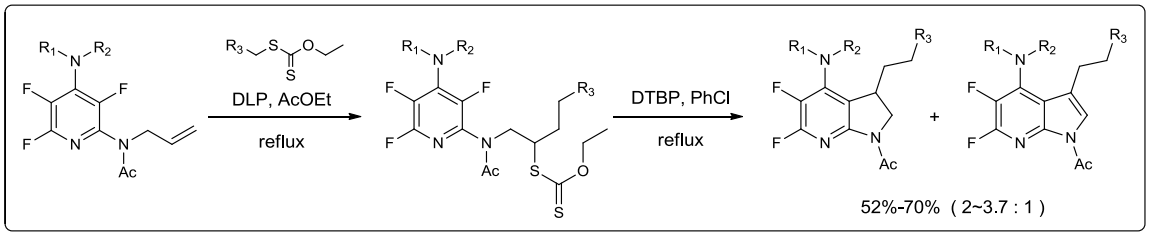
At first, we will briefly introduce the general concepts of radical chemistry (Chapter 1), and then especially the radical chemistry of xanthates which was developed in the laboratory (Chapter 2), to familiarize the reader with the radical xanthate transfer processes.

In Chapter 3, we will describe a novel synthesis of benzazepin-2-ones and 5-arylpiperidin-2-ones using the xanthate transfer technique from simple starting materials, via a seven-membered ring radical cyclization.



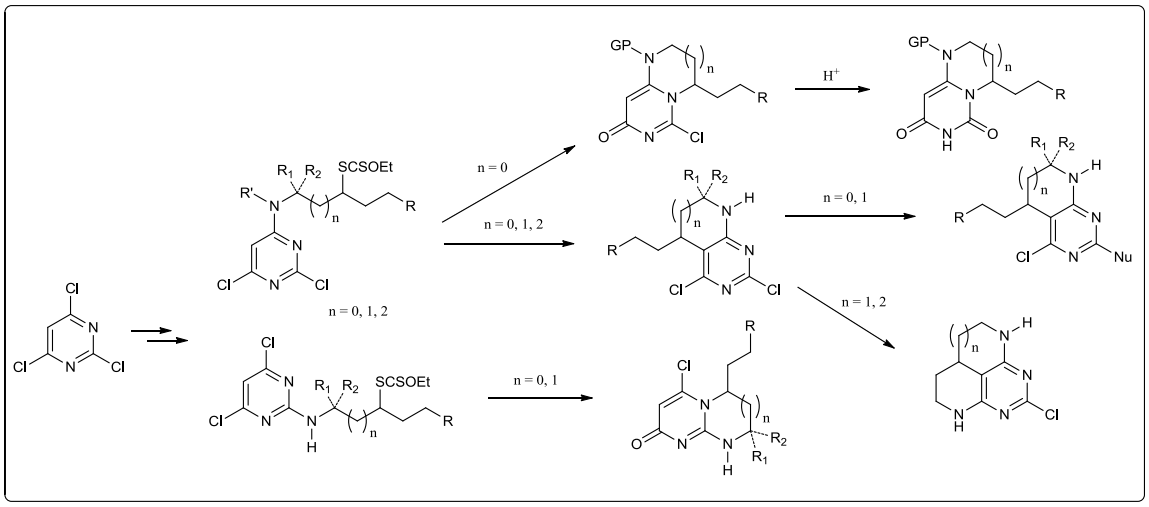
Optimized conditions for the ring closure step afford moderate to excellent yields for this synthesis. Moreover, the ease of introduction of halogen atoms into the aryl group of the products makes it possible to combine this radical process with powerful transition metal catalyzed coupling reactions, allowing the rapid construction of novel libraries with potential use in medicinal chemistry.

In Chapter 4, the concise synthesis of 3,4-disubstituted-5,6-difluoro-7-azaindoles and 7-azaindolines starting from the commercially available pentafluoropyridine will be described.



The formation of these two important families includes the homolytic rupture of a very strong C-F bond, which is extremely rare. The efficiency of this intramolecular radical cyclization was found to be very sensitive to the electronic properties of the C-4 substituents. This approach combines the xanthate transfer radical process with traditional ionic reactions, and provides a convenient access to a diverse library of 7-azaindolines and 7-azaindoles.

In Chapter 5, a direct route to novel polycyclic aza-pyrimidine structures, including 5-, 6-, 7-membered rings, is presented, involving intermolecular radical additions and cyclizations of xanthates.



One of the main developments of this work is the possibility of using substrates which are unprotected at the non-aromatic nitrogen. This methodology could be partially extended to pyridine series. Furthermore, the first radical cyclization onto the heteroaromatic nitrogen atom in a 6-endo-trig manner has also been accomplished. The development of these syntheses provided better understanding of some reaction mechanisms as well as to discover new processes.

Chapter 1

General Introduction to Radical Chemistry

Introduction

The first ever free radical identified in history was the triphenylmethyl radical, which was described in 1900 by Gomberg in his publication "An instance of trivalent carbon: triphenylmethyl".[1] From since then, people started to realize progressively that besides the traditional anions and cations, another neutral species "radicals" also existed and had great potential applications in organic synthesis.

In 1920s, Paneth and Hofeditz first prepared the methyl free radical[2] by heating tetramethyllead in a rapid current of hydrogen under low pressure. Later on, photo-chemical decomposition of alkyl halides and the aliphatic azo compounds was also shown to give free radicals, and the research work in this field rapidly developed.[3]

In 1930s, another remarkable work was published by Kharasch explaining how an anti-Markovnikov orientation could be achieved via free radical chain process, which was defined as the "peroxide effect".[4] During the years of 1950s and 1960s, there were numerous radical transformations studied by many groups. One important discovery involved organotin hydrides, which were shown to have the capability of bringing about the replacement of the halogen atom in alkyl,[5] aryl[6] and acyl[7] halides by hydrogen under mild conditions. In 1962, Kuivila confirmed the existence of a chain mechanism based on free radicals in the reduction of alkyl halides,[8] in which an organotin radical abstracts a halogen atom from the halide in one step, and the resulting alkyl radical abstracts a hydrogen atom from the organotin hydride in the second step (the chain mechanism will be described in detail later in this chapter).

---

[1] Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757-771.
[2] Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, *62*, 1335.
[3] Hey, D. H.; Waters, W. A. *Chem. Rev.* **1937**, *21*, 169-208.
[4] Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc.* **1933**, *55*, 2468-2496.
[5] (a) Noltes, J. G.; Vanderkerk, G. J. M. *Chem. Ind.* **1959**, 294.; (b) Kupchik, E. J.; Connolly, R. E. *J. Org. Chem.* **1961**, *26*, 4747.
[6] (a) Rothman, L. A.; Becker, E. I. *J. Org. Chem.* **1959**, *24*, 294.; (b) Rothman, L. A.; Becker, E. I. *J. Org. Chem.* **1960**, *25*, 2203-2206.
[7] Kuivila, H. G. *J. Org. Chem.* **1960**, *25*, 284-285.
[8] Kuivila, H. G.; Menapace, L. W.; Warner, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 3585.

During the following decades, a variety of other chain and non-chian radical processes were discovered, such as the $S_{RN}1$ reactions (Substitution Radical Nucleophilic Unimolecular)[9], the Minisci alkylation[10] and the Meerwein arylations,[11] etc.

In 1975, the Barton-McCombie deoxygenation of alcohols via xanthates and similar thiocarbonyl derivatives[12] was reported and proved to be one of the most important transformations based on radical chemistry in this period (Chapter 2). In 1983, another important reaction, the decarboxylation of carboxylic acids via the now well known Barton esters[13] was also accomplished (Chapter 1). Later in 1985, the reductive additions of electron-rich radicals to electrophilic alkenes reported by Giese[14] illustrated the potential of carbon-carbon bond formation achieved by a radical strategy. It also proved that polymerization was not the only destination of radical additions to alkenes.

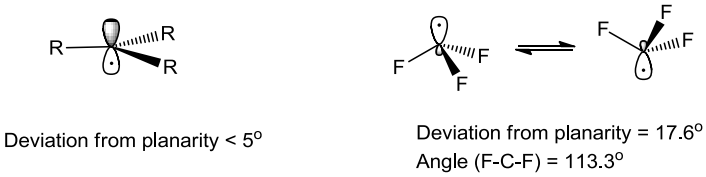
Ever since then, radical chemistry has evolved considerably and its favorable features have become more widely recognized by chemists for solving difficult synthetic problems. One of the most important achievements is the discovery and development of the new radical process with *O*-alkyl dithiocarbonates, or xanthates. This report will focus on understanding and exploring the radical chemistry of xanthates, which was developed in our laboratory. Before we begin the journey with xanthate chemistry, let's review some general concepts about radicals and some important reactions.

[9] Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463.
[10] (a) Minisci, F. *Acc. Chem. Res.* **1975**, 165-171.; (b) Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1
[11] Rondestvedt, C. S. *Org. React.* **1976**, *24*, 225.
[12] Barton, D. H. R.; Mccombie, S. W. *J. Chem. Soc., Perkin Trans.1* **1975**, 1574-1585.
[13] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.
[14] Giese, B. *Angew. Chem. Int. Ed.* **1985**, *24*, 553-565.

Ⅰ. Geometry, stability and reactivity of radicals

1. Geometry of radical

A free radical reaction is a chemical process that involves molecules with unpaired electrons. In most of the cases, radical species generated by homolytic bond cleavages are used as intermediates. EPR studies[15] and theoretical calculations suggest that simple alkyl radicals could be either planar or very shallow pyramids. The barrier to inversion is very small (no more than 4-8 kJ/mol[16]), so very rapid inversion occurs. This kind of radical is defined as a π-radical.



Scheme 1.1 The geometries of π-radical and σ-radical.

However, electronegative substituents on carbon radicals can significantly affect their geometry by increasing the *s*-character of the orbital occupied by the single electron. Analysis of EPR spectra of mono-, di-, and tri-fluoromethyl radicals indicated a progressive distortion from the planarity.[17] For example, the trifluoromethyl radical has almost pure sp^3 hybridization and one of the studies from DFT (Density Functional Theory) calculation with C_{3v} symmetry showed its geometry to be pyramidal.[18] This kind of radical is called σ-radical. Generally it tends to be more electrophilic than a π-radical. Since both of them invert very quickly, in most cases the stereochemical information of the precursors will be lost in a radical process.

---

[15] The distinguishing feature of free radicals is the presence of an unpaired electron. For the purpose of detecting and characterizing them, the most efficient tool is the Electron Paramagnetic Resonance (EPR) spectroscopy, also known as Electron Spin Resonance (ESR) spectroscopy.

[16] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms Fourth Edition* **2001**, Kluwer Academic Plenum Publishers.

[17] (a) Bernardi, F.; Cherry, W.; Shaik, S.; Epiotis, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 1352-1356.; (b) Krusic, P. J.; Meakin, P. *J. Am. Chem. Soc.* **1976**, *98*, 228-230.

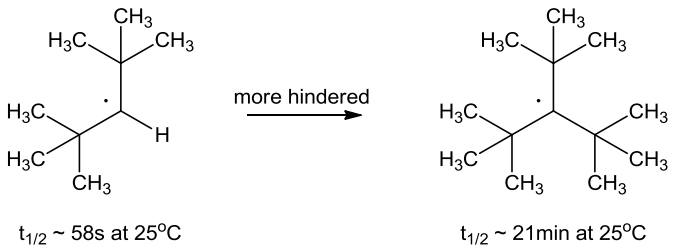
[18] Lund, A.; Gustafsson, H.; Maruani, J.; Shiotani, M. *Spectrochim. Acta, Part A* **2006**, *63*, 830-835.

2. Radical stability and reactivity

Normally free radicals in solution have a very short lifetime since the unpaired electrons are desperate to be paired up again. However, in some special cases, certain structural features, such as steric hindrance and electronic stabilization,[19] can enhance their persistence. The exceptional stability of some persistent radicals normally comes from a mixture of these effects. For example, in the well known commercial chemical product TEMPO, the unpaired electron is delocalized between nitrogen and oxygen with an N-O bond order of 1.5. Besides, the four adjacent methyl groups prevent the disproportionation from taking place. In Scheme 1.2, the right hand side radical, which enjoys the same electronic stablisation as TEMPO is much less persistent because of decomposition through disproportionation.[20]

Scheme 1.2 Electronic conjugation and steric hindrance stabilized radical

Another example is that of di-tert-butylmethyl radical, which has a significantly long half time in the absence of oxygen at 25°C. However, the tri-tert-butylmethyl radical has an even longer lifetime due to both the electronic stabilization and especially the steric hindrance provided by the third tert-butyl group.[21] In this case, the radical is sterically shielded by three bulky tert-butyl groups, making it harder to undergo further reactions.

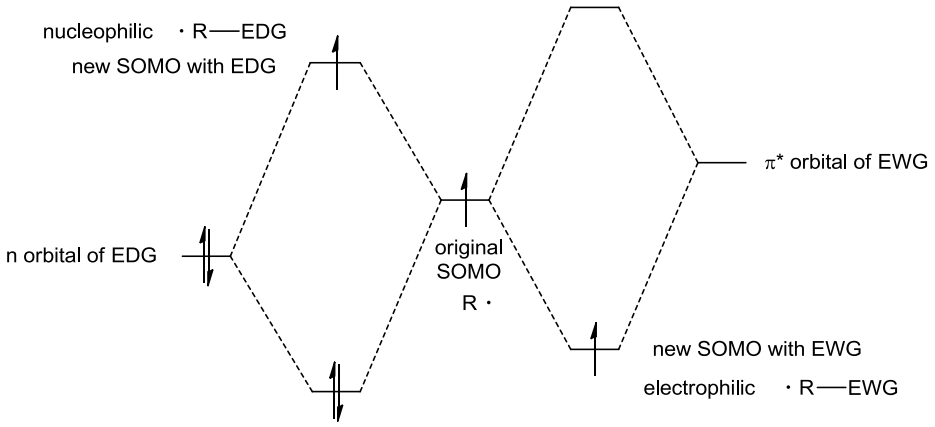


Scheme 1.3 Steric hindrance protection of the tri-tert-butylmethyl radical

[19] It includes adjacent conjugation, electron-withdrawing group (EWG) and electron-donating group (EDG)
[20] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry Second Edition* **2001**, Oxford University
[21] Mendenha.Gd; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 2963-2971.

From a synthetic viewpoint, electronic (polar) factors usually play a more important role than steric hindrance. From a detailed analysis of the interaction between the orbitals of the substituents and the SOMO[22] of the radicals, both EDG and EWG stabilize radicals.

The EDG has a filled *n* orbital with relatively high energy. When it overlaps with the SOMO of a radical, two new molecular orbitals are obtained. Three electrons are then available to fill them, with two electrons decreasing in energy and one electron increasing. As a result, the resulting SOMO is higher in energy than the initial one, but the lone pairs (two electrons) occupy a lower energy orbital than before. One electron rises but two drop in energy, so there is an overall net stabilization of the whole system.



Scheme 1.4 Orbital interaction of single electron with filled and empty orbitals

In a similar manner, we can analyze the interaction between the SOMO of a radical and the low lying empty π* orbital of an EWG. This time only one electron from the original SOMO is available for filling the two new orbitals. As a result, it enters the lower energy orbital which becomes the new SOMO of the whole system. An overall stabilization is achieved since the electron drops in energy.

Although both EDGs and EWGs can stabilize radicals, EDGs tend to raise the energy of the new formed SOMO, while EWGs tend to lower it. As a result, the high energy

[22] The orbital containing the unpaired electron in radicals is called Singly Occupied Molecular Orbital (SOMO)

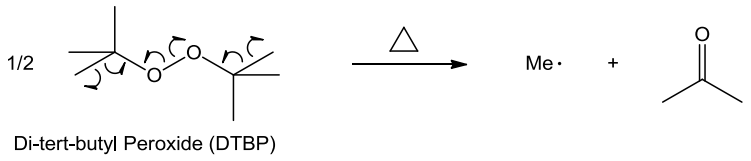
SOMO (with adjacent EDG) has the tendency to give up its unpaired electron and is considered as a radical with nucleophilic character, while the low energy SOMO (adjacent to EWG) tends to accept one electron to pair its single one and is viewed as a radical with electrophilic character. This ambiphilic property enriches the reactivity of radicals, since they can react with both electron-poor and electron-rich species.

From the discussion above, we can see that the persistency of radicals is their natural property. It is associated with the substituents and the geometry. Enhanced persistency means an increased half-life, and normally that means a relatively lower reactivity, especially in dimerization. But the reactivity of radicals is used more to determine their tendency for reacting with the other radicophiles. It depends on the relative positions of the involved molecular orbitals. For a "nucleophilic" radical it depends on the position of its SOMO and the LUMO of the radicophile, while for an "electrophilic" radical it depends on its SOMO and the radicophile's HOMO. The closer the energy levels of the orbitals involved, the higher the reactivities.

Ⅱ. Sources of radicals

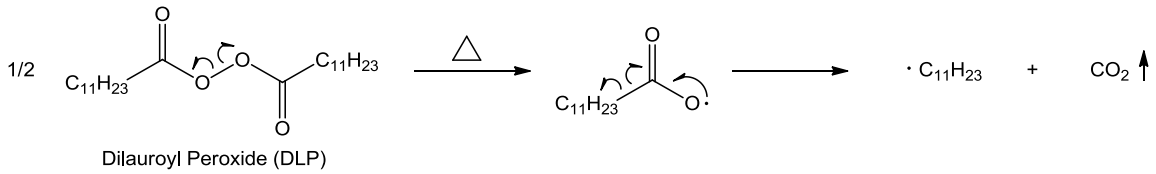
1. Common sources for radicals

Peroxides undergo homolysis of the weak O-O bond relatively easily,[23] and that is why they are commonly used as radical sources in organic synthesis and polymer chemistry. Normally the initiation with peroxides can occur at moderate temperatures. For example, di-tert-butyl peroxide (DTBP) is stable at room temperature but undergoes homolytic cleavage to give methyl radicals beyond 80°C,[24] and more usefully at temperatures around 130°C (half-life ~ 10h).



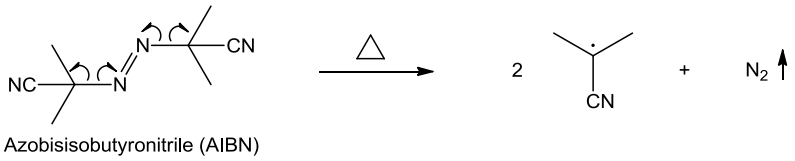
Scheme 1.5 Initiation of DTBP

Diacyl peroxides are also sources of alkyl radicals since the carboxyl radicals which are formed initially lose carbon dioxide rapidly.



Scheme 1.6 Initiation of DLP

Another extensively used radical sources are azo compounds. For example, azobisisobutyronitrile (AIBN) is one of the most freq.uently used precursors to initiate radical chain processes, especially those based on stannanes. The thermal homolysis of AIBN produces nitrogen and nitrile-stabilized radicals.

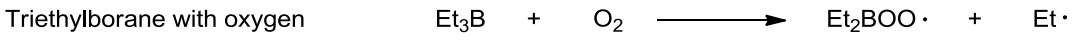


Scheme 1.7 Initiation of AIBN

[23] The dissociation energy for O-O bond in CH_3O-OCH_3 is about 151kJ/mol, while that for H-O bond in water is 498kJ/mol.
[24] The half-time ($t_{1/2}$) of DTBP in benzene at 80°C is 103 days.

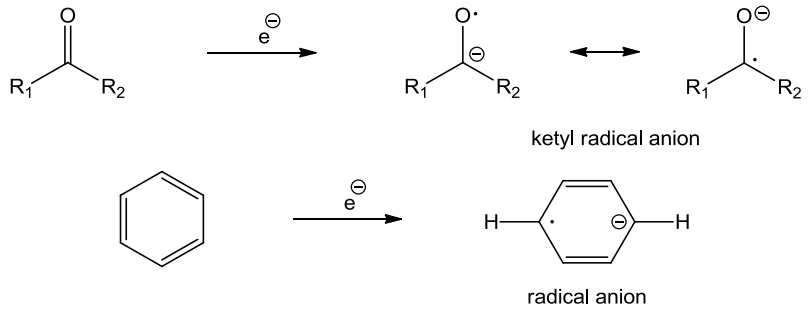
The decomposition of peroxides and azo compounds can also be accomplished by photochemical excitation, since light is a possible energy source for the homolysis of bonds: red light has an associated energy of 167kJ/mol, blue light has about 293kJ/mol, and ultraviolet (200nm) has about 586kJ/mol.

Other radical sources freq.uently used involve organometallic compounds and boron alkyl compounds (such as triethylborane). The former have in some cases weak bonds between carbon and the metals which can easily be homolysed to give carbon centered radicals, while the latter generate alkyl radicals (via peroxide intermediate) when exposed to air (oxygen), even at low temperatures (autoxidation).



Scheme 1.8 Initiation of triethylborane

Another method for generating radicals is based on single electron transfer (SET). The electron normally comes from the dissolving metals like Na, Mg, Zn, or Al. The first example in Scheme 1.9 illustrates the formation of a ketyl radical anion, which is involved in the pinacol coupling reaction and the McMurry reaction.[25] Ketyl radicals produced from the reduction of benzophenone with sodium are used as the desiccant for drying certain solvents.[26] The second example shows that a solvated electron can add to an aromatic ring to give a radical anion, which is the case in the well known Birch reduction.

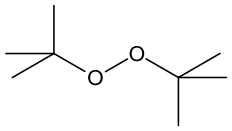
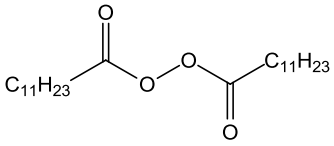
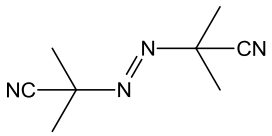
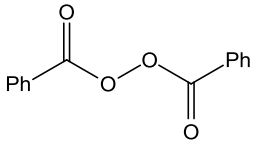
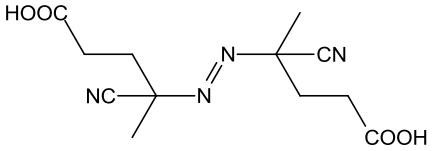


Scheme 1.9 Radical anion formation via single electron transfer

[25] Mcmurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708-4709.
[26] Sodium reduces benzophenone to the soluble ketyl radical, which reacts quickly with the water and oxygen dissolved in the solvent. The deep blue coloration qualitatively indicates dry and oxygen-free conditions.

2. Half-life of radicals

The most important data for evaluating the ability of different initiators is their half-life ($t_{1/2}$). It is the time needed to consume one half of a given quantity of the initiator in a solution at a given temperature. It heavily depends on the bonds that must be broken and the nature of the free radical generated. At the same temperature, half-lives can vary based on the manner in which they are sampled, especially the solvent used.

Initiator	Solvent	Temperature(°C)	$k_d^{27}(s^{-1})$	$t_{1/2}$
 Di-tert-butyl Peroxide (DTBP)	Benzene	100 130	8.8×10^{-7} 3.0×10^{-5}	9d 6.4h
 Di-Lauroyl Peroxide (DLP)	Benzene	40 60 85	4.9×10^{-7} 9.2×10^{-6} 3.8×10^{-4}	16d 21h 30min
 Azobisisobutyronitrile (AIBN)	Benzene	70 100	3.2×10^{-5} 1.5×10^{-3}	6h 8min
 Di-Benzoyl Peroxide (DBP)	Benzene	60 100	2.0×10^{-6} 5.0×10^{-4}	4d 23min
 4,4-Azobis(4-cyanovaleric acid)	Acetone Water	70 69	4.6×10^{-5} 1.9×10^{-5}	4.2h 10h

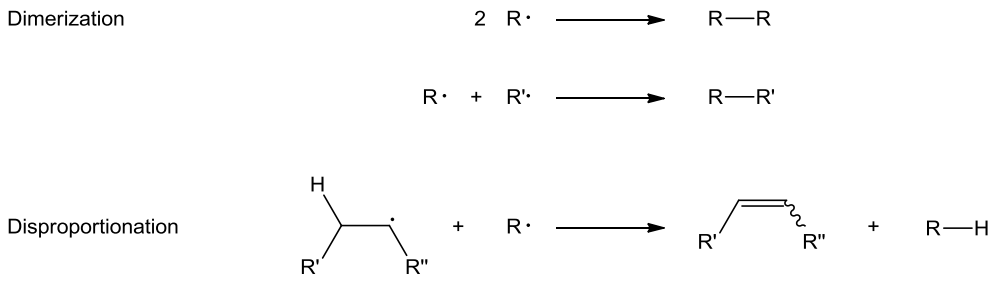
"Decomposition Rates and 10-Hour Half-life Temperatures of Common Thermal Initiators" Polymer Products from Aldrich

Table 1.1 Half-life of some common initiators

Ⅲ. How do radicals react?

a. radical + radical → closed-shell molecule

Radicals without special stabilization rapidly dimerize (with the same or different radicals) or disproportionate. In the disproportionation process, a hydrogen abstraction by one of the radicals leads to an alkane and an alkene.



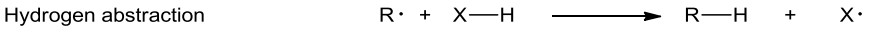
Scheme 1.10 Radical dimerization and disproportionation

b. radical + closed-shell molecule → new radical + new closed-shell molecule

Normally, highly reactive radicals are unselective when reacting with other species. Although they can meet other radicals and dimerize with them, they are more likely to collide with solvent or other closed-shell molecules present in the reaction medium. However, radical-radical interactions are extremely fast. Thus, addition to oxygen is often a process which needs to be avoided in radical synthesis.

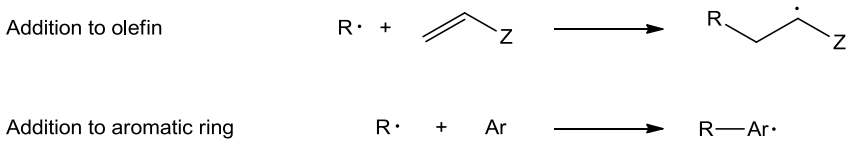
Scheme 1.11 Radical addition to oxygen

Radicals can also rapidly abstract hydrogen atoms from many types of compounds or solvents:



Scheme 1.12 Hydrogen abstraction by a radical

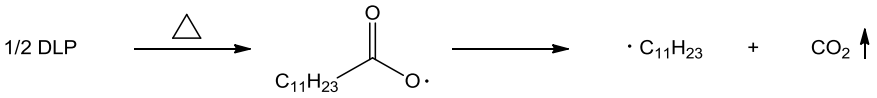
They can also add to olefins and aromatic rings, and this process is more useful from a synthetic viewpoint:



Scheme 1.13 Radical addition to olefin and aromatic ring

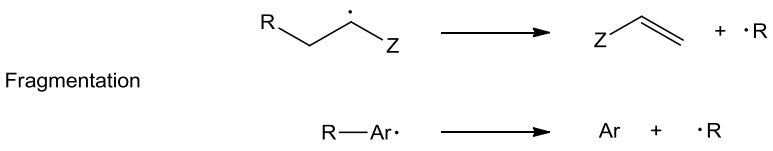
c. radical → new radical + closed-shell molecule

As mentioned above, the thermal dissociation of diacyl peroxides gives first the carboxyl radicals, which fragment rapidly to alkyl radicals, losing carbon dioxide.



Scheme 1.14 Radical generated by fragmentation

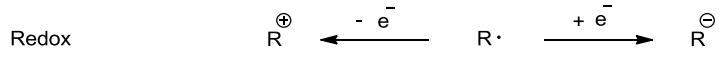
The reverse processes of additions to olefins and aromatic rings also belong to this category:



Scheme 1.15 Radical generated by fragmentation

d. radical $\pm e^-$ → anion or cation

When single electron transfer processes are possible, radicals can form the corresponding cation by losing one electron or form the anion by capturing one electron.

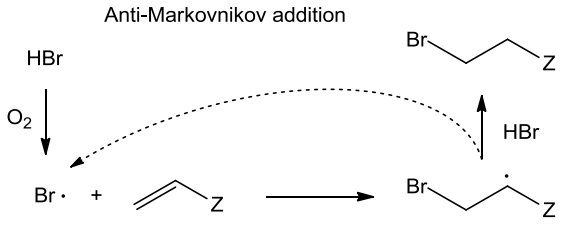


Scheme 1.16 Radical modified by single electron transfer process

Ⅳ. Radical chain processes

1. The mechanism of a radical chain process

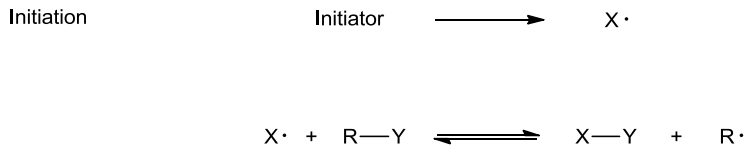
One of the earliest radical chain mechanisms was proposed by Kharasch in the course of his research on the anti-Markovnikov addition of hydrogen bromide to olefins. Adventitious oxygen or peroxide serves as the initiator for the chain process. This early discovery not only established the role of radicals as the reactive intermediates in solution, but also influenced the subseq.uent development of radical chemistry and polymer chemistry. In a radical chain process, three basic concepts are involved: initiation, propagation, and termination.



Scheme 1.17 Kharasch reaction

a. Initiation

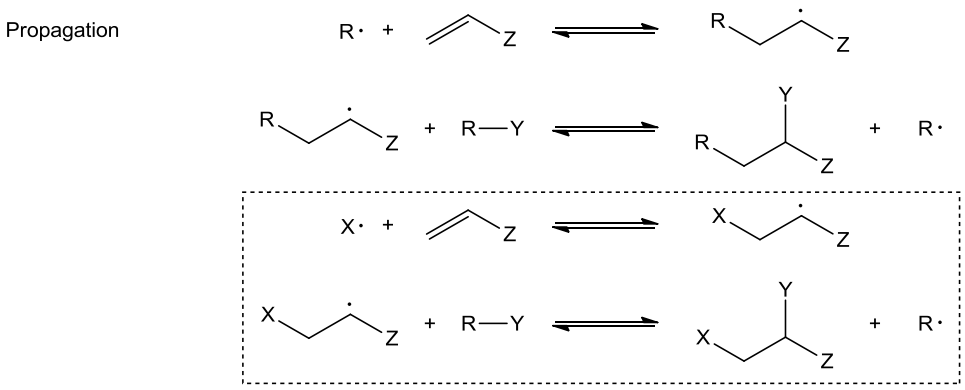
In a chain process, initiation radicals X· can first be introduced into the system by thermal or photochemical dissociation of some common precursors, or through redox processes involving metals. They will then attack the substrate R-Y to generate the new radicals R· for the following reactions.



Scheme 1.18 Initiation of chain processes

b. Propagation

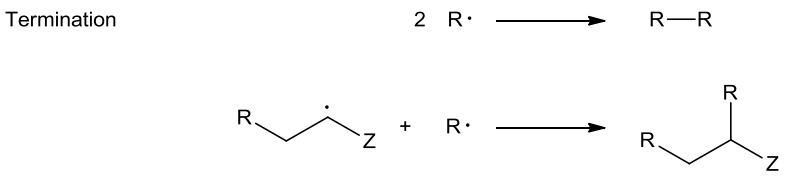
These new radicals R· will then react with a radicophile present in the system, such as an alkene, and form other radicals which will attack R-Y again to give the product and regenerate the R·. Theoretically, only one X· is needed to consume all the starting material. In fact, the initiator is needed in a certain amount, say 5% ~ 10%, in order to complete the chain process. Normally, the attack of initiator X· on the olefin is a side reaction that must be minimized by controlling the relative reactivities.

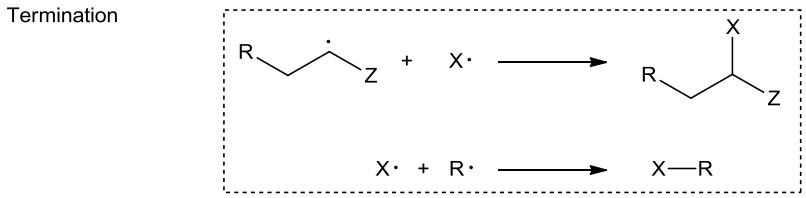


Scheme 1.19 Propagation steps

c. Termination

If the steady-state concentration of the radicals in the system is kept very low, then their recombination becomes rare but still occurs to a certain extent. So this is why it is not in practice possible to complete the reaction with only one X·, and more initiator is needed to start the chains again. The faster the propagation steps, the less initiator is needed and the more insignificant will be the termination steps.



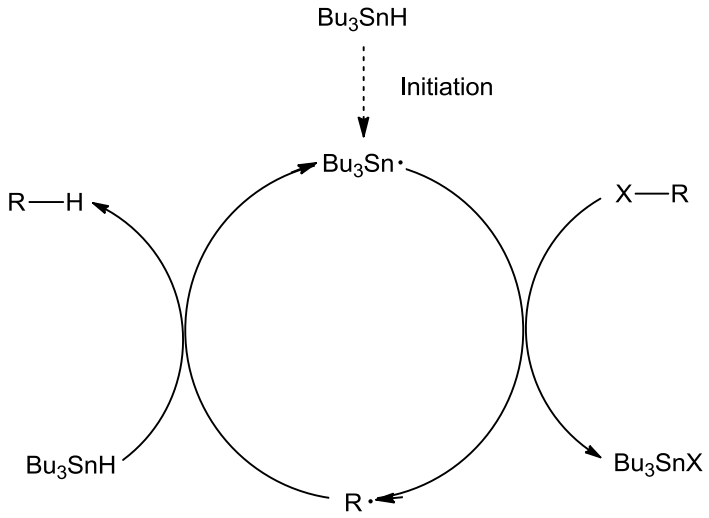


Scheme 1.20 Termination of radicals

2. Applications based on the radical chain processes

a. Triorganotin hydrides

Triorganotin hydrides are the most freq.uently used reagents in the radical chain process. They can convert organic halides and various other groups into the corresponding hydrocarbons.

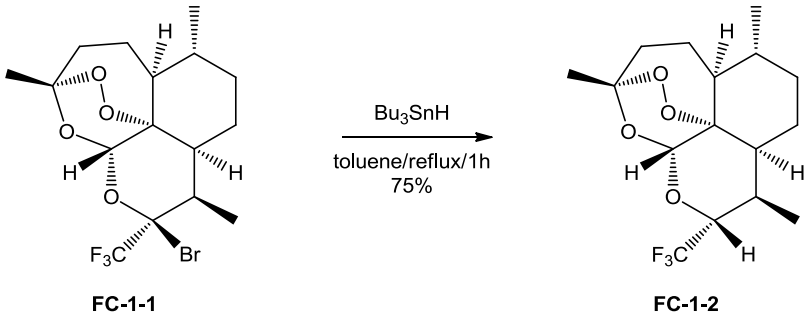


Scheme 1.21 General form of stannane based chain process

Chain reactions involving tributyltin hydride (or tributylstannane) are normally triggered by the nitrile-stabilized radical generated from the thermal homolysis of AIBN. Since the Sn-H bond of Bu_3SnH is not very strong, the relatively unreactive nitrile-stabilized radical can better minimize the side-products compared to the more reactive RO· from peroxides. The stannyl radical can then react with R-X to give the radical R·, which abstracts the hydrogen from the tributyltin hydride to form the hydrocarbon and

simultaneously reproduce the stannyl radical to complete the chain cycle. Here, the R-X can represent many species besides halides (except fluorides), such as sulfides, selenides, isocyanides, nitro compounds, etc.

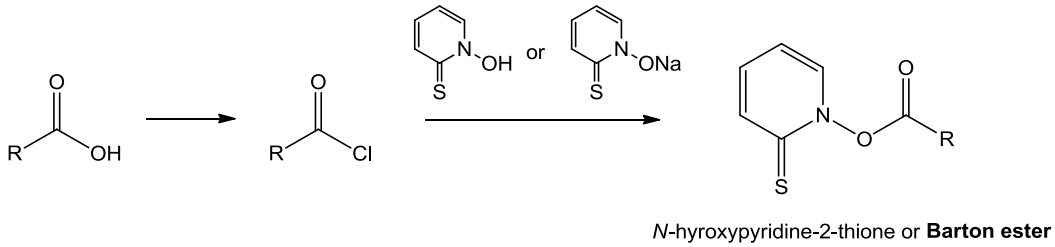
For example, the first synthesis of (trifluoromethyl)deoxoartemisinin **FC-1-2** was accomplished by debromination using tributyltin hydride in the key step.[27] The mild conditions used for this dehalogenation could obviate the possible alteration of the endoperoxide bridge.



Scheme 1.22 Debromination mediated by organotin hydride

b. The Barton decarboxylation

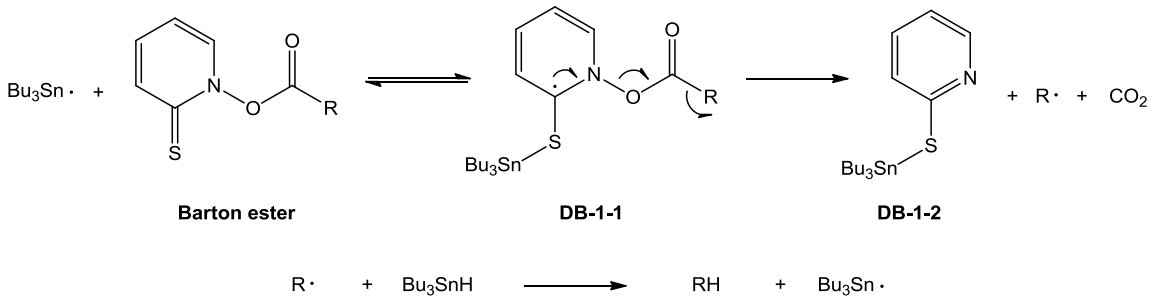
The Barton decarboxylation[13] is a general and powerful method for decarboxylating carboxylic acids discovered by Sir Derek Barton in 1980s. The carboxylic acid is first converted into the corresponding ester of *N*-hyroxypyridine-2-thione or Barton ester by the usual methods for ester synthesis.



Scheme 1.23 Formation of Barton esters

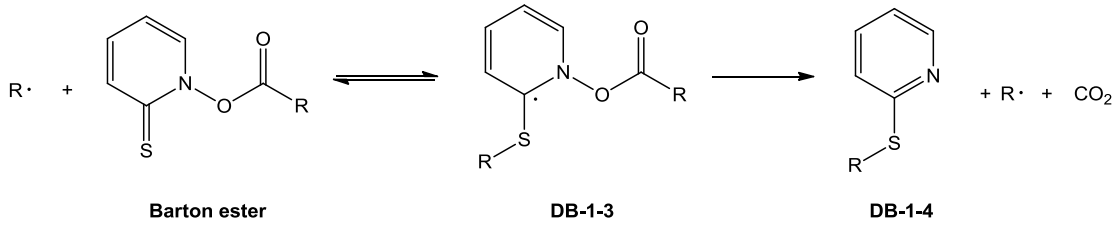
[27] Chorki, F.; Grellepois, F.; Crousse, B.; Hoang, V. D.; Van Hung, N.; Bonnet-Delpon, D.; Begue, J. P. *Org. Lett.* **2002**, *4*, 757-759.

The radical chain process is then triggered by the stannyl radicals from the homolysis of tributyltin hydride initiated by AIBN. The high affinity of the stannyl radical for the thiocarbonyl group will drive it to attack the sulfur of the *N*-hydroxypyridine-2-thione, followed by the homolytic cleavage of the weak N-O bond driven by rearomatization. The carboxyl radical **DB-1-1** formed then undergoes decarboxylation and extrudes carbon dioxide. Finally, the remaining alkyl radical abstracts hydrogen from the tributyltin hydride to form the reduced alkane, and regenerates the stannyl radical to propagate the chain.



Scheme 1.24 The chain process for Barton decarboxylation

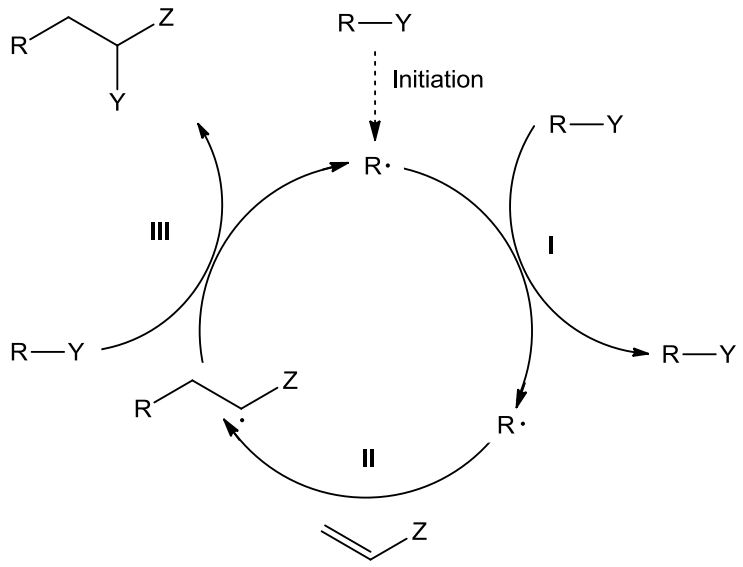
There is a competing route in this process, which involves the attack of the alkyl radical on the thiocarbonyl group to form intermediate **DB-1-3**. The chain is propagated since the alkyl radical is regenerated when this intermediate undergoes fragmentation to give a pyridyl sulfide. This competing pathway can be minimized by proper modifications, such as changing the concentration or temperature.



Scheme 1.25 The background reaction in the Barton decarboxylation

c. Atom and group transfer reactions

Atom and group transfer reactions refer to a broad range of radical additions in which a R-Y species is added across alkenes, alkynes, or other multiply bonded functionalities.[28] The first example is concerned with the C-C bond formation during the addition of CCl_4 to 1-octene in the presence of a radical initiator.[29] Reactions involving transfer of halogens, aryl chalcogens, as well as dithiocarbonyl groups were then later developed. The general mechanism for the atom and group transfer process is shown below.



Scheme 1.26 General mechanism for atom and group transfer process

Process **I** is the reaction between the radical and its precursor R-Y, which is reversible and degenerate. The outcome is needed to emphasize that the radical R· will be present in the medium with a relatively long lifetime, which allows it to react with many kinds of radical traps, even with comparatively unreactive substrates. In process **II** the radical R· has a enough lifetime to react with, for example, unactivated olefins. The new radical generated then undergoes process **III** and gives the final product, as well as regenerating the radical R· to propagate the chain. During all these process, the main deleterious

[28] Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis Volume 1: Basic Principles First Edition* **2001**, WILEY-VCH
[29] Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128-128.

interaction is the hydrogen abstraction between the radicals and the solvent or other side-products. However, these undesired reactions can be obviated or reduced by modifying the various parameters.

Conclusion

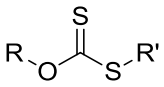
Radical chemistry in organic synthesis is a broad domain and is still under rapid development nowadays. They play an important role in many fields such as polymerization, biochemistry, and many other chemical processes. The short introduction above only covers a tiny fraction, which involves a brief history and some fundamental conceptions and reactions. More detailed processes and relevant cases will be discussed in the following chapters. Chapter 2 will focus mainly on the radical chemistry of xanthates, which was developed mainly in our laborotary.

Chapter 2

The Radical Chemistry of Xanthates

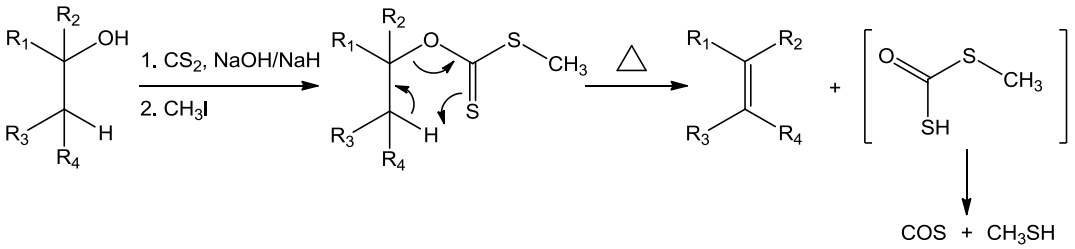
Introduction

Xanthates [30] or dithiocarbonates have the general structure shown in Scheme 2.1. Although they were described first by Zeise almost two centuries ago,[31] their chemistry did not receive much attention for a relatively long period of time.



Scheme 2.1 Structure of Xanthates

One early application of xanthates is the Chugaev elimination, [32] in which the decomposition of *S*-methyl xanthate produces an olefin as well as methanethiol and carbon oxysulfide (Scheme 2.2). This reaction is useful for the overall dehydration of secondary and more rarely tertiary alcohols into the corresponding olefins without rearrangement of the carbon skeleton.



Scheme 2.2 Chugaev elimination (Tschugaeff Olefin Synthesis)

Some applications were also reported in 1965, in which xanthates could serve as photosensitizers in the polymerization of vinyl monomers.[33] However, it is the discovery of the powerful Barton-McCombie deoxygenation in the early 1970s, that revealed xanthates to be such useful intermediates in synthetic radical chemistry. During the past two decades, the degenerative transfer of xanthates was developed mainly in our laboratory and proved to be very effective for the formation of carbon-carbon bonds. This chapter deals mainly with the underlying principles and applications of the xanthate chemistry.

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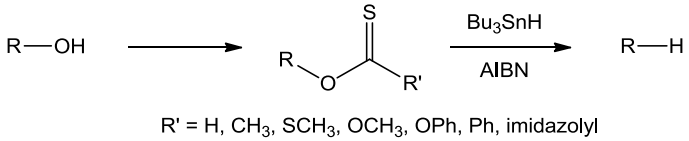
[30] This name comes from Greek which has the meaning of "yellowish, golden".
[31] (a) Zeise, W. C. *J. Chem. Phys.* **1822**, *35*, 173.; (b) Zeise, W. C. *J. Chem. Phys.* **1822**, 36, 1.
[32] Depuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431-457.
[33] Okawara, M.; Nakai, T.; Otsuji, Y.; Imoto, E. *J. Org. Chem.* **1965**, *30*, 2025.

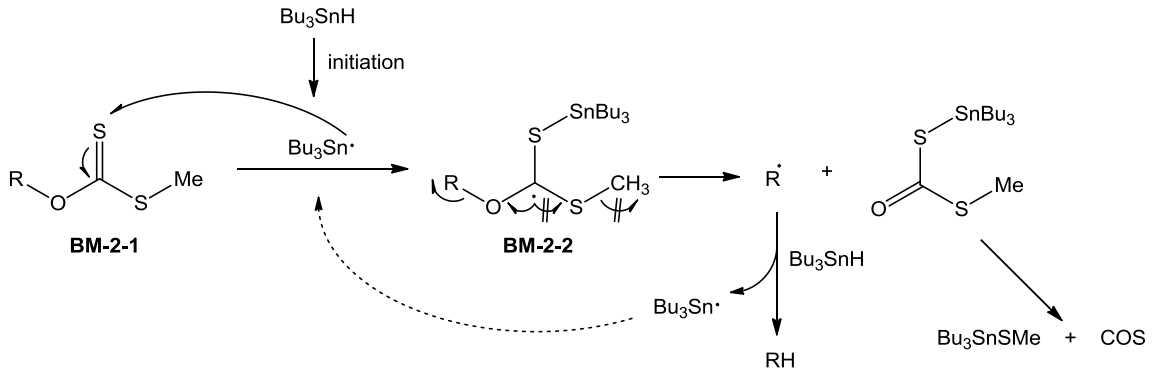
Ⅰ. The Barton-McCombie deoxygenation: mechanism and applications

In 1975, Barton and McCombie discovered an important radical process that can effectively achieve the deoxygenation of the secondary alcohols.[34] It is the most widespread application of xanthates, and is still freq.uently used, especially in the area of carbohydrates and aminoglycosides.



Scheme 2.3 Barton-McCombie deoxygenation

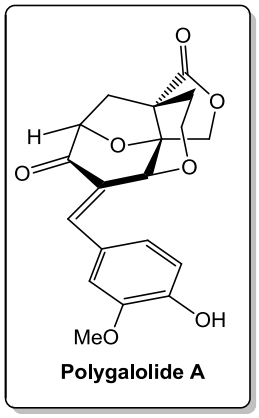
In this reaction, the alcohol is initially converted into the thiocarbonyl derivative then according to the mechanism depicted in Scheme 2.4, it is reduced with Bu_3SnH using a small amount of AIBN as initiator. The tributylstannyl radical attacks the radicophilic thiocarbonyl sulfur of **BM-2-1** to form a strong S-$SnBu_3$ bond and generates a new carbon centered radical **BM-2-2**, which is followed by breaking of the carbon-oxygen bond to complete the deoxygenation. The alternative fragmentation (to break the carbon-sulfur bond) is unlikely to happen since the primary methyl radical is comparatively high in energy. The fragmented carbon radical abstracts hydrogen from the tributyltin hydride to give the desired alkane and new tributylstannyl radical to propagate the chain. The driving force for this transformation is the conversion of a carbon-sulfur double bond to the much stronger carbon-oxygen double bond.

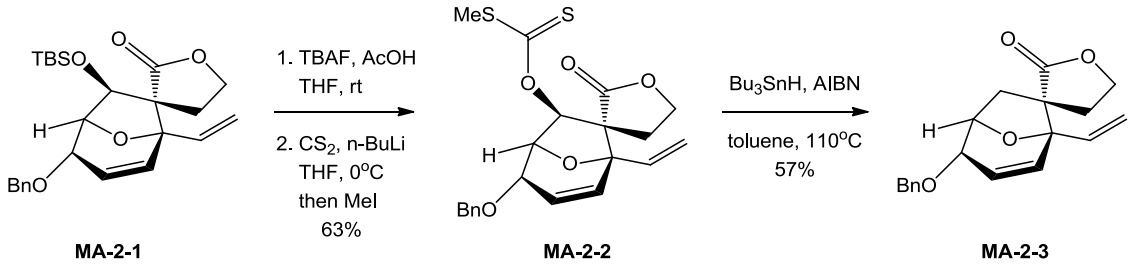


Scheme 2.4 The mechanism of Barton-McCombie deoxygenation

[34] Barton, D. H. R.; Mccombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

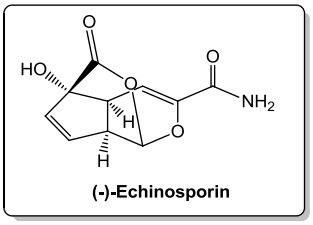
The Barton-McCombie deoxygenation has been very freq.uently used and continues to be applied in present times. For example, in a recent total synthesis of Polygalolide A by Adachi's group[35] (Scheme 2.5), the Barton-McCombie reaction was used to remove the oxygen functionality (OTBS) in **MA-2-1**. Deprotection of the TBS group followed by treatment with *n*-BuLi, CS_2, and MeI afforded the xanthate **MA-2-2**, which was then treated with Bu_3SnH in the presence of AIBN. This furnished the desired key intermediate **MA-2-3**.

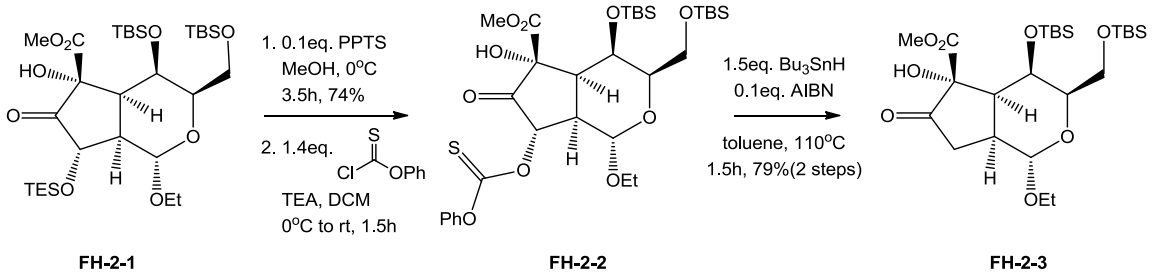




Scheme 2.5 Key deoxygenation in the total synthesis of Polygalolide A

Another example involves a formal synthesis of (-)-Echinosporin by the Hale's group.[36] After detaching the TES group from **FH-2-1**, *O*-phenyl carbonochloridothioate was used as the reagent to form the deoxygenation precursor **FH-2-2**. Standard Barton's conditions were then applied to obtain **FH-2-3**, the intermediate to the target compound.



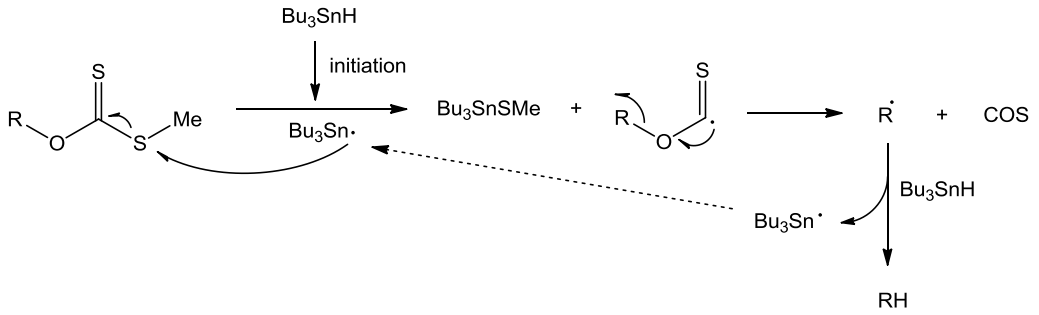


Scheme 2.6 Key deoxygenation step in the total synthesis of (-)-Echinosporin

[35] Adachi, M.; Yamada, H.; Isobe, M.; Nishikawat, T. *Org. Lett.* **2011**, *13*, 6532-6535.
[36] Flasz, J. T.; Hale, K. J. *Org. Lett.* **2012**, *14*, 3024-3027.

Ⅱ. A discovery during a mechanism study

However in 1984, almost 10 years after the discovery of the Barton-McCombie reaction, Barker and Beckwith proposed an alternative pathway which involved the intermediacy of alkoxythiocarbonyl radicals[37] (Scheme 2.7).

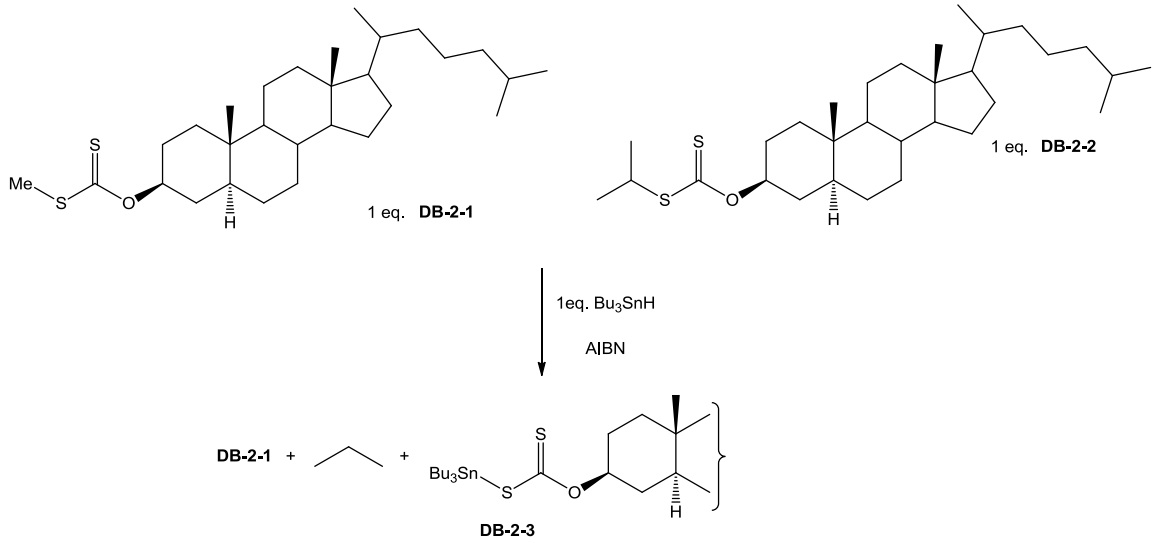


Scheme 2.7 An alternative mechanism of Barton-McCombie deoxygenation

In this alternative route, the tributylstannyl radical initially attacks the sulfide sulfur (S_H2 process) rather than attacking the thiocarbonyl sulfur. An alkoxythiolcarbonyl radical is thus generated and identified by ESR signal. The absence of a carbonyl absorption in IR also seems to support this explanation.

In order to clarify the mechanism, a systematic study was carried by the Barton group (Scheme 2.8). For example, a competition experiment was operated with eq.alent mixtures of **DB-2-1** and **DB-2-2**.[38] When they were treated with one eq.alent of Bu_3SnH at 80°C, the reaction took place within a few minutes with isopropyl derivative **DB-2-2** and gave **DB-2-3** as the sole product. Furthermore, if isopropyl was replaced by a more bulky mesityl group, a similar reaction took place even at room temperature. These phenomena are incompatible in a homolytic substitution process, which is subject to steric hindrance. But in the original mechanism, such observations are reasonable since the attack on the thiocarbonyl group is fast and reversible.

[37] Barker, P. J.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 683.
[38] Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 646-647.

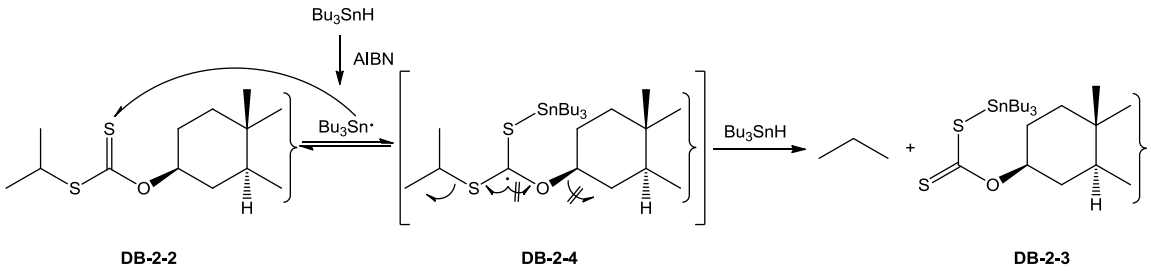


Scheme 2.8 Competitive experiment

Other competition experiments were also performed to exclude the S_H2 mechanism. Furthermore, the absence of the carbonyl absorption in IR could be explained by the fact that the tin thiocarbonate is unstable and extrudes carbonyl sulfide to form the tributyltin methyl sulfide (Scheme 2.7). Moreover, the ESR experiment was conducted under very different conditions compared with the usual deoxygenation process, and thus different pathways can therefore be applied in each case. With all these proofs, conclusion could be made to confirm the original mechanism, with the small but important modification that the addition of the stannyl radicals onto the thiocarbonyl group is both fast and reversible.

Another conclusion could also be drawn with the above experiment: in the rate determining β-scission step, the carbon-sulfur bond is more easily broken than the carbon-oxygen bond, at least kinetically other factors being eq.ual.[39] Since both the isopropyl radical and the 3-cholestannyl radical have similar stabilities, the more favorable cleavage of the carbon-sulfur bond takes place to give propane as the major product.

[39] Zard, S. Z. *Angew.Chem.Int.Ed.* **1997**, *36*, 673-685.



Scheme 2.9 detailed mechanism of the competition experiment

This accidental observation during the mechanistic study opened another door of the xanthates chemistry. Thus, rather than generating radicals by the homolytic cleavage of the carbon-oxygen bond (Barton-McCombie mode), radicals could be produced in a much more general chain process from the reversible scission of the carbon-sulfur bond. This strategy was developed systematically during the past two decades as the degenerative transfer of xanthates, and various carbon-carbon bond formations based on this approach have been achieved.

Ⅲ. Degenerative transfer of xanthates

The degenerative transfer of xanthates is an efficient and convenient method to form alkyl and acyl radicals, and provide them with a long enough lifetime that allow them to add even to un-activated olefins. This cannot normally be achieved by triorganotin hydride chemistry, since the intermolecular addition is much slower than hydrogen abstraction and this large difference in rates cannot be overcome by controlling the concentration. Moreover, this technique uses simple, cheap, and environment friendly reagents rather than the toxic organotin derivatives which also have well-known

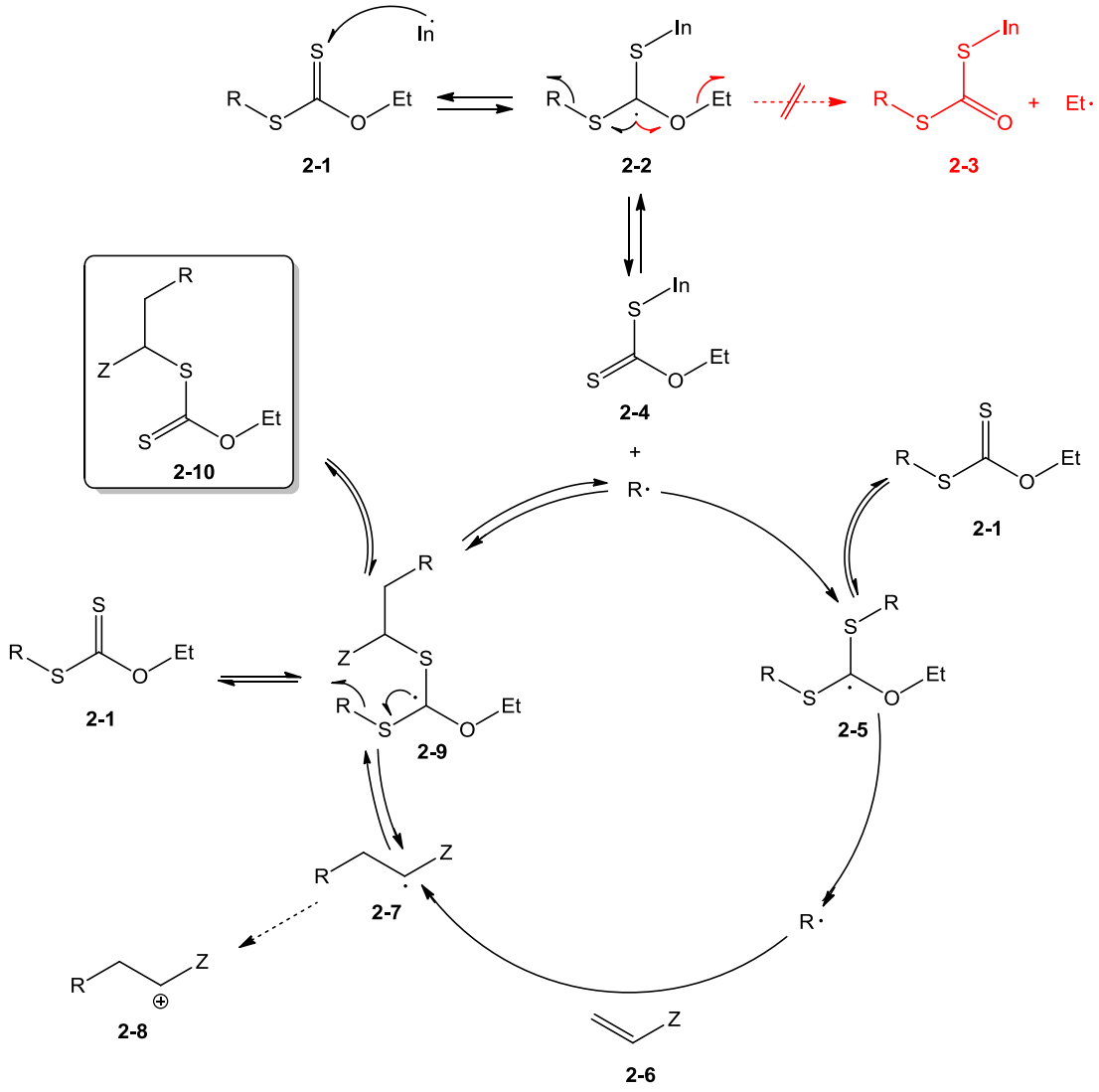
problems with purifications.[40] Other advantages are tolerance for many commonly used functional groups, the need of only a small volume of solvent, and a trivial experimental set-up. Thus, complex and highly functionalized structures can be assembled cleanly and rapidly under mild conditions.

1. Mechanism

The simplified mechanistic manifold for the degenerative transfer of xanthates is shown in Scheme 2.10. Initiation affords a small amount of radicals In· that readily add to xanthate **2-1** and form intermediate **2-2**, which is relatively stable and too hindered to dimerize. This step is in principle reversible but radical **2-2** evolves in a different direction in the bond cleavage: rather than breaking the carbon-oxygen bond to form the adduct **2-3** as in the Barton deoxygenation, intermediate **2-2** undergoes a reversible β-scission via carbon-sulfur cleavage to generate a new radical R· as well as adduct **2-4**. The primary alkyl substituents (methyl, ethyl, etc.) on oxygen make the Barton route unlikely to happen since the primary alkyl radical is relatively high in energy. Therefore the sole macroscopically detectable change with the radical species **2-2** will be through the pathway involving rupture of carbon-sulfur bond.

The radical R· generated during this process can either add reversibly to the thiocarbonyl group of xanthate **2-1**, or add to the olefin traps **2-6** to give another new radical **2-7**. Even un-activated olefins can be used in this reaction, since the radical R· has an effectively long lifetime. A new intermediate **2-9** is then formed by the addition of radical **2-7** to xanthate **2-1**, which can undergo fragmentation (half-headed curly arrows depicted for adduct **2-9**) to generate the desired product **2-10**.

[40] (a) Boyer, I. J. *Toxicology* **1989**, *55*, 253-298; (b) Appel, K. E. *Drug Metab. Rev.* **2004**, *36*, 763-786; (c) Dopp, E.; Hartmann, L. M.; Florea, A. M.; Rettenmeier, A. W.; Hirner, A. V. *Crit. Rev. Toxicol.* **2004**, *34*, 301-333.



Scheme 2.10 Mechanism for the xanthates transfer reaction

In the addition process, the relative stabilities of the starting radical R· and the new adduct radical **2-7** is a key factor. Unlike the Barton deoxygenation, in the xanthate transfer reaction the driving force generated is the addition to the alkene, where a strong σ bonf replaces the weaker π bond. If the new radical **2-7** is more stable than R·, the intermediate **2-9** will prefer returning to **2-7**, which will ultimately add to more alkene **2-6** to form oligomers. Furthermore, the peroxide initiator is able sometimes to oxidize the radical intermediate **2-7** to the cation **2-8**, which can then undergo typical ionic transformations.

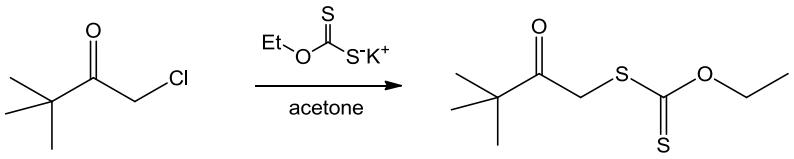
2. Preparation of the xanthates

Three general methods have been used in the present thesis to prepare the req.uisite xanthates: (a) reaction of a xanthate salt with an alkylating agent; (b) radical reaction with a bis-xanthate; and (c) radical addition-transfer of xanthate on an alkene. Based on these methods, a variety of xanthates with different functional groups were conveniently obtained from commercially available materials or easily made products.

a. Reaction of a xanthate salt with an alkylating agent

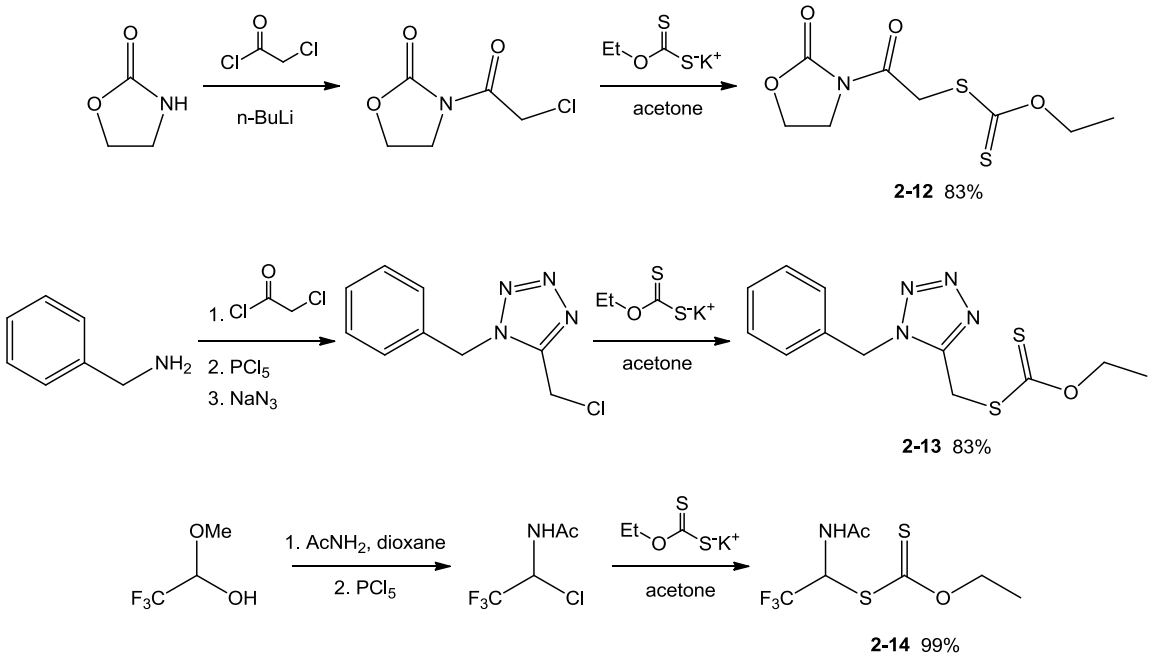
Generally, xanthates can be obtained simply by reaction of a xanthate salt with an alkylating agent RX (X here refers to leaving groups such as halide or sulfonate, etc.). Potassium *O*-ethyl xanthate salt is freq.uently used since it has an excellent nucleophilicity and is commercially available and very cheap.

This approach is efficient but mainly limited to xanthates with primary and secondary R groups. For example, xanthate **2-11** can be readily synthesized from the commercially available 1-chloro-3,3-dimethylbutan-2-one; [41] xanthate **2-12** can be prepared from oxazolidin-2-one in two steps;[42] xanthate **2-13** can be generated from the 5-chloromethyl tetrazole adduct accessibly by a three-steps seq.uence; [43] and xanthate **2-14** can be obtained starting from the hemiacetal of trifluoroacetaldehyde via *N*-(2,2,2-trifluoro-1-chloroethyl)-acetamide.[44]



2-11 90%

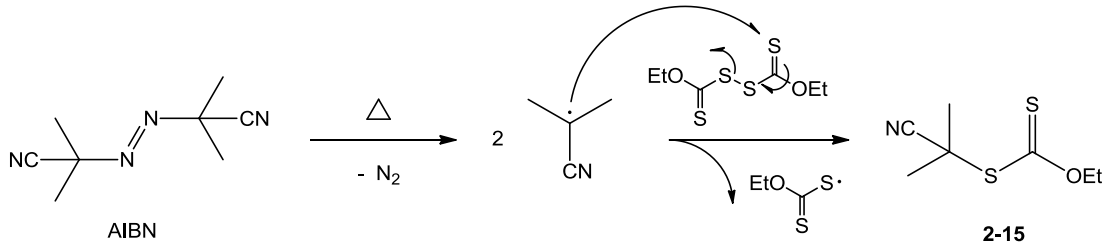
[41] Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295-7298.
[42] Bacqué, E.; Pautrat, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2312-2313.
[43] (a) Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Nakagawa, K. *Chem. Pharm. Bull.* **1989**, *37*, 322-326. ; (b) Biadatti, T.; Quiclet-Sire, B.; Saunier, J. B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 19-22.
[44] (a) Tanaka, K.; Ishiguro, Y.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 661-663. ; (b) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655-2657.



Scheme 2.11 Xanthates generated based on potassium *o*-ethyl xanthate salt

b. Reaction with bis-dithiocarbonates

Since the xanthates with tertiary R group are more hindered and not easily available through the usual nucleophilic substitution, a more efficient route was developed involving radical reaction with symmetrical bis-xanthate (bis-dithiocarbonate). The usual radical source is a slight excess of an azo-compound, such as AIBN. For example, xanthate **2-15** was readily prepared based on this strategy:[45] thermal decomposition of the azo-initiator gives two eq.alents of the same tertiary radicals, which are captured by the bis-xanthate to give the desired product.



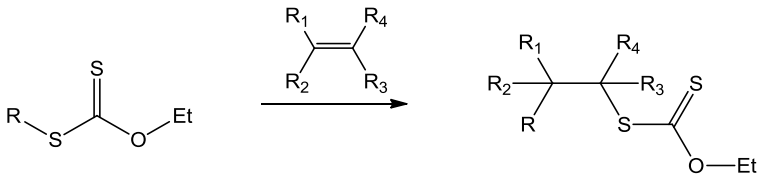
Scheme 2.12 A xanthate generated from a the bis-dithiocarbonate

[45] Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 277-280.

Another reaction involving bis-xanthate is known, namely a nucleophilic substitution by carbanions.[46]

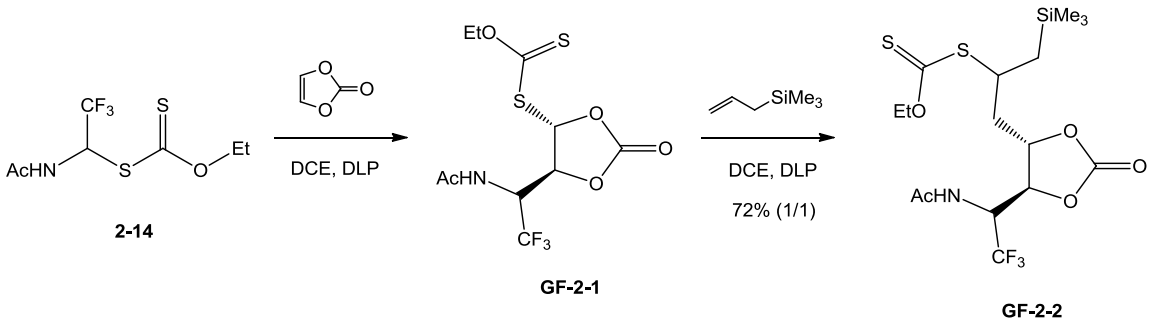
c. Radical addition-transfer of xanthate

One of the useful features of the radical chain addition of xanthates is that the end product is also a xanthate which can be used as a starting material for another radical process. This strategy is usually combined with the other methods and starts with a common and easily made xanthate, a more complex xanthate can then be produced by the radical addition to various olefinic traps.



Scheme 2.13 Radical addition-transfer of xanthate

For example, the previously mentioned xanthate **2-14** can be made to add to vinylene carbonate and the resulting new xanthate **GF-2-1** used as a springboard for accessing more complex xanthates, such as **GF-2-2**.[47] Based on this strategy, various complex xanthates can be constructed from simpler processes.

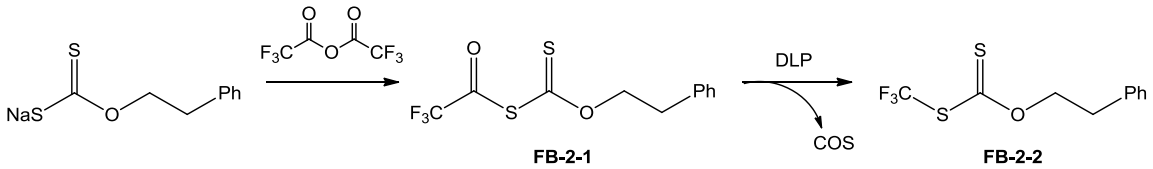


2-14 **GF-2-1** **GF-2-2**

Scheme2.14 Complex xanthates by successive radical addition-transfers

[46] Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett.* **1998**, 1435-1437.
[47] Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655-2657.

Other than the above general methods for preparing xanthates, special strategies were sometimes needed when facing specific cases. For example, in order to make the *S*-trifluoromethyl xanthate **FB-2-2**, direct substitution of a trifluoromethyl halide is not feasible. As shown in Scheme 2.15, a special procedure involving decarbonylation of the *S*-trifluoroacetyl xanthate **FB-2-1** proved to be a reasonable route.[48] Here the reason for using an *O*-phenethyl group to replace the common *O*-ethyl was to avoid having to handle a potentially volatile and perhaps malodorous substance. Although the initial yield was modest as ~40%, it has recently been optimized to up to ~60% with modification of the *O*-alkyl group.[49]



Scheme2.15 Preparation of the *S*-trifluoromethyl xanthate

Other than the methods listed above, there are a number of other routes for the synthesis of xanthates. For example, xanthates containing tertiary carboxyl groups can be prepared via ring-opening of a dichloroepoxide intermediate with a nucleophilic carbodithioate salt as the key step.[50] Conjugate addition of xanthic acid to electrophilic olefins was also reported as an efficient method to synthesize various xanthates.[51] Thioacylation reactions with thiophosgene or 1,1'-thiocarbonyldiimidazole is also documented.[52]

[48] Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069-1071.
[49] Li, S. *Doctoral Work* **2012**
[50] Lai, J. T.; Shea, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4298-4316.
[51] Binot, G.; Quiclet-Sire, B.; Saleh, T.; Zard, S. Z. *Synlett* **2003**, 382-386.
[52] Wood, M. R.; Duncalf, D. J.; Rannard, S. P.; Perrier, S. *Org. Lett.* **2006**, *8*, 553-556.

3. Synthetic potential of the degenerative addition-transfer of xanthates

With xanthate transfer radical chemistry, numerous polycyclic and heterocyclic compounds can be obtained in one-pot reactions or addition-cyclization procedures. Furthermore, the dithiocarbonate group present in the compounds can be modified either by ionic or radical methods. Complex structures and new molecular skeletons can therefore be rapidly constructed.

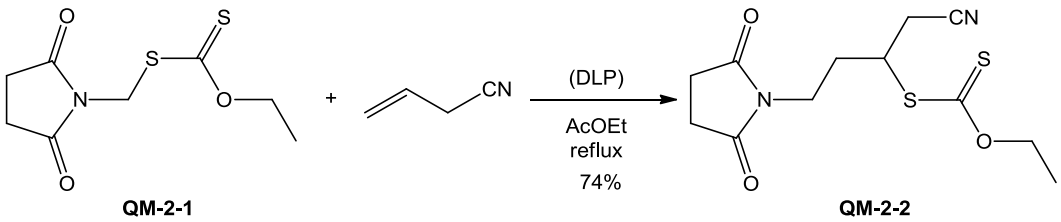
a. Radical Additions

The most important feature of the xanthate transfer process is to provide long-lifetime intermediate active radicals to react with a wide range of alkenes through intermolecular addition. This transformation is possible with a number of xanthates containing various functional groups, including ketones, esters, nitriles, boronates, and even heterocyclic rings.

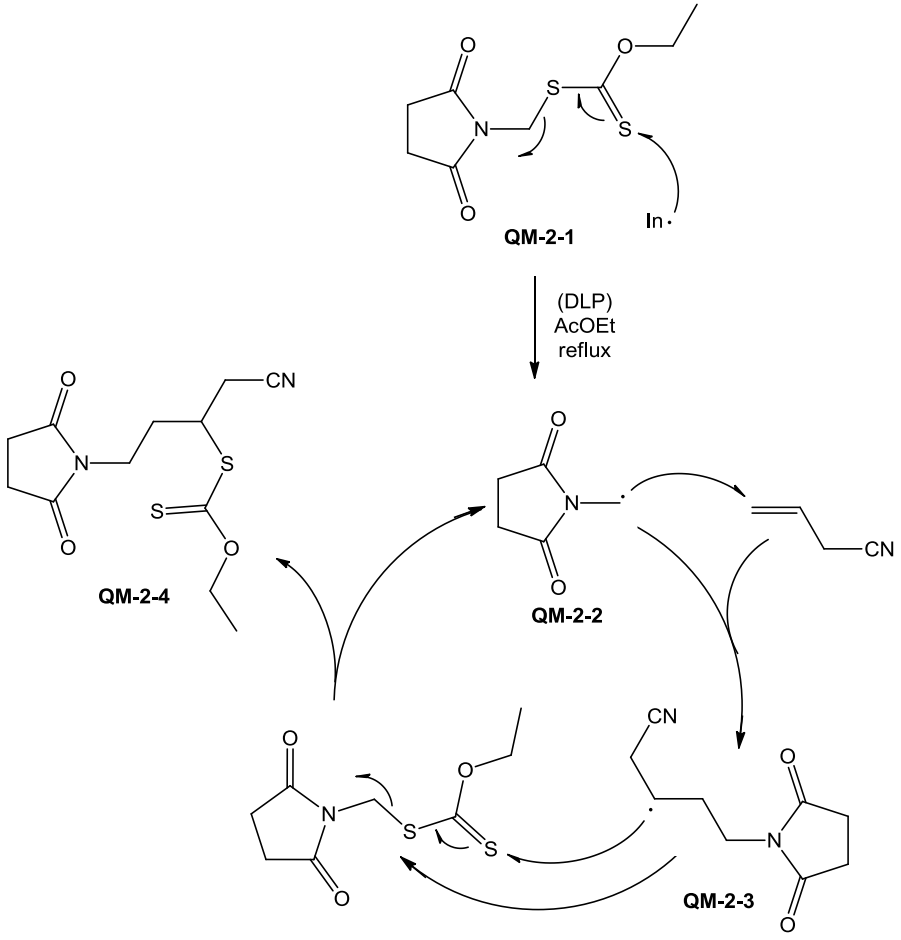
The example below is concerned with a general process established for the regioselective aminomethylation of alkenes.[53] When exposed to DLP, xanthate **QM-2-1** gives rise to radical **QM-2-2** quite efficiently since the thermal decomposition of the peroxide generates ultimately primary undecyl radicals which rapidly add to the thiocarbonyl group, and the intermediate collapses preferentially in the direction of the more stable radicals.

In this reaction, the coupling of the two carbonyls in an imide structure like **QM-2-1** was found to be very important to stabilize the primary aminoalkyl radical, which leads to a clean radical addition to the olefins. However, if only one carbonyl is presented in the xanthate, the desired mono-adduct **QM-2-4** will be replaced by the oligomer. These results confirmed the importance of the relative stabilities of the original radical and the adduct radical in the degenerative transfer of xanthate.

[53] Quiclet-Sire, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279-3282.

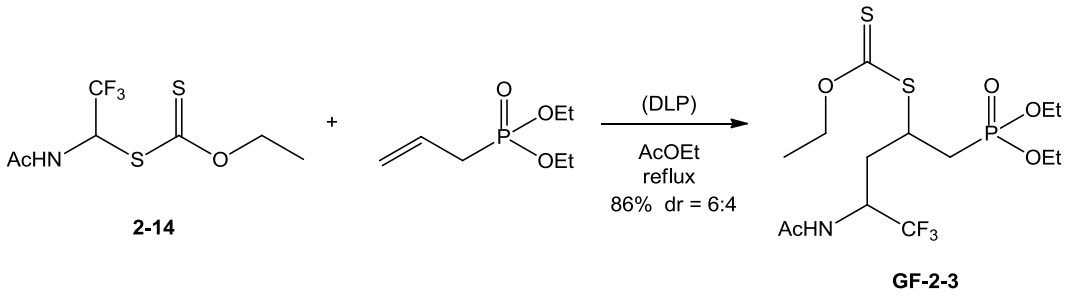


Scheme 2.16 Addition of primary radical to unactivated alkene



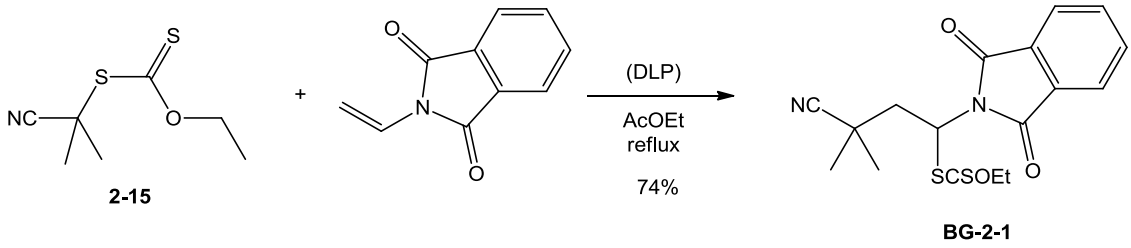
Another example involves the xanthate **2-14** which was mentioned earlier. This xanthate was considered to be an efficient reagent to give a stabilized secondary radical and to introduce the α-trifluoromethylamine motif to many olefinic partners, and which tolerates

various common functional groups.[54] With this approach a variety of fluorinated compounds can be prepared in a practical manner.



Scheme 2.17 Addition of secondary radical to unactivated alkene

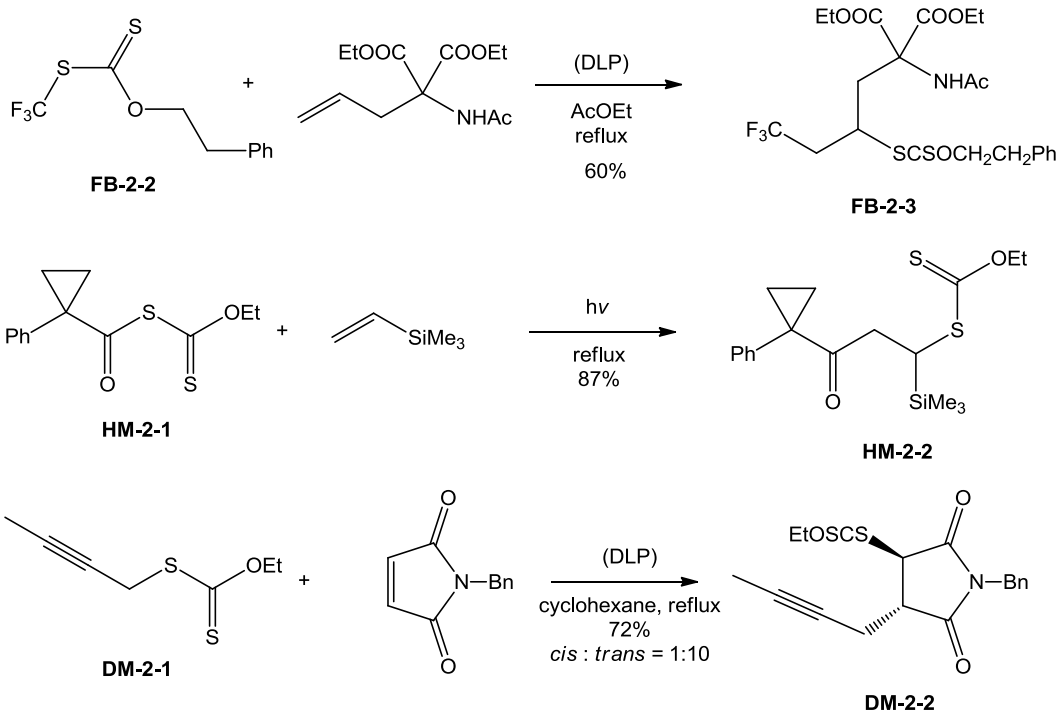
Even hindered tertiary radicals can be obtained from the corresponding xanthates and added to the terminal alkenes to construct the corresponding structures,[55] as illustrated by the example in Scheme 2.18.



Scheme 2.18 Addition of tertiary radical to alkene

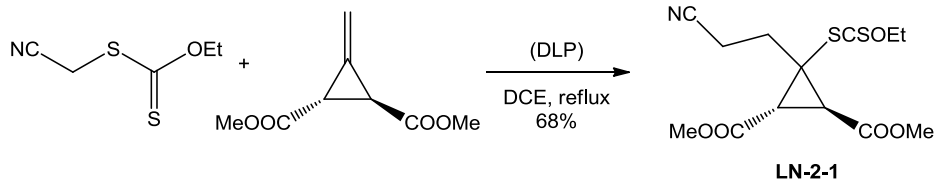
Besides, various special radicals can be generated from the corresponding xanthates, such as trifluoromethyl[48], cyclopropylacyl[56] and propargyl radicals,[57] and captured with different olefinic partners to create functionalized structures not accessible using traditional ionic or organometallic chemistry.

[54] (a) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655-2657; (b) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002-6016.
[55] (a) Quiclet-Sire, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279-3282; (b) Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 277-280.
[56] Heinrich, M. R.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 4969-4972.
[57] Denieul, M. P.; QuicletSire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495-5498.

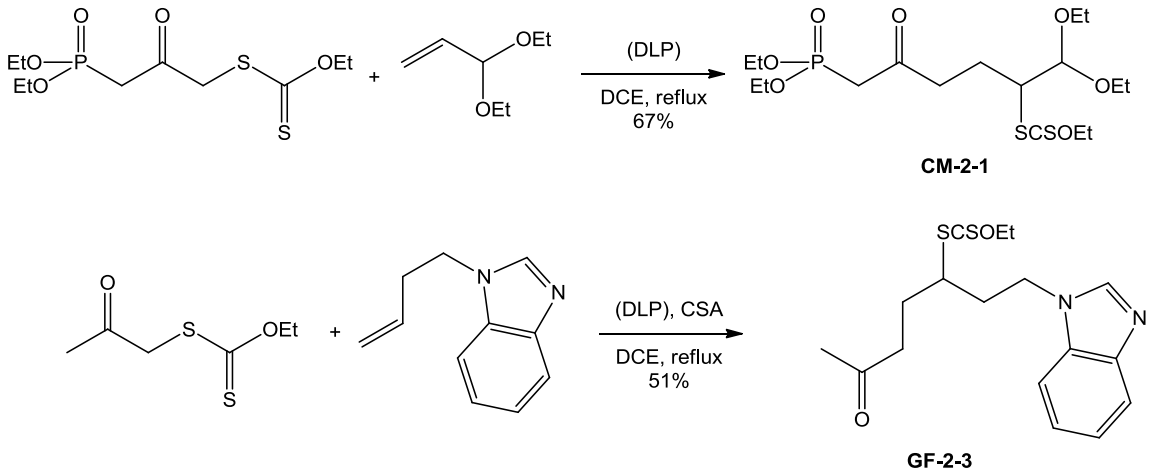


Scheme 2.19 Uncommon radicals generated from xanthates

Another advantage of the xanthate transfer technique is that various functionalized alkenes can be made to react efficiently with xanthates. A selection of examples is displayed in Scheme 2.20 illustrating the compatibility with various substituents.[58] The products thus bear functionality derived from both the starting xanthates and the alkene and can be subseq.uently modified by more traditional reactions. Furthermore, it is often not necessary to protect many of the polar groups typically encountered in synthesis (ketones, alcohols, carboxylic acids, etc.). This represents a considerable advantage of radical processes in general.



[58] (a)Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815-9818; (b) Corbet, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 2861-2864; (c) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345-4348.



Scheme 2.20 Addition of xanthate to different kinds of alkenes

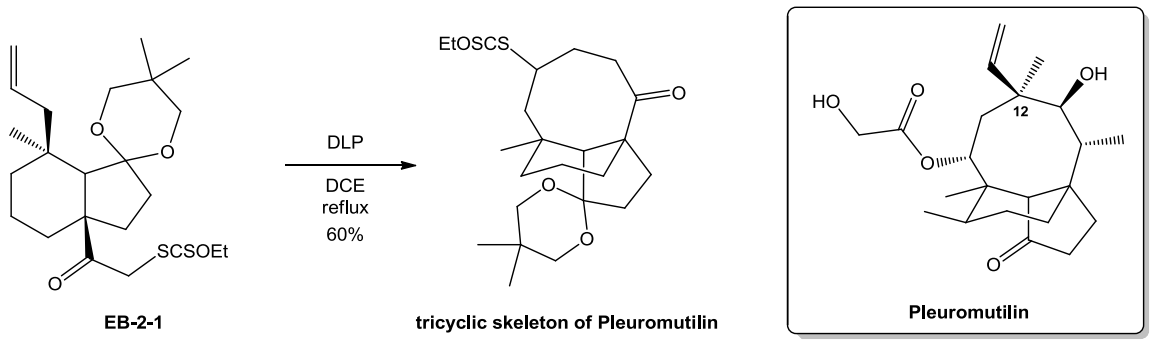
Another important process is the direct addition of xanthates to aromatic systems and this subject will be discussed later in Chapter 5.

b. Radical Cyclisation

Using xanthates as precursors for radical cyclizations turns out to be a particularly efficient strategy to access cyclic compounds as well as polycyclic systems. Based on this strategy, the xanthate group contained in the molecules can be added either to an olefinic partner or to an aromatic ring (or heteroaromatic ring) through an intramolecular process.

1) Ring-closure onto internal alkene

The formation of the eight-membered ring present in Pleuromutilin by direct cyclization of xanthate **EB-2-1** underscores the tremendous synthetic advantages accruing from the relatively long lifetime of radicals generated from xanthates.

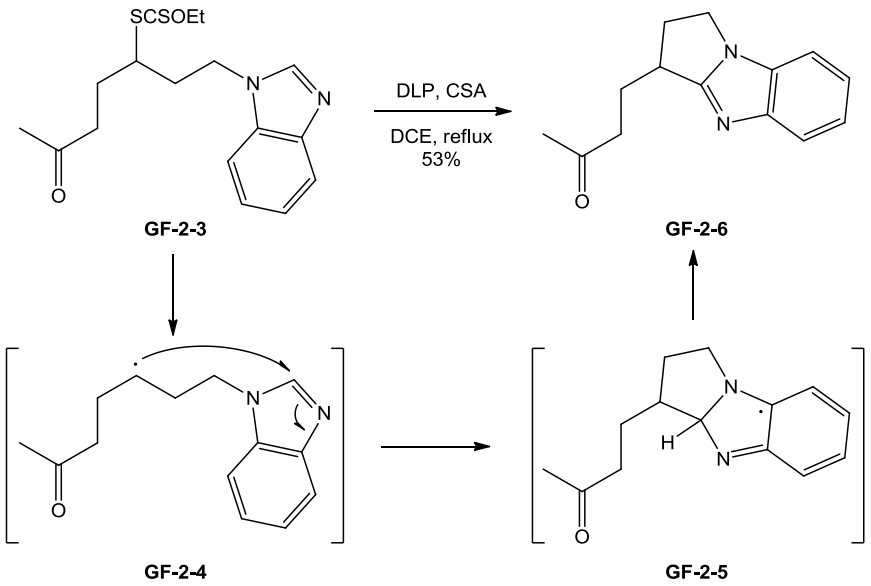


Scheme 2.21 Synthesis of the tricyclic skeleton of Pleuromutilin

2) Ring-closure to aromatic derivatives

We have presented in Scheme 2.20 compound **GF-2-3**, the product of radical addition to 1-(3-butenyl)-benzimidazole. This addition product can in fact be transformed into a more complex molecule by implementing a further radical cyclization by exploiting the presence of the xanthate. Although the radical **GF-2-4** can react with its precursor **GF-2-3**, this process is degenerate. Radical **GF-2-5** is too stabilized to propagate the chain but its conversion to the final product can occur either through dismutation or by oxidation through electron transfer to the peroxide and loss of a proton. Therefore, instead of the submolar amounts of peroxide needed in the radical addition, the cyclization to aromatic

system req.uires stoichiometric quantities. As a result, the tricyclic compound **GF-2-6** was finally obtained through a continuous radical cyclization.[59]

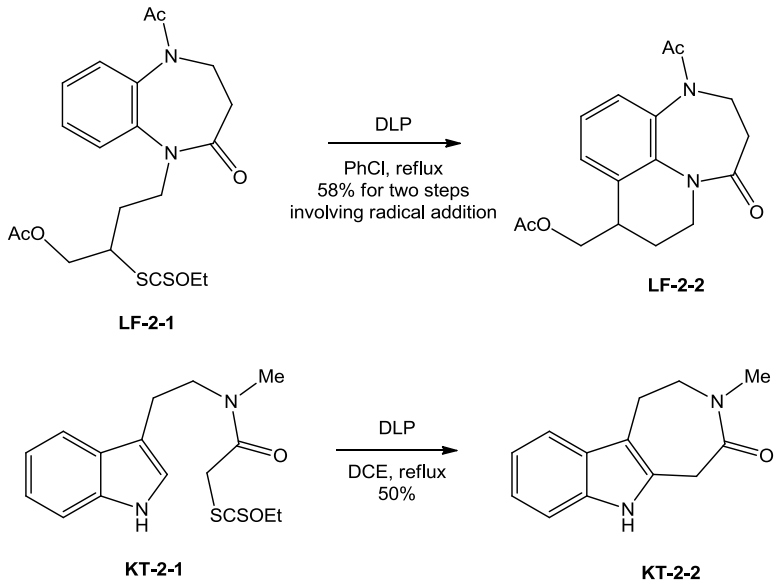


Scheme 2.22 Cyclization of xanthate to five-membered ring

It's worthy to note that the isolation of the radical addition product is not always necessary when the same solvent and initiator are used. The two operations can be carried out in one pot, with only modifying the concentration, since the intermolecular addition prefers a high concentration while the intramolecular cyclization prefers a low concentration. This one-pot procedure simplifies the synthesis of some target molecules or if scale up is considered.

Furthermore, not only five-membered ring can be generated through the intramolecular cyclization of xanthates, larger rings such as six-membered[60] and seven-membered[61] rings are also accessible. With these strategies, various combinations of polycyclic rings can be constructed by modifying the xanthate precursors.

[59] Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345-4348.
[60] Lebreux, F.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2844-2847.
[61] Kaoudi, T.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731.



Scheme 2.23 Radical cyclizations to generate larger rings

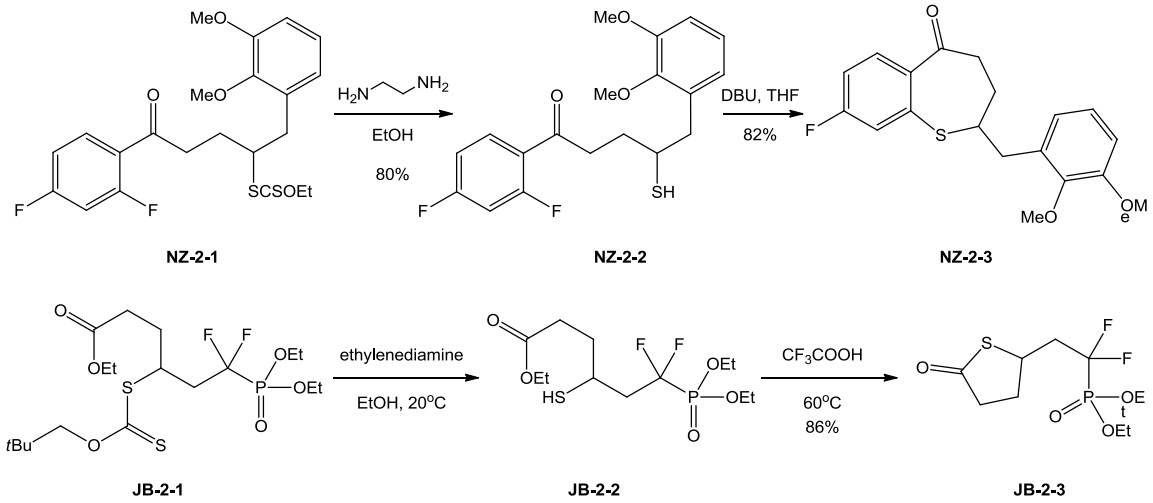
c. Transformation of xanthates into other functional groups

According to the discussion above, radical addition of xanthates to simple un-activated olefins is considered to be a powerful tool for creating carbon-carbon bonds in an intermolecular fashion. However, the addition products still contain the dithiocarbonate functionality which can lead to a number of subseq.uent radical and non-radical transformations. This feature represents a tremendous advantage of xanthate chemistry, since it expands considerably the synthetic possibilities.

1) by ionic methods

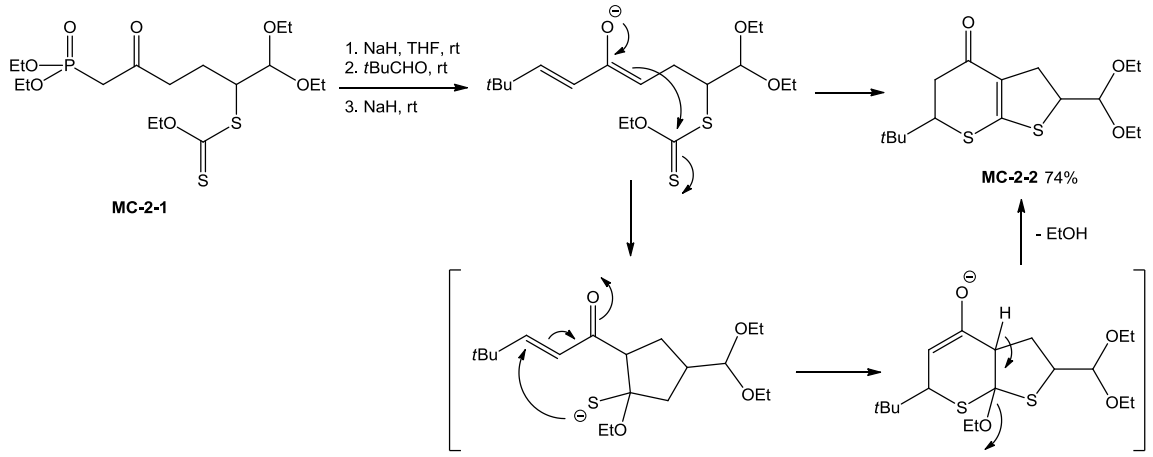
The xanthate group can be readily cleaved by exposure to excess ethylenediamine in ethanol under an inert atmosphere to afford the corresponding thiol. The resulting thiol can be then engaged in nucleophilic substitutions under either basic [62] or acidic [63] conditions to give, for example, benzothiepinone **NZ-2-3** or thiolactone **JB-2-3**.

[62] Boutillier, P.; Quiclet-Sire, B.; Zafar, S. N.; Zard, S. Z. *Tetrahedron-Asymmetry* **2010**, *21*, 1649-1665.
[63] Boivin, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 6877-6880.



Scheme 2.24 Transformation of xanthates to thiols by aminolysis

Furthermore, the dithiocarbonyl moiety can also serve as a building block in the construction of many sulfur containing polycyclic compounds. For example, in combination with the Horner-Wadsworth-Emmons reaction, β-keto-ε-xanthyl phosphonate **MC-2-1** can be transformed into thieno[2,3-b]thiopyran-4-ones **MC-2-2** through a one-pot base-induced intramolecular seq.uence of req.ctions.[64]

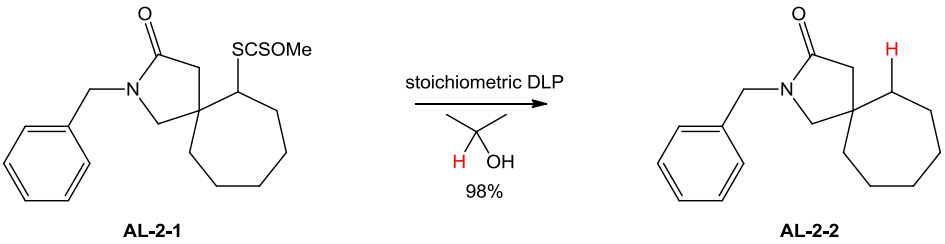


Scheme 2.25 Transformation of xanthates into thieno[2,3-b]thiopyranone

[64] Corbet, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 2861-2864.

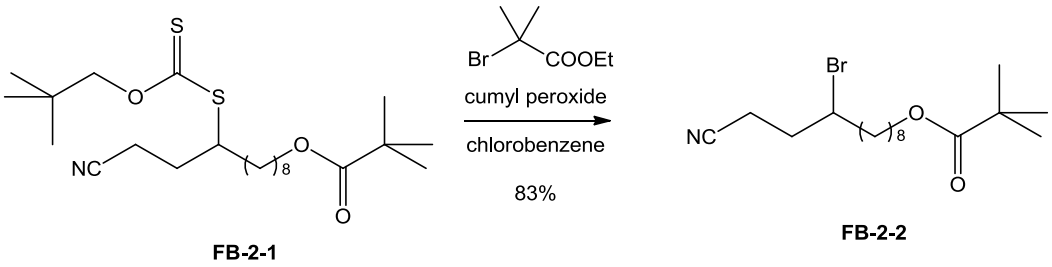
2) by radical methods

Besides ionic transformations, xanthates are capable of participating in a number of different radical processes. For example, a practical reductive dexanthylation was documented in 1996,[65] involving the cleavage of the carbon-sulfur bond in the presence of stoichiometric amounts of lauroyl peroxide in isopropanol. The hydrogen on the tertiary carbon of isopropanol serves as the hydrogen source for this procedure. With this method the dithiocarbonate moiety can be removed from radical addition derivatives, and the resulting alkanes could either be the final products or substrates for subseq.uent ionic chemistry.



Scheme 2.26 Reductive de-xanthylation with DLP-isopropanol

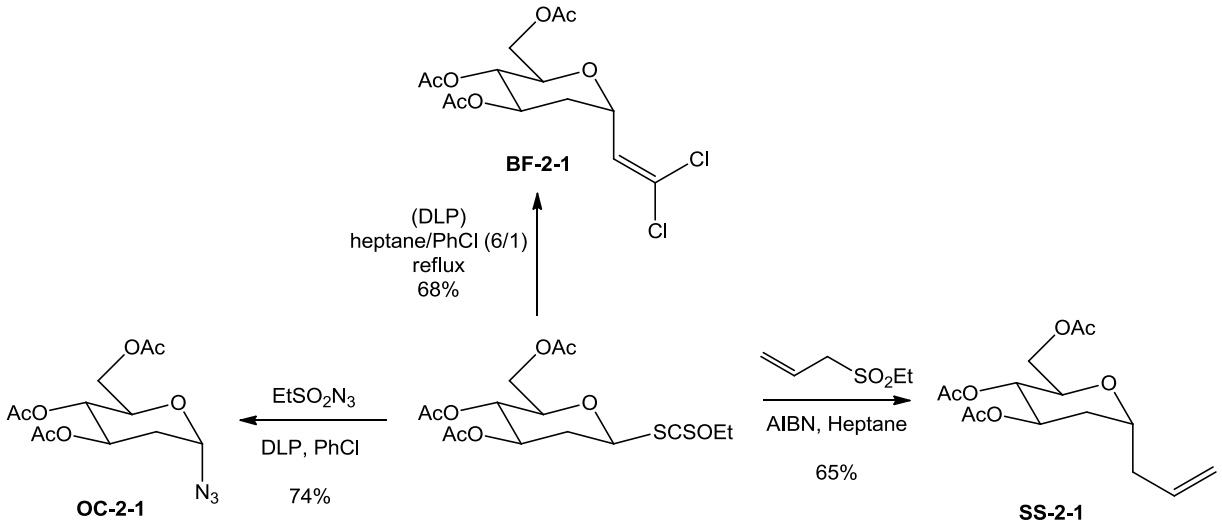
Another reaction is the replacement of a xanthate by a bromine using ethyl bromoisobutyrate as the bromine transfer agent.[66] An example is given in Scheme 2.27.



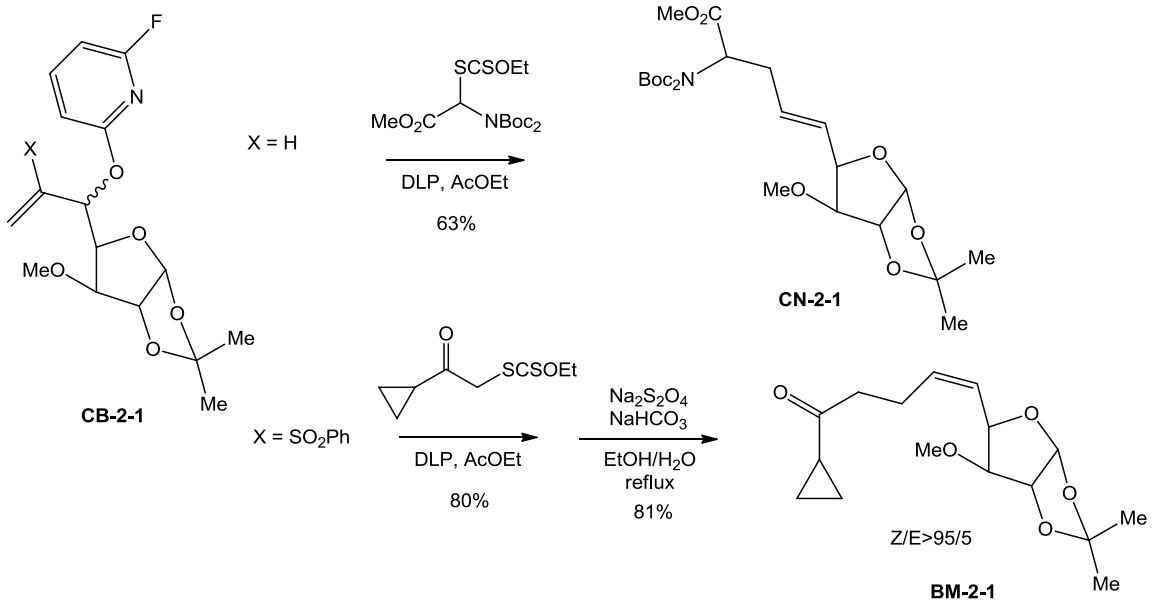
Scheme 2.27 Transformation of xanthate group to bromine

[65] Liard, A.; QuicletSire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877-5880.
[66] Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2002**, 811-813.

Numerous radical based transformations such as allylation,[67] vinylation,[68] azidation,[69] and more complex olefination[70] have also been described. A few representative examples are pictured in Scheme 2.28 and 2.29.



Scheme 2.28 Various transformations of xanthate group

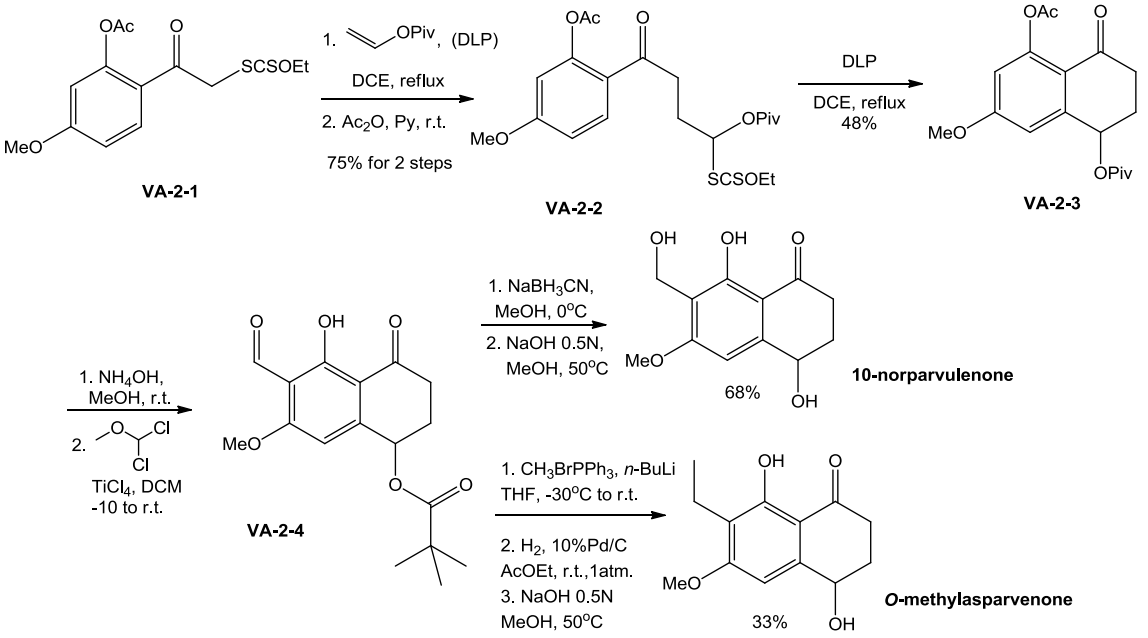


Scheme 2.29 Controlled olefination of xanthate group

[67] Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1998**, *37*, 2864-2866.
[68] Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1999**, *38*, 1943.
[69] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496-6497.
[70] (a) Charrier, N.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2008**, *130*, 8898; (b) Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

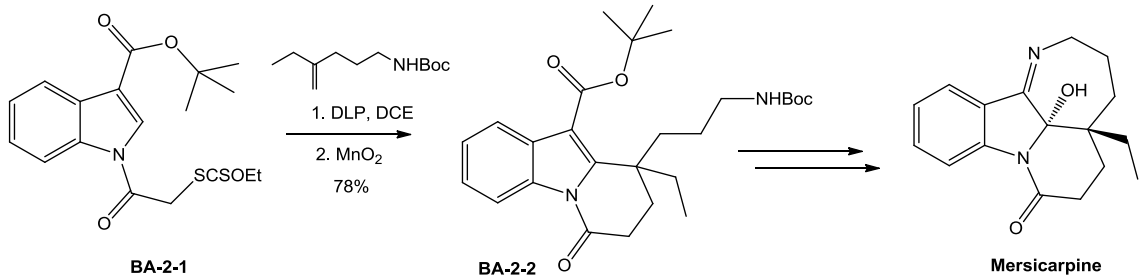
d. Applications to the total synthesis of natural products

Using the xanthate mediated seq.uence of radical addition and cyclization, some natural products could be rapidly constructed. For example, in the total synthesis of two natural products 10-norparvulenone and *O*-methylasparvenone, the xanthate was instrumental in the formation of the key α-tetralone framework[71] (Scheme 2.30).



Scheme 2.30 Total synthesis of 10-norparvulenone and *O*-methylasparvenone

Another example is the intermolecular radical addition-cyclization cascade used in constructing the tricyclic indole structures such as **BA-2-2**, a key intermediate in the synthesis of Mersicarpine (Scheme 2.31). Numerous potential bioactive derivatives can be prepared by simply replacing the alkene partner.[72]



Scheme 2.31 Synthesis of tricyclic indole structures

[71] Vargas, A. C.; Quiclet-Sire, A.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 3717-3719.
[72] Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800-2803.

Conclusion

From the above discussions, we could see that the xanthates exhibit a perfect balance of reactivity, stability and accessibility, and the radical xanthate transfer process has proved to be an efficient method for both intermolecular and intramolecular additions, which can bring together a variety of functional groups under mild conditions. Furthermore, experimental simplicity, absence of heavy and toxic metals, mild and neutral reaction conditions, the possibility of operating under quite concentrated conditions, and the compatibility with a wide range of functional groups, etc. are all advantages that must be underscored. They would be especially useful when large scale preparations are being considered.

Some of the other important applications of xanthates are not included in this section, such as the RAFT (Reversible Addition Fragmentation Transfer) and MADIX (Macromolecular Design by Interchange of the Xanthates), which are considered to be the most powerful technologies for constructing block polymers both in industry and in academia.[73]

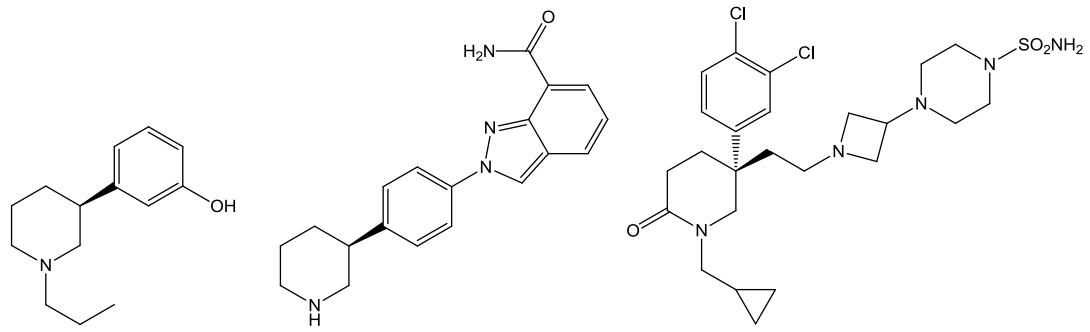
[73] Barner-Kowollik C., *Handbook of RAFT Polymerization* **2008**, WILEY-VCH

Chapter 3

Radical Synthesis of 5-Arylpiperidin-2-ones

Introduction

The piperidine ring is a ubiquitous molecular skeleton, which exists in natural products and synthetic biologically active molecules. A search of the chemical and patent literature shows that several thousands of compounds in clinical and preclinical research are derived from this simple ring system.[74] For instance, as shown in Scheme 3.1, preclamol is the first selective D_2-like dopamine autoreceptor agonist, and such kinds of substances are potential drugs for the treatment of depression and drug addiction, Parkinson's and Alzheimer's diseases, and schizophrenia. MK-4827 developed by Merck is another example of this useful structure, and it has entered clinical trials as an antitumor drug.[75] Piperidinone is less commonly found in the structures of bioactive molecules. However, we can still find it in many molecules which have activities on the central nervous system, such as anticholinergics[76] and antidepressants (e.g. UK-224,671 is a potent selective antagonist of the neurokinin 2 receptor[77]), in diabetic II[78] and in antithrombotic treatments.[79] It is also well documented that piperidin-2-ones are common synthetic precursors for piperidines and biologically important polycyclic alkaloids, such as indolo[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines.[80]



Scheme 3.1 Examples of 3-aryl-piperidine and 5-arylpiperidin-2-one drugs

[74] Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.*, **2000**, *2*, 3679-3681.
[75] Jones, P.; Altamura, S.; Boueres, J.; Ferrigno, F.; Fonsi, M.; Giomini, C.; Lamartina, S.; Monteagudo, E.; Ontoria, J. M.; Orsale, M. V.; Palumbi, M. C.; Pesci, S.; Roscilli, G.; Scarpelli, R.; Schultz-Fademrecht, C.; Toniatti, C.; Rowley, M. *J. Med. Chem.* **2009**, *52*, 7170-7185.
[76] Bishop, D. C.; Cavalla, J. F. *J. Chem. Soc. C* **1966**, 802-805.
[77] MacKenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Newman, S. D.; Jones, B. C. *J. Med. Chem.* **2002**, 45, 5365-5377.
[78] Pei, Z. H.; Li, X. F.; von Geldern, T. W.; et al. *J. Med. Chem.* **2007**, 50, 1983-1987.
[79] Corte, J. R.; Fang, T.; Pinto, D. J. P.; et al. *Bioorg. Med. Chem. Lett.* **2008**, 18, 2845.
[80] Takasu, K.; Nishida, N.; Tomimura, A.; Ihara, M. *J. Org. Chem.*, **2005**, *70*, 3957-3962.

Ⅰ. Synthesis of 5-substituted piperidin-2-ones

1. Oxidation and reduction

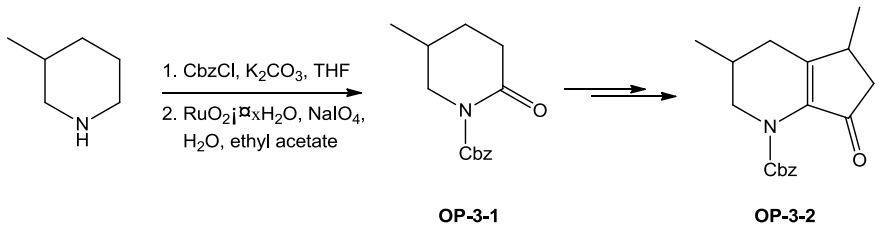
Among all the synthetic strategies for constructing the piperidone skeleton, oxidation of piperidine and reduction of pyridinone are of special importance due to the advantage that no more cyclic structure is added. Therefore, a number of methods were established for these transformations.

a. Oxidation of the piperidine in position-2

Piperidinones are generally the precursors for obtaining piperidines, by reducing the carbonyl group of the ring. As the opposite reactions, the oxidation of piperidines by the mercuric derivatives,[81] a mixture of bromine and acetic acid,[82] and ruthenium oxides[83] are also mentioned in the literature.

For example, Occhiato et al. have mentioned in their publication that the key intermediate piperidin-2-one **OP-3-1** in the synthesis of cyclopenta-fused azacycle **OP-3-2** was prepared by the oxidation of the commercially available 3-methylpiperidine using hydrated RuO_2 in the presence of $NaIO_4$[84] (Scheme 3.2).

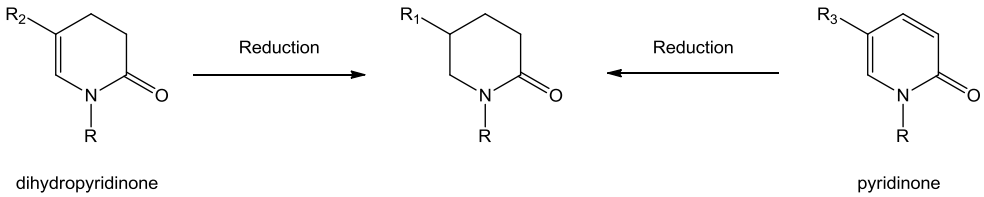
[81] (a) Fujii, T.; Ohba, M.; Yoshifuji, S. *Chem. Pharm. Bull.* **1977**, *25*, 3042-3048. (b) Wenkert, E.; Angell, E. C. *Synth. Commun.* **1988**, *18*, 1331-1337. (c) Bentley, N.; Singh, G.; Howarth, O. W. *Tetrahedron* **1993**, *49*, 4315-4320.
[82] Castro, A.; Juarez, J.; Gnecco, D.; Teran, J. L.; Orea, L.; Bernes, S. *Synth. Commun.* **2006**, *36*, 935-942.
[83] (a) Torii, S.; Inokuchi, T.; Yukawa, T. *Chem. Lett.* **1984**, 1063-1066. (b) Matsumura, Y.; Takeshima, Y.; Okita, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 304-306. (c) Carpes, M. J. S.; Correia, C. R. D. *Tetrahedron Lett.* **2002**, *43*, 741-744.
[84] Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728-9741.



Scheme 3.2 Oxidation of substituted piperidine

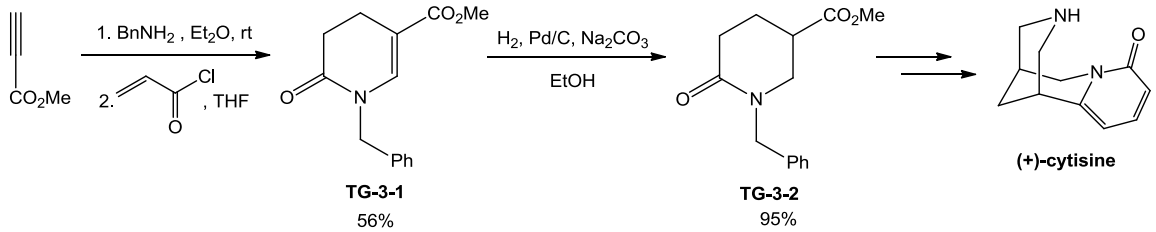
b. Reduction of the pyridinone

As depicted in Scheme 3.3, piperidinones could also be generated from dihydropyridinones and pyridinones by reducing the unsaturated bond(s) of the ring with a hydrogen source.



Scheme 3.3 Reduction of pyridinones

For example, this strategy was applied in a general synthetic route for the construction of lupin alkaloids, such as (+)-cytisine.[85] The 5-substituted-2-piperidone intermediate **TG-3-2** was obtained by partial reduction of the precursor **TG-3-1** with catalytic hydrogenation over palladium.



Scheme 3.3 partial reduction of dihydropyridinone

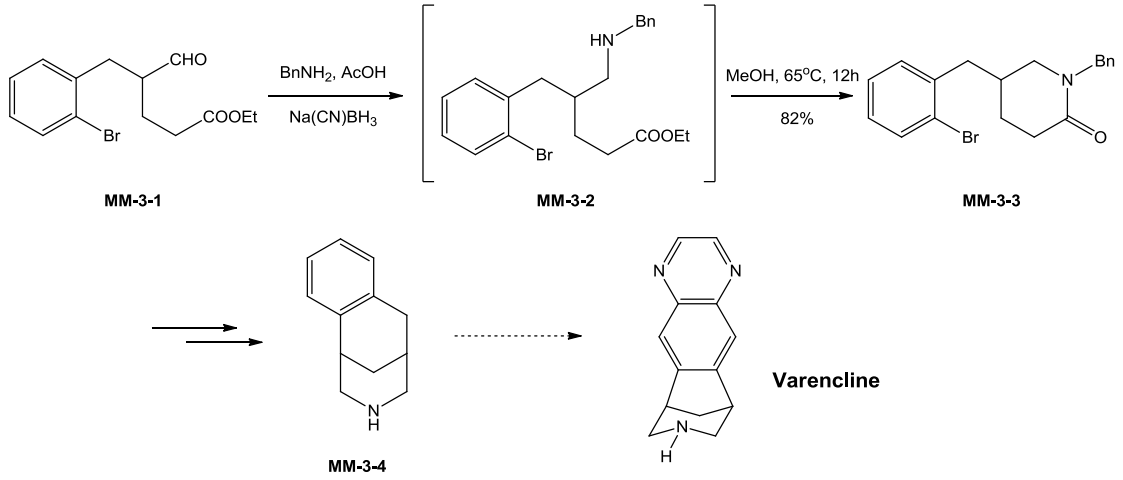
[85] Gray, D. ; Gallagher, T. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2419-2423.

2. Intramolecular C-N bond formations

Intramolecular C-N bond formation is another efficient way to construct 2-piperidone, and a number of studies have focused on this strategy, using intramolecular lactamizations, the Mitsunobu reaction, and Michael addition-cyclization seq.uences, etc.

a. Lactamization of δ-amino carboxylates

Scheme 3.4 depicts a synthetic strategy involving lactamization in an approach to varencline, a drug for smoking cessation. Maier et al. thus reported a method to prepare the precursor of 1,5-methano-3-benzazocines **MM-3-4**, [86] a lead compound in the development of varencline. After the condensation between the aldehyde **MM-3-1** and benzylamine, the imine was then mildly reduced by sodium cyanoborohydride to form the intermediate **MM-3-2**, followed by intramolecular lactamization to generate the piperidin-2-one **MM-3-3**.



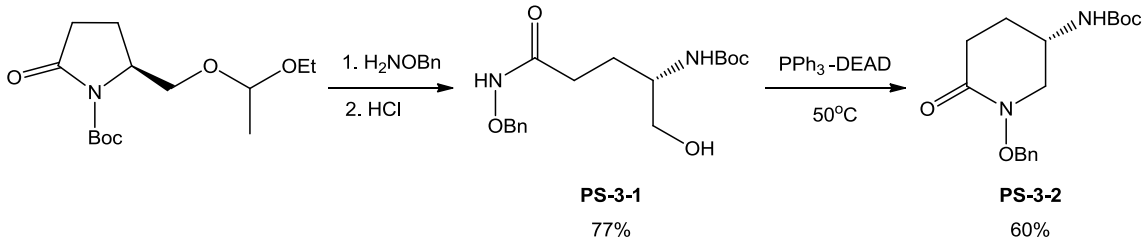
Scheme 3.4 Reductive amination followed by lactam formation

b. Formation of the amide followed by cyclization

This strategy to generate the six-membered ring of piperidin-2-one relies on the formation of an acyclic chain containing an amide, followed by cyclization. There are

[86] Satyanarayana, G.; Maier, M. E. *Tetrahedron* **2008**, *64*, 356-363.

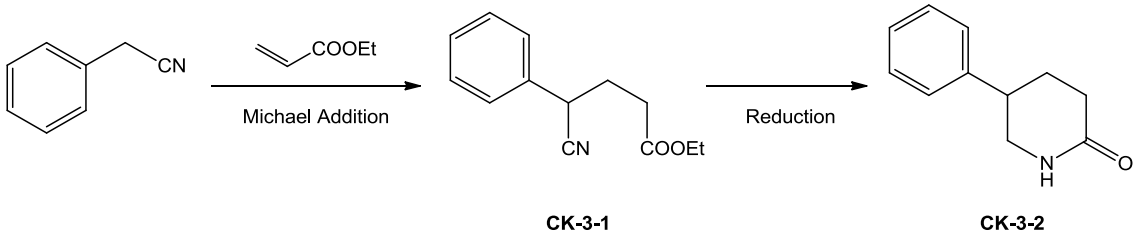
several strategies to conduct the cyclization. For example, the C-N bond could be formed by the direct replacement of a mesylate group with the nitrogen of the amide.[87] The photocyclization of a compound that contain an active methylene can also furnish the ring of piperidin-2-one.[88] Another method is based on the application of the Mitsunobu reaction on an open-chain amido-alcohol, such as **PS-3-1**, as displayed in Scheme 3.5.[89]



Scheme 3.5 Intramolecular Mitsunobu reaction based on an amido-alcohol

c. Michael addition and cyclization seq.uence

The last strategy cited here is to create the C-N bond by a seq.uence of Michael addition and cyclization. For instance, Koelsch developed a synthetic route to efficiently construct piperidin-2-ones, as depicted in Scheme 3.6.[90] Michael addition of benzonitrile to an unsaturated acrylate ester produces cyano-ester **CK-3-1**, which is transformed to a primary amine by catalytic reduction, followed by a spontaneous cyclization with the ester group to form piperidin-2-one **CK-3-2**.



Scheme 3.6 Seq.uence of Michael addition and cyclization

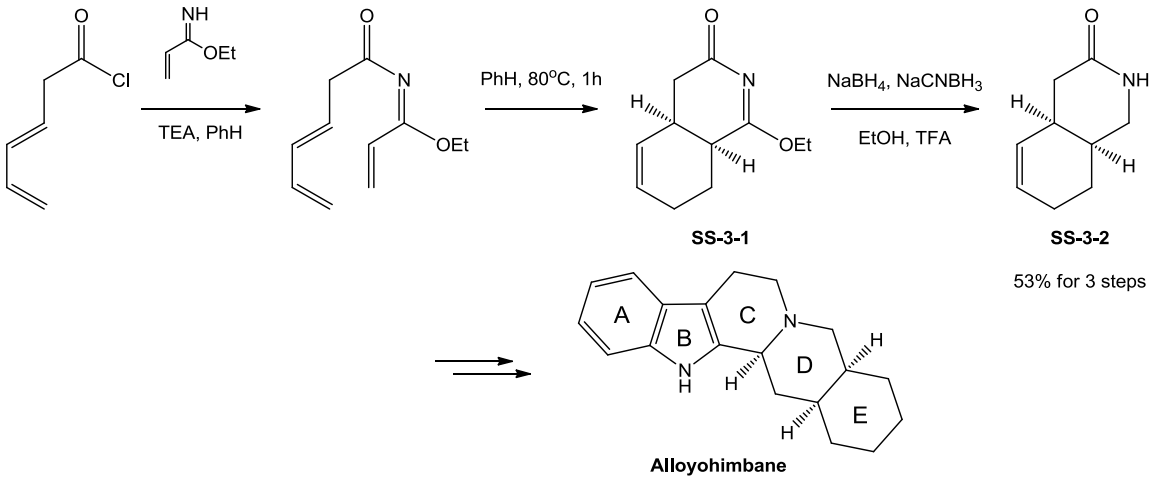
[87] Danieli, B.; Lesma, G.; Macecchini, S.; Passarella, D.; Silvani, A. *Tetrahedron Asymmetry* **1999**, *10*, 4057-4064.
[88] Lindemann, U.; Reck, G.; Wulff-Molder, D.; Wessig, P. *Tetrahedron* **1998**, *54*, 2529-2544.
[89] (a) Olsen, R. K.; Ramasamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527-3534. (b) Panday, S. K.; Langlois, N. *Tetrahedron Lett.* **1995**, *36*, 8205-8208.
[90] Koelsch, C. F. *J. Am. Chem. Soc.*, **1943**, *65*, 2093-2095

3. Intramolecular C-C bond formations

In addition to the intramolecular C-N bond formation, C-C bond can also be created with a similar strategy based on an intramolecular process, such as the Diels-Alder reaction and the Ring-Closing Metathesis (RCM).

a. Intramolecular Diels-Alder reaction

An approach to the synthesis of the DE rings of the yohimbinoid alkaloids, such as alloyohimbane, has been described by Shea et al.[91] employing an intramolecular Diels-Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates. This cycloaddition afforded a high proportion of the *cis*-fused hexahydroisoquinolone **SS-3-1** in good yield, which could be reduced to provide the 4,5-disubstituted piperidin-2-one **SS-3-2**.

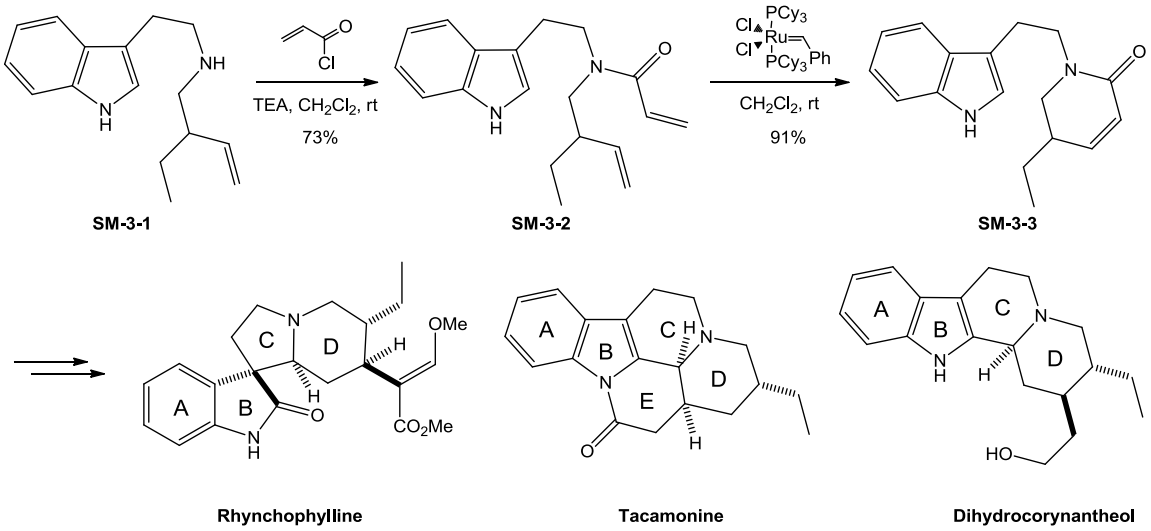


Scheme 3.7 Diels-Alder reaction using *N*-acylvinyl imidates

[91] Sparks, S. M.; Shea, K. J. *Tetrahedron Lett.* **2000**, *41*, 6721-6724.

b. Metathesis cyclization

RCM is also an efficient way for this synthetic purpose. For instance, following the work of different groups,[92] Martin and his co-workers developed an expedient route to form the unsaturated lactam **SM-3-3**, which involved the intramolecular metathesis of the tryptamine derivative **SM-3-2** using first generation Grubbs catalyst.[93] Serving as the key intermediate for the synthesis of various alkaloids (ring D), **SM-3-3** could be easily reduced to give the substituted piperidin-2-ones (Scheme 3.8).



Scheme 3.8 Metathesis cyclization to form the precursor of piperidin-2-ones

[92] (a) Arrayas, R. G.; Alcudia, A.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 3381-3383. (b) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron Asymmetry* **2001**, *12*, 2621-2624. (c) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056-9062. (d) Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185-1192.

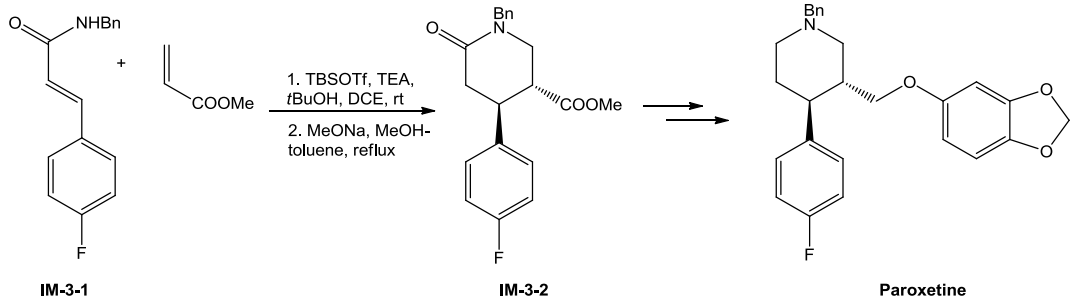
[93] Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547-6561.

4. Intermolecular processes

Apart from the above intramolecular reactions, intermolecular processes are also capable of leading to the piperidine-2-one framework. Two examples of intermolecular Diels-Alder reaction and multicomponent process are presented below to illustrate this alternative synthetic route.

a. Intermolecular Diels-Alder reaction

Ihara and his co-workers used a [4+2] cycloaddition of an unsaturated amide **IM-3-1** with methyl acrylate to form the six-membered ring skeleton of the 4,5-disubstituted-2-piperidone **IM-3-2**. This method can be used effectively to synthesize the functionally complex piperidines, such as Paroxetine, an antidepressant.[94]



IM-3-1 IM-3-2 Paroxetine

Scheme 3.9 Intermolecular Diels-Alder reaction to form substituted 2-piperidone

b. Multi-component reaction

Multi-component reactions allow the rapid building up of functionalized molecules in a one-pot operation, with high bond forming efficiency and minimal functional group manipulation. In this respect, Landais and his co-workers have developed three- and four-component reactions to synthesize the multi-substituted-2-piperidones through a formal [2 + 2 + 2] process.[95]

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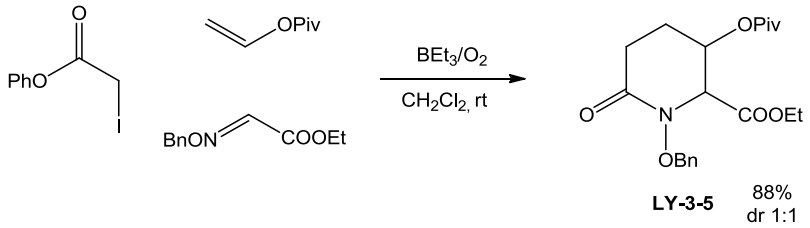
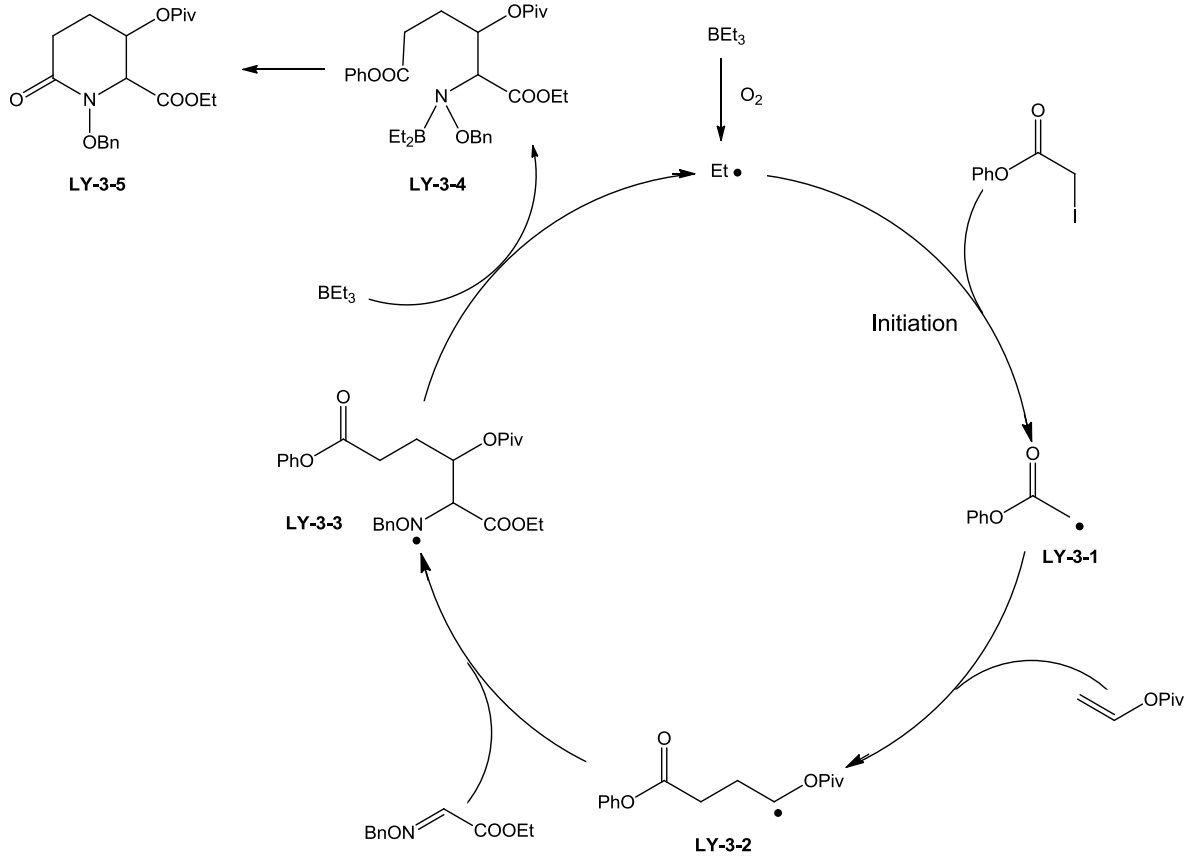
[94] (a) Takasu, K.; Nishida, N.; Ihara, M. *Tetrahedron Lett.* **2003**, *44*, 7429-7432. (b) Takasu, K.; Nishida, N.; Ihara, M. *Synthesis Stuttgart* **2004**, 2222-2225. (c) Takasu, K.; Nishida, N.; Tomimura, A.; Ihara, M. *J. Org. Chem.* **2005**, *70*, 3957-3962.

[95] Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662-12663.



Scheme3.10 Three-component reaction to synthesize the substituted 2-piperidone

This method is based on a tandem radical intermolecular additions-lactamization seq.uence, starting from readily available reagents. After the initiation with triethylborane and oxygen, the stabilized radical **LY-3-1** reacts with vinyl pivalate to give a new nucleophilic carbon centered radical **LY-3-2**, which is then trapped by the protected oxime. Two C-C bonds are formed during these two intermolecular radical events, and the seq.uence is terminated by the formation of the C-N bond via an irreversible ionic ring closure.



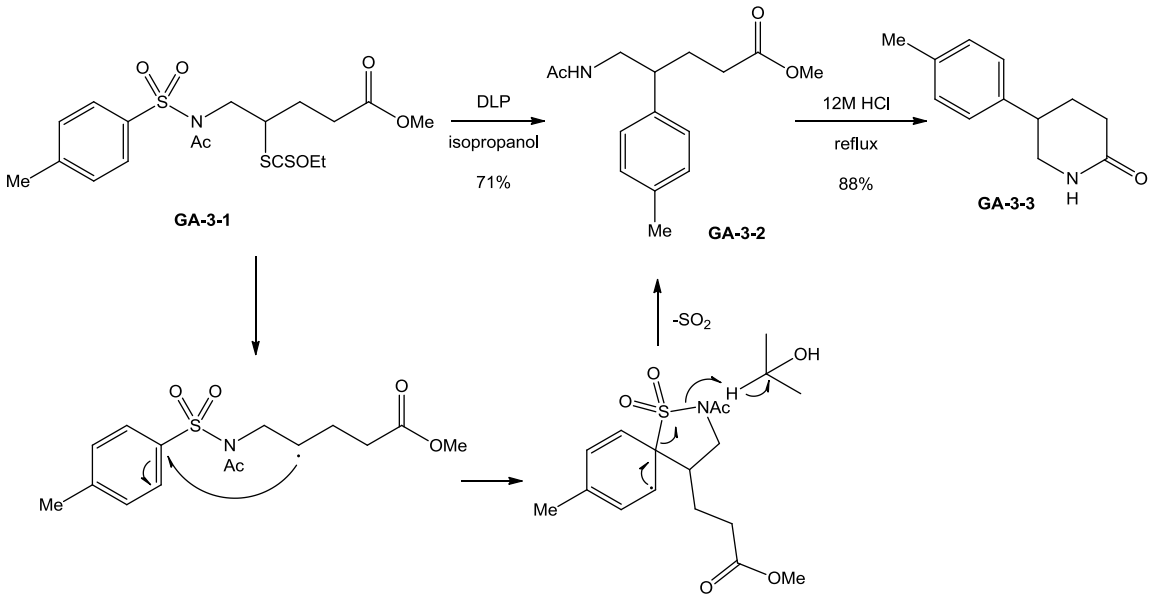
Scheme 3.11 Mechanism of the three-component reaction proposed by Landais

Ⅱ. Desulfonylative radical ring closure onto aromatics: synthesis of benzazepin-2-ones and 5-arylpiperidin-2-ones

1. Investigation of 5-arylpiperidin-2-one synthesis

a. Initial strategy to synthesize 5-arylpiperidin-2-ones

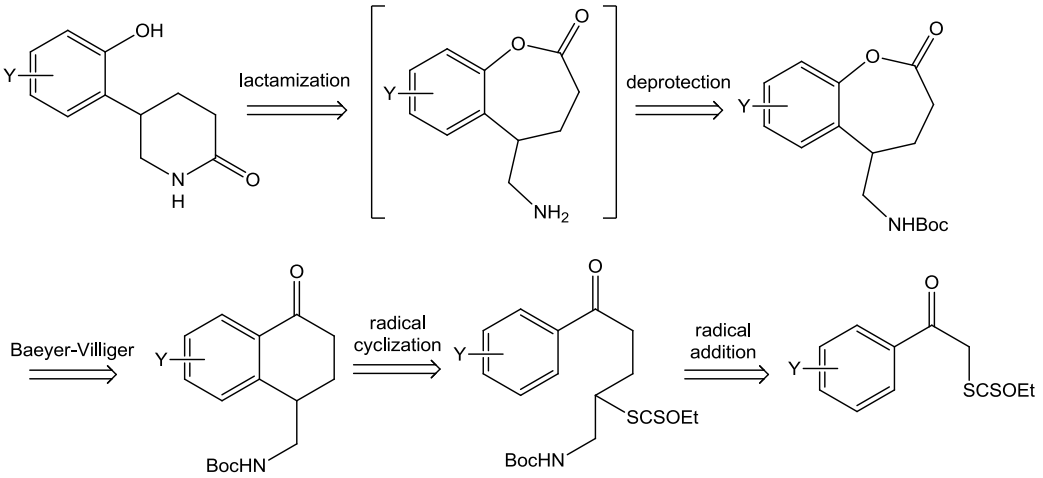
As stated in the introduction of part I, the arylpiperidin-2-one moiety widely exists in bioactive molecules. In order to investigate its synthesis through the radical chemistry of xanthates, a route to 5-arylpiperidin-2-one involving a radical 1,4-aryl migration was studied previously in our group[96] (Scheme 3.12).



Scheme 3.12 Synthesis of 5-arylpiperidin-2-one via 1,4-aryl migration

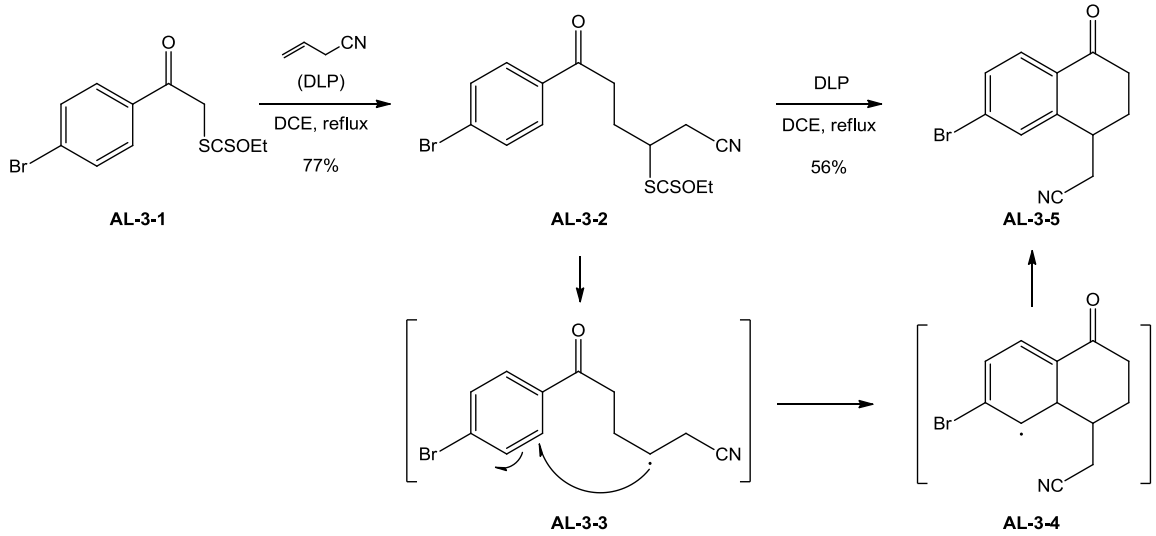
In continuation of this work, an alternative strategy to 5-arylpiperidin-2-ones was next conceived. This route involves the initial formation of an *α*-tetralone, followed by a Baeyer-Villiger oxidation, and finally a spontaneous lactamization after liberating the protected amine (Scheme 3.13).

[96] (a) Gheorghe, A.; Quiclet-Sire, N.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, 7, 1653-1656; (b) Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007**, 63, 7187-7212.



Scheme 3.13 Retrosynthesis for 5-arylpiperidin-2-one

The study commenced with the synthesis of the α-tetralone motif. In a previous work,[97] *α*-tetralone derivatives like **AL-3-5** could be readily prepared from an addition-cyclization seq.uence of the substituted *S*-phenacyl xanthate **AL-3-1** (Scheme 3.14). A variety of olefinic traps can also be incorporated into this seq.uence and the substituents on the acetophenone moiety can be both electron withdrawing and electron donating groups.

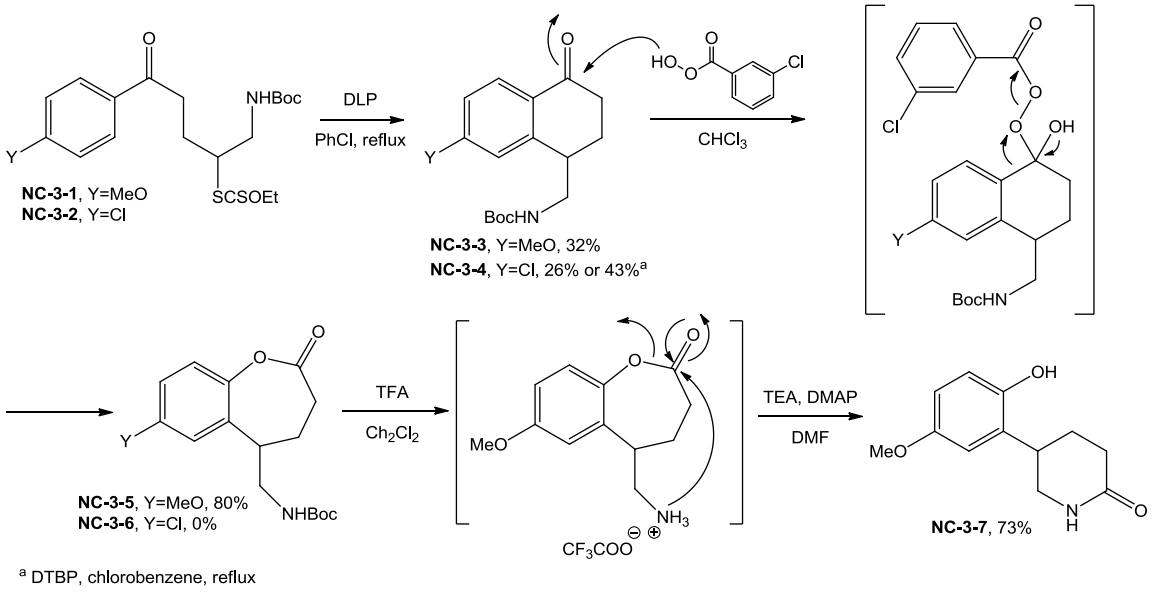


Scheme 3.14 Synthesis of an *α*-tetralone

[97] Liard, A.; QuicletSire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759-1762.

It is worth mentioning that this type of cyclization is relatively slow and thus cannot be achieved by the other radical processes. In the initial procedure, the α-tetralone **AL-3-5** was generated by portionwise addition of DLP to a refluxing solution of **AL-3-2** in DCE over 37 hours. Later, it was found more expedient to heat the intermediate xanthate in the higher boiling point chlorobenzene and to add the DLP over a shorter period, since its half-life is much shorter at ~130°C. This allowed a faster operation and the yields were usually comparable.

We thus applied this procedure in our own approach (Scheme 3.15). The corresponding precursors **NC-3-1** and **NC-3-2** were readily obtained starting with *S*-phenacyl xanthates and Boc-protected allylamine. However, although the intermolecular radical addition proceeded efficiently, the ring closure step leading to tetralones **NC-3-3** and **NC-3-4** gave varying and also lower yields compared to earlier work.



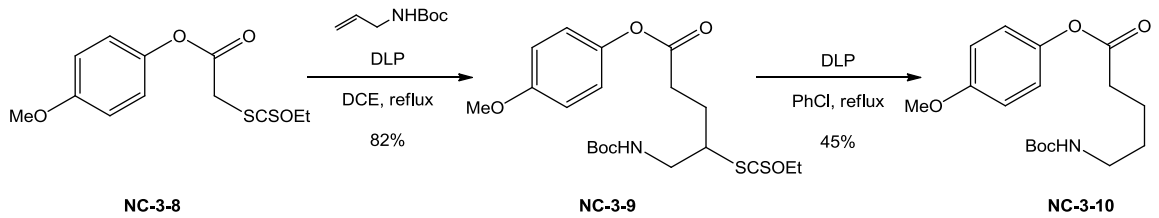
Scheme 3.15 Initial strategy to synthesize the 5-arylpiperidin-2-one

Partial destruction of the Boc-protected amine by the co-produced lauric acid at the high reaction temperature could be responsible for this setback. When the DLP was replaced with DTBP, which does not give any acidic products upon thermolysis or induced decomposition, the yield of tetralone was significantly increased. For example, the

cyclization of **NC-3-2** performed originally with DLP (0.1eq. every 15min, 0.03M in chlorobenzene) gave tetralone **NC-3-4** in 26% yield. By using DTBP (5eq. at the beginning, 0.1M in chlorobenzene), the yield was improved by almost two folds to 43%.[98]

Unfortunately, the subseq.uent ring expansion by the Baeyer-Villiger oxidation afforded variable results. In the case of the methoxy substituted tetralone **NC-3-3**, treatment with *m*-chloroperoxybenzoic acid (3.0eq. *m*CPBA, 0.1M in chloroform) furnished the desired lactone **NC-3-5** in good yield. In contrast, the chlorine substituted analog did not give any lactone **NC-3-6** under identical conditions. No clear explanation for this unexpected discrepancy can be put forward at the moment.

With lactone **NC-3-5** in hand, the deprotection of the amide group followed by rearrangement of the free amine intermediate afforded the final 5-arylpiperidin-2-one **NC-3-7** in good yield. It is worth noting that an attempt to obviate the capricious Baeyer-Villiger oxidation[99] by direct cyclization of xanthate precursor **NC-3-9** failed completely (Scheme 3.16), presumably because of a disfavored *s-trans* conformation of the ester motif. Prematurely reduced product **NC-3-10** was generated instead of the desired bicyclic lactone.

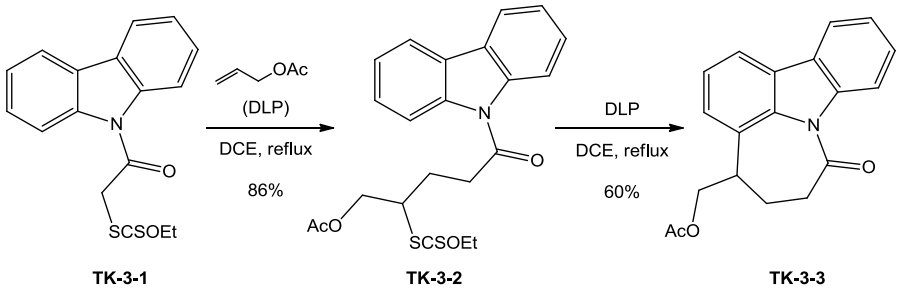


Scheme 3.16 Attempt to obviate Baeyer-Villiger oxidation

[98] Charrier, N. *PhD thesis* Ecole Polytechnique, **2008**.
[99] ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105-4123.

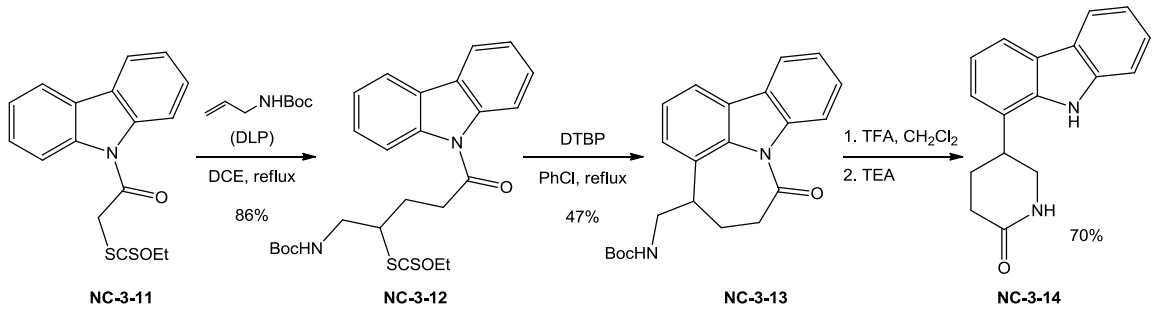
b. An improved synthetic strategy involving a mesylate as the protecting group

Faced with this unexpected setback, we examined another potentially efficient strategy inspired by an earlier work.[100] This strategy is based on the accessibility of benzazepinone derivatives such as **TK-3-3** by direct radical ring closure (Scheme 3.17).



Scheme 3.17 Synthesis of benzazepinone **TK-3-3** by direct radical cyclization

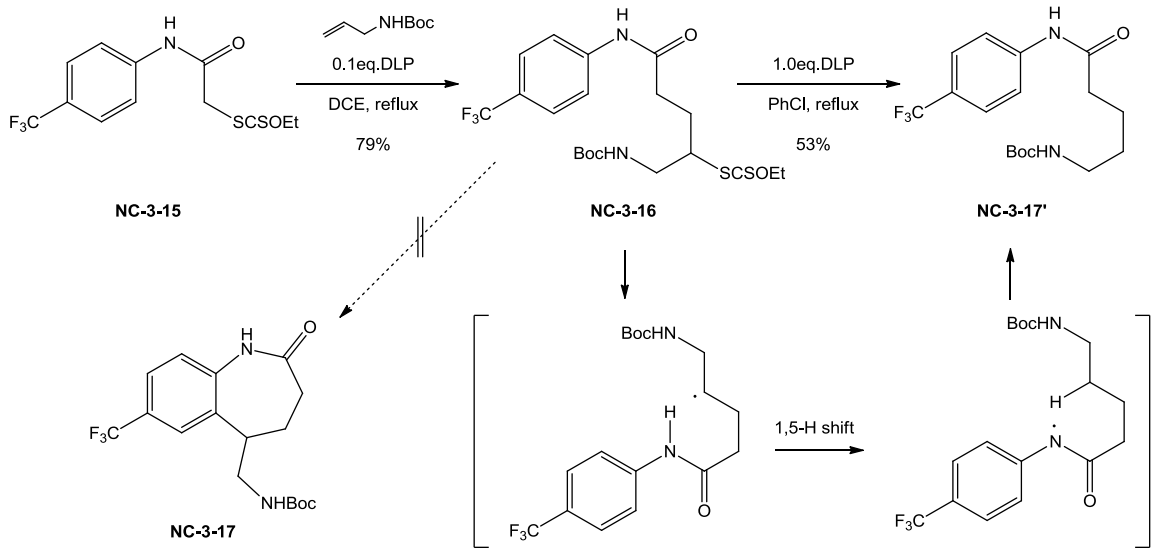
As depicted in Scheme 3.18, the radical addition of the xanthate **NC-3-11** to the Boc-protected allylamine furnished a high yield of the normal adduct **NC-3-12**. In view of the discussion above regarding the fragile Boc group, DTBP was used as the initiator in refluxing chlorobenzene to accomplish the cyclization and this gave benzazepinone **NC-3-13** in a yield of 47%. Finally, after deprotecting the amide group with TFA, spontaneous rearrangement of the free amine afforded efficiently the more stable piperidine-2-one **NC-3-14**.



Scheme 3.18 Improved strategy to synthesize the 5-arylpiperidin-2-one

[100] Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731.

This first success encouraged us to extend this approach to anilines. Unfortunately, as shown in Scheme 3.19, the synthesis starting from commercially available 4-trifluoromethylaniline was not successful: instead of the desired cyclization product benzazepinone **NC-3-17**, only the reduced compound **NC-3-17'** was isolated.



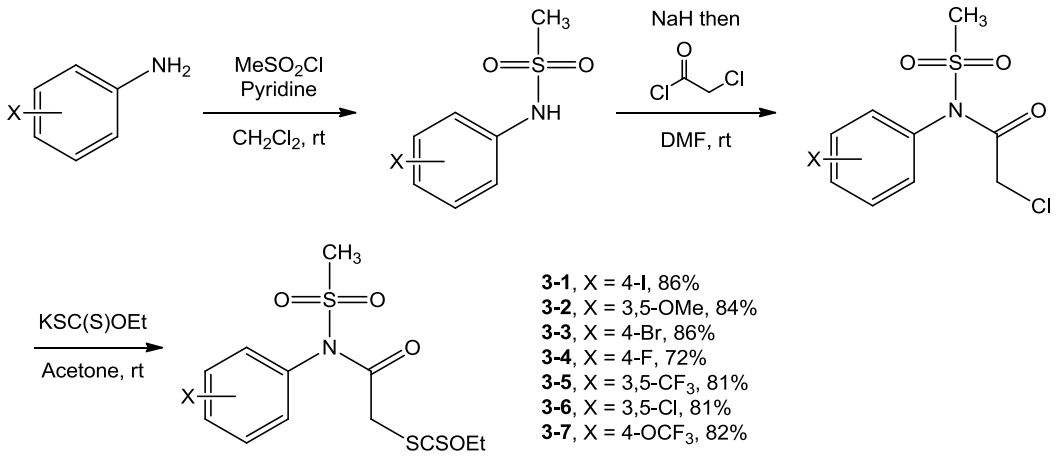
Scheme 3.19 Failure of the cyclization by a possible 1,5-hydrogen shift

Since a 1,5-hydrogen migration could be responsible for this failure, we decided to place a substituent on the nitrogen of the aniline moiety. A mesyl group was selected to avoid rotamers that complicate spectroscopic analyses on one hand, and to facilitate the transamidation step by improving the leaving group ability of the aniline nitrogen on the other.

2. Results and optimizations

a. Unexpected loss of mesyl group during the radical cyclization

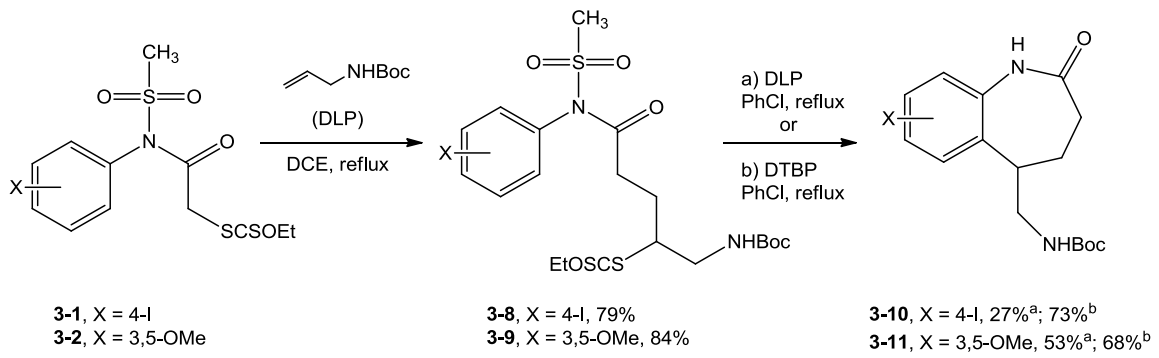
As outlined in Scheme 3.20, various substituted anilines were first protected as the corresponding sulfonamides using methanesulfonyl chloride. This protection diminished the reactivity of the aniline nitrogen and it was necessary to deprotonate the sulfonamides using sodium hydride to generate the anion, prior to reaction with chloroacetyl chloride and displacement of the chlorine with potassium *O*-ethyl xanthate salt to form the desired xanthates **3-1** to **3-7**.



Scheme 3.20 Formation of the xanthate precursor

The following intermolecular addition to Boc-protected allylamine proceeded uneventfully to give the corresponding adducts **3-8** and **3-9** in high yields. However, when the ring closure was performed by heating them with DLP in refluxing chlorobenzene, we were surprised to find that *the sulfonamide group was absent* in the products **3-10** and **3-11** which were obtained with yields of 53% and 27% respectively[101] (Scheme 3.21). Moreover, if the initiator was replaced by DTBP, which did not release the deleterious lauric acid, we were pleased to find that the yields of benzazepinones improved significantly to a respectable 68% and 73%.

[101] This phenomenon was first observed by Dr. Charrier, N.



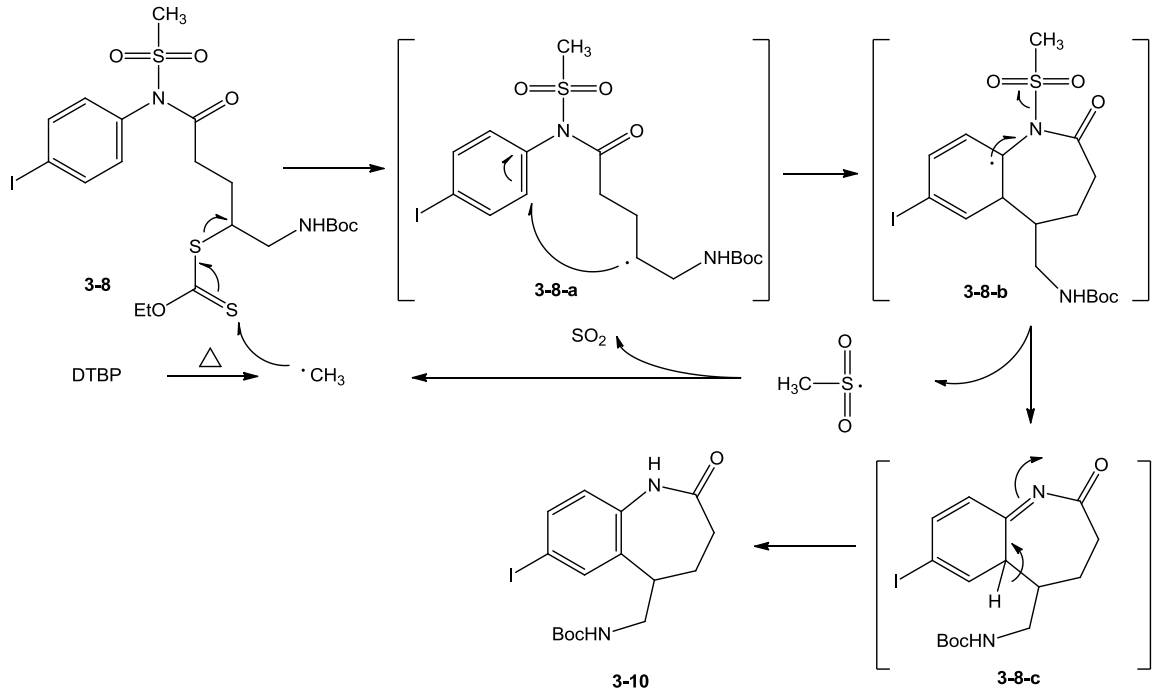
3-1, X = 4-I
3-2, X = 3,5-OMe

3-8, X = 4-I, 79%
3-9, X = 3,5-OMe, 84%

3-10, X = 4-I, 27%[a]; 73%[b]
3-11, X = 3,5-OMe, 53%[a]; 68%[b]

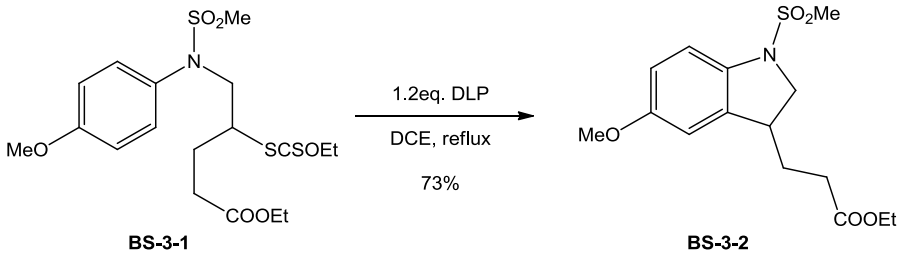
Scheme 3.21 Unexpected loss of the mesyle group

The mechanism of this ring closure step is outlined for xanthate **3-8** in Scheme 3.22. The methyl radical from DTBP attacks the sulfur to create a new radical intermediate **3-8-a**, which cyclizes onto the aromatic ring and forms another new bicyclic radical **3-8-b**. Extrusion of methylsulfonyl radical and phototropic shift finally gives rise to the observed benzazepinone **3-10**. The methylsulfonyl radical extrudes one molecule of sulfur dioxide and generates another methyl radical which participates in propagating the radical chain.



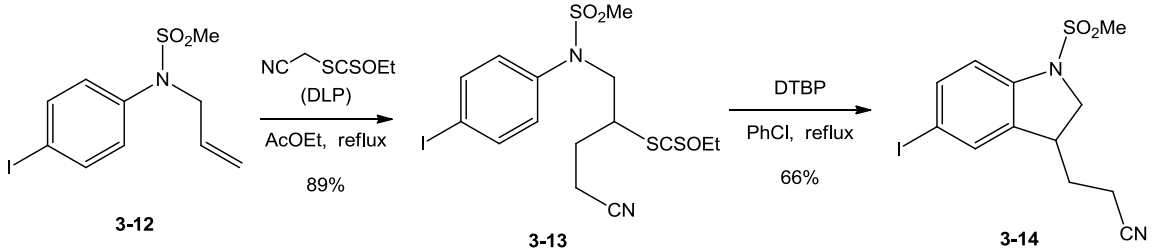
Scheme 3.22 Mechanism for the cyclization of xanthate **3-8**

The mesyle group was used extensively in our laboratory in the synthesis of indolines,[102] yet no such fragmentation was hitherto observed. For instance, the xanthate precursor **BS-3-1** was used in the synthesis of the corresponding indoline, and the mesyle protecting group remained in the cyclized compound **BS-3-2**[103] (Scheme 3.23).



Scheme 3.23 Synthesis of substituted 5-methoxyindoline with mesyl protection

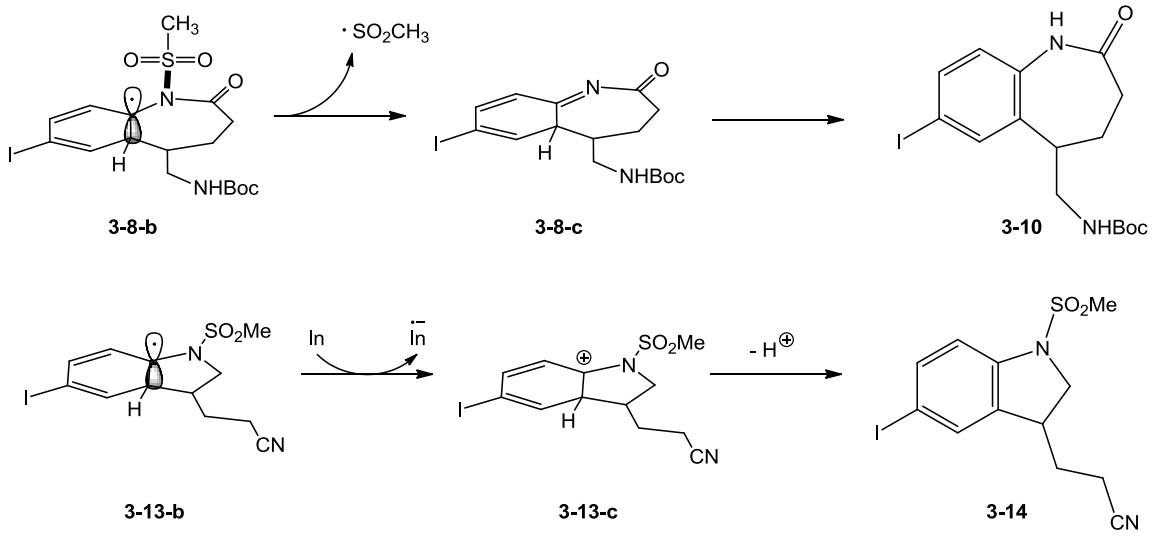
For a more direct comparison, the corresponding cyclization was performed under identical conditions as above with xanthate **3-12**, which was obtained by addition of cyanomethyl xanthate to *N*-allyl-*N*-methanesulfonyl-4-iodoaniline (Scheme 3.24). As expected, no desulfonylated indoline was formed; the cyclization furnished the *N*-methanesulfonylindoline **3-14** as the sole product in 66% yield.



Scheme 3.24 Synthesis of substituted 5-iodoindoline with Mesyl protection

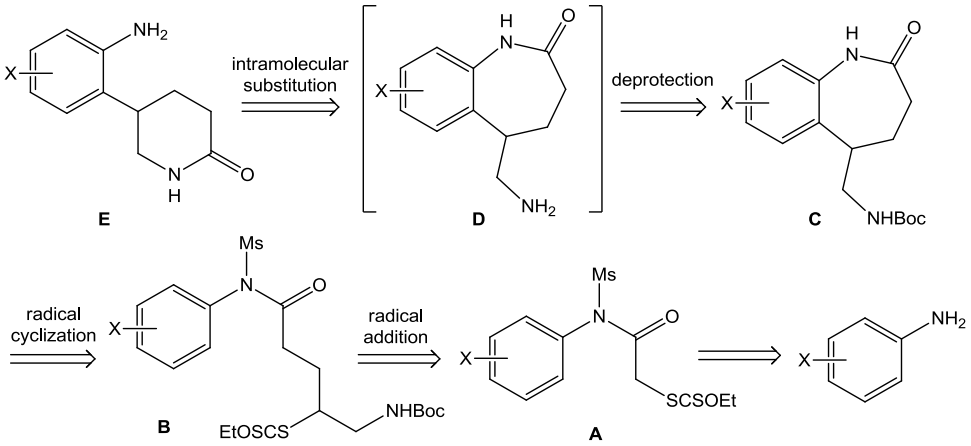
One plausible explanation is that the more flexible benzazepinone structure in the intermediate **3-8-b** allows the correct alignment of the single electron containing orbital with the nitrogen-sulfur antibonding orbital and thus allows the scission to occur (Scheme 3.25). In contrast, a similar arrangement in the intermediate radical **3-13-b** of the smaller indoline ring is more difficult and more energy is needed due to the significantly more strained five-membered ring.

[102] Ly, T. M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533-2536.
[103] Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Chem. Commun.* **2002**, 1692.



Scheme 3.25 Comparative mechanisms for the cyclizations

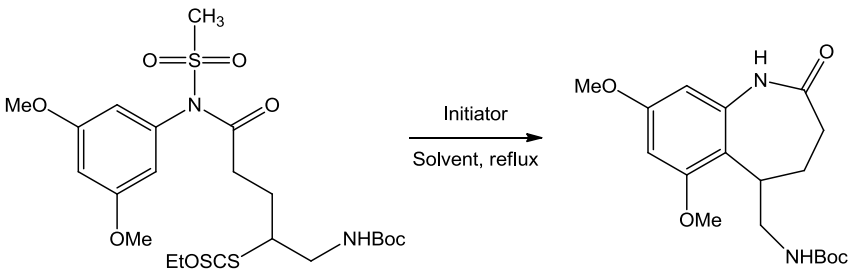
The loss of the sulfonamide group eliminated the need for a subseq.uent deprotection step and fortunately had no deleterious effect on the rest of the seq.uence. The eq.uilibrium still favored the formation of the desired 5-arylpiperidin-2-ones. Based on this successful seq.uence, we decided to expand the range of the substrates in order to make this strategy more versatile for application. The modified retrosynthesic route is displayed in Scheme 3.26: xanthates **A** arise from substituted anilines by mesylation, chloroacetylation and nucleophilic substitution with potassium *O*-ethyl xanthate salt. Addition-cyclization of the xanthates with Boc-protected allylamine produce benzazepinone **C**, and finally, Boc-deprotection followed by rearrangement of the free amine **D** leads to the desired 5-arylpiperidin-2-ones **E**.



Scheme 3.26 Retosynthesis of 5-arylpiperidin-2-one

b. Optimization of the ring closure by dilution and addition of base

Initial experiments confirmed the choice of chlorobenzene as the solvent and DTBP as the initiator for the ring closure step. As summarized in Table 3.1, three different conditions involving ethyl acetate and chlorobenzene as well as DLP and DTBP were tested for adduct **3-9**. According to the results, we could see that at a fixed concentration, the best yields of up to ~70% were obtained with the combination of DTBP and chlorobenzene. Such a good yield is not often achieved for the radical cyclizations on aromatic rings leading to the direct fusion of a seven-membered ring. In the proposed mechanism sulfur dioxide is expelled as a co-product, and the use of high boiling point solvent could promote this process. As for the initiator, besides the advantage of no acidic by-product released as discussed before, the long half-life (~10h in 130°C) and the absence of undecyl xanthate by-product add to the convenience of this method.



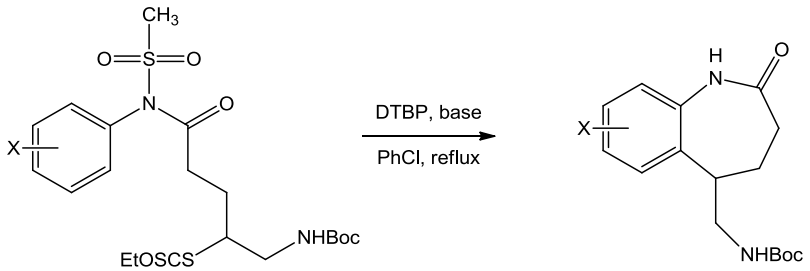
3-9 **3-11**

Initiator	Introduced condition	Solvent	Concentration	Yield
DLP	20%/60min	Ethyl acetate	0.1M	47%
DLP	20%/60min	Chlorobenzene	0.1M	53%
DTBP	5eq. at the beginning	Chlorobenzene	0.1M	68%

Table 3.1 Cyclization of xanthate **3-9**

In order to maximize the yield of this key step, other comparative experiments were carried out under various conditions, and two optimizations were generally realized. The first improvement was accomplished by lowering the concentration of the reaction

mixture. Normally, diluting the medium is preferred in a unimolecular process. Undesired intermolecular processes are thus minimized and therefore lead to better results. For example, as illustrated in Table 3.2, the general yields for the cyclization of xanthate **3-15** were almost doubled when the concentration was changed from 0.1M (entry 1 and 2) to 0.02M (entry 3 and 4). It is worth noting that in the cyclization of xanthate **3-16**, a further two-fold dilution from 0.02M (entry 8) to 0.01M (entry 9) did not seem to alter the yield significantly.

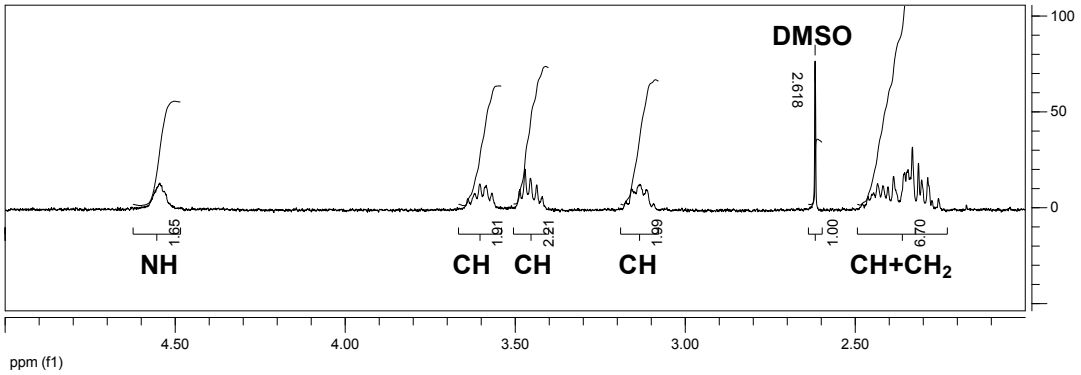


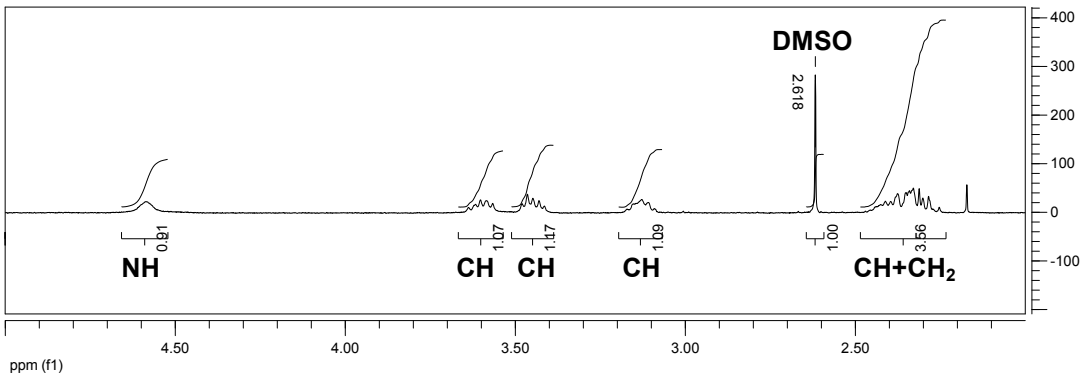
Entry	Xanthate	X	Concentration	2,6-lutidine	Yield	Product
1	**3-15**	4-Br	0.1M	0	24%	**3-20**
2	**3-15**	4-Br	0.1M	0.5 eq.	32%	**3-20**
3	**3-15**	4-Br	0.02M	0	43%	**3-20**
4	**3-15**	4-Br	0.02M	0.5 eq.	56%	**3-20**
5	**3-15**	4-Br	0.02M	1.0 eq.	49%	**3-20**
6	**3-16**	4-F	0.1M	0	13%	**3-21**
7	**3-16**	4-F	0.02M	0.5 eq.	51%	**3-21**
8	**3-16**	4-F	0.02M	1.0 eq.	57%	**3-21**
9	**3-16**	4-F	0.01M	1.0 eq.	56%	**3-21**
10	**3-17**	3,5-CF_3	0.02M	0	43%	**3-22**
11	**3-17**	3,5-CF_3	0.02M	0.5 eq.	35%	**3-22**
12	**3-17**	3,5-CF_3	0.02M	1.0 eq.	26%	**3-22**

Table 3.2 Cyclizations of xanthates **3-15** to **3-17**

Another optimization was realized by adding small amount of base in order to neutrolise any traces of hydrogen chloride that could arise from radical addition to the chlorobenzene solvent and which could cause the destruction of the Boc group. 2,6-Lutidine was chosen because of its weak basicity (pK_a ~ 6.60) and its moderate nucleophilicity blocked by the methyl groups. As revealed in Table 3.2, 0.5 eq.alent of 2,6-lutidine was used as the additive base in the cyclization of **3-15** (entries 2 and 4), and for both concentrations a modest improvement in the yield was observed.

However, an increase in the amount of base to 1.0 eq.alent proved to be ambiguous or even harmful to the cyclization process (entries 5 and 12). The reasons are not clear yet, but may have to do with the nucleophilicity of 2,6-lutidine. Although 2,6-lutidine is weakly nucleophilic and sterically hindered, several hours of heating in refluxing chlorobenzene could still have a negative effect on either the intermediate or on the final product. A preliminary test was operated with **3-20** which was heated with 2~3 eq.alent of 2,6-lutidine in refluxing chlorobenzene for 2 hours. High boiling DMSO (bp~189°C) was added at the beginning as an internal standard as shown in the spectra of Scheme 3.27. We can see that after heating with base, the integration indicates that almost half the starting material is lost in the reaction medium. 2,6-Lutidine must therefore be used with care in these cyclization and , if needed, perhaps replaced with the more bulky 2,6-di-*t*-butylpyridine.



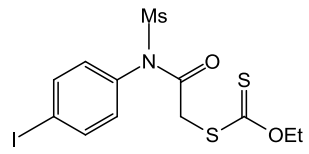
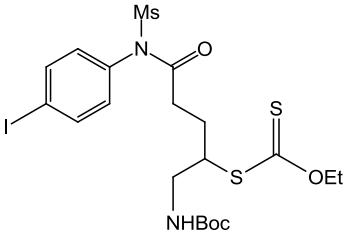
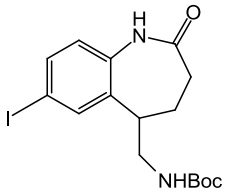
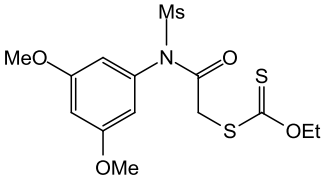
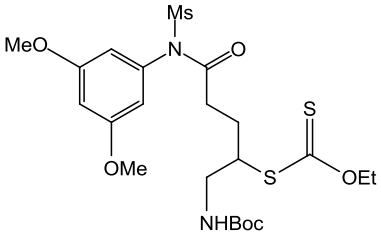
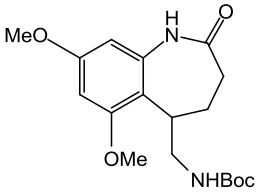
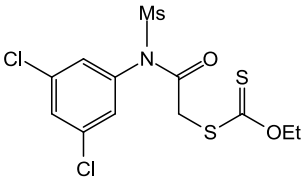
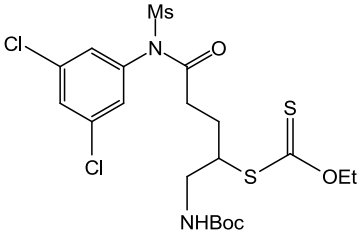
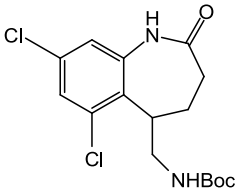
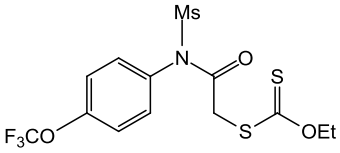
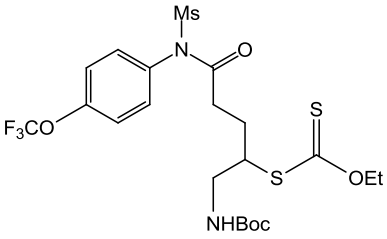
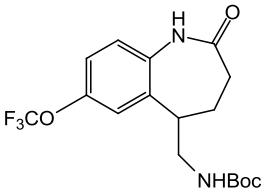


Scheme 3.27 Influence of 2,6-lutidine with DMSO as the internal standard

With these optimized conditions, various benzazepinones were generated in moderate to good yields from a range of anilines (Table 3.3). As mentioned above, the req.uired xanthate precursors were prepared from various substituted anilines by mesyl group protection, chloroacetylation of the nitrogen, and nucleophilic substitution with xanthate salt. One advantage of this seq.uence was that it can be performed without purification between each step, and the final xanthates could be obtained by simple recrystallization. The synthesis of the precursors can therefore be easily scaled up.

The examples cited in Table 3.3 give an idea of the scope and functional group tolerance of this approach. As for substituents of the starting anilines, both electron withdrawing (e.g. chloride, bromide, etc.) and electron donating (e.g. methoxy) groups could be tolerated, thus significantly expanding the utility of this method. It is also worth mentioning that in the former case, a classical Friedel-Craft mode of cyclization would be difficult with these deactivated aromatic rings.[104] Moreover, the presence of an aromatic bromide and iodide allows further modification to the products through the rich transition metal catalyzed coupling reactions.

[104] K.M. Johnston, R.G. Shotter *Tetrahedron* **1974**, *30*, 4059-4064.

xanthates	addition products	cyclisation products
 **3-1**	 **3-8** 79%	 **3-10** a: 73%; b: 75%
 **3-2**	 **3-9** 84%	 **3-11** a: 68%; b: 81%
 **3-6**	 **3-18** 81%	 **3-23** a: 41%; b: 59%
 **3-7**	 **3-19** 82%	 **3-24** a: 20%; b: 38%

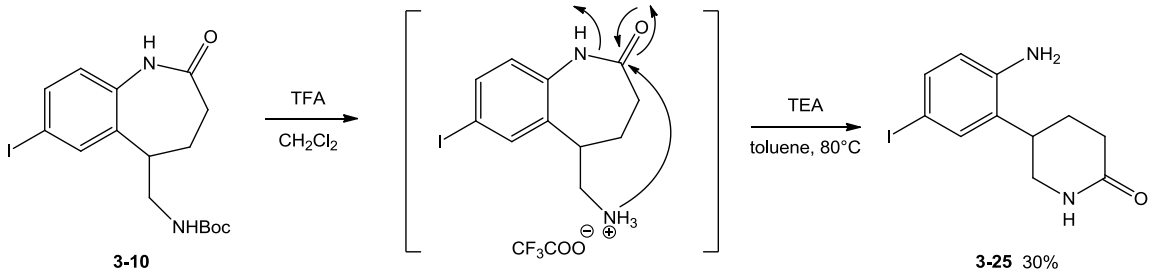
a. 5.0 eq.DTBP, 0.1 M in chlorobenzene

b. 5.0 eq.DTBP and 1.0 eq. 2,6-lutidine, 0.02 M in chlorobenzene

Table 3.3 Results of the radical additions and cyclizations

c. Rearrangement leading to 5-arylpiperidin-2-ones

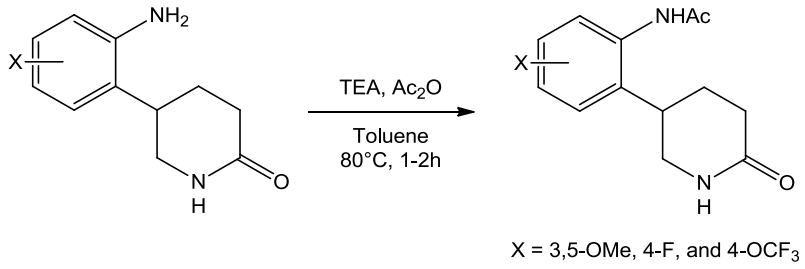
In order to convert the benzazepin-2-ones into piperidin-2-ones, the *tert*-butyl carbamate was deprotected by a solution of 30% TFA in DCM, and the resulting amine trifluoroacetate salt was neutralized by TEA in toluene. The liberated primary amine spontaneously reacted with the carbonyl to open the seven-membered ring and gave the arylpiperidin-2-one as the final product. For example, in the case of **3-10**, the above seq.uence afforded the desired 5-arylpiperidin-2-one **3-25** with a yield of 30% for two steps (Scheme 3.28).



3-10 **3-25** 30%

Scheme 3.28 Synthesis the 5-arylpiperidin-2-one

We observed that some of the products will change color from white to pink indicating that oxidation occurring on the substituted anilines to some extent. Thus, for the compounds which were sensitive to air, protection of the aniline was accomplished by acetylation with TEA and acetic anhydride to provide more stable derivatives (Scheme 3.29).



Scheme 3.29 Acetylation of 5-arylpiperidin-2-ones

What is particularly noteworthy is that some of the final unprotected products were found to be unstable to oxidation during the flash chromatography purification and extensive loss as compared with the TLC estimation appeared unavoidable. However, since both

the protected and the unprotected 5-arylpiperidin-2-ones were insoluble in the usual solvents, e.g. DCM, EtOAc, or even acetone, purification could be simply accomplished by centrifugation. In fact, the final products were thus seperated and washed with the corresponding cold solvent to afford the pure material in modest to excellent yields (Table 3.4)

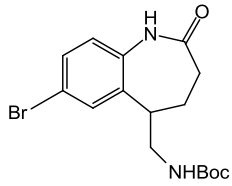
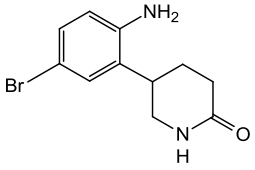
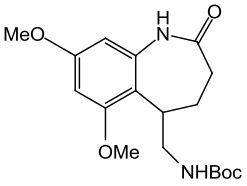
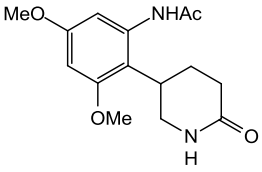
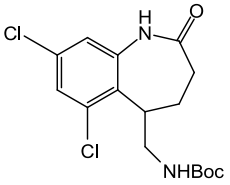
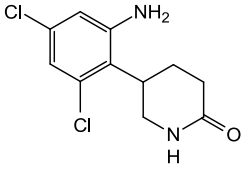
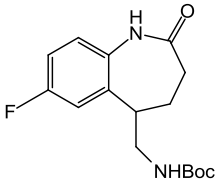
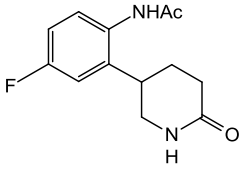
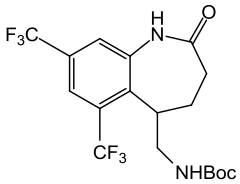
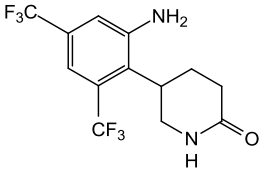
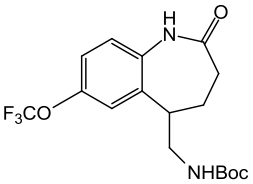
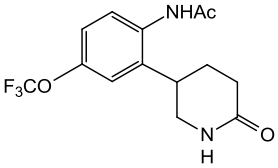
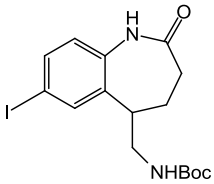
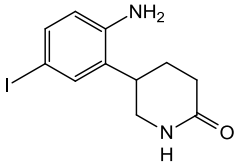
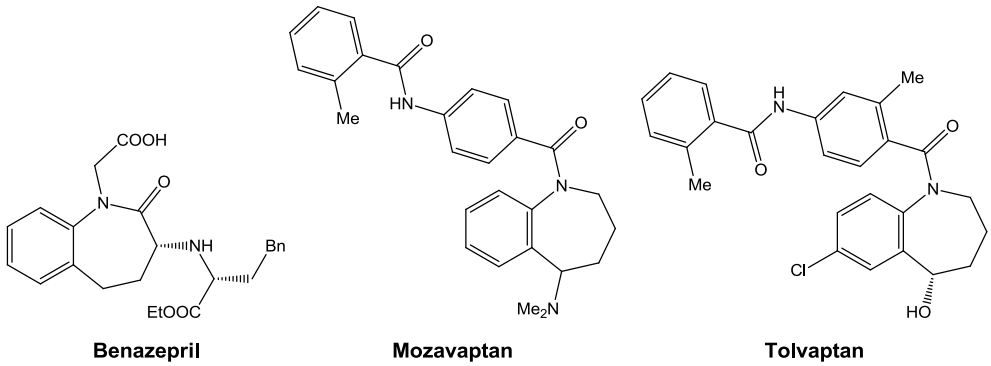
Cyclization product	Rearrangement product	Cyclization product	Rearrangement product
 **3-20**	 **3-27** 83%	 **3-11**	 **3-26** 34%[a]
 **3-23**	 **3-30** 81%	 **3-21**	 **3-28** 30%[a]
 **3-22**	 **3-29** 56%	 **3-24**	 **3-31** 49%[a]
 **3-10**	 **3-25** 30%		a. Yields including acetylation

Table 3.4 Results for generating the 5-arylpiperidin-2-ones

d. Generalization of the synthesis of benzazepin-2-ones

Although the original purpose of this work was to synthesize the arylpiperidin-2-ones through a radical pathway, the bicyclic intermediates are themselves of great medical potential since they belong to one of the most studied classes of pharmacophores. For instance, benazepril[105] is a medication used to treat high blood pressure (hypertension), congestive heart failure, and chronic renal failure. Mozavaptan (OPC-31260)[106] is a vasopressin receptor antagonist and tolvaptan[107] is a selective, competitive vasopressin receptor 2 antagonist, both of which are used to treat hyponatremia (Scheme 3.30).



Scheme 3.30 Examples of biologically active benzazepinones

The Boc-protected allylamine can therefore be replaced by other olefins in the above transformations, thus providing a simple way for introducing various functional groups into the side-chain of the bicyclic benzazepinone skeleton.

Three examples using this strategy were achieved by changing the olefins as well as by modifying the substitution pattern of the aromatic ring in the xanthates, as displayed in Table 3.5 with the yields shown below the structures. Different functional groups ranging from an ester group to silane or boronate were included in these *N*-unsubstituted benzazepinones. From our experience in the xanthate mediated radical addition-

[105] Yu, L. T.; Huang, J. L.; Chang, C. Y.; Yang, T. K. *Molecules* **2006**, *11*, 641-648
[106] Kondo, K.; Ogawa, H.; Yamashita, H.; Miyamoto, H.; Tanaka, M.; Nakaya, K.; Kitano, K.; Yamamura, Y.; Nakamura, S.; Onogawa, T.; Mori, T.; Tominaga, M. *Bioorg. Med. Chem.* **1999**, *7*, 1743-1754.
[107] Kondo, K.; Ogawa, H.; Shinohara, T.; Kurimura, M.; Tanada, Y.; Kan, K.; Yamashita, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Mori, T.; Tominaga, M.; Itai, A. *J. Med. Chem.* **2000**, *43*, 4388-4397.

cyclization seq.uence, many other groups which were not examined in this study would also be compatible with this approach. It is worth stressing that the rapid synthesis of the boronate substituted benzazepinone **3-36** is particularly interesting since such derivatives would be exceedingly tedious to make by the traditional routes.

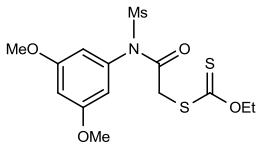
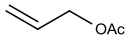
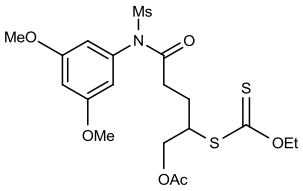
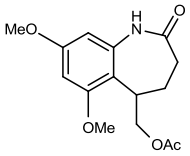
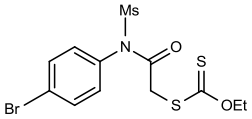
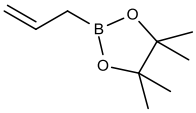
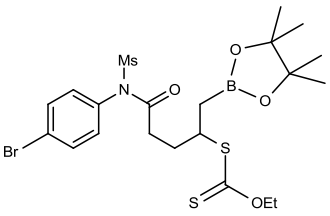
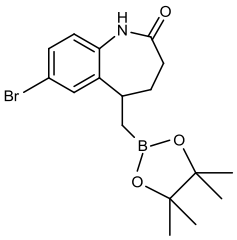
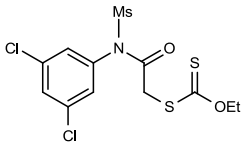
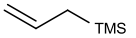
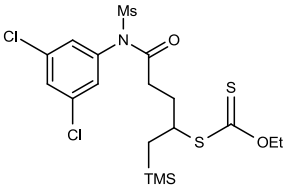
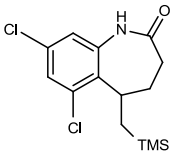
Xanthates	Alkenes	Addition products	Cyclisation products
 **3-2**		 **3-32** 70%	 **3-35** 64%
 **3-3**		 **3-33** 84%	 **3-36** 45%
 **3-6**		 **3-34** 96%	 **3-37** 68%

Table 3.5 Results of the expanded bicyclic benzazepinones

Another point worth emphasizing about this present route is that the alternative access to *N-unsubstituted* benzazepinones by direct radical cyclization of secondary amide xanthates cannot be achieved. The reasons are not clear yet, but it is probably due to competing 1,5-hydrogen shifts and/or unfavorable conformation as discussed in Scheme 3.19. With this in mind, our approach is of particular importance since numerous functionalized benzazepinones become readily available within five easy steps starting from cheap commercial reagents.

Conclusion

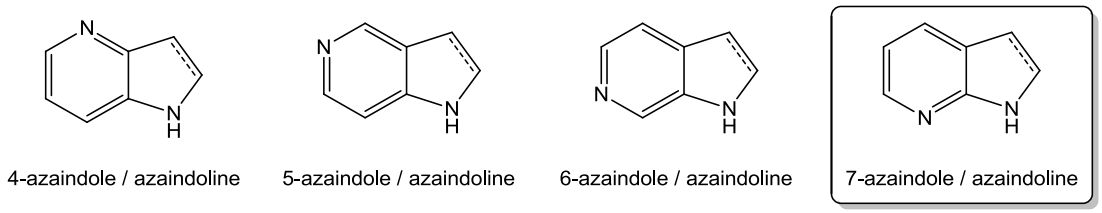
In summary, we have established a concise access combining simplicity, cheapness, convergence, and flexibility to both benzazepinones and 5-arylpiperidin-2-ones, unsubstituted on the nitrogen of the ring. In the key step of radical cyclization, methanesulfonyl radical is extruded from the intermediates and *N*-unsubstituted benzazepinones were generated in moderate to excellent yields under partially optimized conditions. This method demonstrates the potential of the xanthates technique in providing biologically active compounds which are not readily available by traditional methods. Furthermore, one notable advantage of this synthesis is the presence of halogen atoms in the products, which makes it possible to combine the radical reaction with some of the most powerful transition metal catalyzed processes, such as the Heck, Suzuki, Sonogashira and Buchwald-Hartwig reactions. They represent therefore interesting scaffolds for the pharmaceutical industry.

Chapter 4

Radical Synthesis of 7-Azaindolines and 7-Azaindoles

Introduction

The azaindole ring system is a structural motif present in a variety of natural products, pharmaceuticals, and diverse synthetic intermediates. Compared to the analogous, more common indoles, azaindoles are supposed to overcome some of their drawbacks such as poor water solubility.[108] The related azaindolines, which are less common in the literature, are also pharmaceutically interesting derivatives[109] as well as important precursors to the corresponding azaindoles. As depicted in Scheme 4.1, replacing one carbon atom at positions 4 to 7 of indoles or indolines with an sp^2-hybridized nitrogen gives the so-called 4-, 5-, 6-, and 7-azaindoles or azaindolines, respectively.[110] Most of these one-nitrogen analogs of indoles are synthetic products, although some of them exist in nature.

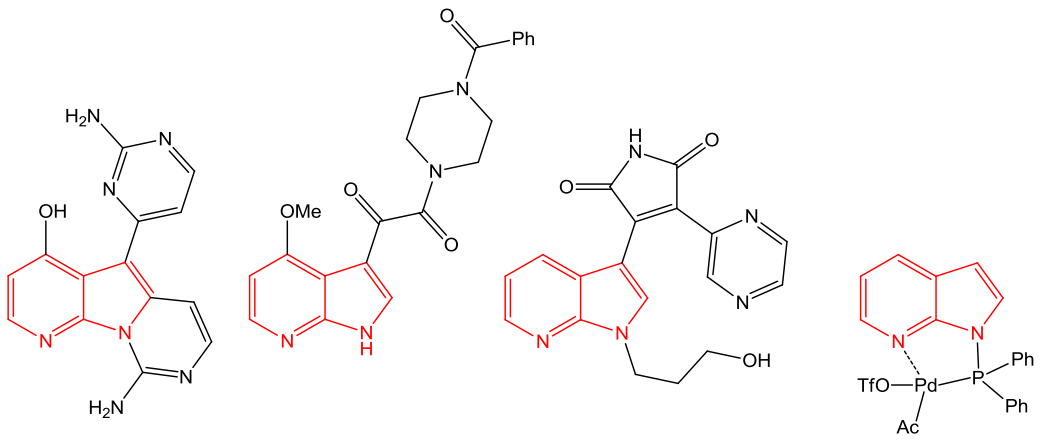


Scheme 4.1 Structures of azaindole and azaindoline

Among all these isomeric structures, 7-azaindoles have attracted more attention due to their physicochemical and pharmacological properties. They can be considered as bioisosteres of indoles or purines. The supplementary nitrogen makes the 7-azaindole a stronger base (pK_a=4.59)[111] than indole and provides a skeleton containing the hydrogen-bond donor/acceptor in a rigid three-atom arrangement.[112] But in contrast to indoles, which are widely present in nature, 7-azaindoles are only contained in a few natural products and most of them are found in alkaloids from the Variolin family. For instance, Variolin B which was isolated from the marine sponge *Kirkpatrickia varialosa*, displays

[108] Schirok, H. *Synlett* **2005**, 1255-1258.
[109] Southon, I.W.; Buckingham, J. *Dictionary of Alkaloids* **1989**, Chapman and Hall, London.
[110] For a review on the synthesis and reactivity of 4-, 5-, and 6-azaindoles, see: Popowycz, F.; Merour, J. Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689-8707 and references cited therein.
[111] Adler T. K.; Albert A. *J. Chem. Soc.* **1965**, 2531.
[112] Zheng, X.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 3777.

strong in vitro activity against the P388 murine leukaemia cell line as well as moderate antiviral activity[113] (Scheme 4.2).



Scheme 4.2 Representative 7-azaindole derivatives

Unnatural bioactive 7-azaindoles in contrast are also freq.uently exploited in the design of biologically interesting molecules. For example, BMS-378806 is found to be a prototype of novel HIV attachment inhibitors that block the first step of HIV-1 entry into cells.[114] Hydroxypropyl-substituted 7-azaindolylmaleimide, which behaves as a specific Glycogen synthase kinase 3β (GSK-3β) inhibitor, has a potential usage for the treatment of elevated levels of GSK-3β related diseases.[115] Furthermore, due to the two adjacent nitrogen atoms, 7-azaindole derivatives also have good coordination ability which is very useful in inorganic chemistry.[116] For example, new palladium complexes with the azaindolyl-phosphine ligand were developed as active catalysts for the co-polymerization of CO and ethene. For all these reasons, chemists are increasingly interested in these compounds, and many relevant synthetic methods have been developed.

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[113] (a) Perry, N. B., Ettouati, L., Litaudon, M., Blunt, J. W., Munro, M. H. G., Parkin, S., Hope, H. *Tetrahedron* **1994**, *50*, 3987 ; (b) Trimurtulu, G., Faulkner, D. J., Perry, N. B., Ettouati, L., Litaudon, M., Blunt, J. W., Munro, M. H. G., Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993 ; (c) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 8697-8699.; (d) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z. L.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120-1132

[114] Yang, Z.; Zadjura, L.; D'Arienzo, C.; Marino, A.; Santone, K.; Klunk, L.; Greene, D.; Lin, P. F.; Colonno, R.; Wang, T.; Meanwell, N.; Hansel, S. *Biopharm. Drug Dispos.* **2005**, *26*, 387-402.

[115] O'Neill, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H. C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G. H. *Bioorg. Med. Chem.* **2004**, *12*, 3167-3185.

[116] See for example: (a) Tani, K.; Sakurai, H.; Fujii, H.; Hirao, T. *J. Organomet. Chem.***2004**, *689*, 1665-1674.; (b) Burrows, A. D.; Mahon, M. F.; Varrone, M. *J. Chem. Soc., Dalton Trans.* **2003**, *24*, 4718-4730.

This chapter aims to present a novel synthesis of 7-azaindoles and 7-azaindolines based on xanthate technology, which was developed in our laboratory during the past years. In order to give a general idea related to our work, the existing methodologies for synthesizing these useful structures are briefly summarized in the first part.[117] An efficient method for preparing 5,6-difluoro-4-substituted 7-azaindoles and 7-azaindolines by an uncommon radical *ipso*-substitution of a C-F bond will then be described in detail.

Ⅰ. Synthesis of 7-azaindole derivatives

Compared to indoles and indolines, the corresponding azaindoles and azaindolines are far more challenging to prepare, especially in highly functionalized forms. Although a variety of related compounds have been prepared and characterized[118] during the past decades, the general synthetic routes to these simple heterocycles are somewhat limited. In this part, we will summarize in detail the methods used for the synthesis of 7-azaindoles, in order to give the readers an overview of this area. Related methods to generate azaindolines are disregarded here since they have been summarized by Dr. Laurent Petit in his thesis.

7-azaindole contains one pyridine-like nitrogen atom in the six-membered ring which behaves as a π and σ acceptor, and one pyrrole-like nitrogen atom in the five-membered ring which acts as a π donor and σ acceptor.[119] Thus the property of 7-azaindole is governed by the involvement in their condensed bicyclic system of two *N*-heteroatomic rings with opposite π-electron effects: pyridine with a deficiency of π-electrons and pyrrole with an excess of π-electrons.

---

[117] For a review on the synthesis and reactivity of 7-azaindole (a) Merour, J. Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471-506.; (b) Popowycz, F.; Routier, S.; Joseph, B.; Merour, J. Y. *Tetrahedron* **2007**, *63*, 1031-1064.; (c) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z. L.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120-1132.

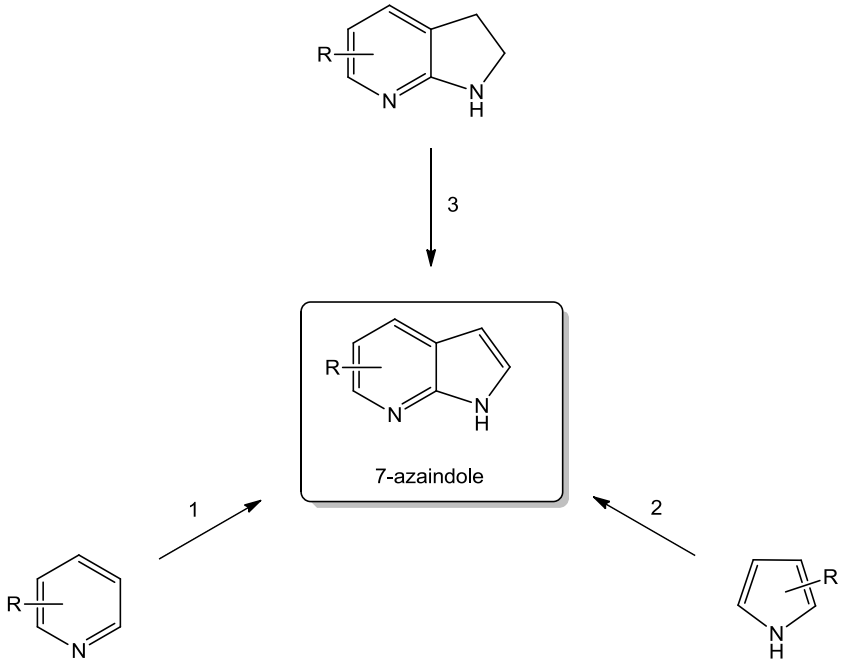
[118] Bailey, W. F.; Salgaonkar, P. D.; Brubaker, J. D.; Sharma, V. *Org. Lett.* **2008**, *10*, 1071-1074. and references cited therein.

[119] Ciureanu M. *Rev. Roum. Chim.* **1976**, *21*, 1007.

Many classical methods for preparing the indole moiety, such as the Fischer reaction,[120] the Madelung cyclization,[121] and the Reissert reaction[122] are usually not applicable or less efficient for the synthesis of azaindoles. The electron poor nature of the pyridine nucleus alters the property of the π-system and thus affects the formation of azaindoles using these traditional methods.

Generally there are three strategies to synthesize this bicyclic skeleton (Scheme 4.3):

1. by creating the pyrrole rings from substituted pyridine derivatives;
2. by generating the pyridine rings on substituted pyrroles;
3. by oxidizing the corresponding 7-azaindolines.



Scheme 4.3 Three general strategies in synthesizing 7-azaindoles

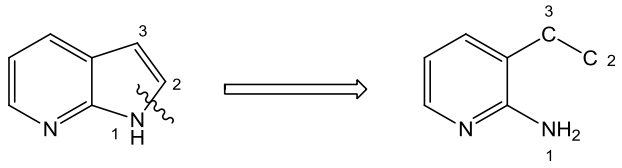
[120] (a) Fischer, E.; Jourdan, F. *Ber. Bunsen-Ges. Phys. Chem.***1883**, *16*, 2241. ; (b) Robinson, B. *Chem. Rev.* **1963**, *63*, 373.
[121] Madelung, W. *Ber. Bunsen-Ges. Phys. Chem.***1912**, *45*, 1128.
[122] Reissert, A. *Ber. Bunsen-Ges. Phys. Chem.***1897**, *30*, 1030.

1. Pyrrolo annulation into preformed pyridine rings

From a synthetic point of view, the most freq.uently employed strategy for 7-azaindole synthesis starts with preformed pyridine derivatives, followed by the formation of pyrrole rings. Generally, three kinds of substituted pyridines could serve as the precursor of this strategy: 3-substituted-2-aminopyridines, 3-(2-aminoethyl)-pyridines, and 3-halo-2-aminopyridines.

a. Construction of 7-azaindoles via 3-alkyl/vinyl/alkynyl -2-aminopyridines

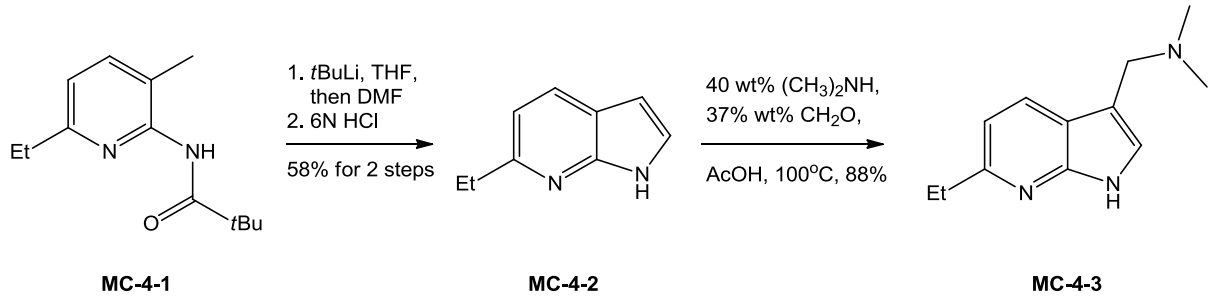
7-azaindoles can be constructed by forming the C(2)-N(1) bond as indicated in the retrosynthetic analysis (Scheme 4.4). This disconnection leads back to 3-substituted-2-aminopyridines, in which the substituents could be alkyl, vinyl, and alkynyl, etc. a number of lithiation methods have been reported based on this retrosynthesis.



Scheme 4.4 Synthesis of 7-azaindole from 3-substituted-2-aminopyridines

The first example involves the lithiation of 3-methyl-2-aminopyridine.[123] Acylation of 6-ethyl-2-aminopyridine with pivaloyl chloride, followed by alkylation with methyl iodide gives the 3-methyl substituted pyridine **MC-4-1**. Treatment with *tert*-butyl lithium provides the bis-anion which, after quenching with DMF and hydrolysis, furnishes the intermediate aldehyde. Cyclization with 6N hydrochloric acid then affords the desired 7-azaindole **MC-4-2** in synthetically useful yield.

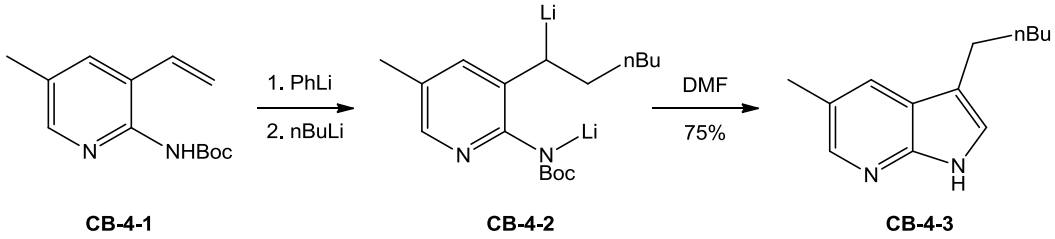
[123] Van Zandt, M. C.; Doan, B.; Sawicki, D. R.; Sredy, J.; Podjarny, A. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2006-2008.



Scheme 4.5 Synthesis of 7-azaindole from 3-methyl-2-aminopyridine

It is worth noting that in this synthesis, the C(2)-C(3) bond is formed before the C(2)-N(1) bond formation. An alternative bond-forming seq.uence, eg. C(2)-N(1) bond formation followed by intramolecular C(2)-C(3) bond formation, represents the traditional Madelung synthesis which generally req.uires very harsh conditions and has a very limited scope in azaindole synthesis.[124]

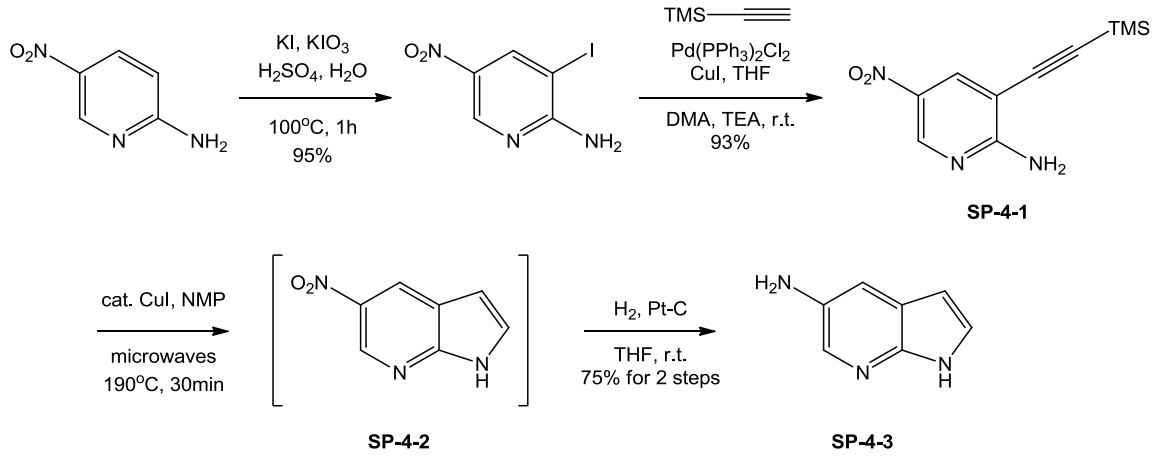
O'Shea described another synthesis of 7-azaindoles from 3-vinyl-2-aminopyridine, which involves a controlled lithiation of the vinyl double bond as the key synthetic step.[125] The starting material **CB-4-1** is obtained in high yields by the Suzuki-Miyaura cross coupling of substituted 3-bromo-2-aminopyridine with the 2,4,6-trivinyl-cyclotriboroxane-pyridine complex (not shown in Scheme 4.6). After that, the reaction of substituted 3-vinyl-2-aminopyridine with phenyl and butyl organolithiums[126] followed by addition of suitable electrophiles leads to the desired 7-azaindole **CB-4-3**. Replacement of DMF by other electrophiles, such as nitriles, opens up access to a wide range of 2,3-difunctionalized 7-azaindoles in modest to good yields.



Scheme 4.6 Synthesis of 7-azaindole from 3-vinyl-2-aminopyridine

[124] Turner J.A. *J. Org. Chem.* **1983**, *48*, 3401.
[125] Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935-1938.
[126] In order to avoid the ineffective vinyl carbolithiation, NH deprotonation was first carried out with phenyllithium prior to treatment with an alkyllithium.

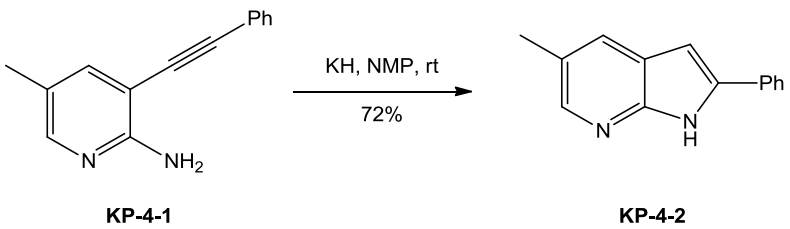
Although the lithiation of pyridine systems has been extensively employed, other methods have also been studied for the synthesis of 7-azaindoles. For example, Pearson and co-workers investigated the microwave-assisted CuI catalyzed cyclization of 3-alkynyl-2-aminopyridine **SP-4-1**, which was derived from the Sonogashira coupling of the unprotected 3-iodo-2-aminopyridine precursor and trimethylsilylacetylene, in the synthesis of 5-amino-7-azaindole **SP-4-3**.[127] It was found that the microwave-promoted process provided a faster reaction than the original thermal conditions.[128]



Scheme 4.7 Synthesis of 7-azaindole from 3-alkynyl-2-aminopyridine

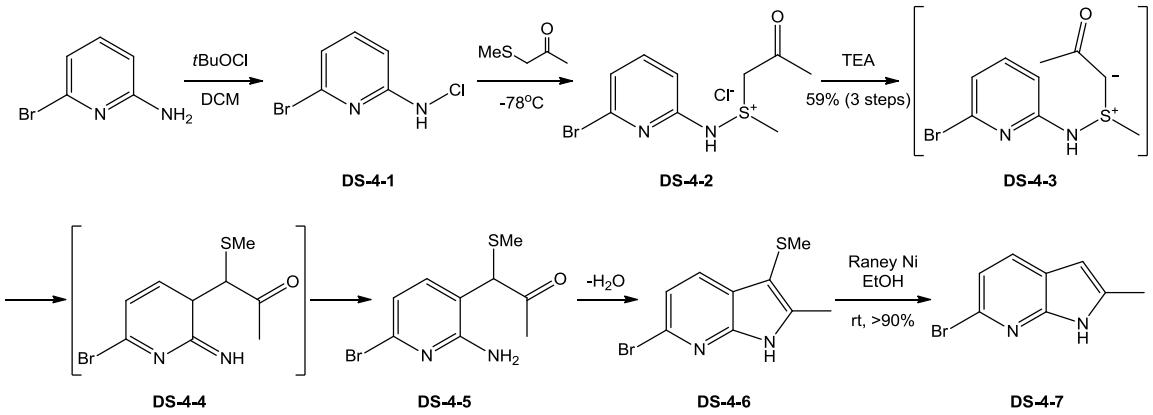
Nevertheless, this method usually req.uires quite harsh conditions (e.g. 80-190°C in a polar solvent). In order to optimize this synthesis with milder conditions, several new processes have been developed. For example, Knochel and co-workers reported a similar synthesis of 7-azaindole via the intramolecular addition of nitrogen nucleophiles to a triple bond, mediated by potassium or cesium bases in *N*-methylpyrrolidinone.[129] The method employs 3-alkynyl-2-aminopyridine as the ring closure precursor, and proceeds by a 5-*endo-dig* cyclization under mild conditions. As depicted in Scheme 4.8, 5-methyl-3-(phenylethynyl)-2-aminopyridine **KP-4-1** affords subseq.uently 5-methyl-2-phenyl-7-azaindole **KP-4-2** in 72% yield. This approach could also serve as a general strategy for preparing 2-substituted indoles.

[127] Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503-2506.
[128] (a) V. Kumar, J. A. Dority, E. R. Bacon, B. Singh and G. Y. Lesher, *J. Org. Chem.*, **1992**, 57, 6995.; (b) L. Xu, I. R. Lewis, S. K. Davidsen and J. B. Summers, *Tetrahedron Lett.*, **1998**, 39, 5159.
[129] (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488.; (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571-1587.; (c) Sun, L. P.; Huang, X. H.; Wang, J. X. *J. Chin. Chem. Soc.* **2007**, *54*, 569-573.



Scheme 4.8 Synthesis of 7-azaindole by 5-*endo-dig* cyclization

The last example cited here is based on the Gassman indole synthesis. Merck researchers reported a convenient process to prepare 7-azaindole from 2-aminopyridine and keto sulfides via a Sommelet-Hauser type rearrangement.[130]

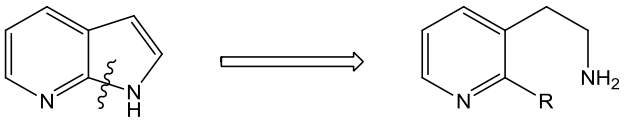


Scheme 4.9 Gassman-based route to substituted 7-azaindoles

This one pot reaction is divided into three steps. The first step is the oxidation of the 2-aminopyridine using *tert*-butyl hypochlorite to give chloramine **DS-4-1**. The second is the addition of the ketone to give the sulfonium ion **DS-4-2** which is typically done at low temperatures. The final step is the addition of base. Upon warming to room temperature, the base deprotonates the sulfonium ion and forms the sulfonium ylide **DS-4-3**, which rapidly undergoes a [2,3]-sigmatropic rearrangement to give ketone **DS-4-5**, which in turn undergoes a facile condensation to give the desired 3-thiomethyl-7-azaindole **DS-4-6**. Treatment with Raney Ni in ethanol provides the desulfurized 7-azaindole **DS-4-7** in a near quantitative yield.

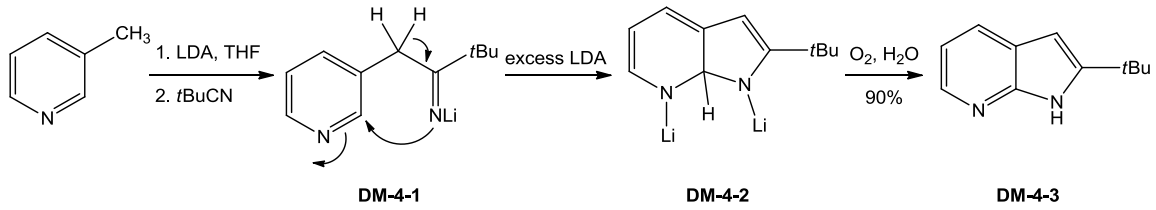
[130] (a) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590–591; (b) Debenham, S. D.; Chan, A.; Liu, K.; Price, K.; Wood, H. B. *Tetrahedron Lett.* **2005**, *46*, 2283–2285.

b. Construction of 7-azaindoles from 3-(2-aminoethyl)-pyridine derivatives



Scheme 4.10 Synthesis of 7-azaindole from 3-(2-aminoethyl)-pyridines

Rather than starting from the 2-aminopyridines, another effective synthesis uses the 3-(2-aminoethyl)-pyridine derivatives as the key intermediate. For example, Wakefield and his co-workers developed a one pot synthesis of 7-azaindole involving the metalation of 3-picoline and subseq.uent addition of nitriles.[131] As shown in Scheme 4.11, the lithium anion of 3-picoline with pivalonitrile gives intermediate **DM-4-1**, which readily cyclizes onto the pyridine ring in the presence of an excess of strong base. The intermediate is then oxidized to afford 2-substituted-7-azaindole **DM-4-3**. The cyclization is highly regioselective for the C-2 of pyridine. The isomeric azaindole resulting from ring closure onto the C-4 position was also observed as a by-product (5-azaindole) in trace amounts.

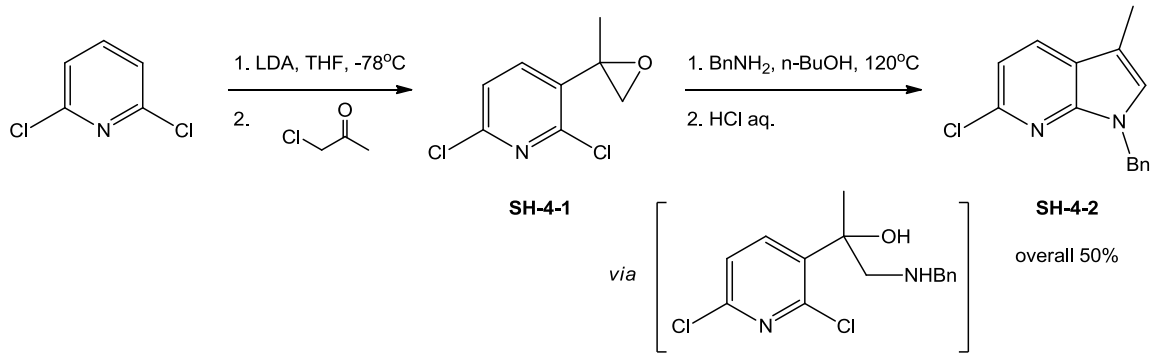


Scheme 4.11 Synthesis of 7-azaindole from 3-picoline

Another example of this strategy involves the nucleophilic cyclization of 2-chloro-3-ethylaminopyridine derivatives, which was reported by Schirok in 2005.[132] This approach proved to be an efficient way for preparing 3-substituted-6-chloro-7-azaindoles, such as **SH-4-2** (Scheme 4.12). After deprotonation of 2,6-dichloropyridine at the C-3 position with LDA, the addition of chloroacetone directly led to epoxide intermediate **SH-4-1**,

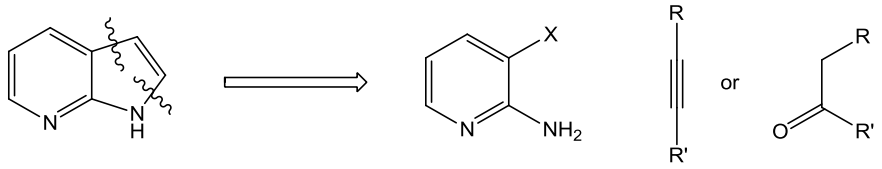
[131] (a) Davis, M. L.; Wakefield, B. J.; Wardell, J. A. *Tetrahedron* **1992**, *48*, 939-952.; (b) Ma, Y.; Breslin, S.; Keresztes, I.; Lobkovsky, E.; Collum, D. B. *J. Org. Chem.* **2008**, *73*, 9610-9618.
[132] Schirok, H. *Synlett* **2005**, 1255-1258.

which was then treated with primary amines (e.g. benzylamine), followed by acidification with HCl to furnish the target compound.



Scheme 4.12 Synthesis of a 7-azaindole via 2-chloro-3-ethylaminopyridine

c. Construction of 7-azaindoles via heteroannulation of 3-halo-2-aminopyridine



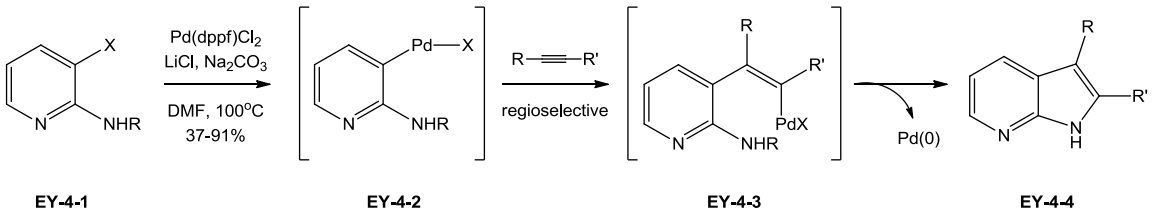
Scheme 4.13 Synthesis of 7-azaindole from 3-halo-2-aminopyridines

As a result of the rapid development in transition metal catalyzed cross-coupling reactions, palladium catalysis has been extensively employed in the synthesis of azaindole scaffold. For example, the 3-alkynyl-2-aminopyridine mentioned above as the precursor for 7-azaindoles, is prepared via the Sonogashiha coupling of aryl halides with *terminal* alkynes.

Moreover, the palladium-catalyzed heteroannulation of *internal* alkynes has also been applied to the construction of azaindoles (Scheme 4.13). This strategy was originally reported by Larock in 1990s for indole synthesis,[133] and later developed for the synthesis

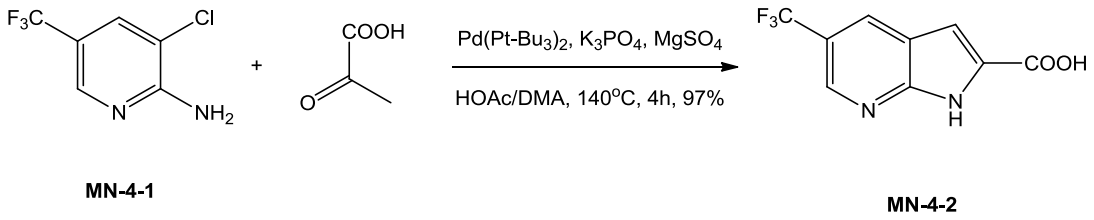
[133] R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, **1991**, 113, 6689.

of azaindoles.[134] For example, Yum and co-workers carried out extensive studies on this heteroannulation strategy for preparing 7-azaindole (Scheme 4.14). In this reaction, the use of LiCl and certain nitrogen protecting groups (alkyl and aryl groups) were found to be crucial for obtaining good yields. It worth noting that a high regioselectivity was obtained for most of the alkynes, with the more sterically bulky group (R') at the C(2) position.



Scheme 4.14 Palladium-catalyzed heteroannulation to prepare 7-azaindoles

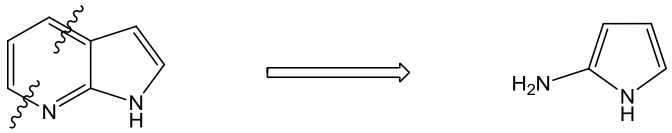
As shown in Scheme 4.13, the palladium-catalyzed annulation of 3-halo-2-aminopyridines with regular ketones has also been used to synthesize azaindoles. Generally, the reaction starts with enamine formation followed by an intramolecular Heck reaction. For example, Nazare and co-workers reported an effective synthetic route for preparing a 7-azaindole via the direct annulation of 5-trifluoromethyl-3-chloro-2-aminopyridine **MN-4-1** with 2-oxopropanoic acid[135] (Scheme 4.15). The use of Pd(P*t*-$Bu_3)_2$ as catalyst and a K_3PO_4-HOAc base-additive mixture was found to be essential for obtaining high yields.



Scheme 4.15 Palladium-catalyzed annulation of 3-halo-2-aminopyridines with ketones

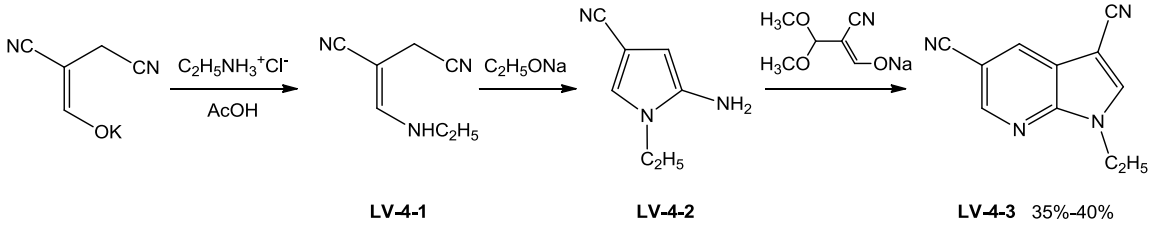
[134] (a) D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz and L. A. Cohen, Tetrahedron Lett., **1993**, 34, 2823; (b) S. S. Park, J.-K. Choi and E. K. Yum, *Tetrahedron Lett.*, **1998**, 39, 627; (c) M. S. Lee and E. K. Yum, *Bull. Korean Chem. Soc.*, **2002**, 23, 535.
[135] Nazare, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 4526-4528.

2. Pyridine ring formation starting from substituted pyrrole derivatives



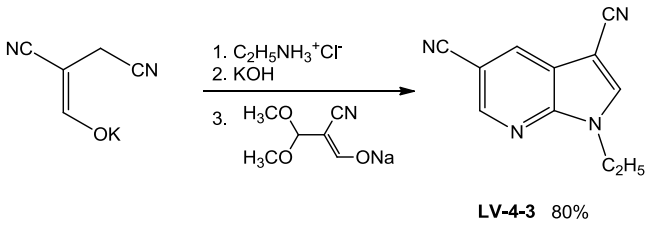
Scheme 4.16 Synthesis of 7-azaindole from substituted pyrroles

Although most of the syntheses of 7-azaindoles have pyridine derivatives as starting materials, some preparations starting from a pyrrole moiety have also been reported. Early work around this strategy can be traced back to the 1970s, albeit the yields for the key steps were unsatisfactory.[136] In 1994, Quéguiner described an improved synthesis of 3,5-disubstituted 7-azaindoles from the 2-aminopyrrole derivative **LV-4-2** and the sodium salt of 3,3-dimethoxy-2-fromylpropanenitrile[137] (Scheme 4.17).



Scheme 4.17 Synthesis of 7-azaindole **LV-4-3** based on a 2-aminopyrrole

Later on, further optimized one pot procedures were developed proceeding in synthetically useful yields, whereby enamine **LV-4-1** is not isolated and the pH kept under careful control (pH > 9).

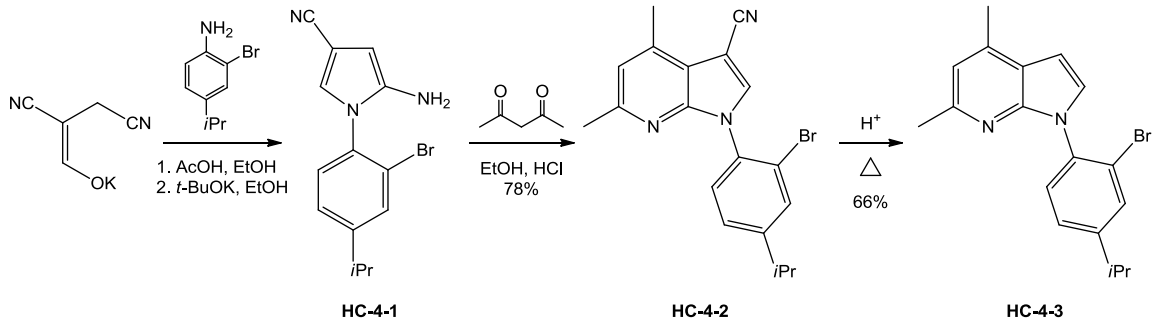


Scheme 4.18 One pot procedure for the same synthesis of **LV-4-3**

[136] (a) Abramenko, P. I. *Zh. Vse. Khim. Obshchest.* **1973**, *18*, 715; (b) Gilchrist et al. Chem. Abstr. **1974**, *80*, 95788; (c) Brodrick A., Wibberley D.G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1910

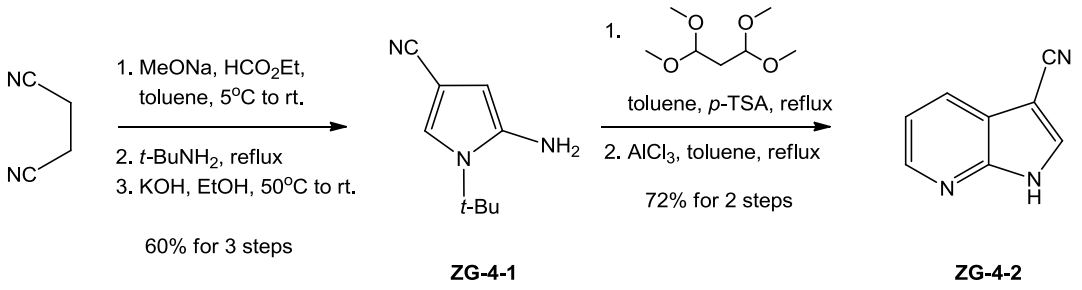
[137] Levacher V., Leroy C., Dupas G., Bourguignon J., Quéguiner G. *Synth. Commun.* **1994**, *24*, 2697

Based on the process for preparing intermediate aminopyrrole derivatives, **HC-4-3** an antagonist of the corticotropin-releasing hormone receptor, which had shown clinically beneficial properties in combating anxiety and depression, was generated from **HC-4-1** in two steps (Scheme 4.19). In acidic medium, bicyclic 7-azaindole **HC-4-2** is first obtained from 4-cyano-2-aminopyrrole and acetylacetone in good yield. Subseq.uent hydrolysis and final decarboxylation afford **HC-4-3** in 66% yield.[138]



Scheme 4.19 Synthesis of bioactive 7-azaindole **HC-4-3**

Recently, a new optimized synthesis of **ZG-4-2** was achieved by the reaction of 4-cyano-2-aminopyrrole with 1,1,3,3-tetramethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid, followed by removal of the *tert*-butyl group using $AlCl_3$.[139] The key aminopyrrole intermediate **ZG-4-1** was prepared from the inexpensive succinonitrile and ethyl formate in a three steps' procedure. This cost-effective synthesis can be regarded as suitable for industrial production.

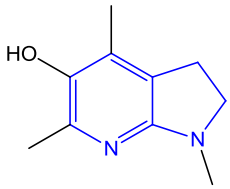


Scheme 4.20 Optimized cost-effective synthesis of 7-azaindole **ZG-4-2**

[138] Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Nemeth, G. A.; Arvanitis, A.; Cheeseman, R. S.; Chorvat, R. J.; Ciganek, E.; Christos, T. E.; Gilligan, P. J.; Krenitsky, P.; Scholfield, E.; Strucely, P. *J. Med. Chem*. **1999**, *42*, 819.
[139] Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. *Org. Process Res. Dev*. **2003**, *7*, 209-213.

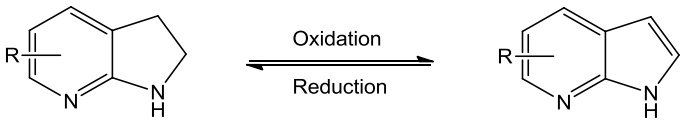
3. Oxidation of the corresponding 7-azaindolines

7-azaindolines, possessing the 7-azaindole structure with a saturated C(2)-C(3) bond, are also an important family of compounds. For example, 1,4,6-trimethyl-5-hydroxy-7-azaindoline was reported to be an efficient antioxidant, which displayed 88-fold larger inhibition rate constants than R-Tocopherol (a form of vitamin E) in quenching the oxidation of methyl linoleate in benzene solution.[140]



Scheme 4.21 Tocopherol-like antioxidant

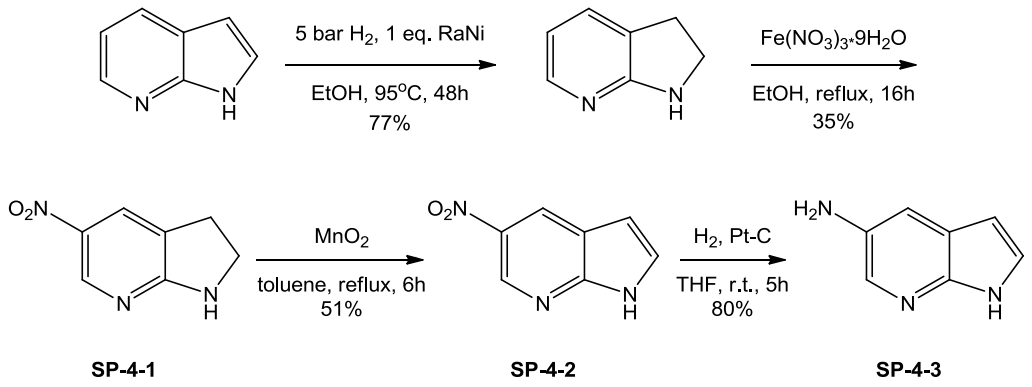
By oxidation or dehydrogenation, 7-azaindolines can be converted into the corresponding 7-azaindoles. Thus, an alternative strategy for generating 7-azaindoles is to oxidize the related 7-azaindoline derivatives.



Scheme 4.22 7-azaindoline and 7-azaindole transformation

Since the 3-position of 7-azaindole is most susceptible to electrophilic attack, blocking the pyrrole ring by introducing 7-azaindoline is a promising approach for certain syntheses. In 1959, with the aim of installing a substitution on the pyridine ring, Robinson reported a procedure to prepare 5-amino-7-azaindole with a 21% overall yield in four steps from 7-azaindoline.[141] More recently, chemists at AstraZeneca optimized this procedure starting from commercially available 7-azaindole[142] (Scheme 4.23).

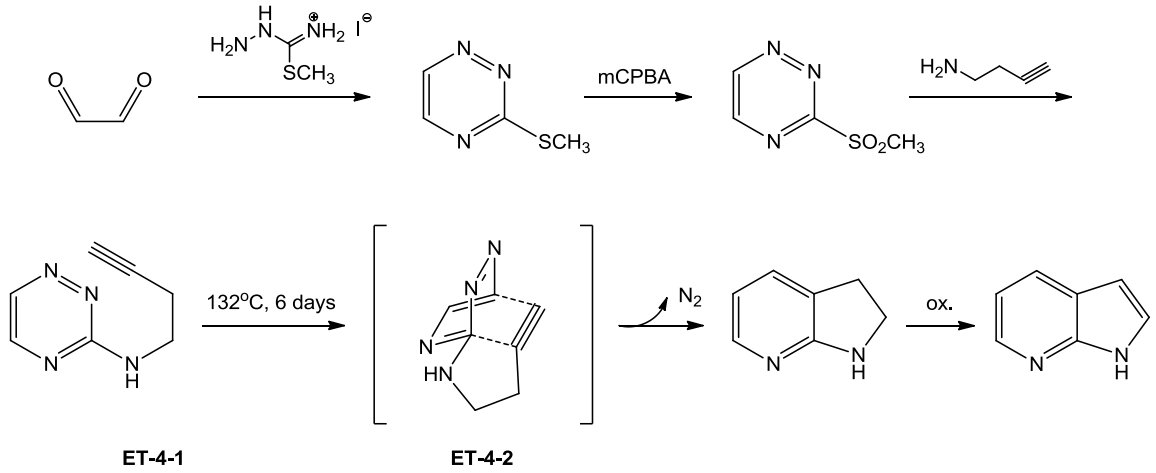
[140] Lu, J.; Cai, X. Q.; Hecht, S. M. *Org. Lett.* **2010**, *12*, 5189-5191.
[141] M. Robinson, *J. Am. Chem. Soc.* **1959**, 743
[142] Pearson, S. E.; Nandan, S. *Synthesis Stuttgart* **2005**, 2503-2506, and references cited therein.



Scheme 4.23 Optimized Robinson procedure by chemists at AstraZeneca

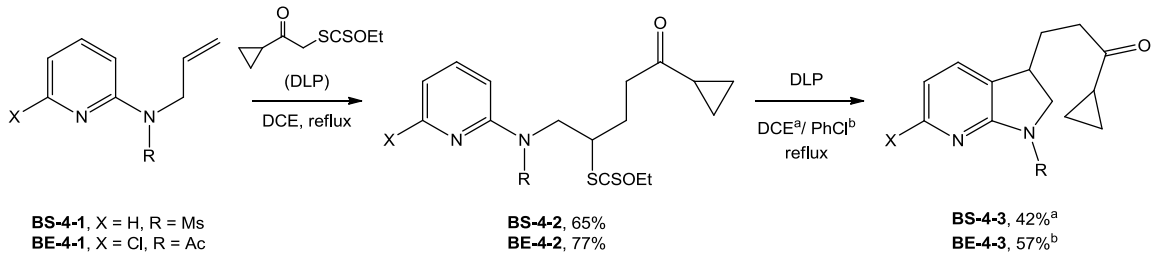
7-azaindoline can be generated via many types of reactions, such as reductive 5-exo aryl radical cyclization,[143] intramolecular carbolithiation of aryllithiums,[144] intramolecular inverse electron demand Diels-Alder reaction,[145] and many other processes.[146] For example, condensation of 1,2-dicarbonyl compounds with *S*-methylthio-semicarbazide smoothly provides the 3-methylthio-1,2,4-triazine, which is subseq.uently oxidized with *m*CPBA to the 3-methylsulfonyl-1,2,4-triazine.[147] Nucleophilic displacement of methylsulfinate with 4-aminobutyne in DMF affords the triazolo compound **ET-4-1**. The latter undergoes intramolecular cycloaddition via the intermediate **ET-4-2** in refluxing bromobenzene to yield the 7-azaindoline.[148] Final aromatization with DDQ furnishes the 7-azaindole.[149] However, this strategy is sometimes limited when preparing more elaborate 7-azaindoles due to the high temperature req.uired for the Diels-Alder reaction.

[143] Viswanathan, Rajesh; Prabhakaran, Erode N.; Plotkin, Michael A.; Johnston, Jeffrey N., *J. Am. Chem. Soc.*, **2003**, *125*, 163-168.
[144] W.F. Bailey, P.D. Salgaonkar, J.D. Brubaker, V. Sharma, *Org. Lett.* **2008**, *10*, 1071.
[145] Taylor, E. C. *Bull. Soc. Chim. Belg.* **1988**, *97*, 599.
[146] Dr. Petit, L. *PhD thesis* Ecole Polytechnique, **2008**.
[147] Taylor E. C., Macor J. E. *Tetrahedron Lett*. **1986**, *27*, 431
[148] Taylor E. C., Pont J. L. *Tetrahedron Lett*. **1987**, *28*, 379
[149] Merour J.Y., Joseph B. *Curr. Org. Chem.* **2001**, *5*, 471-506



Scheme 4.24 Intramolecular inverse electron demand Diels-Alder process

In our laboratory, the synthesis of 7-azaindolines has also been extensively explored based on the radical chemistry of xanthates. Many syntheses have been realized by direct radical cyclization of related substituted pyridine precursors. For example, as displayed in Scheme 4.25, following the seq.uence of intermolecular addition and intramolecular cyclization to the pyridine nucleus, 7-azaindolines **BS-4-3** and **BE-4-3** were obtained with yields of 42% and 57% respectively.[150] These early studies were important since they showed that the nitrogen of pyridine was not deleterious to the xanthate precursor if its nucleophilicity could be blocked by appropriate substituents.



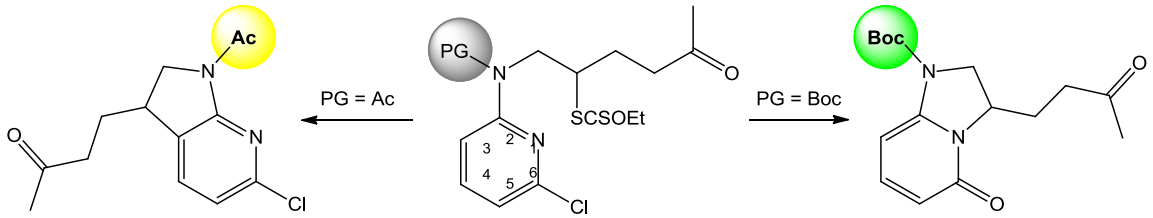
Scheme 4.25 Synthesis of 7-azaindolines by radical addition-cyclization

[150] (a) Ly, T. M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533-2536; (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671-3674.

Ⅱ. Synthesis of 7-azaindoles and 7-azaindolines by an uncommon radical *ipso*-substitution of a C-F bond

1. Discovery of an unexpected radical *ipso*-substitution-demethylation

"In chemistry, minor and seemingly harmless modifications can have a profound effect on reactivity".[151] During a study of pyridine based substrates, a dramatic effect on the regioselectivity was found in the radical cyclization of substrates such as **BE-4-2** (Scheme 4.25), which indicated that the protecting groups on the extranuclear nitrogen played a significantly important role in the regioselectivity.[152] As shown in Scheme 4.26, when an acetyl group is present in the precursor xanthate **EQ.-4-1**, the radical cyclization proceeds on C-3 and gives the 7-azaindoline **EQ.-4-2**. However, if the side chain nitrogen is protected by a Boc group, the radical cyclization takes place on the ring nitrogen to give the corresponding pyridinone **EQ.-4-3**. It was also noticed that the Boc group can be replaced by a smaller carbamyl group, and the presence of halogen substitutions like chlorine or fluorine is necessary in this selective process.[153] This special regioselectivity will be further discussed in the next chapter.

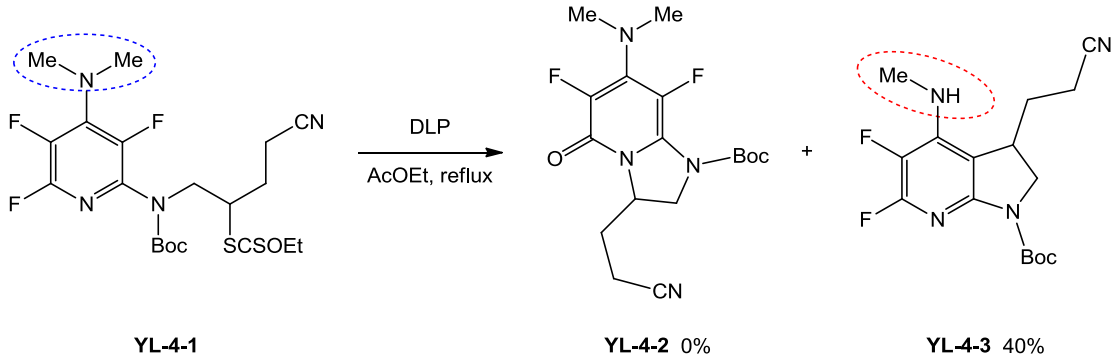


Scheme 4.26 Divergent radical cyclization on a pyridine ring

In the attempt to expand the scope of this unexpected transformation as well as generate more mechanistic information, a related radical process of another derivative **YL-4-1** was

[151] Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 3426-3429.
[152] El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, 4422-4424.
[153] In the case of chlorine, the cyclization to nitrogen worked better than fluorine.

examined, with the idea of using fluorine substituent to block the aromatic carbon and thus force the radical to cyclize on the pyridine nitrogen[154] (Scheme 4.27).



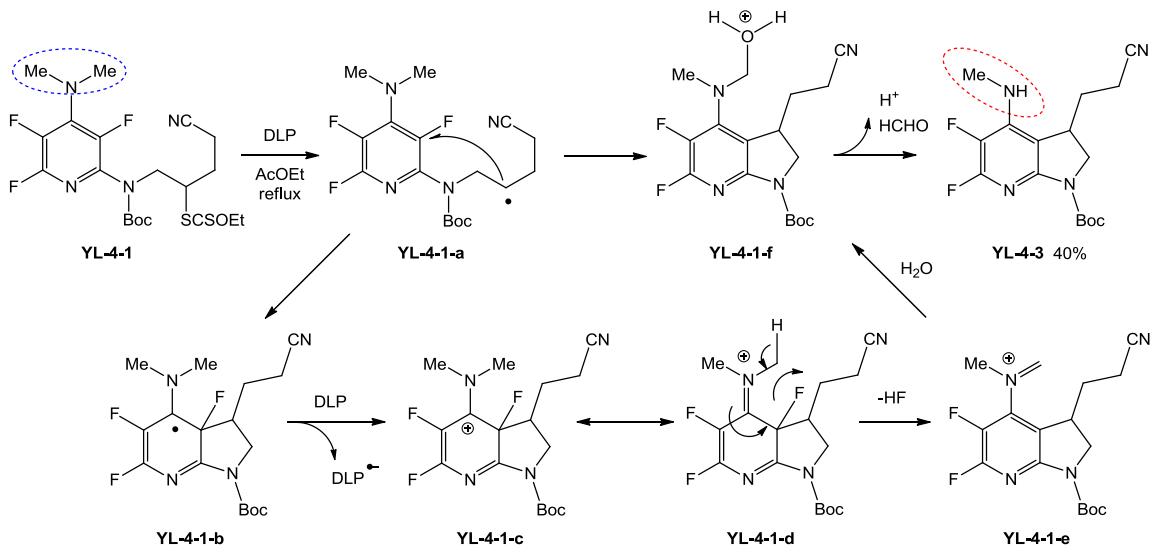
YL-4-1 **YL-4-2** 0% **YL-4-3** 40%

Scheme 4.27 Unexpected radical *ipso*-substitution-demethylation

However, the cyclization did not proceed as expected on the pyridine nitrogen to furnish the corresponding pyridinone **YL-4-2**. Instead, bicyclic azaindoline **YL-4-3** was surprisingly generated in a modest yield, with loss of the *ortho*-fluorine atom as well as one of the methyl groups from the dimethylamino substituent on C-4 (Scheme 4.27).

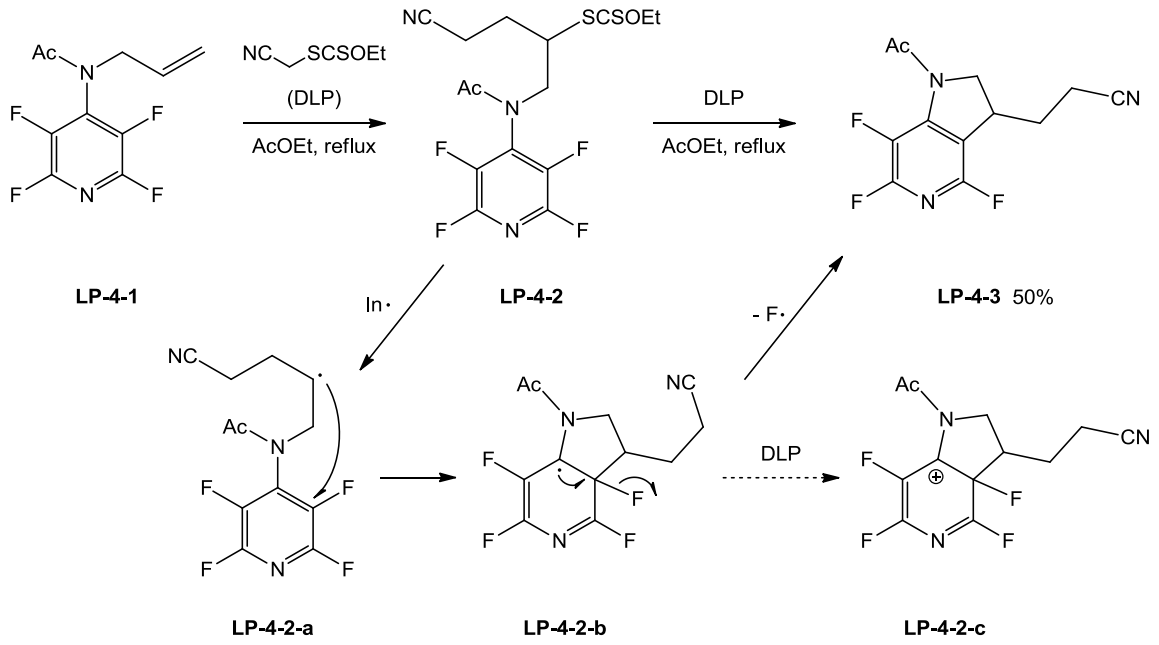
A plausible mechanism is depicted below to explain the formation of the azaindoline (Scheme 4.28). After initiation, the radical species **YL-4-1-a** undergoes an *ipso*-substitution on the *ortho*-carbon next to the extra-nucleus nitrogen to give an intermediate radical **YL-4-1-b**, which is then oxidized by the peroxide to form an allylic cation **YL-4-1-c**. This intermediate cation is destabilized by the adjacent electron withdrawing fluorines, but stabilized by the two exocyclic nitrogen substituents. After losing the hydrogen fluoride as depicted, an iminium species **YL-4-1-e** is obtained which is readily hydrolyzed upon workup to complete the demethylation and give the final azaindoline **YL-4-3**.

[154] (a) Laot, Y.; Petit, L.; Ngoc, D. M. T.; Zard, S. Z. *Aust. J. Chem.* **2011**, *64*, 416-425; (b) Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 3426-3429.



Scheme 4.28 A plausible mechanism for the unexpected cyclization

A modification to the substrate of **YL-4-1** was made by our colleagues later on, which installed the xanthate-containing side chain directly at C-4, as illustrated in Scheme 4.29. In this way, the cation **LP-4-2-c** which is generated from the *ipso*-substituted intermediate **LP-4-2-b**, would not be stabilized by a second nitrogen substituent and the 5-azaindoline **LP-4-3** is thus obtained with a reasonable yield after losing the fluorine atom.



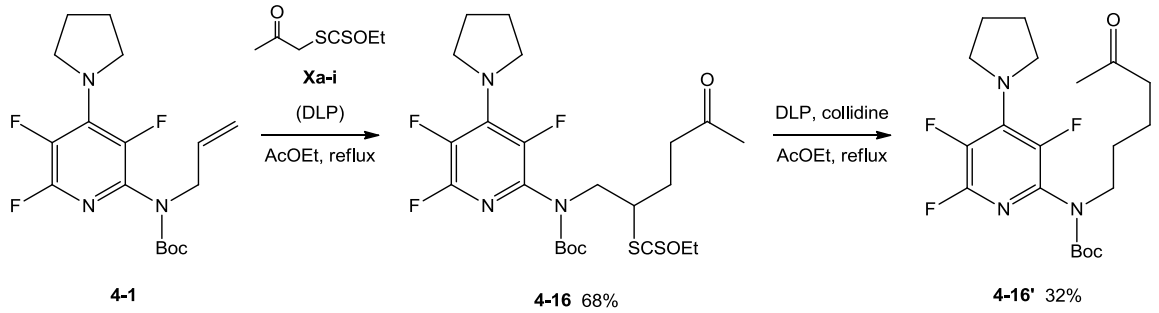
Scheme 4.29 Synthesis of 5-azaindoline by radical *ipso*-substitution of C-F

2. Clarification of the mechanism

In order to confirm the proposed mechanism for the *ipso*-substitution-demethylation and perhaps gain some additional mechanistic insight into this reaction, a related study was carried out with the substrates in which the dimethylamino substituent was replaced by pyrrolidyl and piperidyl group. With these modifications, further information might be acquired from the changes in the substituent rings.

a. With pyrrolidyl substituted precursors

At this point, xanthate precursor **4-16** was readily prepared by radical addition of xanthate **Xa-i** to the Boc-protected *N*-allylaminopyridine **4-1**, which was obtained following the general procedures [155] starting from the commercially available pentafluoropyridine. However, a complicated reaction mixture was obtained from the exposure of **4-16** to the action of dilauroyl peroxide in AcOEt, and only 32% of prematurely reduced material **4-16'** was isolated and identified (Scheme 4.30). An observation based on NMR analysis was that deprotection occurred to the molecules in the reaction mixture. The Boc-protecting group was partially destroyed by the acidic side-products in the medium.



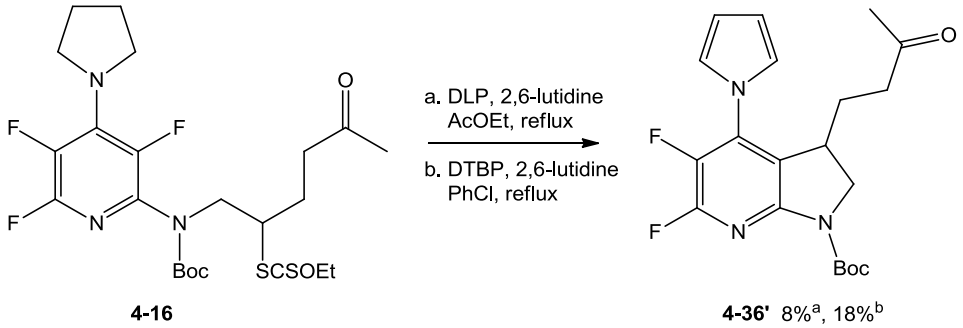
Scheme 4.30 Radical cyclization of xanthate **4-16**

We then attempted to employ another initiator DTBP, which does not produce any acidic product upon thermolysis or induced decomposition, and replaced the collidine with a

[155] See page 135 for the general procedure in preparing olefinic precursors.

slightly less basic 2,6-lutidine as the hydrogen fluoride scavenger. Higher boiling point chlorobenzene was also employed to match the half-life of the initiator DTBP, which can be added all at once at the beginning.

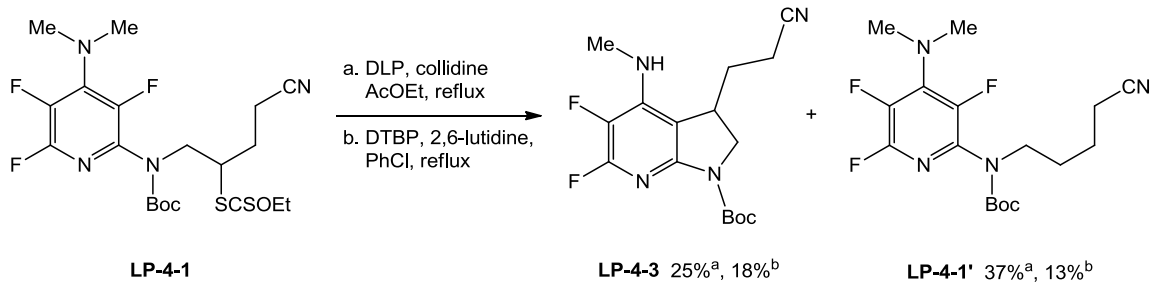
When the starting material was completely consumed, the solvent was removed under reduced pressure and the residue was purified by flash chromatography. Surprisingly, the cyclization this time of **4-16** was successful, affording an unexpected azaindoline **4-36'**, *the pyrrolidyl at C-4 was replaced by a pyrrolyl group* (Scheme 4.31). Although the yield for ring closure was far from being useful from a preparative standpoint, the observation of this transformation was still encouraging.[156] We also repeated the former conditions with DLP in AcOEt and got 28% of **4-16'** as well as 8% of the cyclized compound **4-36'** which was not identified previously in the complicated reaction mixture.



Scheme 4.31 Radical cyclization of xanthate **4-16**

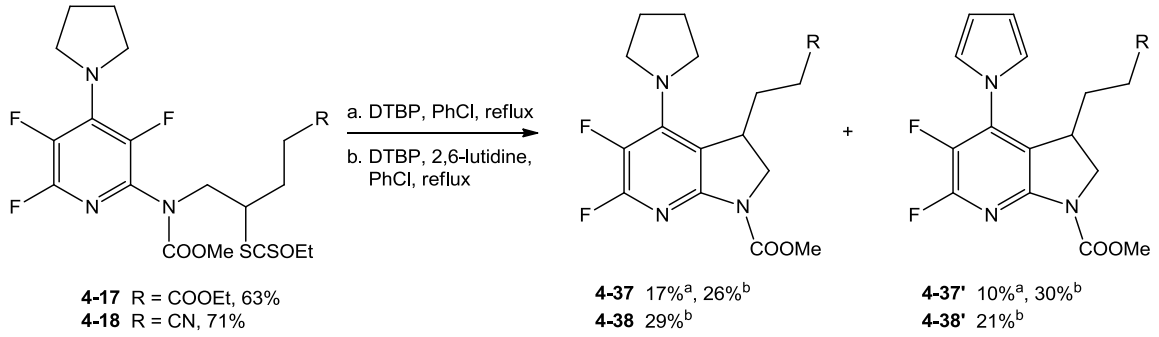
Based on this new observation, the radical cyclization of **LP-4-1** was repeated with the new conditions (see Scheme 4.32). For a more direct comparison, the cyclization was also repeated with the original method and furnished 25% of **LP-4-3** with 37% reduced material. However, with the new method only 18% of **LP-4-3** and 13% of reduced material were obtained. Based on the mechanism proposed above, the decrease of yield in generating **LP-4-3** was reasonable since DLP is a better oxidant than DTBP, and lower temperature as well as long heating duration also favors the formation of cation species. Furthermore, the relative instability of Boc group towards prolonged heating at high temperature could also be responsible for the low yield.

[156] Unfortunately, the possibly formed prematurely reduced material was not collected for a better comparison of the relative rates for the transformations.



Scheme 4.32 Unexpected radical *ipso*-substitution-demethylation

Significant improvement was observed by replacing the relatively sensitive Boc group[157] with a similar but more robust methoxycarbonyl group. With this modification, xanthate precursors **4-17** and **4-18** were readily prepared and subjected to the radical cyclization (Scheme 4.33). Even more surprising was that this time not only the yield of pyrrolyl substituted product **4-37'** jumped from 18% to 30%, but a second pyrrolidyl substituted 7-azaindoline **4-37** was also generated in a yield of 26%. At this point, the reaction resulted in a relatively efficient ring closure with an overall yield of 50% ~ 56%.

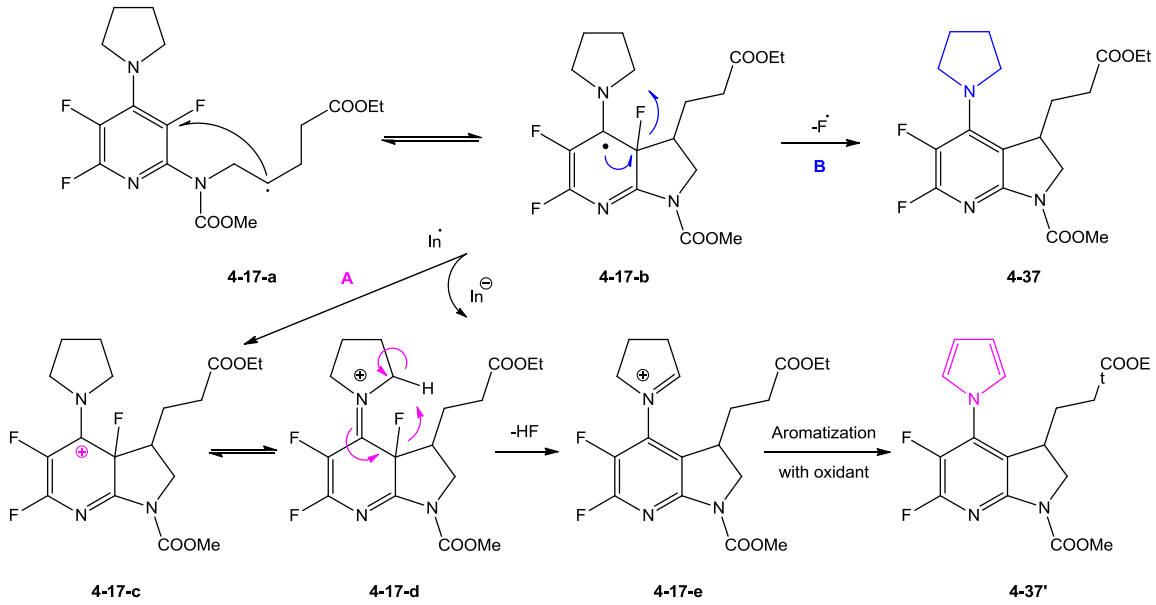


Scheme 4.33 Radical cyclizations with a different protecting group

It is worth mentioning that as indicated above, the cyclization of **4-17** in chlorobenzene without an additive base gave rise to a dark colored medium at the end of the heating period. The ensuing purification was somewhat laborious and only furnished 17% of **4-37** as well as 10% of **4-37'**. However, with the addition of base as the hydrogen fluoride scavenger, the reaction was not only cleaner but also gave a higher yield of the desired azaindolines **4-37** and **4-37'**.

[157] The deprotection of Boc group can be achieved under thermal conditions; El Kazzouli, S.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 8575-8577, and references cited therein.

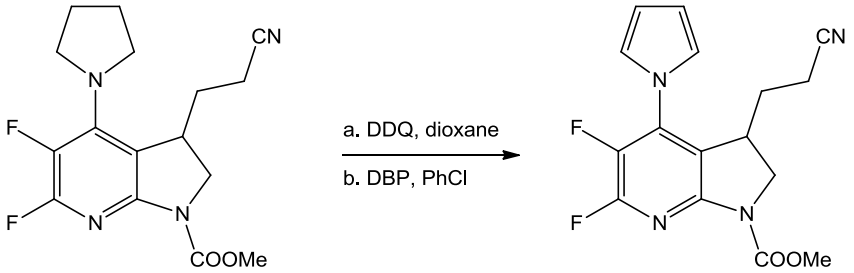
A revised mechanism for this transformation can now be proposed as shown in Scheme 4.34. The first pathway (Path A) includes a cationic intermediate **4-17-c**, which is generated by electron transfer to the peroxide, followed by elimination of hydrogen fluoride and aromatization by further oxidation by the peroxide. The second pathway (Path B) starts with the radical attack at the C-3 of pyridine and ends by loss of a fluorine atom directly from intermediate **4-17-b**. This process is favored by a high temperature.



Scheme 4.34 Radical cyclization of xanthate **4-17**

Although an overall ring closure yield of 50% ~ 60% was realized, the specificity of the reaction was still dashed by the fact that two products were generated in the ratio of ~1:1. A better transformation leading to one major compound either by oxidation or reduction had to be developed.[158] Experiments aimed at oxidizing the pyrrolidyl derivative **4-38** to pyrrolyl derivative **4-38'** were carried out with DDQ, but failed. We then tried benzoyl peroxide (DBP) in refluxing chlorobenzene as an oxidant for **4-38** (Scheme 4.35). We were pleased to find that the desired product **4-38'** was isolated in a modest yield of 38%.

[158] Robison, M. M.; Butler, F. P.; Robison, B. L. *J. Am. Chem. Soc.* **1957**, *79*, 2573-2578.



4-38 **4-38'** 0%[a], 38%[b]

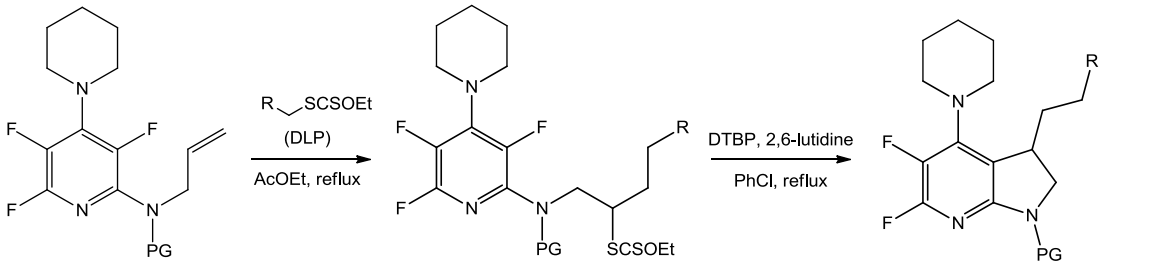
Scheme 4.35 Non-optimized oxidation of **4-38**

We didn't go any further than this, since this transformation was not the target of our project. However, these preliminary results showed that with optimized reagents and conditions, a one-pot seq.uence of cyclization-oxidation could in principle be realized, giving 4-pyrrolyl-7-azaindoline specifically.

b. With piperidyl substituted precursors

In order to figure out whether there would be any similar changes to the C-4 substituent, a larger nitrogen ring was installed on the xanthate precursors. At this point, we studied the piperidyl substituted olefinic precursors **4-3** and **4-4**, which were prepared from pentafluoropyridine by two steps of substitution followed by the corresponding protection.[159] They were then employed to perform initial comparative studies. The radical addition was accomplished using the standard procedure with DLP in refluxing AcOEt and afforded the xanthates **4-19**, **4-20** and **4-21** in reasonable yields (Scheme 4.36). The subseq.uent cyclizations then gave 7-azaindolines **4-39**, **4-40** and **4-41** in similar yields for all three cases.[160]

[159] See page 135 for the general procedure in preparing olefinic precursors.
[160] An important difference between the cyclizations of **4-19** and **4-21** was found later which will be discussed in page 132.



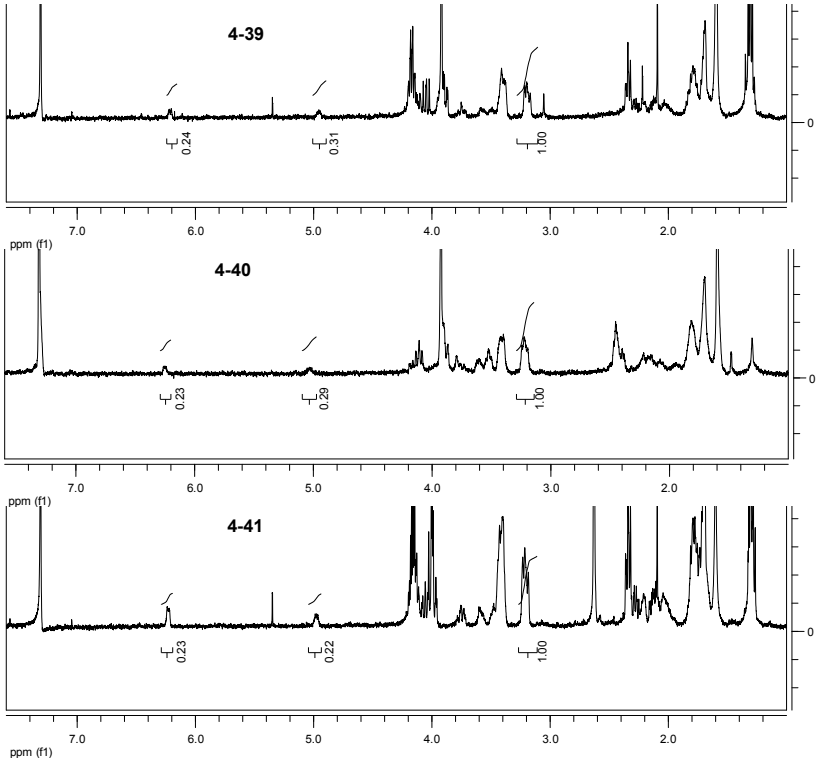
4-3, PG = COOMe
4-4, PG = Ac

4-19, PG = COOMe, R = COOEt, 61%
4-20, PG = COOMe, R = CN, 75%
4-21, PG = Ac, R = COOEt, 56%

4-39, PG = COOMe, R = COOEt, 33%
4-40, PG = COOMe, R = CN, 27%
4-41, PG = Ac, R = COOEt, 31%

Scheme 4.36 Radical cyclizations with piperidyl substituted precursor

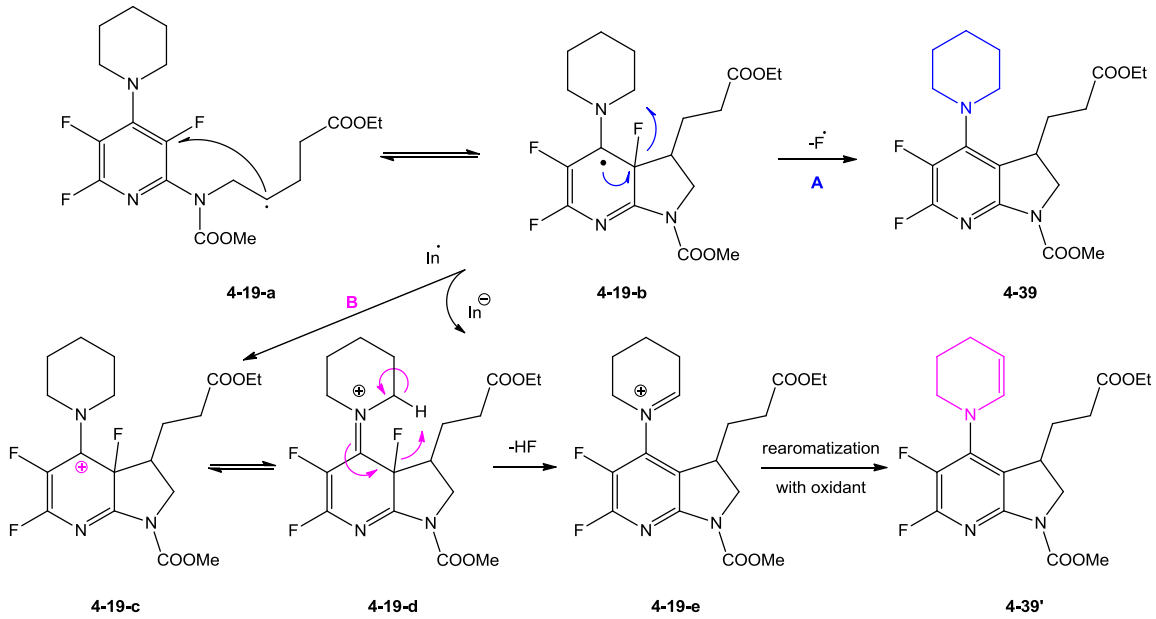
However, it was interesting that the products were isolated in a somewhat impure state, indicated by the presence of two correlated eq.alent impurity peaks[161] at δ~6.20 and δ~4.95 (Scheme 4.37). Two rounds of purification were needed to remove these peaks in order to get the clean spectra for these three products.



Scheme 4.37 ^{1}H NMR spectra of the 7-azaindolines from the first purification

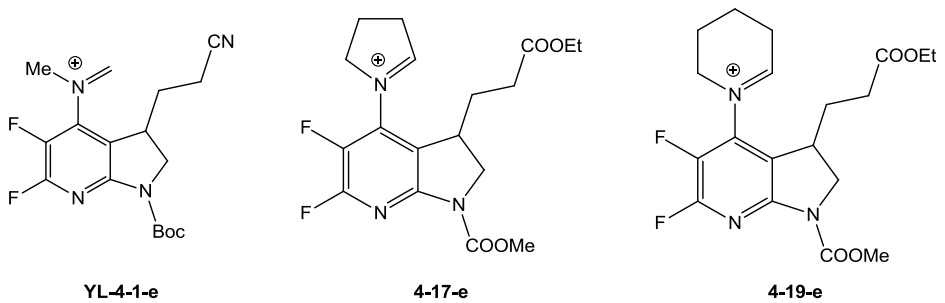
[161] ^{1}H Cosy NMR confirmed that the two peaks were correlated.

Based on the previous discussion of the mechanism, the enamine species with piperidyl substitution could also be formed. Although it was not isolated to be completely characterized, the indirect proof from NMR analyses partially confirmed its existence.



Scheme 4.38 Radical cyclization of xanthate **4-19**

It should be noted that none of the product from Path A was obtained when we repeated the cyclization of **YL-4-1**, two products in similar yields were produced from the cyclization of **4-17**, and less product from Path B was observed from the cyclization of **4-19**. The reasons underlying this behavior are not clear yet. In the case of **YL-4-1-e** only hydrolysis can take place to give the demethylated product, while in the case of **4-17-e**, further oxidation furnishes a stable pyrrole. For **4-19-e**, the iminium cannot easily proceed to an aromatic structure nor does it hydrolyse cleanly. In the absence of a good mass balance for the reaction, we cannot draw solid conclusions.

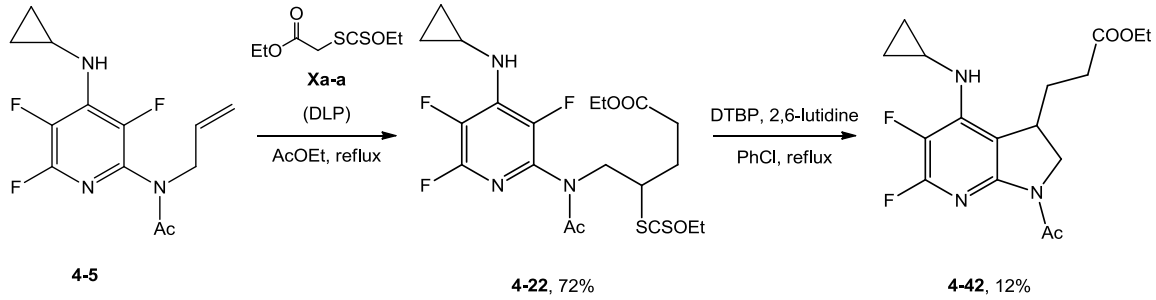


Scheme 4.39 Imines intermediates with different C-4 substitutions

3. Further investigations of the scope

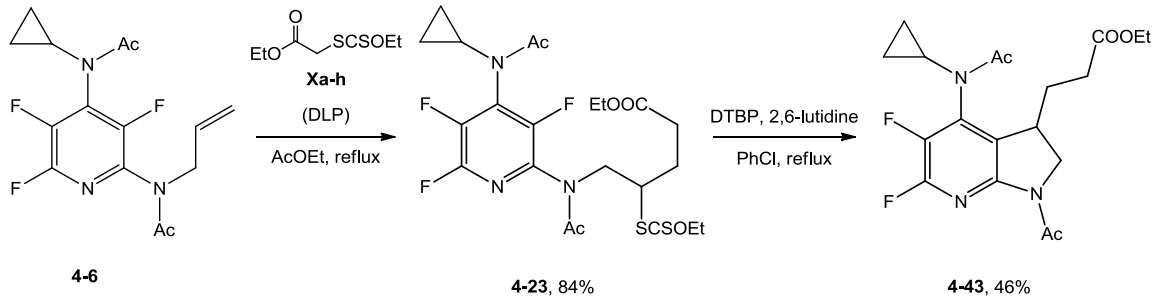
a. Discovery of another product: 7-azaindole

With the aim of further investigating the influence of substituted ring size, another cyclic substituent cyclopropylamine was chosen at C-4, and the standard radical addition-cyclization procedure was applied to olefin **4-5** using xanthate **Xa-h** (Scheme 4.40). Unfortunately, a complicated reaction mixture was obtained and only 12% of 7-azaindoline **4-42** could be isolated.



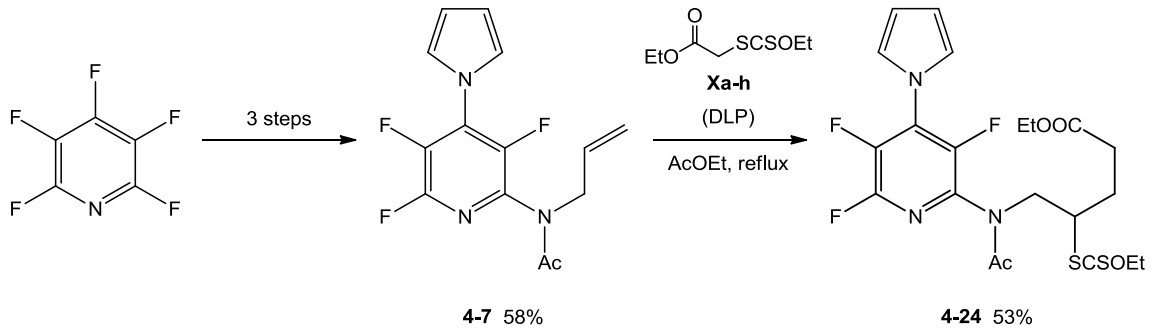
Scheme 4.40 Radical cyclizations with smaller ring substitution

During the preparation of olefin **4-5**, the bis-acetylated adduct **4-6** was also obtained. Although this compound was just a by-product and the intrinsic electron withdrawing nature of the substituent should destabilize the cationic intermediate (c.f. **4-19-c**), it was nevertheless worth a try, as it was already available. Thus, the addition-cyclization seq.uence was applied to **4-6** as shown in Scheme 4.41 and, surprisingly, this time the desired azaindoline **4-43** was isolated in a yield up to 46%!



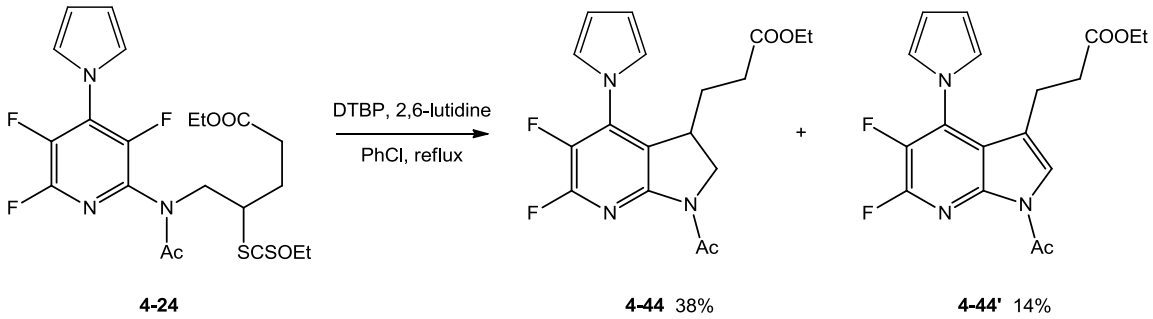
Scheme 4.41 Radical cyclizations with bis-acetylated precursor

This observation reminded us that with an electron withdrawing substituent at C-4, the nucleophilic radical addition followed by a β-scission ("Path B") becomes dominant. With this idea in mind, we then examined another olefinic precursor **4-7** incorporating a weaker electron-releasing pyrrolyl substituent at the C-4. This olefinic precursor was accessible through substitution of pentafluoropyridine with pyrrole, then with *N*-allylamine followed by acetylation (Scheme 4.42). The subseq.uent radical addition was realized with xanthate **Xa-h** in a reasonable yield to give the xanthate **4-24**.



Scheme 4.42 Preparation of xanthate precursor **4-24**

Xanthate precursor **4-24** was then subjected to the usual conditions with an even more surprising result (Scheme 4.43). From the radical cyclization we isolated the expected 7-azaindoline **4-44** in a modest yield (38%); however, we also observed another spot on the TLC plate adjacent to the starting material. Usually such spots correspond to the prematurely reduced material (i.e. the xanthate group simply replaced with hydrogen) as these side-products are difficult to avoid when difficult cyclization are involved. However, it was not the case this time. One new product, *7-azaindole* **4-44'**, was obtained in a yield of 14% thus raising the total yield of cyclized products to 52%.



Scheme 4.43 Radical cyclization of **4-24**

b. A more complete view of the mechanism

The discovery of 7-azaindole **4-44'** not only increased the ring closure efficiency, but also made this synthesis more versatile. However, a question arose automatically: how was this 7-azaindole formed? We therefore repeated the cyclization of **4-24** with an increased amount of DTBP under similar concentration in chlorobenzene[162] (Table 4.1).

Entry	DTBP	Concentration in PhCl	**4-44**	**4-44'**	Total yield	**4-44'/4-44**
1	3.5 equiv.	0.07M	51%	trace	51%	~ 0
2	5.0 equiv.	0.05M	38%	14%	52%	0.37
3	15.0 equiv.	0.05M	35%	21%	56%	0.60

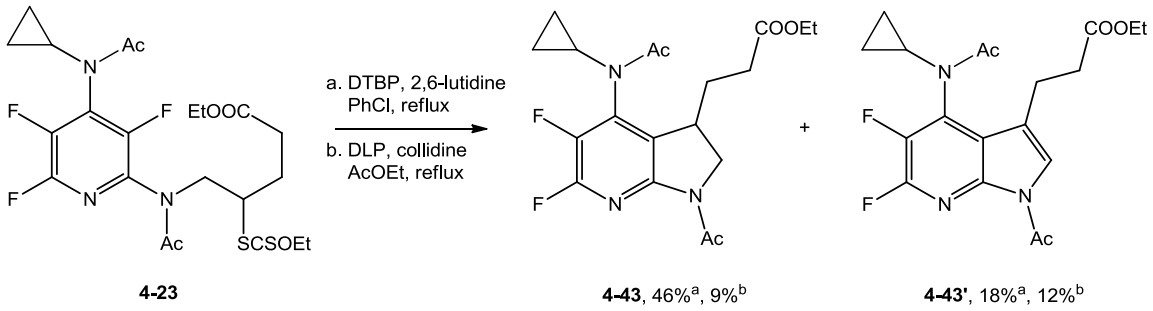
Table 4.1 Analyses of the role of DTBP

It is clear that when more DTBP is added, the total yield for cyclization was gently increased and the ratio of **4-44'** to **4-44** increased as well. Thus, the 7-azaindole was very likely generated from 7-azaindoline via partial oxidation by DTBP in refluxing chlorobenzene.[163]

Anyway, this newly found 7-azaindole was derived from a reasonably efficient ring closure of the electron-accepting group substituted xanthate **4-24**. In that case, a similar compound should be generated from the cyclization of xanthate **4-23**, which also has an electron-withdrawing *N*-substituent at C-4. In fact, when we re-examined a minor fraction, which was previously thought to be the prematurely reduced material, the corresponding 7-azaindole **4-43'** was identified with a yield of 18%. Conseq.uently, the actual yield for cyclization is now a respectable 64% (Scheme 4.44).

[162] In the first two entries, DTBP was added once and the reaction took about 3h; while in the third, DTBP was added twice, 10.0 eq. for 4h and then 5.0 eq. for 1h

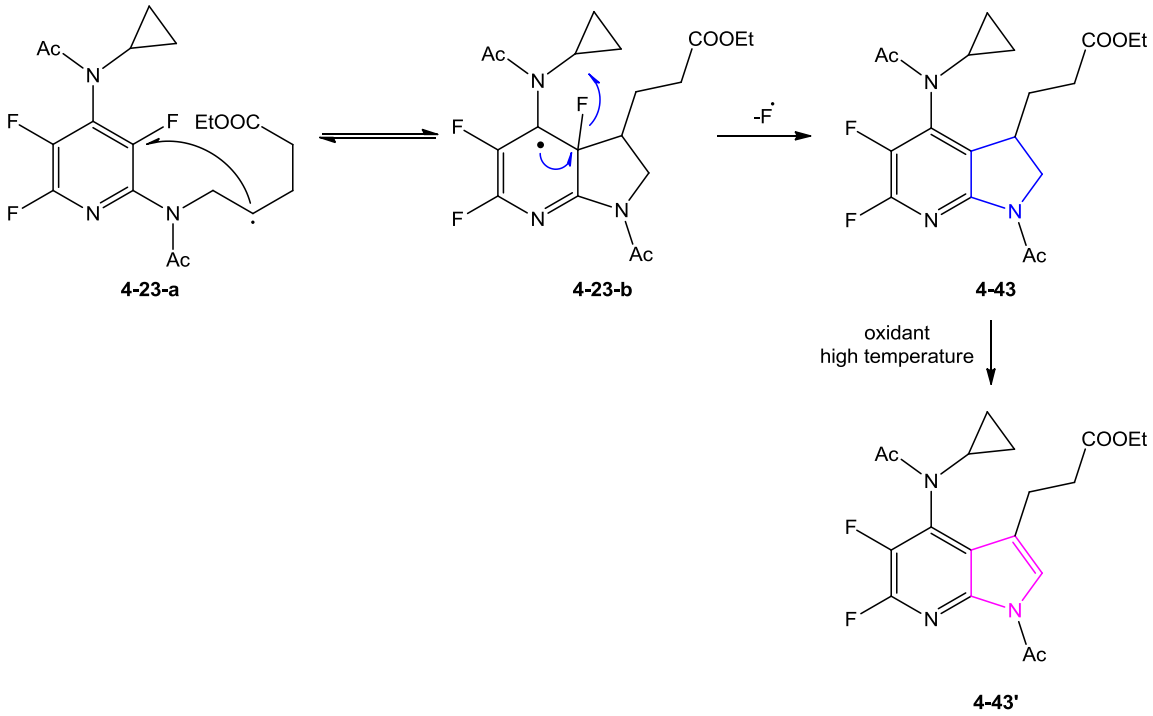
[163] Later, we tried the oxidation of **4-47** with benzoyl peroxide (DBP), a more powerful oxidant. However, only part of the 7-azaindoline was oxidized to the corresponding 7-azaindole **4-47'**. A more efficient oxidation will be discussed in the next part.



4-23 **4-43**, 46%[a], 9%[b] **4-43'**, 18%[a], 12%[b]

Scheme 4.44 Recover of the 7-azaindole **4-43'**

Furthermore, we also repeated the cyclization of **4-23** under the former conditions (b) with DLP in refluxing AcOEt. Although poor yields were obtained, it was interesting that 7-azaindole **4-43'** was also isolated, even as the major product. None of the corresponding 7-azaindole was observed during the early study with C-4 EDG substituent under these conditions, which meant that the C-4 EWG was not only essential for improving the cyclization, but also important to the oxidation step (Scheme 4.45).



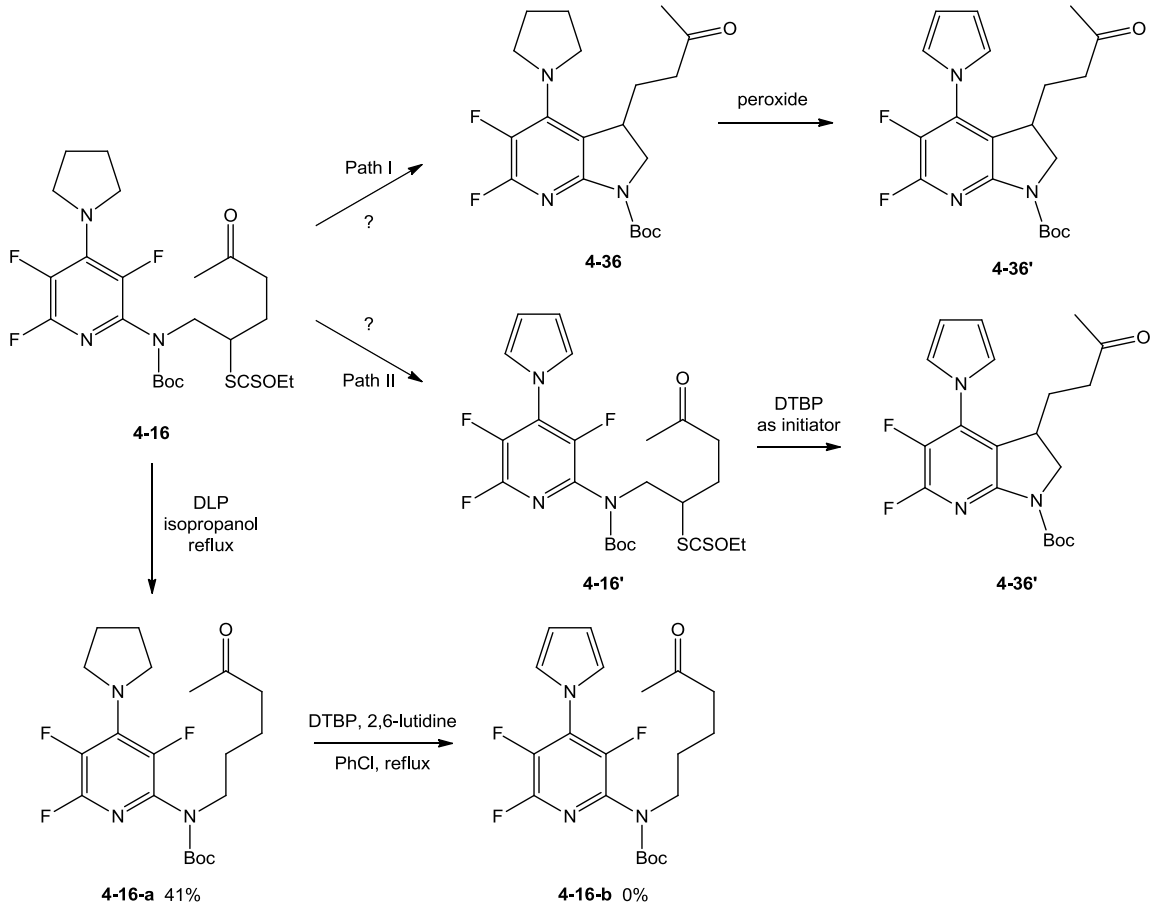
4-23-a **4-23-b** **4-43** **4-43'**

Scheme 4.45 Mechanism for obtaining **4-43** and **4-43'**

c. Clarification of two previous results

1) When the pyrrolidyl was oxidized to the pyrrolyl?

Since the cyclization of **4-24** gave a much improved overall yield for ring-closure, could the pyrrolyl substituted 7-azaindoline **4-36'** be derived from the cyclization of a pre-oxidized xanthate **4-16'**? If so, the mechanism for this reaction should be modified by adding the Path II depicted in Scheme 4.46, which includes the seq.uence of pre-oxidation and radical *ipso*-substitution.



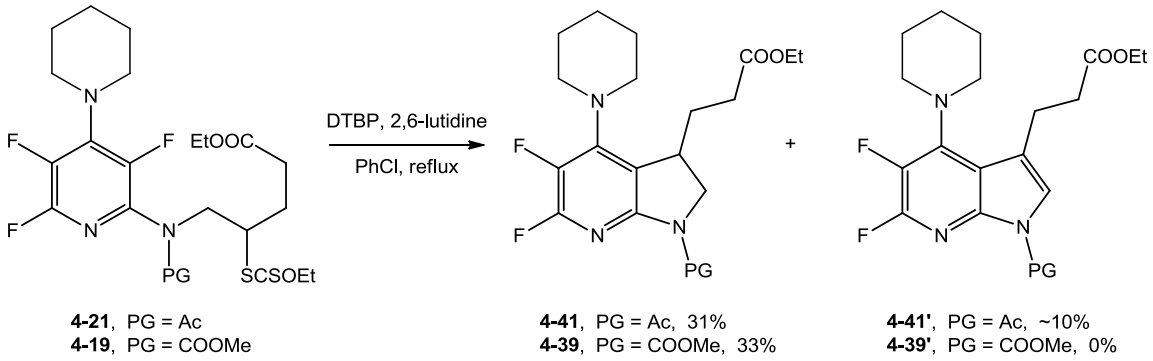
Scheme 4.46 Alternative possibility for generating **4-36'**

At this point, direct oxidation of the pyrrolidyl substituted derivative **4-16-a** was attempted under usual radical cyclization conditions. As shown in Scheme 4.46, the xanthate group in **4-16** was reductively removed by treatment with a stoichiometric

amount of DLP in isopropanol. Then same conditions for the cyclization were applied to compound **4-16-a**. However, no trace of an oxidized compound **4-16-b** was observed, which therefore excludes this possible pathway and confirmes previous analysis.

2) The role of the nitrogen protecting group at C-2

Another "lost" 7-azaindole **4-41'** was also discovered in a yield of 10% when we carefully re-examined residues from two previous experiments (Scheme 4.47). Interestingly, no azaindole was observed in the cyclization of COOMe-protected xanthate precursor **4-19**, which indicated that the electronic modification to the pyridine nucleus by the C-2 *N*-substituent also contributed to the efficiency in ring closure as well as to the ease of oxidation leading to the 7-azaindole.[164]

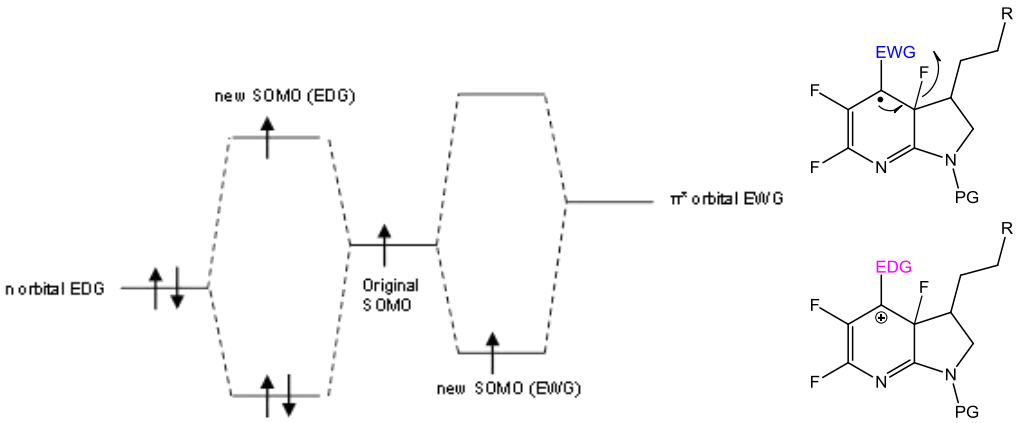


Scheme 4.47 Radical cyclization of piperidine substituted xanthates

[164] Further studies with the trifluoroacetate CF_3CO-protected xanthates were pursued by Mr. Ling QIN.

d. Further rationalization

In the light of the above studies, the processes involved in this transformation were now clearer. Electronic modification to the pyridine nucleus with EWGs in C-4 and C-2 promotes the radical cyclization by facilitating the first attack of secondary alkyl (nucleophilic) radical to an electron-poor ring. The radicals formed in the transition state are stabilized by both EWGs and EDGs (Scheme 4.48). However, the SOMOs of these radicals have different proclivities towards oxidation to the corresponding cations, and this leads to two different reaction pathways.



Scheme 4.48 Possible explanation by Frontier Molecular Orbital Theory

In the case of an EWG substituent, the newly formed radical is less inclined to proceed to the cation by electron-transfer to the peroxide, but it is still stabilized and capable of undergoing homolytic rupture of the C-F bond which permits aromatization to take place.

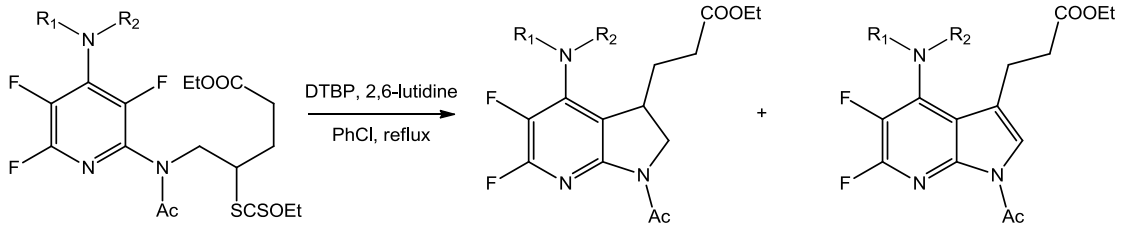
However, the newly formed SOMO with an EDG substituent is more likely to undergo oxidation to the cation, allowing at least partially following the path leading to aromatization ultimately by ionic elimination of hydrogen fluoride.

Furthermore, the use of a high boiling solvent speeds up the rate of *ipso*-substitution[165] but, more importantly, speeds up considerably the rate of fragmentation of the C-F bond. This fragmentation step has a high positive entropy and therefore is very sensitive to

[165] The reactions proceeded >10h in refluxing AcOEt while <3h in refluxing chlorobenzene

temperature ($\Delta G = \Delta H - T\Delta S$). In the present case, the C-F bond is very strong and does not fragment easily in a homolytic manner. A high temperature and the powerful driving force of the aromatization are necessary.

With a better appreciation of the factors governing the process, we examined the behavior of other C-4 *N*-substituents. As depicted in Scheme 4.49, simple functional groups, such as methyl, hydrogen, acetyl and mesyl were employed in these syntheses.



4-25, R_1 = Ac, R_2 = Me, 84%
4-26, R_1 = Ac, R_2 = H, 63%
4-27, R_1 = Ms, R_2 = Me, 71%
4-22, *R_1 = cyclopropyl, R_2 = H, 72%*

4-45, R_1 = Ac, R_2 = Me, 44%
4-46, R_1 = Ac, R_2 = H, 50%
4-47, R_1 = Ms, R_2 = Me, 43%
4-42, *R_1 = cyclopropyl, R_2 = H, 12%*

4-45', R_1 = Ac, R_2 = Me, 15%
4-46', R_1 = Ac, R_2 = H, 20%
4-47', R_1 = Ms, R_2 = Me, 18%
4-42', *R_1 = cyclopropyl, R_2 = H, 0%*

Scheme 4.49 Radical cyclization examples

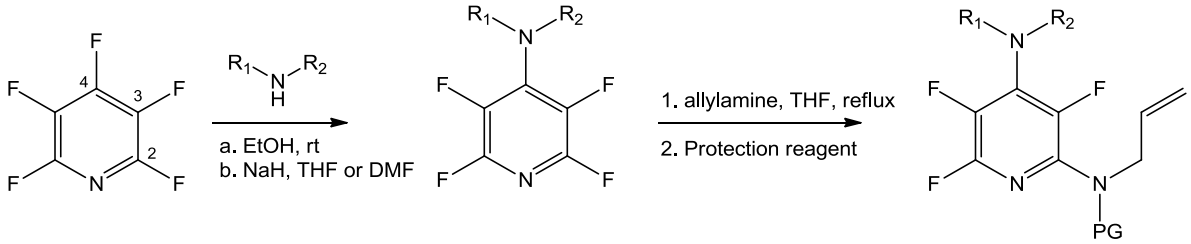
From these results we could see that as long as one C-4 *N*-substituent is electron-withdrawing, the desired cyclized products are readily obtained in good combined yields. It should be noted that in comparing the cyclization of **4-22** and **4-26**, both of the substrates contain hydrogen on the C-4 nitrogen. In the case of **4-26** which has an EWG at C-4 nitrogen, cyclization proceedes via the *ipso*-substitution with extrusion of a fluorine atom without interference from the amide proton; whereas in the case of **4-22**, the absence of an EWG favors oxidation of the cyclized radical leading to many side reactions involving the strained cyclopropyl group and thus resulting in a very low yield of 7-azaindoline **4-42**.

4. Diversity and perspectives

Based on the previous study, we decided to expand the scope of this synthesis by introducing yet more different C-4 substituents as well as the diverse functional groups on the xanthate partners. We also explored briefly the possibility of extending this approach to 1,2,3,4-tetrahydro-1,8-naphthyridines (piperidopyridines).

a. Further examples

A number of diverse substrates were prepared by reacting pentafluoropyridine with various amines, anilines, and nitrogen heteroaromatic compounds. Pentafluoropyridine usually reacts first at C-4 and then at C-2.[166] Depending on the strength of the nucleophiles, the substitution was accomplished by either stirring the mixture of pentafluoropyridine with the nucleophile in ethanol, or by slowly adding a pre-deprotonated nitrogen-containing component to the solution of pentafluoropyridine in anhydrous THF. Normally the substitution was rapid and quantitative, but sometimes a second substitution at the C-2 was observed which lowered the yields.[167] It is worth mentioning that since the pentafluoropyridine is volatile and very electron deficient, this reaction could not be easily monitored by NMR or TLC analyses.



Scheme 4.50 General synthesis of the olefinic precursors

In the second substitution step with allyamine, consistent results were obtained although the reactivities were different according to the C-4 substitution. For instance, in the case

[166] (a) Hargreaves, C. A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *Tetrahedron* **2007**, *63*, 5204-5211; (b) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119-2183.

[167] For example, during the preparation of **4-3** and **4-4**, double substitutions gave 6% of 1,1'-(3,5,6-trifluoropyridine-2,4-diyl)dipiperidine as a yellow oil.

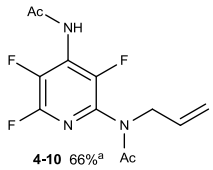
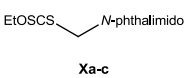
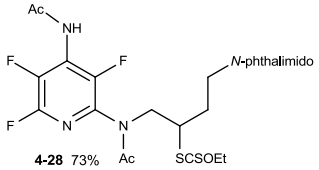
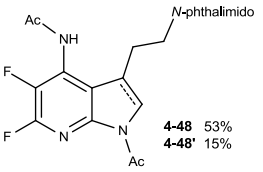
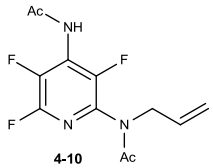
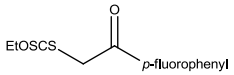
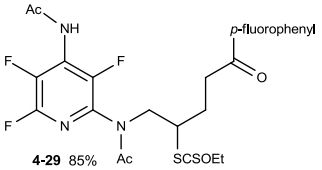
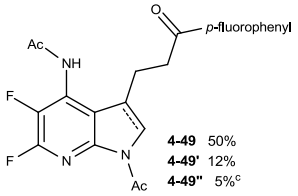
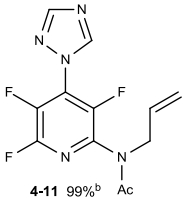
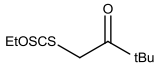
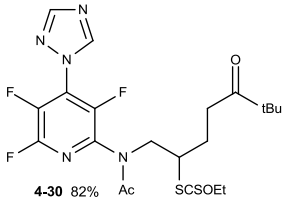
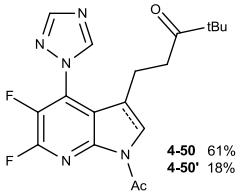
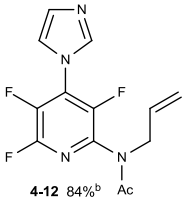
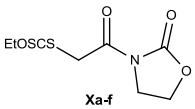
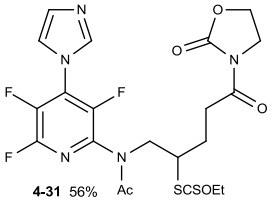
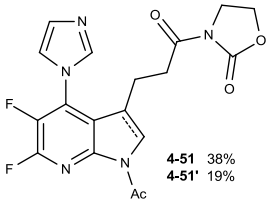
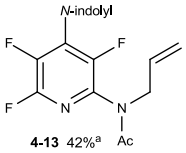
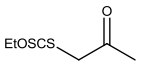
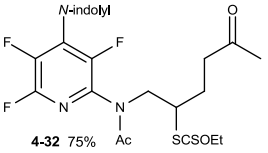
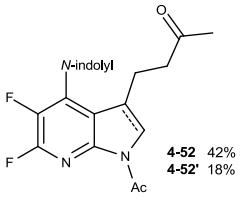
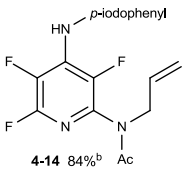
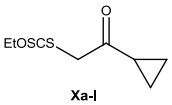
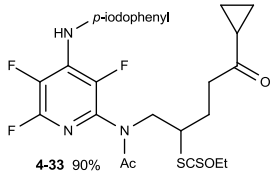
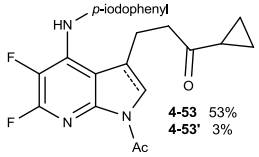
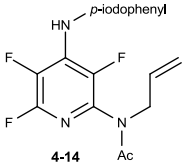
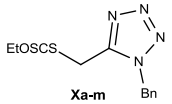
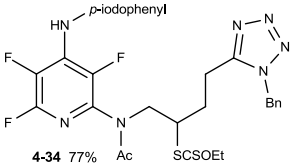
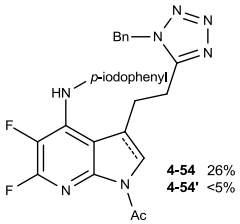
of an EDG substituent (eg. dimethylamine, cyclopropylamine, pyrolidine or piperidine), the electrophilic character at C-2 was decreased and the substitution normally took 3 to 6 days. However, when EWGs were installed at C 4, the substitution of allylamine is much easier and took only 1 hour at most.

Finally, the protection of 2-pyridyl allylamine was preformed with Boc anhydride, methyl chloroformate or acetyl chloride to give the desired olefinic precursors in moderate to good yields.[168]

Various 7-azaindolines and 7-azaindoles were prepared by radical addition and cyclization as shown by the results listed in Table 4.2. The radical addition step gave yields from 56% to 84% (see experimental part), and the intrinsically difficult cyclization afforded quite respectable yields ranging from 52% to 79%. The possibility of introducing different substituents by modifying both the xanthates and the nitrogen containing nucleophiles allowed ultimately access to a broad assortment of novel fluoro-7-azaindolines and fluoro-7-azaindoles. It should be noted that functionalities like the important azole subunits[169] also proved compatible with our synthesis.

It is also interesting to note that in the cyclization of **4-29**, a small amount (5%) of tetralone was isolated arising from cyclization of the intermediate radical on the phenyl ring instead of on the pyridine nucleus. This indicates that the rate of *ipso*-closure on the pyridine ring while being a difficult process, is still faster than the ring-closure leading to a six-membered tetralone. The fact that the xanthate technology also allows the construction of tetralones,[170] a process extensively studied in our laboratory, is a testimony to its immense synthetic potential.

[168] These one-pot three steps reactions were carried out without optimization.
[169] Azoles are freq.uently present in biologically active compounds. For instance, the marketed drug rizatriptan (trade name Maxalt) is used in the treatment of migraine and contains a triazole motif.
[170] Liard, A.; QuicletSire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759-1762.

Olefinic precursors	Xanthates	Addition products	Cyclization products
 **4-10** 66%[a]	 **Xa-c**	 **4-28** 73%	 **4-48** 53% **4-48'** 15%
 **4-10**	 **Xa-g**	 **4-29** 85%	 **4-49** 50% **4-49'** 12% **4-49''** 5%[c]
 **4-11** 99%[b]	 **Xa-d**	 **4-30** 82%	 **4-50** 61% **4-50'** 18%
 **4-12** 84%[b]	 **Xa-f**	 **4-31** 56%	 **4-51** 38% **4-51'** 19%
 **4-13** 42%[a]	 **Xa-i**	 **4-32** 75%	 **4-52** 42% **4-52'** 18%
 **4-14** 84%[b]	 **Xa-l**	 **4-33** 90%	 **4-53** 53% **4-53'** 3%
 **4-14**	 **Xa-m**	 **4-34** 77%	 **4-54** 26% **4-54'** <5%

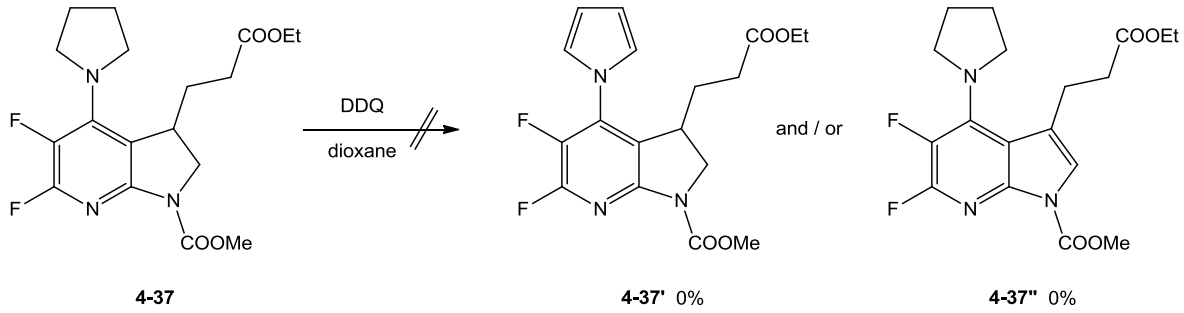
a. Non-optimised yields over four steps; c. Stucture not shown in the table, which was the product from the cylization to fluorophenyl
b. Yields over three steps; d. Stucture not shown in the table, which was the 7-azaindole **4-54'** with tetrazole ring-opening

Table 4.2 Synthesis of various 7-Azaindoles and 7-Azaindolines

b. Optimization of the reaction selectivity

The process we have developed furnishes a mixture of 7-azaindoline and 7-azaindole. From a synthetic standpoint, it would be useful if the azaindoline could be cleanly oxidized into the azaindole.

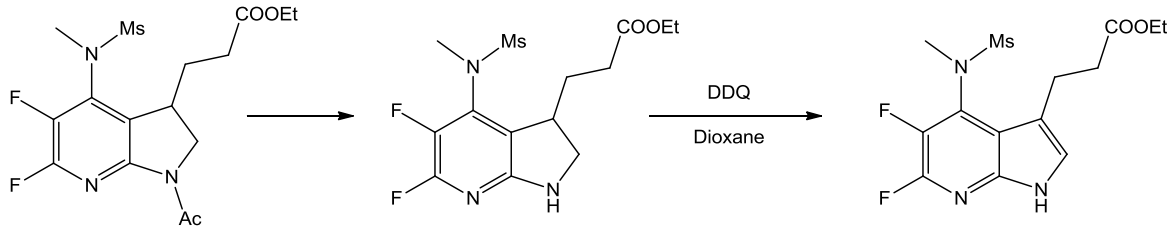
By analogy with a related transformation on a non-fluorinated analog,[171] we first examined DDQ as the oxidant to access the 7-azaindole. Thus pyrrolidyl substituted 7-azaindoline **4-37** was chosen to test the oxidation with DDQ in dioxane (Scheme 4.51). Any form of oxidation was interesting, no matter which nitrogen-containing ring is modified.



4-37 **4-37'** 0% **4-37"** 0%

Scheme 4.51 Oxidation of **4-37** with DDQ

In the event, no oxidation was observed under these conditions. We also examined the unprotected azaindoline **4-47-a** which should be easier to oxidize, but reaction was obscured[172] (Scheme 4.52).



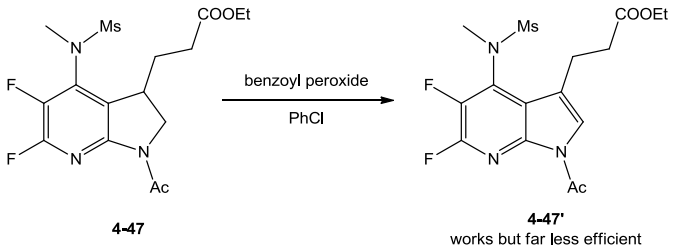
4-47 **4-47-a** **4-47'-a** 0%

Scheme 4.52 Oxidation of **4-47** with DDQ after deprotection

[171] El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, 4422-4424.
[172] In a later study, this condition was succeeded with substrate **4-52-a**, but far less efficient (see Scheme 4.54, condition a).

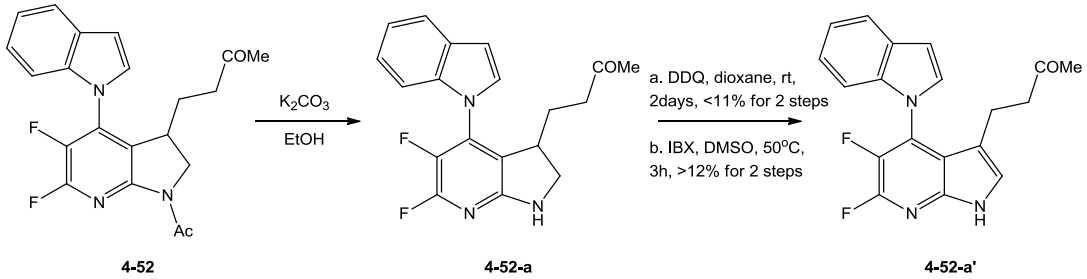
From these preliminary tests, we could see that the presence of the electronegative fluorine atoms strongly deactivate the 7-azaindoline core. Thus DDQ was not a sufficiently powerful reagent to oxidize these compounds.

Since we noted that the amount of 7-azaindoles increased generally with further additions of DTBP into the reaction medium, we decided to try the oxidation with benzoyl peroxide (DBP), which is a more potent oxidizing agent as compared with DTBP.



Scheme 4.53 Oxidation of **4-47** with DBP

Although no quantitative results were generated, we did observe the formation of the corresponding 7-azaindole **4-47'** in the reaction medium according to TLC analysis. However, it was still not efficient enough to be employed to completely finish this transformation.

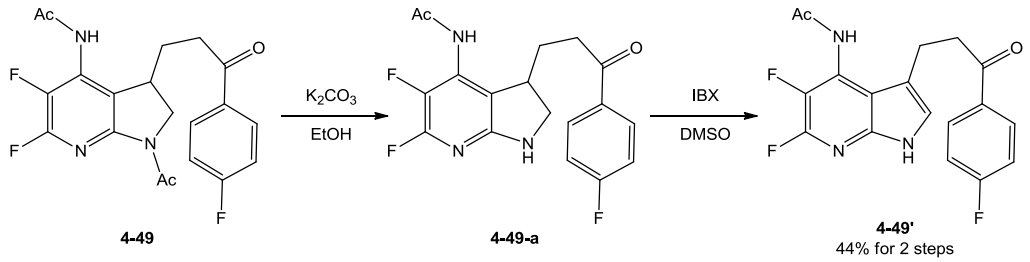


Scheme 4.54 Oxidation of **4-52-a** with different oxidants

Finally, we decided to use the *o*-iodoxybenzoic acid (IBX) in DMSO, which was employed previously in a related case in our laboratory. This reagent system was developed by Nicolaou[173] as an oxidant for indolines. An overall 12% of yield was obtained in the oxidation of compound **4-52** into the 1-*H*-7-azaindole **4-52-a'**. This preliminary test was performed with a very limited quantity, which explains partly the low overall yield. In contrast, when the same procedure was used to oxidize another

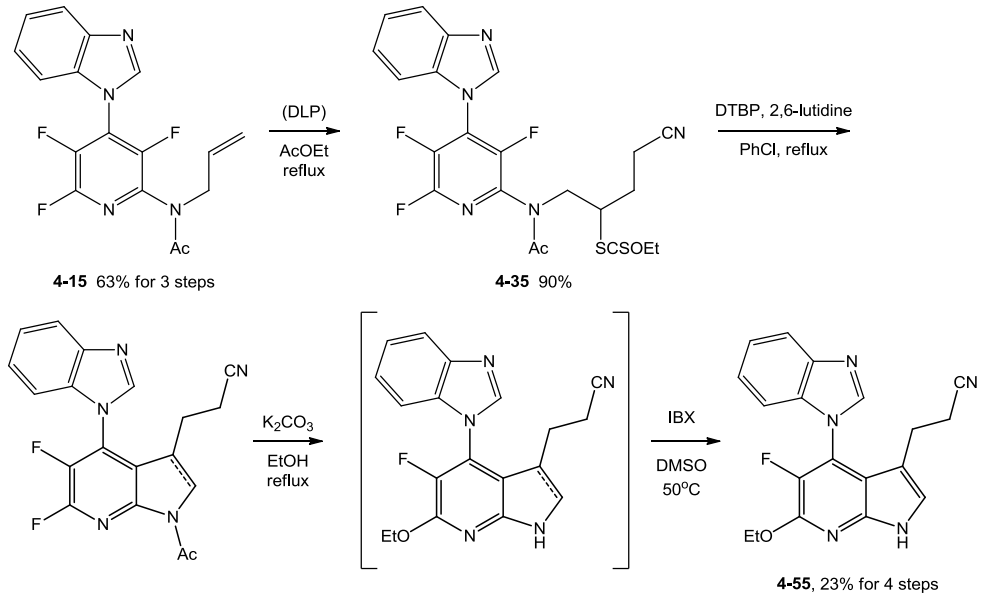
[173] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192 and references therein.

substrate **4-49**, a more satisfactory yield of 44% was achieved for the two steps (Scheme 4.55).



Scheme 4.55 Oxidation of **4-49-a** with IBX in DMSO

To extend this oxidation as well as to make this seq.uence more practical, we tried to perform the cyclization, deprotection, and oxidation all in one-pot.



Scheme 4.56 One-pot synthesis of 1-*H*-7-azaindole **4-55**

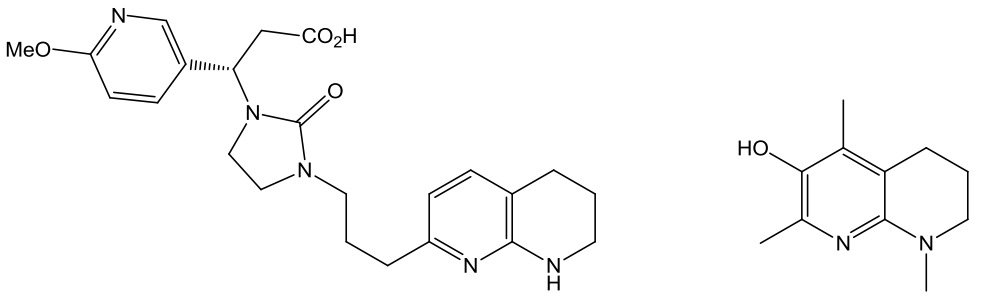
1-*H*-7-Azaindole **4-55** was obtained in a modest yield for four steps. It is interesting to note that the fluorine atom at C-6 was substituted by an ethoxy group in the deacetylation step, which was carried out in ethanol as solvent. The C-6 fluorine is selectively substituted by various nucleophiles in these systems. The adjacent C-5 fluorine is not

activated by the nitrogen of the pyridine nucleus and remains intact.[174] We did not go any further to explore the chemistry of the final 7-azaindolines and 7-azaindoles.

[174] Laot, Y.; Petit, L.; Ngoc, D. M. T.; Zard, S. Z. *Australian Journal of Chemistry* **2011**, *64*, 416-425. references 13 cited therein

c. Preliminary study towards the synthesis of piperidopyridine

As an extension of this approach, we examined the possibility of using a similar procedure to prepare piperidopyridine derivatives, which also exhibit interesting activities in the pharmaceutical domain.[175] For example, as shown on the left hand side of Scheme 4.57, the 7-substituted-piperidopyridine developed by Merck was identified as a selective antagonist of the $\alpha_v\beta_3$ receptor with a potential usage for the prevention and treatment of osteoporosis.[176] The multi-substituted-piperidopyridine on the right hand side of Scheme 4.57 is an efficient antioxidant, displaying a 28-fold larger inhibition rate constants relative to R-Tocopherol, a form of vitamin E, in quenching the oxidation of methyl linoleate in benzene solution.[177]

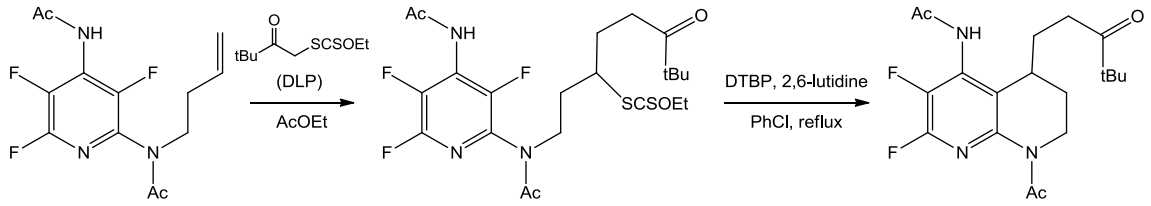


Scheme 4.57 Examples of bioactive piperidopyridines

Based on the successful radical cyclization to create a five-membered ring fused pyridine, a similar transformation with the aim of constructing a six-membered ring fused pyridine was also tested. As shown in Scheme 4.58, the synthesis of the piperidopyridine **4-58** was accomplished by the cyclization of precursor **4-57**, prepared by a similar procedure starting from pentafluoropyridine and 3-buten-1-amine. In the event, the radical addition step proceeded well, but treatment of xanthate **4-57** with DTBP under the usual

[175] The general preparation of this molecular skeleton has been summarized in the thesis of Dr. M. El Qacemi. Here we just present an updated progress towards these compounds using our methodology.
[176] Hutchinson, J. H.; Hatczenko, W.; Brashear, K. M.; Breslin, M. J.; Coleman, P. J.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Fisher, J. E.; Hartman, G. D.; Huff, J. R.; Kimmel, D. B.; Leu, C. T.; Meissner, R. S.; Merkle, K.; Nagy, R.; Pennypacker, B.; Perkins, J. J.; Prueksaritanont, T.; Rodan, G. A.; Varga, S. L.; Wesolowski, G. A.; Zartman, A. E.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2003**, *46*, 4790-4798.
[177] Lu, J.; Cai, X. Q.; Hecht, S. M. *Org. Lett.* **2010**, *12*, 5189-5191.

conditions afforded the expected product in a normally low yield (~16%). Since the radical cyclization leading to a six-membered ring is less favored than that forming a five-membered ring, hydrogen abstraction from the medium could seriously compete with the desired process. Optimization of this synthesis will be continued by Mr. Ling QIN.



4-56 67% for 3 steps **4-57** 43% **4-58** 16%

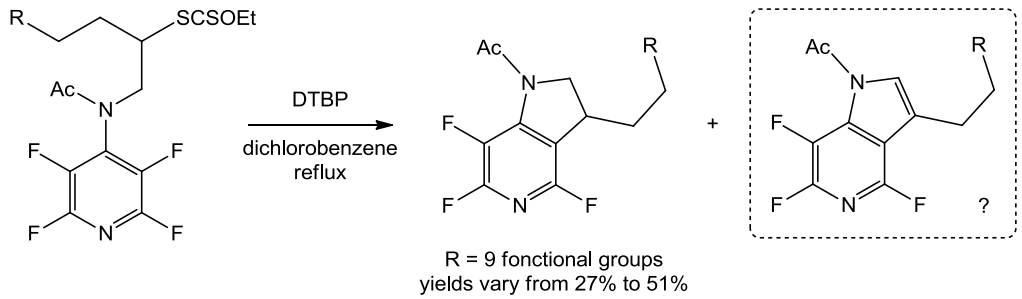
Scheme 4.58 Piperidopyridine generated via radical *ipso*-substitution (non-optimized)

Conclusion

In summary, we have described a useful route to an uncommon class of fluorinated heterocyclic derivatives which could be of significant interests.[178] In the structures that we have prepared, diversity can be introduced by modifying the substituent at C-4 in the first step; by modifying the amine side-chain in the second step; by modifying the xanthate partner; and by modifying the nucleophile during substitution of the fluorine at C-6. A vast library of analogs can thus be readily obtained.

From a fundamental standpoint, this work has demonstrated the efficient homolytic rupture of the strong C-F bond [179] under mild conditions. Such fragmentations are extremely rare and in fact hardly documented in the literature. The very success in accomplishing such a different process is a testimony to the power of the radical chemistry of xanthates.

The previous work concerning the synthesis of the related trifluoro-5-azaindolines used the same initiator in a higher boiling point solvent. There is therefore the possibility that the corresponding trifluoro-5-azaindoles were also produced in the reaction but were overlooked. The reported yields of the 5-azaindolines vary from 27% to 51%, but could be a little higher if the corresponding 5-azaindoles are indeed formed (Scheme 4.55).



Scheme 4.55 Synthesis of 5-azaindolines by radical *ipso*-substitution of C-F

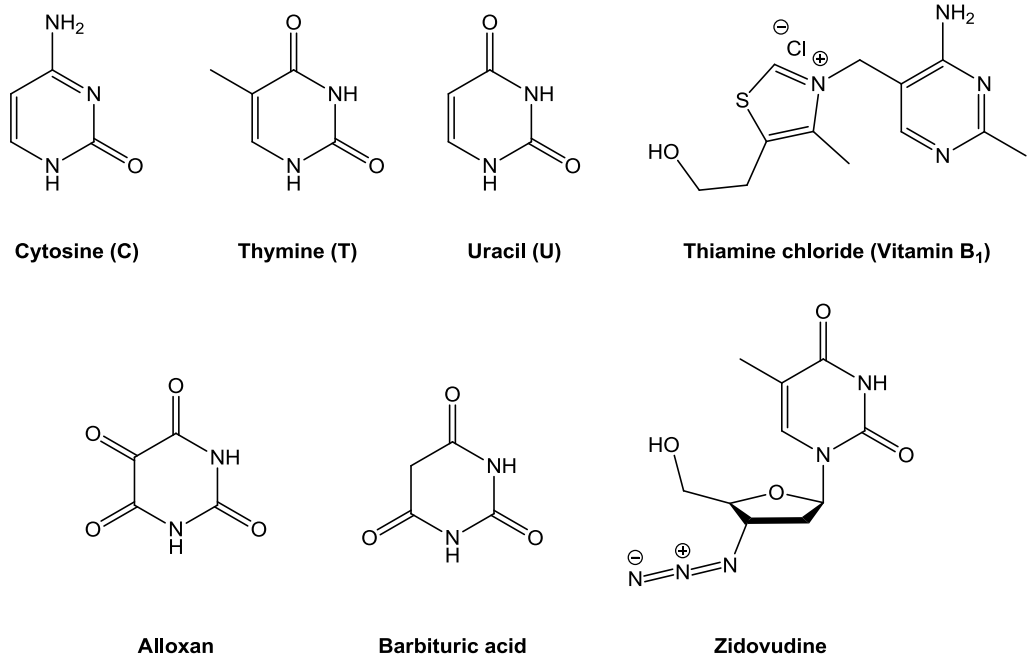
[178] A rapid growth of interest in fluoro-organics has occurred in many areas of application, including polymers, materials, specialty solvents, performance fluids, medicinal agents, agrochemicals and numerous reagents and intermediates for chemical synthesis. For example, in the pharmaceutical industry, about 20% of commercialized drugs contain fluorine since even one single atom can improve its chemical reactivity.
[179] Bond energy: ***C-F*** **485 kJmol^{-1}**, C-H 411 kJmol^{-1}, C-C 346 kJmol^{-1}, C-Cl 327 kJmol^{-1}

Chapter 5

Radical Synthesis of Pyrimidine Derivatives

Introduction

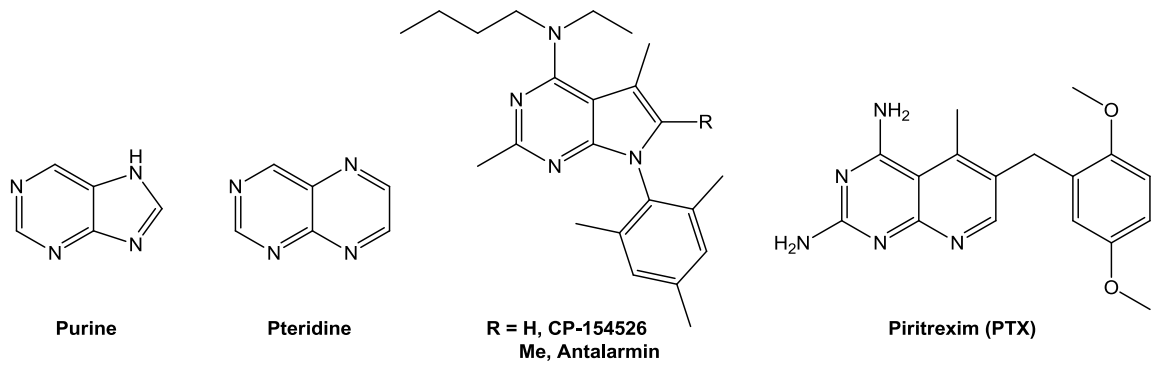
The pyrimidine ring can be seen as an amidine moiety incorporated into a diazine system (1,3-diazine). It has wide occurrence in nature as substituted and ring fused compounds or as their related pyrimidone derivatives, including the nucleotides, thiamines and alloxans. Such motifs are also found in many synthetic compounds such as barbiturates, P-3A,[180] bleomycin A_2,[181] and the HIV drug, zidovudine.[182]



Scheme 5.1 Biological active pyrimidine derivatives

The bicyclic derivatives based on pyrimidine rings are of significant interest to the field of modern biological organic chemistry. They are widely distributed in natural products and have important biological activity. It is sufficient to note that such biologically important compounds as purines and pteridines are related to bicyclic pyrimidines.

[180] (a) Boger, D. L.; Honda, T.; Menezes, R. F.; Colletti, S. L.; Dang, Q.; Yang, W. J. *J. Am. Chem. Soc.* **1994**, *116*, 82-92. (b) Boger, D. L.; Dang, Q. *J. Org. Chem.* **1992**, *57*, 1631-1633.
[181] Boger, D. L.; Menezes, R. F.; Dang, Q. *J. Org. Chem.* **1992**, *57*, 4333-4336.
[182] Lagoja, I. M. *Chem. Biodivers.* **2005**, *2*, 1-50.



Scheme 5.2 Biological active bicyclic pyrimidines

For example, CP-154526 is one of the first CRF-1 antagonists[183] and shows high affinity as well as interesting signs of *in vivo* activity in animal models of anxiety and depression. The bicyclic pyrimidine core is substituted in the top region of this molecule, and the aromatic nitrogen serves as the H-bond acceptor.[184] Piritrexim (PTX)[185] is a clinically tested compound against PCP[186] in AIDS patients and is currently used for the treatment of this opportunistic infection.

This chapter will focus on the application of the radical chemistry of xanthates to the modification of the pyrimidine nucleus. Relevant methodologies for constructing the bicyclic aza-pyrimidines are briefly summarized in the first part. In the second part, a dramatic effect of the protecting group on the regioselectivity of the radical cyclization in the pyridine and pyrimidine series will be discussed in detail. Next, efficient methods to access novel polycyclic aza-pyrimidine structures including 5, 6, and 7-membered rings, are described involving radical addition and cyclization of xanthates. Finally, preliminary results concerning radical additions to the heteroaromatic nitrogen to create six-membered rings will be presented.

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[183] Corticotropin-releasing factor (CRF), a 41 amino acid peptide synthesized by specific hypothalamic nuclei in the brain, was originally isolated by Wale in 1981 from ovine hypothalamus. The identification of CRF-1 antagonists is an attractive therapeutic approach for the treatment of depression and anxiety.

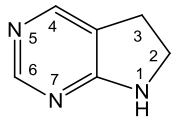
[184] (a) Gentile, G.; Di Fabio, R.; Pavone, F.; Sabbatini, F. M.; St-Denis, Y.; Zampori, M. G.; Vitulli, G.; Worby, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5218-5221.; (b) Zorrilla, E. P.; Koob, G. F. *Drug Discov. Today* **2010**, *15*, 371-383.

[185] (a) Kovacs, J. A.; Allegra, C. J.; Swan, J. C.; Drake, J. C.; Parrillo, J. E.; Chabner, B. A.; Masur, H. *Antimicrob. Agents Chemother.* **1988**, *32*, 430-433.; (b) Gangjee, A.; Devraj, R.; Queener, S. F. *J. Med. Chem.* **1997**, *40*, 470-478.

[186] Pneumocystis pneumonia (PCP) is a form of pneumonia caused by yeast-like fungus.

Ⅰ. Synthesis of bicyclic aza-pyrimidine derivatives

1. Five-membered ring fused bicyclic aza-pyrimidines (5,7-diazaindolines)



Scheme 5.1 5,7-diazaindoline

Generally, there are four synthetic strategies for constructing the five-membered ring fused bicyclic aza-pyrimidines. The first method is to build up the pyrimidine part after synthesizing the functionalized five-membered pyrrole or pyrrolidine rings. [187] Alternatively, one can also construct the five-membered ring unit starting with the pyrimidine derivatives.[188] Another approach employs the Diels-Alder reaction starting from 1,3,5-triazines, which can also be applied to synthesize the six-membered ring fused bicyclic aza-pyrimidines as we will discuss in detail later.[189] In addition, reduction of diazaindoles can give the corresponding diazaindolines.[190] The detailed synthetic routes for the above strategies are not presented here in order to avoid a lengthy literature study. More information about this subject can be found in the doctoral thesis of Dr. L. Petit.

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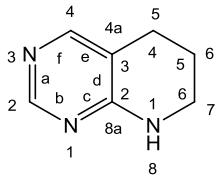
[187] (a) Takahata, H.; Nakajima, T.; Yamazaki, T. *Synthesis Stuttgart* **1983**, 226-228. (b) Sonoda, M.; Kuriyama, N.; Tomioka, Y.; Yamazaki, M. *Chem. Pharm. Bull.* **1986**, *34*, 886-892. (c) Aso, K.; Hitaka, T.; Yukishige, K.; Ootsu, K.; Akimoto, H. *Chem. Pharm. Bull.* **1995**, *43*, 256-261. (d) Kuyper, L. F.; Garvey, J. M.; Baccanari, D. P.; Champness, J. N.; Stammers, D. K.; Beddell, C. R. *Bioorg. Med. Chem.* **1996**, *4*, 593-602. (e) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 1177-1179.

[188] (a) St-Denis, Y.; Di Fabio, R.; Bernasconi, G.; Castiglioni, E.; Contini, S.; Donati, D.; Fazzolari, E.; Gentile, G.; Ghirlanda, D.; Marchionni, C.; Messina, F.; Micheli, F.; Pavone, F.; Pasquarello, A.; Sabbatini, F. M.; Zampori, M. G.; Arban, R.; Vitulli, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3713-3716. (b) Choi, H. S.; Wang, Z. C.; Richmond, W.; He, X. H.; Yang, K. Y.; Jiang, T.; Sim, T. B.; Karanewsky, D.; Gu, X. J.; Zhou, V.; Liu, Y.; Ohmori, O.; Caldwell, J.; Gray, N.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2173-2176. (c) Kempson, J.; Pitts, W. J.; Barbosa, J.; Guo, J. Q.; Omotoso, O.; Watson, A.; Stebbins, K.; Starling, G. C.; Dodd, J. H.; Barrish, J. C.; Felix, R.; Fischer, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1829-1833. (d) Boros, E. E.; Thompson, J. B.; Katamreddy, S. R.; Carpenter, A. J. *J. Org. Chem.* **2009**, *74*, 3587-3590.

[189] Boger, D. L.; Kochanny, M. J. *J. Org. Chem.* **1994**, *59*, 4950-4955.

[190] (a) Shih, C.; Gossett, L. S. *Heterocycles* **1993**, *35*, 825-841. (b) Amarnath, V.; Madhav, R. *Synthesis Stuttgart* **1974**, 837-859. (c) Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. *Synlett* **2005**, 3121-3125. (d) Song, J. H. J.; Tan, Z. L.; Reeves, J. T.; Fandrick, D. R.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 3952-3954. (e) Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. *J. Org. Chem.* **2010**, *75*, 11-15.

2. Six-membered ring fused bicyclic aza-pyrimidines (piperido[2,3-*d*]pyrimidines)

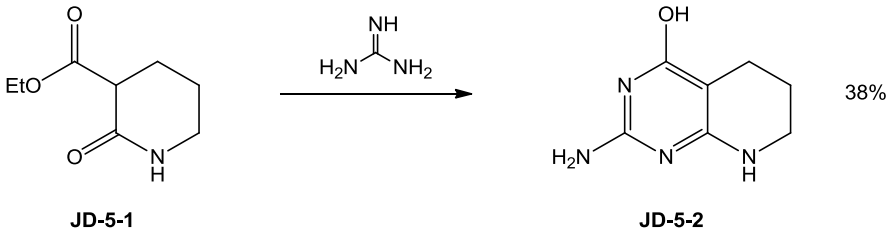


Scheme 5.2 Piperido[2,3-*d*]pyrimidines

Piperido[2,3-*d*]pyrimidine or triazanaphthalene is a saturated six-membered ring fused bicyclic aza-pyrimidine. Similar to 5,7-diazaindoline, the synthesis of this structure could be based on four general strategies.

a. Condensation of functionalized piperidines

The condensation of guanidine with a β-ketoester represents one of the most useful and general methods for preparing the pyrimidine ring. As an extension of this strategy, the first condensation of guanidine with a β-amidoester to form the bicyclic piperido[2,3-*d*]pyrimidine was achieved by DeGraw[191] in his investigations on the synthesis of **JD-5-2**.

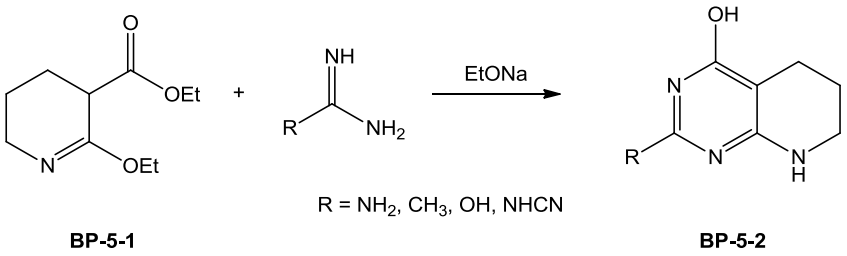


Scheme 5.3 Condensation of guanidine with a β-amidoester

A series of 2-substituted 4-hydroxy-piperido[2,3-*d*]pyrimidines **BP-5-2** were synthesized by reacting the lactim ether of 3-carboethoxy-2-piperidone **BP-5-1** with guanidine, acetimidamide, carbamimidic acid, and 1-cyanoguanidine, in yields of 58%, 49%, 44%,

[191] Degraw, J.; Goodman, L. *Can. J. Chem.-Revue Canadienne De Chimie* **1963**, *41*, 3137

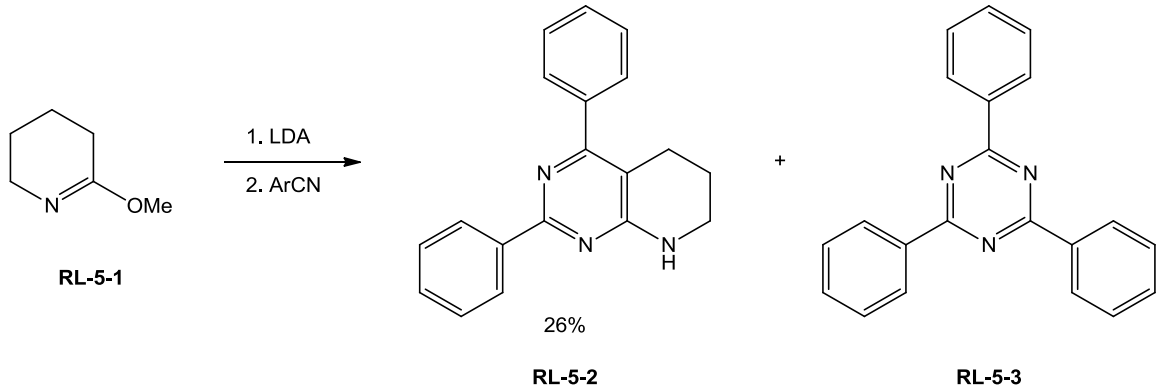
and 19% respectively.[192] These structural analogs of pteridones are of interest on account of their biological activity.



Scheme 5.4 Synthesis of 2-substituted 4-hydroxy-piperido[2,3-*d*]pyrimidines

Although the guanidine cyclization route is often used for constructing the pyrimidine ring in various synthetic approaches, they often req.uire use of problematic intermediates that have low solubility. To overcome this shortcoming, other methods were explored.

O-Methyl-δ-valerolactim **RL-5-1** is readily generated from the corresponding lactam. C-Acylation occurred when it was treated firstly with lithium diisopropylamide (LDA) and then with an aromatic nitrile in benzene solution. The piperido[2,3-*d*]pyrimidine **RL-5-2** was obtained along with 2,4,6-triaryltriazines **RL-5-3** as the side-product.[193] A 2+2+2 component combination was proposed for this transformation.[194]

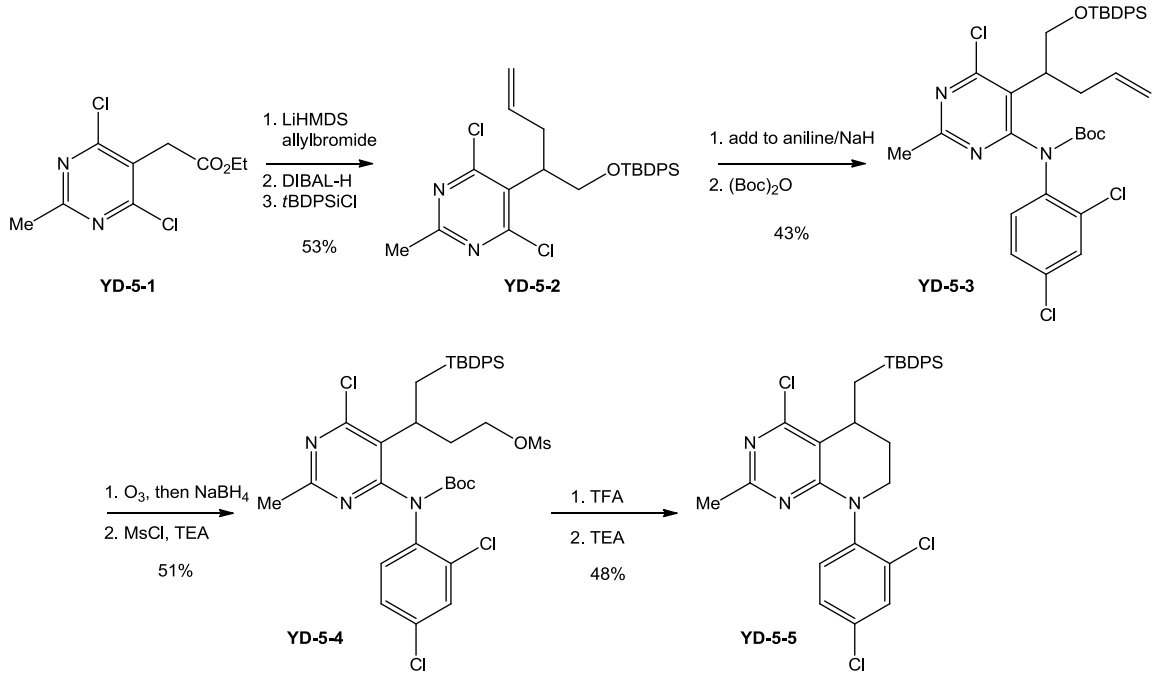


Scheme 5.5 Three component reaction for preparing **RL-5-2**

[192] Pyatin, B. M.; Glushkov, R. G. *Pharm. Chem. J.* **1968**, 488
[193] Lalonde, R. T.; Elkafrawy, A.; Muhammad, N.; Oatis, J. E. *J. Org. Chem.* **1977**, *42*, 1808-1809.
[194] Morita, K.; Kobayashi, S.; Shimadzu, H.; Ochiai, M. *Tetrahedron Lett.* **1970**, 11, 861

b. Intramolecular ring closure on substituted pyrimidines

A synthetic procedure for the preparation of tetraazaacenaphthylene[195] was described in Scheme 5.6 The functionalized pyrimidine **YD-5-1** was readily obtained by condensation of acetamidine hydrochloride with 2-ethoxycarbonyl–succinic acid diethyl ester.[196] Allylation followed by reduction of the ethyl ester yielded an alcohol, which was protected by a *tert*-butyldiphenylsilyl group to give **YD-5-2**. Nucleophilic aromatic substitution with dichloroaniline followed by protection of the amino group by a Boc group gave intermediate **YD-5-3**. Ozonolysis followed by reductive workup gave the intermediate alcohol, which reacted with methanesulfonyl chloride in the presence of TEA to give **YD-5-4**. This mesylate then underwent cleavage of the Boc group, followed by treatment with TEA to give the desired substituted piperidinopyrimidines **YD-5-5**.

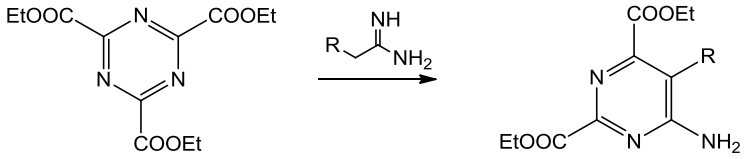


Scheme 5.6 Synthesis of substituted piperidinopyrimidines **YD-5-5**

[195] St-Denis, Y.; Di Fabio, R.; Bernasconi, G.; Castiglioni, E.; Contini, S.; Donati, D.; Fazzolari, E.; Gentile, G.; Ghirlanda, D.; Marchionni, C.; Messina, F.; Micheli, F.; Pavone, F.; Pasquarello, A.; Sabbatini, F. M.; Zampori, M. G.; Arban, R.; Vitulli, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3713-3716.
[196] Chen, Y.L. WO 95/33750 A1, **1995**.; Chen, Y.L. US 5962479 A, **1999**.

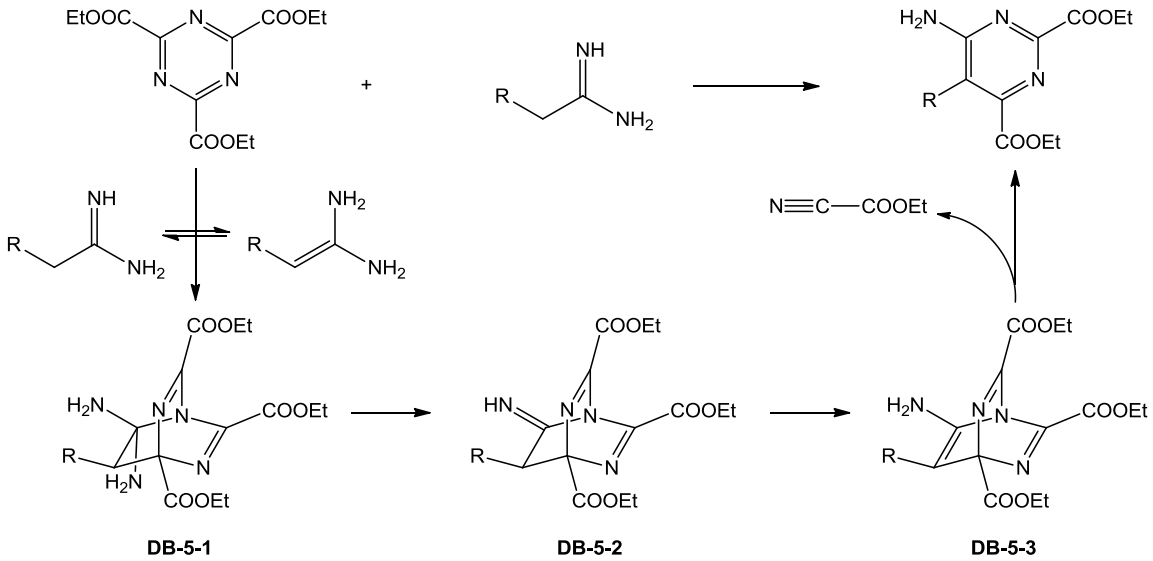
c. Inverse electron demand Diels-Alder reaction of heterocyclic azadienes

This strategy employs the inverse electron demand Diels-Alder reaction of electron-deficient heteroaromatic azadienes (1,3,5-triazine) with amidines.[197] The general transformation in this reaction is shown below (Scheme 5.7).



Scheme 5.7 Formation of pyrimidines via an inverse electron demand Diels-Alder reaction

The mechanism of this reaction is outlined below (Scheme 5.8). It starts from *in situ* tautomerization of an amidine into its corresponding 1,1-diaminoethene. Subseq.uently, it is trapped by the symmetrical 1,3,5-triazine through a [4+2] cycloaddition and loses ammonia from the initial intermediate **DB-5-1** to give the corresponding imine **DB-5-2**. An imine to enamine **DB-5-3** tautomerization followed by a retro Diels-Alder with elimination of ethyl cyanoformate finally gives the desired 4-aminopyrimidine.

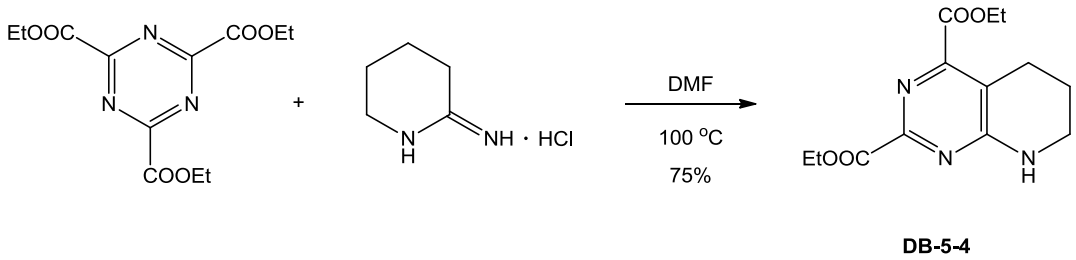


Scheme 5.8 Details of the route using the inverse electron demand Diels-Alder reaction

[197] (a) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745-5754.; (b) Boger, D. L.; Kochanny, M. J. *J. Org. Chem.* **1994**, *59*, 4950-4955.

Generally, the reaction proceeds smoothly in polar aprotic solvents including DMF under modest thermal reaction conditions (80-120°C). Heating (>80°C) is req.uired to promote the amidine tautomerization and accelerate the loss of ethyl cyanoformate leading to the aromatic pyrimidine ring. Both acyclic and cyclic amidines are capable of undergoing this cycloaddition, although slightly lower yields were observed with cyclic amidines. The reaction is completely regioselective. Furthermore, the amidine hydrochloride salts proved to be more efficient for this conversion than the corresponding free bases.

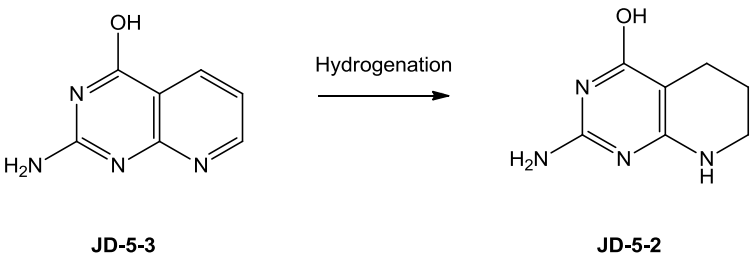
With this strategy, highly substituted and functionalized pyrimidine derivatives can be obtained, such as (+)-P-3A, bleomycin A_2, as well as bicyclic compounds related to our subject (Scheme 5.9).



Scheme 5.9 Formation of **DB-5-4** via a Diels-Alder reaction

d. Reduction of pyrido[2,3-*d*]pyrimidines

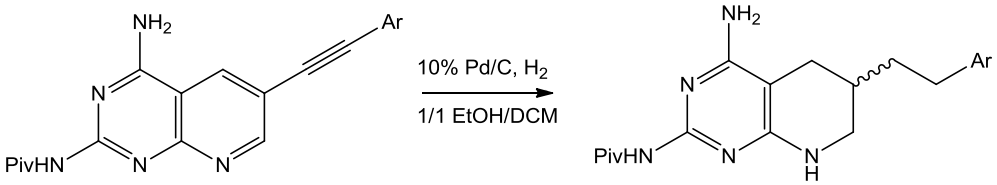
Piperido[2,3-*d*]pyrimidines may be seen as 5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidines, the hydrogenated derivatives of the corresponding pyrido[2,3-*d*]pyrimidines. An early catalytic reduction of 2-amino-4-hydroxypyrido[2,3-*d*]pyrimidine **JD-5-3** was investigated in order to confirm the structure of **JD-5-2** produced in condensation mentioned above. When an aqueous suspension of **JD-5-3** was treated with hydrogen at atmospheric pressure over platinum oxide, approximately 2 moles of hydrogen were absorbed and the corresponding piperido[2,3-*d*]pyrimidine **JD-5-2** was smoothly generated.



JD-5-3 **JD-5-2**

Scheme 5.10 Piperido[2,3-*d*]pyrimidine formed by reduction

This method appears to be more convenient and is widely used in generating piperido[2,3-*d*]pyrimidines. For example, in the course of synthesizing a series of 2,4-diaminopyrido[2,3-*d*]pyrimidine based antifolates, useful as antineoplastic and antiarthritic agents,[198] piperido[2,3-d]pyrimidine **LG-5-2** was obtained by hydrogenation of precursor **LG-5-1**.



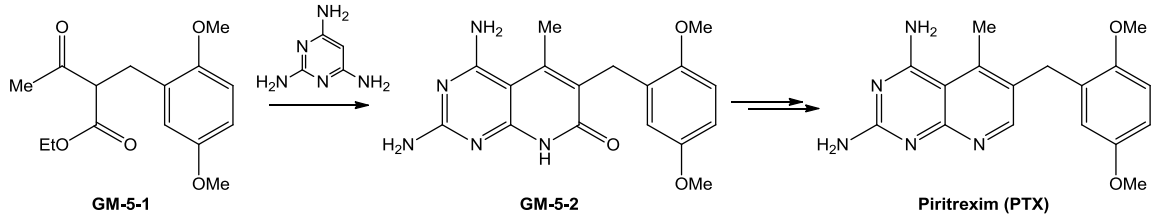
LG-5-1 **LG-5-2**
78%

Scheme 5.11 Piperido[2,3-d]pyrimidine **LG-5-2** generated by hydrogenation

Synthesis of aromatic derivatives of pyrido[2,3-d]pyrimidines has been better investigated due to their biological significance. Generally, these structures could be elaborated by two methods, either from derivatives of 2,3-disubstituted pyridines[199] or from 4-aminopyrimidines.[200] For example, the well known nonclassical antifolate Piritrexim (PTX) was synthesized by Grivsky as a lipophilic analog of the anticancer

[198] Gossett, L. S.; Habeck, L. L.; Shackelford, K. A.; Mendelsohn, L. G.; Gates, S. B.; Worzalla, J. F.; Self, T. D.; Theobald, K. S.; Andis, S. L.; Schultz, R. M.; Shih, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 75-78.
[199] (a) Degraw, J. I.; Christie, P. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. *J. Med. Chem.* **1990**, *33*, 673-677. (b) Vercek, B.; Leban, I.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1979**, *44*, 1695-1699. (c) Kuyper, L. F.; Garvey, J. M.; Baccanari, D. P.; Champness, J. N.; Stammers, D. K.; Beddell, C. R. *Bioorg. Med. Chem.* **1996**, *4*, 593-602.
[200] (a) Gangjee, A.; Devraj, R.; Queener, S. F. *J. Med. Chem.* **1997**, *40*, 470-478.; (b) Rosowsky, A.; Chen, H.; Fu, H. M.; Queener, S. F. *Bioorg. Med. Chem.* **2003**, *11*, 59-67.

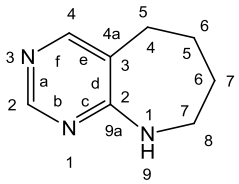
drug MTX.[201] In this synthesis, ethyl 2-(2,5-dimethoxybenzyl)-3-oxobutanoate **GM-5-1** is condensed with 2,4,6-triaminopyrimidine to afford the bicyclic lactam **GM-5-2**, whereupon dehydrative chlorination followed by catalytic dechlorination yields PTX.[202] Three other synthetic routes to PTX have also been reported in the literature,[203] all of which use the same strategy for constructing the diaminopyridopyrimidine by condensation of the substituted pyridine and guanidine.



Scheme 5.12 Synthesis of Piritrexim

Further syntheses of pyrido[2,3-d]pyrimidines are not included in this section because of limited space.

3. Seven-membered ring fused bicyclic aza-pyrimidines (6,7,8,9-tetrahydro-5H-pyrimido[4,5-*b*]azepanes)



Scheme 5.13 Pyrimido[4,5-*b*]azepine

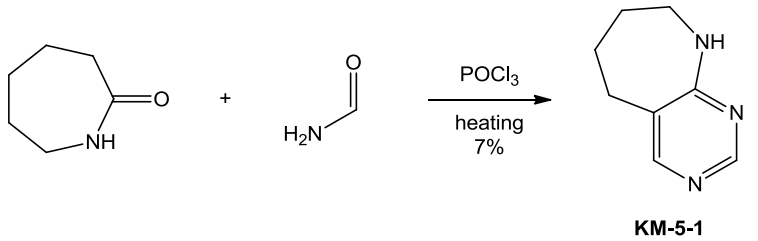
Pyrimido[4,5-*b*]azepine as pictured in Scheme 5.13 has a bicyclic structure based on a seven-membered ring fused to a pyrimidine nucleus. Such compounds have potential

[201] Methotrexate (MTX) is an antimetabolite and antifolate drug. It is used in treatment of cancer, autoimmune diseases, ectopic pregnancy, and for the induction of medical abortions.
[202] Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327-329.
[203] (a) Hill, J. A.; Wisowaty, J. C.; Darnofall, M. E. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 1119-1130. (b) Troschutz, R.; Zink, M.; Gnibl, R. *J. Heterocycl. Chem.* **1999**, *36*, 703-706.; (c) Chan, D. C. M.; Rosowsky, A. *J. Org. Chem.* **2005**, *70*, 1364-1368.

applications in medicinal chemistry but, although some derivatives are commercially available, the strategies for their synthesis are very limited. Generally, these compounds can be constructed by three pathways: pyrimidine formation on a functionalized azepane; intramolecular ring closure of a functionalized side chain on a pyrimidine; and multi-component reactions.

a. Pyrimidine formation on a functionalized azepane

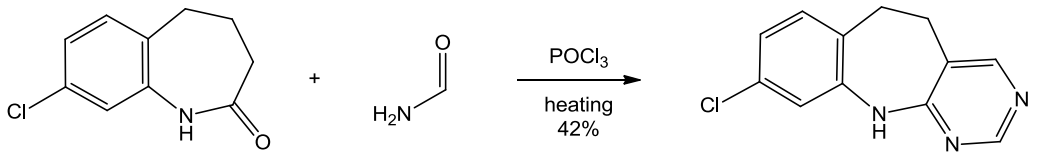
In 1970, Morita and co-workers described a one-pot method to synthesize pyrimidoazepine **KM-5-1** by heating azepan-2-one and 2 eq.alents of formamide in the presence of phosphorus oxychloride. They successfully formed the desired product but in a very low yield.



KM-5-1

Scheme 5.14 One-pot synthesis of pyrimidoazepine **KM-5-1**

In 1973, Kobayashi improved this one-step strategy by introducing an aromatic ring on the azepan-2-one.[204] The reactivity was dramatically affected by the substituents on the supplementary aromatic ring. The highest yield turned out to be 42%, which is still relatively low.

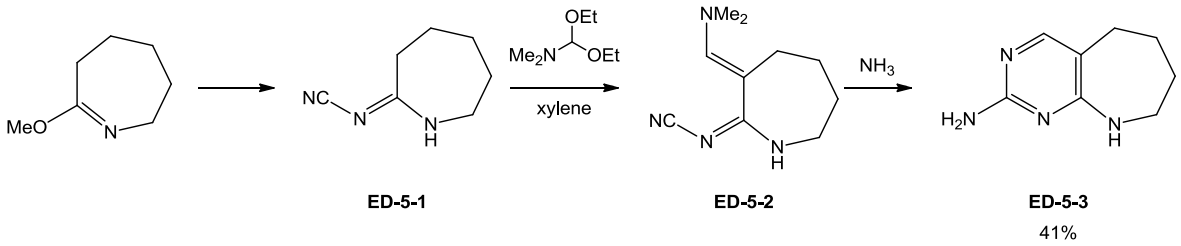


KS-5-1

Scheme 5.15 One-pot method to synthesize pyrimidoazepine **KS-5-1**

[204] Kobayash.S *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2835-2839.

Since amidines are convenient for obtaining pyrimidine structures, another approach to synthesize the bicyclic pyrimidoazepine is based on these starting materials which are shown below.[205] Heating *N*-cyanoamidine with 1,1-diethoxy-*N*,*N*-dimethylmethanamine in dry xylene leads to formation of 3-dimethylaminomethylene-2-*N*-cyanoimino-hexahydroazepine **ED-5-2**. The *N*-cyano group and the enamino double bond of this intermediate enaminoamidine favor closure to the pyrimidine ring. Therefore, condensation by heating **ED-5-2** with NH_3 produces the desired 2-amino-6,7,8,9-tetrahydropyrimido[4,5-b]-5H-azepine **ED-5-3**. This method could also be applied to the synthesis of 2-amino-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine and other related compounds.

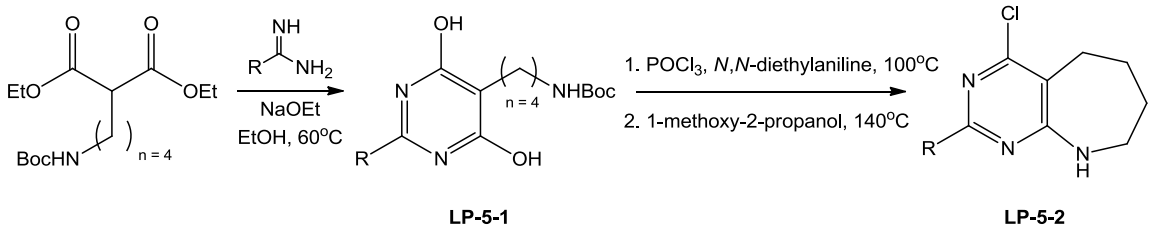


Scheme 5.16 Synthesis of pyrimidoazepine **ED-5-3**

b. Intramolecular closure of a side chain on a pyrimidine ring

In the searching for potential new drugs for COPD[206] treatment, 6,7,8,9-tetrahydro-5H-pyrimido[4,5-*b*]azepine derivative was synthesized via the intermediacy of a side chain substituted 4,6-dihydroxypyrimidine **LP-5-1**, acquired by condensation of 2-substituted dialkylmalonate with amidine mediated by sodium ethoxide. Reaction with phosphorus oxychloride in the presence of *N*,*N*-diethylaniline afforded the deprotected 4,6-dihydroxypyrimidine, which was then heated at high temperature to give the desired cyclized compound **LP-5-2**.[207]

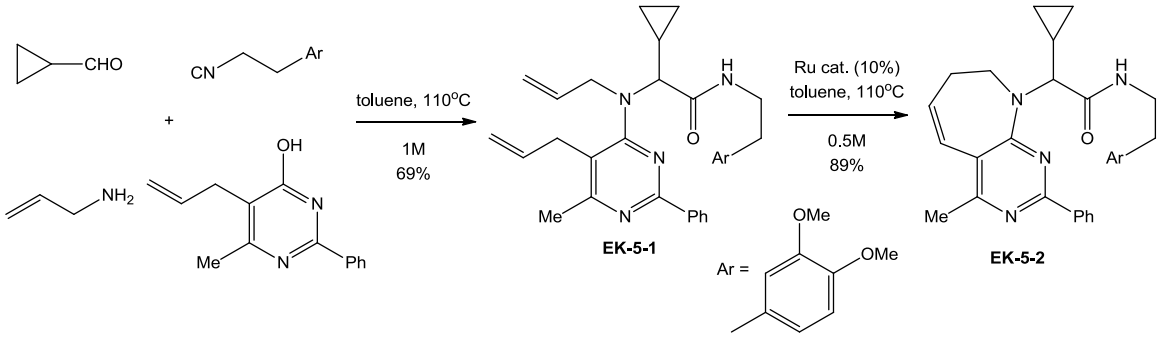
[205] Dozorova, E. N.; Grizik, S. I.; Persianova, I. V.; Syubaev, R. D.; Shvarts, G. Y.; Granik, V. G. *Khimiko-Farmatsevticheskii Zhurnal* **1985**, *19*, 154-158.
[206] Chronic obstructive pulmonary disease (COPD) is a pair of commonly co-existing diseases of the lungs in which the airways become narrowed.
[207] Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Durieu, W.; Gillard, M.; Lebon, F.; Lengele, S.; Quere, L.; van Keulen, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1834-1839.



Scheme 5.17 Synthesis of pyrimidoazepines **LP-5-2** by intramolecular cyclization

c. Multi-component reaction

More recently, El Kaim and co-workers[208] reported an ugi-smiles-metathesis strategy toward the synthesis of pyrimidoazepines. This method involved Ugi-Smiles coupling followed by ring-closure metathesis which was catalyzed by the Hoveyda-Grubbs second generation catalyst. They successfully obtained the desired pyrimidoazepines in a synthetically useful yield.



Scheme 5.18 Synthesis of pyrimidoazepine via an Ugi-Smiles/RCM combination

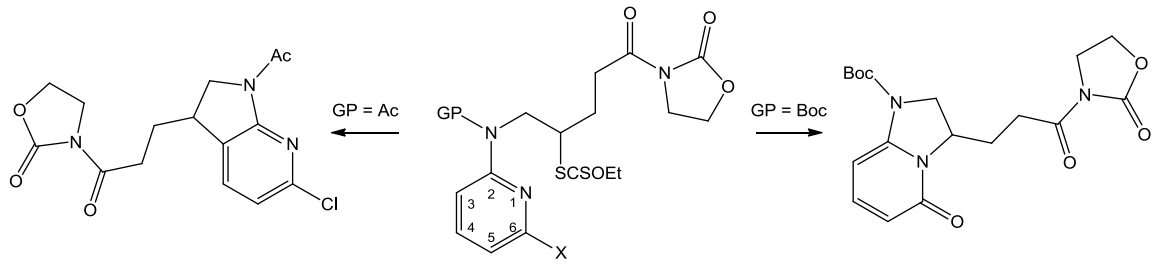
[208] El Kaim, L.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835-5838.

Ⅱ. Synthesis of bicyclic aza-pyrimidines using xanthates

1. Investigation of the "carbamate puzzle"[209]

a. An unusual radical addition to the heteroaromatic nitrogen

In 2005, our colleagues made a remarkable and very surprising observation while studying a new approach to azaindolines and related substances.[152] As shown in Scheme 5.19, when an acetyl group was present in the precursor xanthate **EQ.-5-1**, the radical cyclization proceeded as expected on C-3 to give the 7-azaindoline **EQ.-5-2**. However, when the side chain nitrogen was protected by a carbamyl group, the radical cyclization mainly take place on the ring nitrogen to give the corresponding pyridinone **EQ.-5-3** as the major product, although a very small amount of the analogous azaindoline was observed. It was established that the presence of a halogen such as chlorine or fluorine on C-6 was necessary for this process. The cyclization onto nitrogen worked slightly better with a chlorine substituent.



EQ-5-2, 66%

EQ-5-1-a, GP = Ac, X = Cl
EQ-5-1-b, GP = Boc, X = Cl
EQ-5-1-c, GP = Boc, X = F

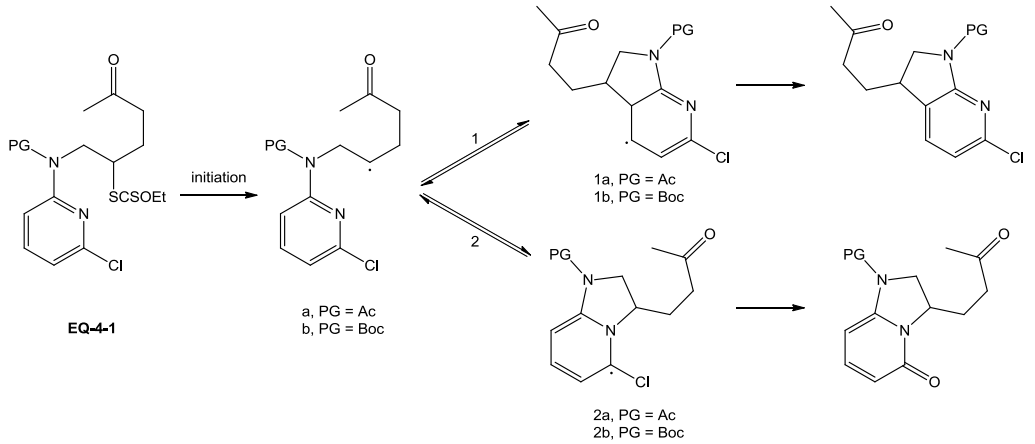
EQ-5-3, X = Cl, 63%
X = F, 25%

Scheme 5.19 Dramatic effect of the protecting group on the regioselectivity

A theoretical analysis was carried out in order to have a better understanding of this selectivity,[210] but no completely satisfactory explanation has yet emerged.

[209] Zard, S. Z. *J. Phys. Org. Chem.* **2012**, *25*, 953-964.
[210] We wish to acknowledge in this respect our collaboration on the theoretical aspects with Dr. Michelle Coote at Australian National University.

As illustrated in Scheme 5.20, the formation of pyridinone and azaindoline can arise through ring closure of radicals ***a*** and ***b***, where ***a*** stands for PG = Ac (Acetyl) and ***b*** for PG = Boc (*t*-butoxycarbonyl) group. Each of radicals of ***a*** and ***b*** can proceed to ***1a*** or ***2a*** and ***1b*** or ***2b*** by reactions ***1*** and ***2*** respectively. Reaction ***1*** is the attack to C atom of pyridine ring while reaction ***2*** is the attack to N atom of the ring.



Scheme 5.20 Theoretical analysis

Table 5.1 showed a summary of thermodynamic and kinetic study[211] of reactions ***1*** and ***2***. The barrier energies for conversion of ***a*** to ***2a*** and ***b*** to ***2b*** (attack to N atom) are less than those for conversion of ***a*** to ***1a*** and ***b*** to ***1b*** (attack to C atom). However the difference between barrier energies for the case of PG = Boc is more than that of PG = Ac (approximately 10 kJ.mol^{-1}).

	$\Delta G^{\#}$ kJ.mol^{-1}	ΔG kJ.mol^{-1}
a ⟶ 1a	53.0	-40.9
a ⟶ 2a	37.4	-36.7
b ⟶ 1b	73.2	-16.2
b ⟶ 2b	46.7	-28.8

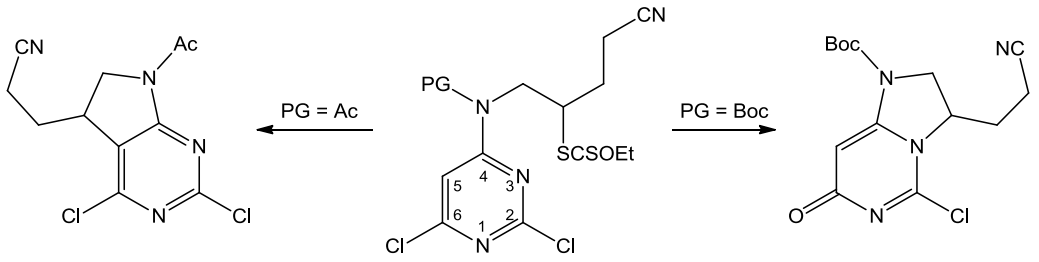
Table 5.1 Thermodynamic and kinetic analyses

[211] Computational details: careful conformational search have been performed for both radicals of ***a*** and ***b*** using B3LYP/6-31G(d) level of theory. 160 different conformers for ***b*** and 45 conformers for ***a*** have been fully optimised. The most stable conformer has been selected for further calculations. Figure 1 shows the optimised structures of radicals a and b. Transition structures for reactions 1 and 2 for four cases (***a*** → ***1a*** , ***a*** → ***2a*** , ***b*** → ***1b*** and ***b*** → ***2b***) have been carefully trapped using freq.uency calculations. Large imaginary freq.uencies of -496.5, -502.0, -499.6, -494.4 cm^{-1} have been found for studied transition states, respectively. The B3-LYP/6-31G(d) thermodynamic corrections were then used in conjunction with the ROMP2/6-311+G(3df,2p) energy to calculate a Gibbs free energy *G* and the barriers. Harmonic oscillator approximation has been used for freq.uency calculations.

From a kinetic point of view, reaction ***2***, which is the attack on the N atom, is faster in both cases. However from thermodynamic point of view, reaction ***1*** is more favourable than reaction ***2*** for ***a*** (PG = Ac) while reaction ***2*** is more favourable than reaction ***1*** for the case of ***b*** (PG = Boc). This means that although the barrier for conversion of ***a*** $\rightarrow$ ***2a*** is less than the barrier for conversion ***a*** $\rightarrow$ ***1a***, the conversion of ***a*** $\rightarrow$ ***1a*** is thermodynamically more favourable. This implies that the radical attack in both cases is reversible. The conversion of ***b*** $\rightarrow$ ***2b*** is favored by both kinetic and thermodynamic effects, i.e. a smaller energetic barrier and a greater stability for ***2b***.

However, results from our later study were not completely in harmony with the theoretical analysis above, and other factors need perhaps to be be included in explaining this unexpected phenomenon.

The same tendency was also found later in the pyrimidine series.[212] The normal cyclization product diazaindoline **LP-5-2** was obtained when an acetyl group was used. However, when it was changed to a Boc group, the generated carbon radical in the intermediate preferred to attack the adjacent heteroaromatic nitrogen rather than the carbon.



LP-5-2 54%

LP-5-1-a, PG = Ac
LP-5-1-b, PG = Boc

LP-5-3 43%

Scheme 5.21 Unusual regioselectivity in the pyrimidine series

A preliminary experiment indicated that a mixture of *C*-cyclised product **LP-5-2'**[213] (14%) and two regioisomeric *N*-cyclised products (**LP-5-3** 43% and **LP-5-3'** 9%) were obtained. It mentioned briefly that the last two regioisomeric products were difficult to separate and

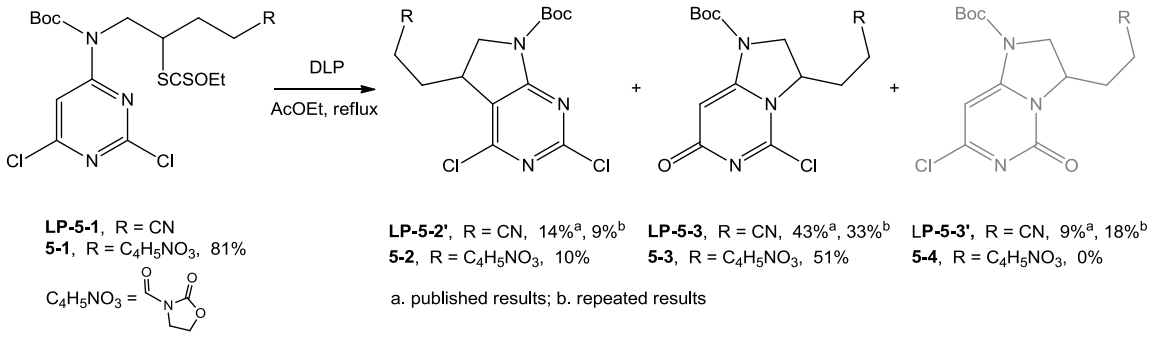
[212] Laot, Y.; Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784-5786.
[213] Similar structure to **LP-5-2** but with Boc protection instead of Ac, which is not shown in Scheme 5.21

only the major one **LP-5-3** was obtained in sufficiently pure form for complete characterisation. In principle, the two *N*-cyclized products were supposed to be derived from the attack of the laurate anion to either of the allylic cation formed in position C-2 or C-6. And since the C-6 was less hindered than C-2, the former was the major product.

b. Identification of the minor *N*-cyclized product

Before further investigating the underlying reasons for this uncommon regioselectivity, we corrected the structure of the unidentified product **LP-5-3'**.

When we repeated this reaction, the *C*-cyclised product and the two *N*-cyclised products were isolated in very different yields, 9%(**LP-5-2'**), 33%(**LP-5-3**), and 18%(**LP-5-3'**). In particular, the ratio of the two regioisomeric pyrimidinones changed from 4.8 to 1.8. It is very strange to have such different ratios for the same reaction under identical conditions.



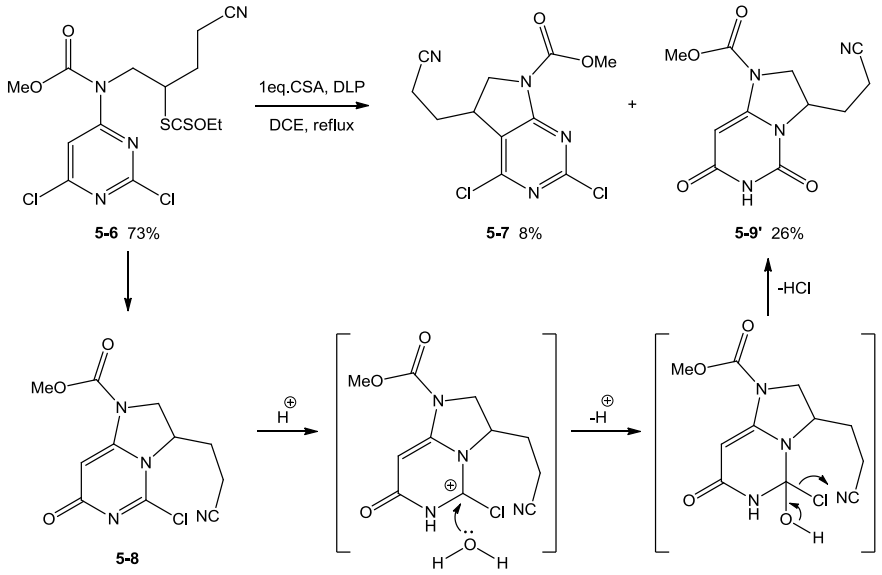
Scheme 5.22 Radical cyclization with unusual regioselectivity

We next examined the same cyclization but changing the size of the terminal group (2-oxooxazolidine-3-carbonyl). Surprisingly, no second regioisomeric *N*-cyclized product was observed, but only the normal diazaindoline **5-2** and pyrimidinone **5-3** were isolated in yields of 10% and 51%, respectively (Scheme 5.22).

Two points should be emphasized here. First, a strong dependence on the size of the side chain was observed, which was not found in the previous pyridine ring cyclization. Second, the *N*-cyclized products (**LP-5-3** and **LP-5-3'**) in the original and repeated

reactions had a similar combined yield (published result 52%, and repeated result 51%). If the unidentified compound **LP-5-3'** was derived from the pyrimidinone **LP-5-3** during purification (acidic medium) or storage (exposure to air), both of the above observations would seem to be reasonable.

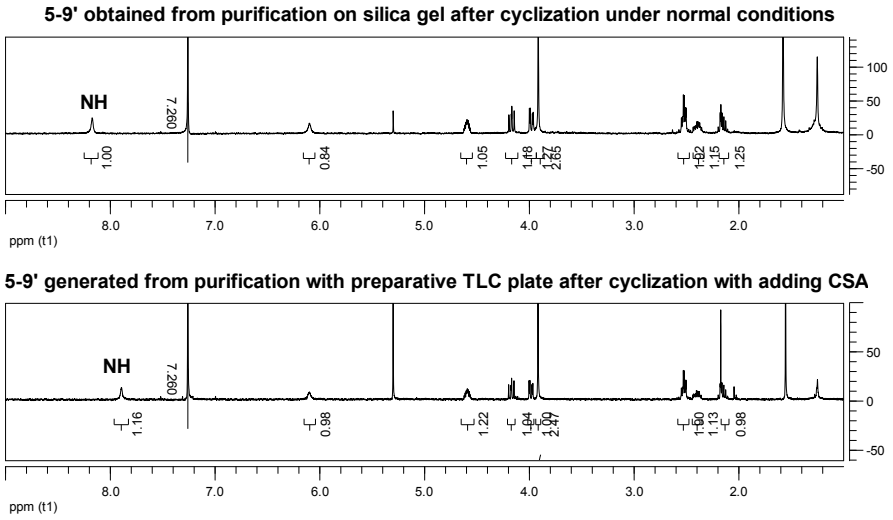
Therefore, we designed another reaction (Scheme 5.23) in order to evaluate the influence of an acidic medium.[214] A methoxycarbonyl protecting group was selected to replace the acid sensitive Boc group. Dichloroethane was used here to overcome a possible problem of solubility caused by salt formation.



Scheme 5.23 Regioselective radical cyclization in the presence of camphorsulfonic acid

Surprisingly, instead of two spread spots at the bottom of the monitoring TLC, one concentrated spot was observed with a similar R_f to the unidentified compound. This compound was ultimately isolated and found to possess structure of **5-9'**, and its ^{1}H NMR spectrum was coinsident with the previous unidentified compound, which was obtained from the purification on silica gel after radical cyclization under normal conditions (Scheme 5.24).

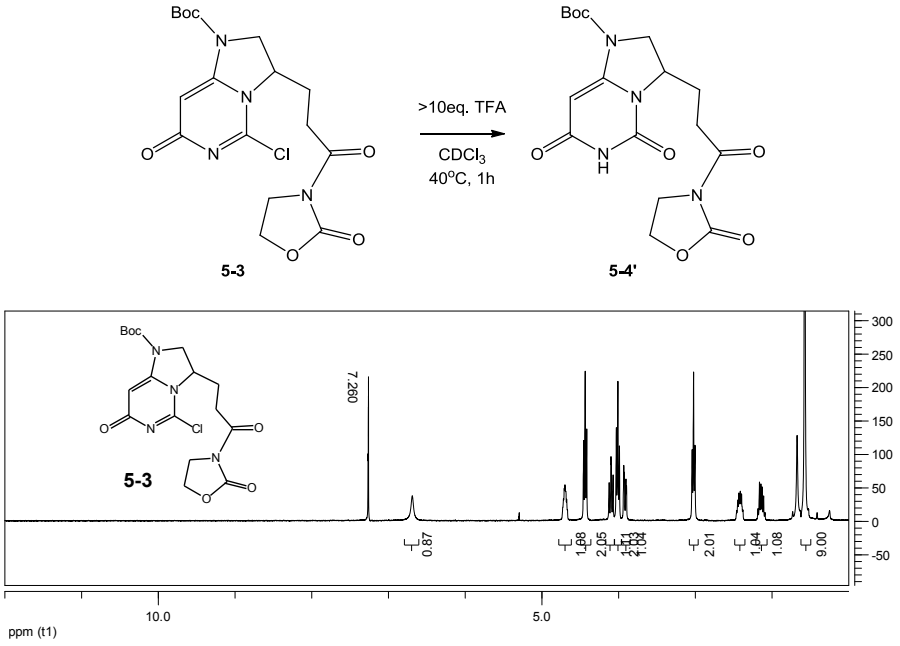
[214] Camphorsulfonic acid was added to protonate the pyrimidine ring.

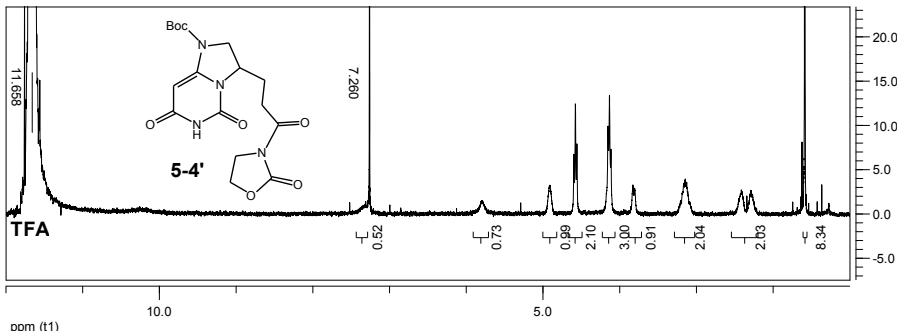


Scheme 5.24 ^{1}H NMR comparison of **5-9'** prepared from different conditions

This result confirmed the previous hypothesis that a further modification happened to pyrimidinone **5-8**. In the presence of acid, a cationic species is readily formed by protonation and is then attacked by moisture to give the corresponding 2,3-dihydro-imidazo[1,2-*c*]pyrimidine-5,7(1*H*, 6*H*)-dione **5-9'** after elimination of a chlorine atom (Scheme 5.23).

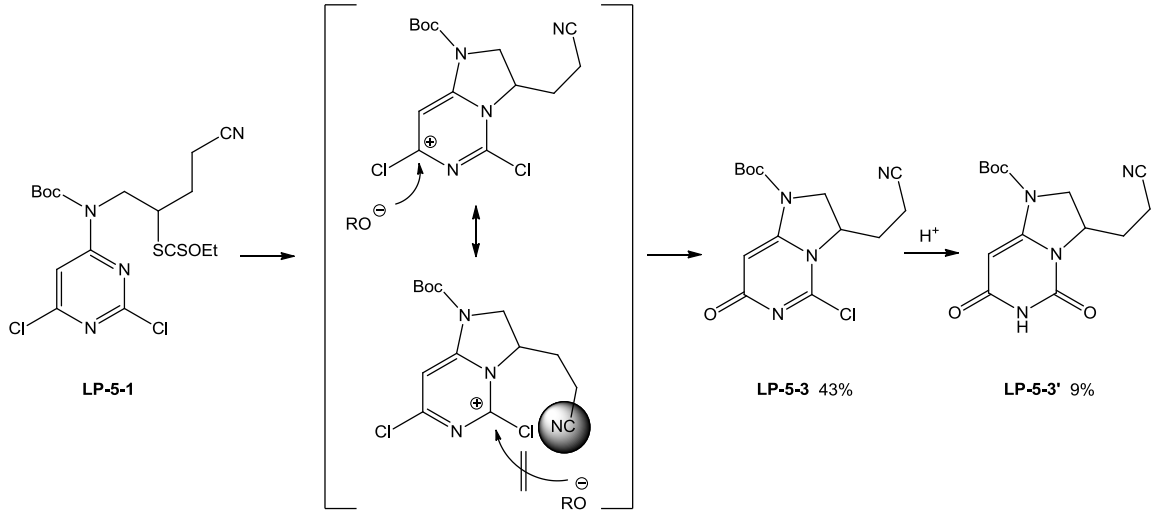
This proposed mechanism was confirmed by the simple test of treating the pyrimidinone **5-3** with trifluoroacetic acid in an NMR tube (Scheme 5.25).





Scheme 5.25 Qualitative NMR analysis of **5-3** with TFA

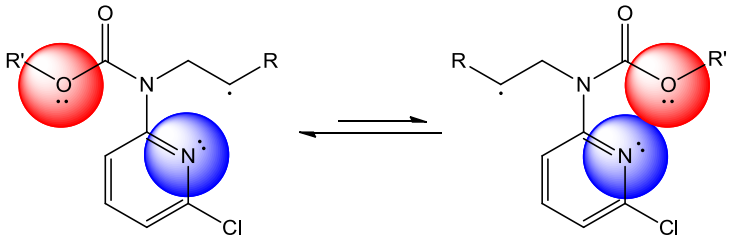
Based on the analysis above, we can now modify the previous picture as outlined in Scheme 5.26, where the second *N*-cyclized product **LP-5-3'** is in fact derived from the hydrolysis of **LP-5-3**. Therefore, a selective synthesis of bicyclic imidazo[1,2-*c*]pyrimidine-dione derivatives could be achieved in principle by hydrolysis with acid following the radical cyclization.



Scheme 5.26 Modified radical cyclization of **LP-5-1** (*C*-cyclized product not shown)

c. Further investigations of the regioselectivity with various protecting groups

As we know, both amides and carbamates exhibit the approximately planar N-C=O framework, which is responsible for their rotation barriers.[215] However, the additional oxygen of the carbamate functional group exerts unique steric and electronic perturbation.[216] Conseq.uently, the regioselectivity in the previous pyridine series could be explained by the dipole-dipole interaction[217] between the additional oxygen of the carbamate and the pyridine nitrogen. This interaction might force the alkoxy portion of the carbamate group to rotate to the opposite side, as shown in Scheme 5.27. The radical generated on the side chain thus has a better chance to approach the adjacent nitrogen and to form the C-N bond.

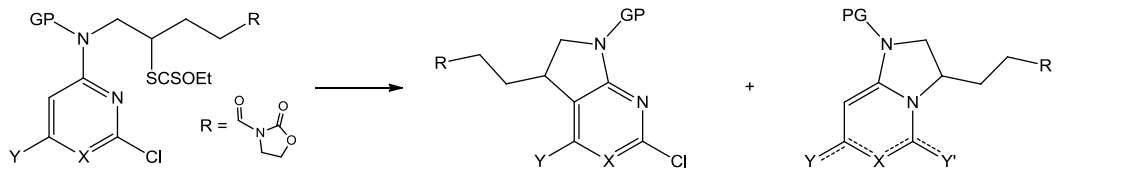


Scheme 5.27 Dipole-dipole interaction between carbamate and pyridine nitrogen

However, since later we observed the same but lower regioselectivity in the pyrimidine series (Scheme 5.28), this explanation started to become less persuasive. Since the two nitrogen and chlorine atoms render the dichloropyrimidine ring more electron-deficient than the chloropyridine ring, the C(Ar)-N bond in **5-1** must be slightly shorter than that of **EQ.-5-1**. The conseq.uence of this difference should result in a better regioselectivity in the pyrimidine series, which is clearly not the case. Although both the reactant and the products could be deprotected due to the somewhat fragile Boc group,[218] and this might

[215] The barrier for rotation in carbamates is around 16kcal/mol, which is usually 3-4 kcal/mol (about 15-20%) lower than that for the corresponding amide. For more information, see: (a) Kost, D.; Kornberg, N. *Tetrahedron Lett.* **1978**, 3275-3276. (b) Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426-2427. (c) Rablen, P. R. *J. Org. Chem.* **2000**, *65*, 7930-7937.
[216] Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426-2427.
[217] Deetz, M. J.; Forbes, C. C.; Jonas, M.; Malerich, J. P.; Smith, B. D.; Wiest, O. *J. Org. Chem.* **2002**, *67*, 3949-3952.
[218] Thermal decomposition of Boc group was observed under similar conditions.

alter the selectivity, other factors besides electrostatic repulsion should still be explored. At the same time, since the dipole-dipole interactions between the amide oxygen and the pyridine or pyrimidine nitrogen could not be completely neglected, the lack of nitrogen cyclized products from the acetyl protected xanthates **EQ.-5-1** and **LP-5-1** was hard to understand on the basis of dipole-dipole repulsion.



EQ-5-1, X = C, Y = H, PG = Boc
EQ-5-4, X = C, Y = H, PG = CO_2Me
5-1, X = N, Y = Cl, PG = Boc, 81%

EQ-5-5, X = C, Y = H, PG = Boc, 0%
EQ-5-6, X = C, Y = H, PG = CO_2Me, <8%
5-2, X = N, Y = Cl, PG = Boc, 10%

EQ-5-7, X = C, Y = H, Y' = O, PG = Boc, 63%
EQ-5-8, X = C, Y = H, Y' = O, PG = CO_2Me, 69%
5-3, X = N, Y = O, Y' = Cl, PG = Boc, 51%

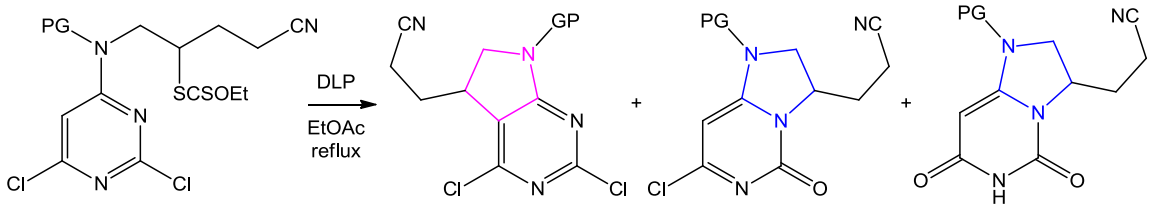
Scheme 5.28 Regioselectivity comparison with different ring systems

Furthermore, according to the theoretical analysis which was presented above,[219] this regioselectivity could be rationalized in the case of Boc group, while the results were not solid enough for the acetyl protecting group.

Since the reason for this unexpected effect of the nitrogen protecting group was still unclear, we carried out additional experiments in order to understand better this phenomenon. Some preliminary conclusions might be drawn from these studies, and more detailed investigations are still ongoing.

In order to confirm the unique role of the carbamate group, we undertook additional experiments to compare with other protecting groups. In some cases, the compounds were difficult to separate and only the major product could be completely characterized. The general tendency is summarized in Table 5.2. The pyrimidones were the only major products isolated when carbamyl groups were used for protecting the extranulear nitrogen. A similar proportion of each kind of cyclization was found in both cases, which excludes a steric influence of the bulky *tert*-butyl group. Various functional groups introduced by the xanthate partner also proved to be unrelated to this effect.

[219] See pages 161 to 162

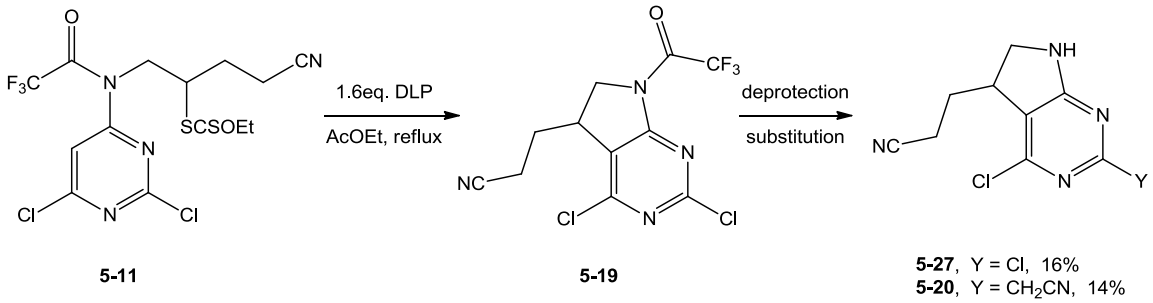


Xanthate precursors	Protecting groups	C-cyclized products	N-cyclized products	Hydrolysis products
LP-5-4 79%	Ac	**LP-5-5** 54%	0%	–
5-10 91%	Boc	**5-16** 9%	**5-17** 33%	**5-18'** 18%
5-6 73%	CO_2Me	**5-7** 6%	**5-8** 5%	**5-9'** 29%
5-11[a]	$COCF_3$	**5-19** 30%[b]	0%	–
5-14 74%	SO_2Me	**5-21** 36%	0%	–
5-15 92%	Me	**5-22** 54%	0%	–

a. One-pot addition-cyclization sequence without isolation of the intermediate;
b. Half of the C-cyclized product was transformed into **5-20**, probably derived from the radical addition of the overdosed **Xa-a** (See Scheme 5.29)

Table 5.2 Regioselective cyclization with different protecting groups

Groups with very different electronic properties such as acetyl and methyl on precursors **LP-5-4** and **5-15** were examined. However, both of these substrates gave the corresponding diazaindolines **LP-5-5** and **5-22** in similar yields. The electronic property of the protecting groups is apparently not responsible for the regioselectivity. The mesyl group was also tried but its cyclization led to complex mixtures which were difficult to analyze. Only the major product **5-21** could be obtained in enough purity for complete characterization. Nevertheless, no evidence pointed to the formation of the corresponding pyrimidone.



5-11 **5-19**

5-27, Y = Cl, 16%
5-20, Y = CH_2CN, 14%

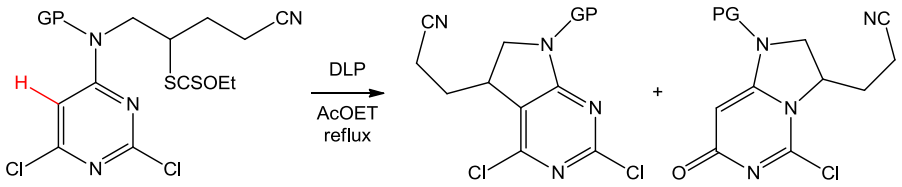
Scheme 5.29 Radical cyclization of trifluoromethylcarbonyl protected xanthate **5-11**

Moreover, we also tested the more electron-withdrawing trifluoromethylcarbonyl protected xanthate **5-11** in a one-pot addition-cyclization seq.uence under standard conditions (Scheme 5.29). The *C*-cyclized compound was obtained in an overall yield of 30%, with no evidence supporting the existence of *N*-cyclized products.

Based on all the observation above, the carbamyl protecting groups clearly plays a special role in this regioselectivity, and a more detailed study will concentrate on this moiety.

d. Preliminary evidence for an enhanced intramolecular hydrogen bond

Occasionally, we found a strange tendency in the ^{1}H NMR chemical shift of the aromatic hydrogens in the xanthate precursors. As depicted in Table 5.3, the general trend was that when an EDG (such as methyl) was substituted at the extranuclear nitrogen, the corresponding ^{1}H NMR signal of the C-5 hydrogen appeared at relatively high field; while if an EWG (such as acetyl) was attached to the nitrogen, downfield shifts were well recognized. This observation coincided with our knowledge that an electron-donating alkyl group leads to increased shielding of the hydrogen while electron-withdrawing substituents lead to deshielding.



Xanthate precursors	Protecting group	^{1}H NMR for aromatic H	^{13}C NMR for C-5	C/N-cyclized ratios
LP-5-4	Ac	7.75	112.2	54 / 0
5-10	Boc	8.05	110.3	9 / 51
5-6	COOMe	8.06	110.3	6 / 34
5-11	$COCF_3$	7.59	–	30 / 0
5-14	SO_2Me	7.53	108.0	36 / 0
5-15	Me	6.39	99.8	54 / 0

Table 5.3 Dramatic effect of the protecting group for regioselectivity

However, we noticed that the chemical shifts of the aromatic hydrogens in carbamyl protected xanthates (**5-10** and **5-6**) showed unexpected downfield shifts with respect to the other analogs.[220] Since the *N*-cyclized product was only observed with a carbamyl protecting group, we wondered if these two phenomena could be related.

Similar observations were also acquired when we examined other precursor xanthates which belonged to the same family (with different chain lengths and different position of the extranuclear nitrogen). We focused only on acetyl and Boc groups. As shown in Table 5.4, a similar tendency was found when the extranuclear nitrogen is positioned at C-4 of the pyrimidine, regardless of the chain length. But when it was installed at C-2, a similar chemical shifts were found for both protecting groups. Therefore, a regiochemical influence obviously arises from the substituent of the extranulear nitrogen.

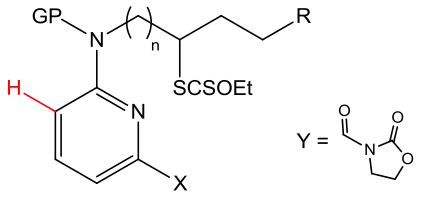
Xanthate precursors	Protecting group	^{1}H NMR for aromatic H	^{13}C NMR for C-5
LP-5-4	Ac	7.75	112.2
5-10	Boc	8.05	110.3
5-48-a	Ac	7.97	111.6
5-48-b	Boc	8.10	110.1
5-103	Ac	7.07	115.3
5-104	Boc	7.02	115.1

Table 5.4 Chemical shifts of the relevant xanthates with pyrimidine rings

It is worth mentioning that since the acetyl group is more electron-withdrawing, its deshielding effect should normally cause a more downfield shift for the signals. This theoretical prediction is generally correct for the C-5 position, as shown in Table 5.3 and 5.4. However, in the case of aromatic hydrogens, it is correct only when the protecting groups were away from the C-5 position (**5-103** and **5-104**).

[220] Theoretically, since acetyl group is more electron-withdrawing, more downfield shift should be found when an acetyl group is used. Therefore, such contrary shifts to low field with carbamyl groups cannot be ascribed only to its moderately electron-withdrawing character.

We further examined the related precursor xanthates with pyridine ring, since a regiochemical issue also existed in this series. As shown in Table 5.5, the unusual downfield shifts of the aromatic hydrogens were observed only when the carbamyl protecting groups were used, without regard to the chain functionalities or the halogen substitutions.



Xanthate precursors	R	X	n	Protecting group	^{1}H NMR for aromatic H
EQ-5-1-b	Y	Cl	1	Boc	7.57
EQ-5-4	Y	Cl	1	CO_2Me	7.59
EQ-5-1-a	Y	Cl	1	Ac	7.29
EQ-5-1-c	Y	F	1	Boc	7.58
5-62	CO_2Et	F	3	Boc	7.60
5-63	CO_2Et	F	3	Ac	7.21
5-56	CO_2Et	F	3	H	6.17

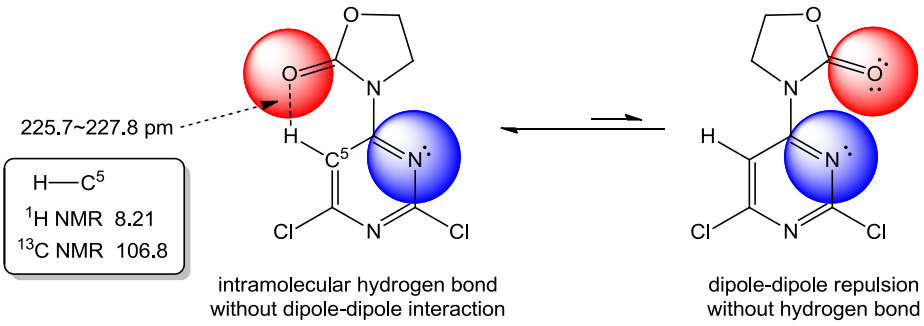
Table 5.5 Chemical shifts of the relevant xanthates in the pyridine series

Based on the comparison, the electronic property of the adjacent substituent seemed not to be the only reason to cause this strange trend in hydrogen chemical shifts. This may be an indication that the rotamer with the carbonyl oxygen near the C-5 hydrogen is greatly dominant causing a downfield shift in the signal. A weak hydrogen bonding could even be present.

In fact, intramolecular hydrogen bonding in related structures was observed by Zanda's group in the X-ray diffraction study of the single crystals of 3-(2,6-dichloro-pyrimidin-4-yl)oxazolidin-2-one.[221] Since C–H groups can act as weak hydrogen bond donors,[222] one important structural feature of this molecule in the solid-phase is the presence of an intramolecular C—H·····O hydrogen bond, involving the pyrimidine C-5 hydrogen and the

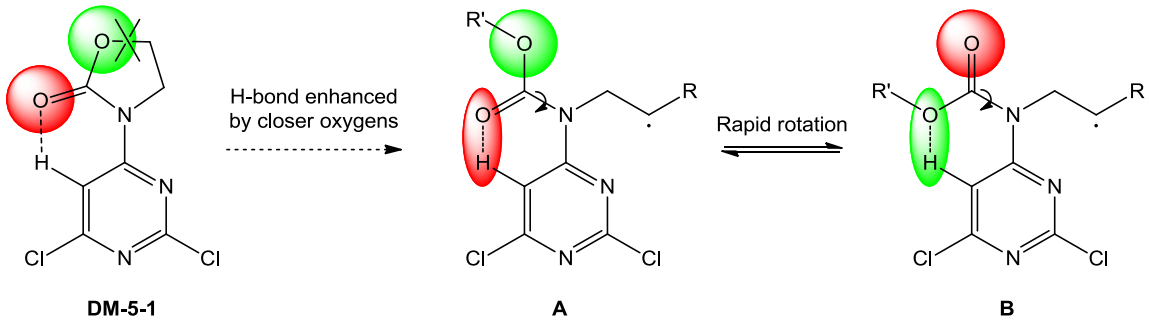
[221] Montebugnoli, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, *58*, 2147-2153.
[222] Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441-449.

carbonyl oxygen.[223] Furthermore, the predominance of the *s-trans* arrangement between the oxazolidone C=O and the pyrimidine C=N in $CDCl_3$ solution was also observed, which is in accordance with the previous hypothesis of the unfavorable dipole-dipole interactions between C=O and C=N in the *s-cis* conformation.



Scheme 5.30 H-bond in 4-*N*-alkoxycarbonyl-amino 2,6-dichloropyrimidine

Although theoretical studies suggest that the carbonyl oxygen of carbamates is a relatively weaker hydrogen bond acceptor than the amide carbonyl,[224] an enhanced intramolecular hydrogen bond could still be formed between the carbamate group and the pyrimidine-ring hydrogen.



Scheme 5.31 Possible intramolecular H-bonding directing the regiochemistry

As shown in Scheme 5.30 and 5.31, the intramolecular hydrogen bond in **DM-5-1** was observed and estimated to be 2.257~2.278Å.[221] If the oxazolidone ring is disconnected,

[223] (a) Steiner, T. *Chem. Commun.* **1997**, 727-734.; (b) Steiner, T.; Desiraju, G. R. *Chem. Commun.* **1998**, 891-892. (c) Mazik, M.; Blaser, D.; Boese, R. *Tetrahedron Lett.* **2000**, *41*, 5827.
[224] Bandekar, J.; Okuzumi, Y. *THEOCHEM.* **1993**, *100*, 113-122.

the intramolecular hydrogen bond would be enhanced by the closer carbonyl oxygen (**A**) as well as the liberated ether-like oxygen (**B**).

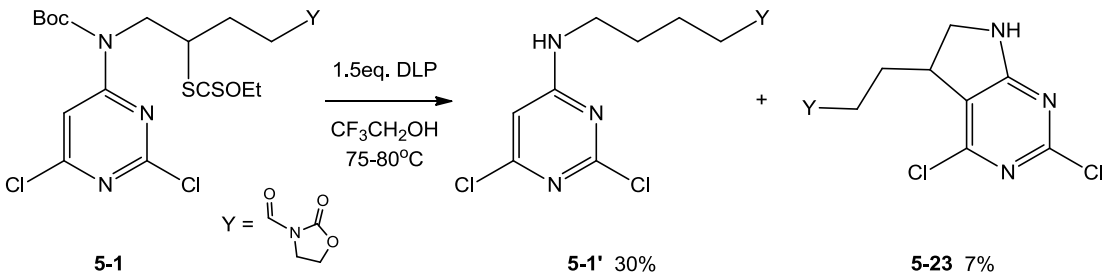
Furthermore, the strong electron-withdrawing feature of the dichloropyrimidine ring also dramatically lowers the rotation barrier of the carbamate, which should facilitate the formation of the hydrogen bond. This enhanced intramolecular hydrogen bond could in part explain the previous regioselectivity.

According to the above observation, we propose a possible explanation for the regiochemistry. The xanthate precursor possesses a predominant conformation to cyclize on the heteroaromatic nitrogen as shown in Scheme 5.31 (**A** and **B**). The general electron deficiency of the pyrimidine ring, increased by the presence of the two chlorine substituents, also shortens the C(4)-N bond and extends the C(carbonyl)-N bond, which leads to an overall lower rotation barrier of the carbamate moiety. Therefore, rapid rotation allows the two oxygens of the carbamate group to form alternating hydrogen bonds and thus enhance the bond strength in the neutral reaction medium. In the case of an amide, the hydrogen bond is not strong enough since only one oxygen can interact with the aromatic hydrogen. Furthermore, the dipole-dipole repulsion between the heteroaromatic nitrogen and the carbonyl oxygen must not be neglected.

e. Preliminary study in evaluating the mechanistic hypothesis

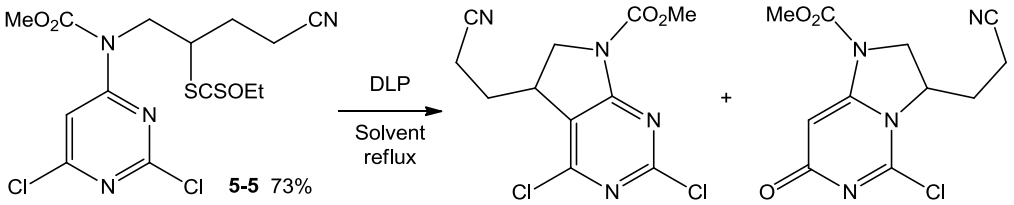
Evidence for this hypothesis was partly adduced by performing the reaction in solvents which can disturb the hydrogen bonding by interacting with the carbamate oxygens. Therefore, *tert*-butanol (pKa~17.0) and trifluoroethanol (pKa~12.5) were chosen for this study. An attempt at testing the cyclization with a Boc protected extranuclear nitrogen was unsuccessful, since the acid sensitive Boc group was lost in refluxing trifluoroethanol before the desired cyclization[225] took place (Scheme 5.32).

[225] The yields of prematurely reduced material and the *C*-cyclized product are similar to those of the cyclization with unprotected xanthate precursor, see page 179.



Scheme 5.32 Unsuccessful test with Boc protected substrate

Conseq.uently, a methoxycarbonyl was employed as the protecting group. As shown in Table 5.6, with increasing acidity of solvents, the proportion of the "normal" *C*-cyclized product increased significantly.



Solvent	Solvent acidity	*C*-cyclized product	*N*-cyclized product	C-cyclization percentage[b]
AcOEt	$CH_3COOCH_2CH_3$ pKa~25	6%	34%[a]	15% ~ 20%
*t*BuOH	$(CH_3)COH$ pKa~17	16%	35%	25% ~ 31%
TFE	CF_3CH_2OH pKa~12.5	18%	20%	43% ~ 47%

[a] Hydrolysis product (imidazo[1,2-c]pyrimidine-dione) is included with a yield of 7%

[b] C-cyclization percentage = ***C*-cyclized product** / **total cyclized products**, which is an estimation based on both of the yields and the crude ratio observed in ^1H NMR.

Table 5.6 Radical cyclization of xanthate **5-5** in different solvents

Since the acidic proton of the solvent is supposed to interact with the carbamate oxygens and thus weaken the intramolecular hydrogen bond and formation of the *N*-cyclized product should therefore be disturbed to different extents according to the acidity. This prediction is in agreement with the results listed in Table 5.6

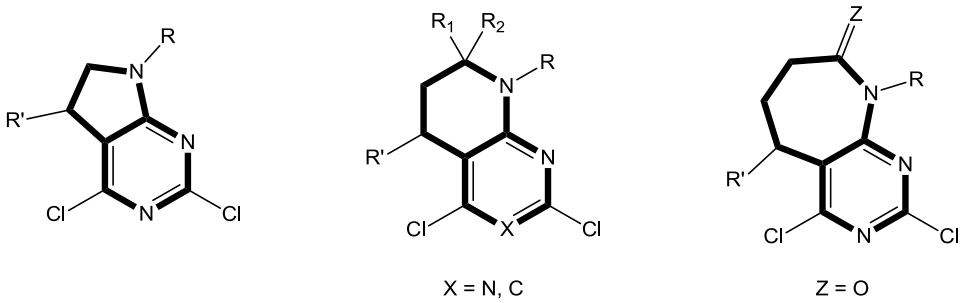
Up to now, we have proposed a hypothesis to explain the "carbamate puzzle", and all related indirect evidence seems to point in the right direction. Some studies still need to be done. For example, according to the hypothesis, the sulfonamide which has two

oxygens should also have an enhanced intramolecular hydrogen bonding. But a complex mixture was obtained and only the *C*-cyclized product was observed in a moderate yield. Thus, it might be necessary to further examine this reaction by collecting and analyzing each product in the reaction medium. More information might be gained with the similar but more electronegative trifluorosulfonamide substituted xanthate precursor. Another possibility is to use a base to disturb the hydrogen bonding by interacting with the polarized hydrogen.[226]

[226] This study is being pursued by Mr. Ling QIN.

2. Synthesis of bicyclic aza-pyrimidines and related derivatives

The above studies have underscored the important role played by protecting groups on the extranuclear nitrogen in the outcome of the radical cyclization process. However, we had never tried the cyclization without protecting the extranuclear nitrogen. We therefore embarked on an investigation of the radical cyclization without protecting group, and this resulted in an interesting approach to a wide range of bicyclic and tricyclic structures (Scheme 5.33).



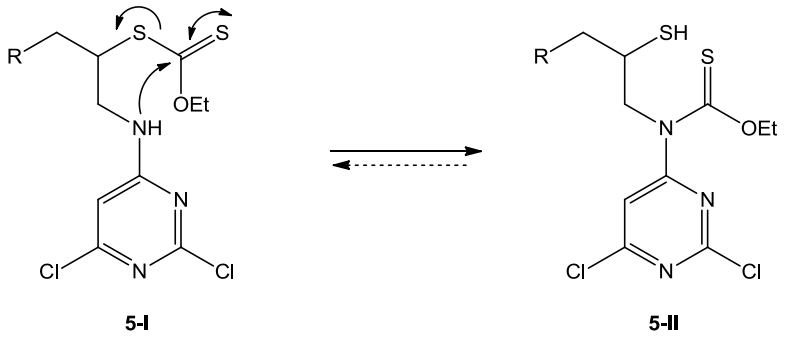
Scheme 5.33 Bicyclic pyrimidine and pyridine fused saturated *N*-containing rings

a. Synthesis of 5,7-diazaindolines without protecting groups

As shown above in Table 5.2, *C*-cyclized products could be obtained in modest to good yields according to the different extranulear nitrogen protecting groups. Thus *N*-acetylated 5,7-diazaindoline derivatives with various pendant functional groups had already been obtained in good yield by our colleagues.[216] *N*-Cyclized products could also be prepared in synthetically useful yields (>50%) starting with Boc protected xanthate precursors, followed by hydrolysis to the pyrimidone.

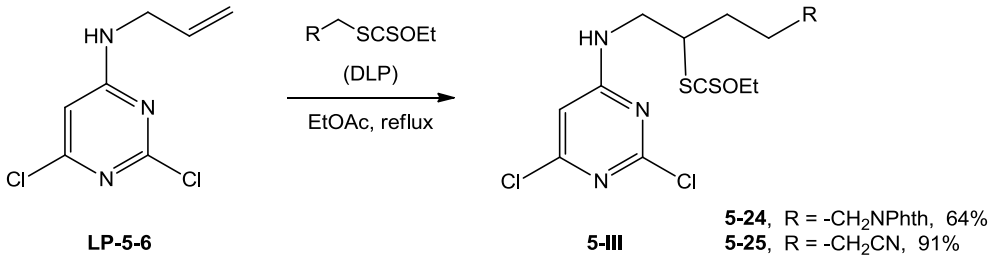
However, we had not attempted these cyclizations without protecting the extranuclear nitrogen. In fact, the original reason for installing a protecting group was to avoid any possible nucleophilic attack on the xanthate moiety. For instance, if an intramolecular

attack occurs to the alkoxythiocarbonyl group of **5-I**, the resulting thiol **5-II** would react as a serious inhibitor for the following radical process.[227]



Scheme 5.34 Undesired intramolecular ionic attack on the alkoxythiocarbonyl group

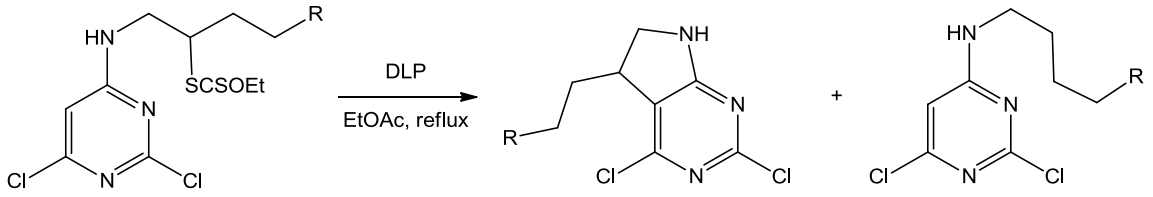
However, curiosity drove us to think about the outcome in the absence of the protection. Therefore we decided to test the cyclization on the unprotected substrate **5-III** using the usual experimental conditions. Two precursors (**5-24**[228] and **5-25**) were indeed readily obtained in good yield by DLP initiated radical addition of *S*-phthalimidomethyl and cyanomethyl xanthates on the unprotected *N*-allylamino-dichloropyrimidine **LP-5-6** (Scheme 5.35).



Scheme 5.35 Preparation of the cyclization precursors

Unfortunately, the subseq.uent radical cyclizations into diazaindolines **5-26** and **5-27** proceeded unexpectedly in low yields. Most of the xanthate precursors were prematurely reduced by hydrogen abstraction from the solvent and thus formed the undesired compounds **5-26'** and **5-27'** (Scheme 5.36).

[227] Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671-3674.
[228] Secondary products were found while preparing **5-24**, which opened another door for intramolecular radical additions to heteroaromatic rings. The details of this side reaction will be discussed in page 189.



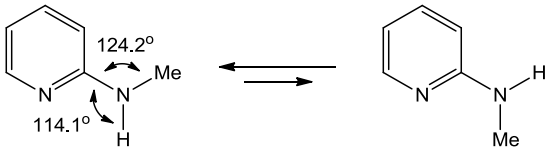
5-24, R = NPhth, 64%
5-25, R = CN, 91%

5-26, R = NPhth, 11%
5-27, R = CN, 13%

5-26', R = NPhth, 28%
5-27', R = CN, 40%

Scheme 5.36 Formation of five-membered ring fused pyrimidines without protection

The formation of five-membered rings by radical cyclization is usually the most efficient process. The reasons for the inefficient formation of diazaindoline **5-3** and **5-4** are not clear but may be related to an increased C-N-C(Ar) bond angles compared with the protected analogs. Since no values are available for the compounds in hand, the C-N-C(Ar) bond angle of the closely related 4-methylaminopyridine is used to illustrate this tendency.



Scheme 5.37 Related bond angles of 4-methylaminopyridine

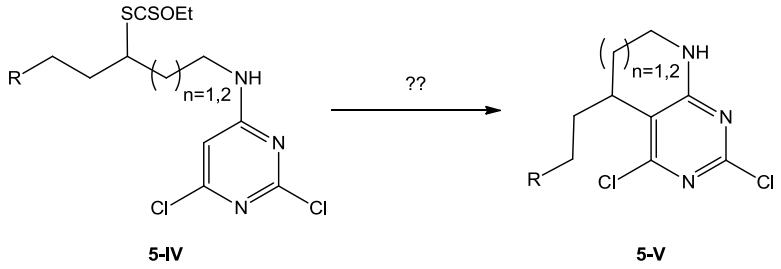
As shown in Scheme 5.37, the calculated bond angle for 4-methylaminopyridine is 124.2° which is larger than the 120° of a theoretical pure sp^2-hybridized extranuclear nitrogen.[229] The substituted side chain of **5-III** is more bulky than a small methyl group, thus this bond angle is expected to be even bigger in our case. The large opening of the C-N-C(Ar) angle places the carbon centered radical further away from the pyrimidine nucleus and the strain in the transition state leading to a fused five-membered ring would be significantly increased.

Although no efficient five-membered ring cyclization was achieved, one positive aspect of these preliminary experiments was that the feared thiol was in fact not observed. That meant that the problematic *S*- to *N*-migration of the alkoxythiocarbonyl group did not

[229] Akai, N.; Ohno, K.; Aida, M. *J. Photochem. Photobiol. A* **2007**, *187*, 113.

occur to any deleterious level during both the intermolecular and the intramolecular radical steps. It appears therefore that the electron-withdrawing effect of the dichloropyrimidine ring decreases sufficiently the nucleophilicity of the extranuclear nitrogen and obviates the need for its protection.

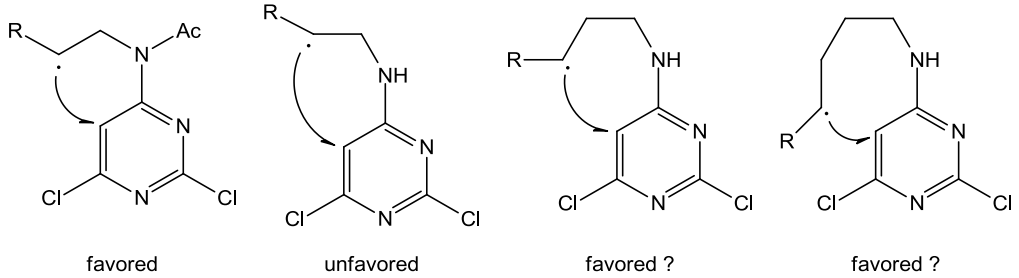
Furthermore, the fact that cyclization did proceed in the case of xanthates **5-III**, albeit in modest yield, encouraged us to examine the behavior of the higher homologues **5-IV**. As shown in Scheme 5.38, the cyclization in these cases would lead to piperidopyrimidine (n=1) and pyrimidoazepine (n=2).



5-IV **5-V**

Scheme 5.38 Designed cyclization of the higher homologue **5-IV**

In contrast to the somewhat unfavorable formation of 5,7-diazaindolines, larger ring cyclization might be favored since the generated radical is more flexible in approaching the pyrimidine ring (Scheme 5.39). This phenomenon is well documented in radical cyclizations.[230] Thus, we expected the desired cyclization would take place better in the homologous series.

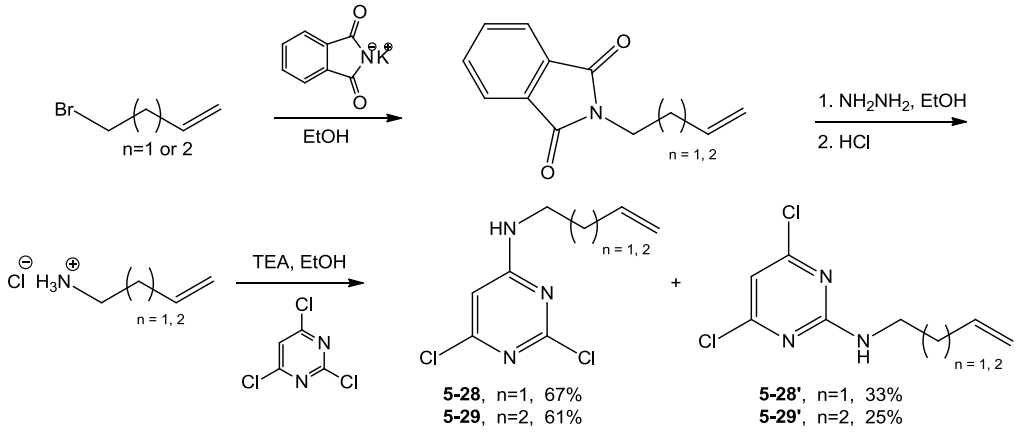


Scheme 5.39 Radical cyclizations in the homologous series

[230] Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651-3655.

b. A route to unprotected bicyclic aza-pyrimidine derivatives

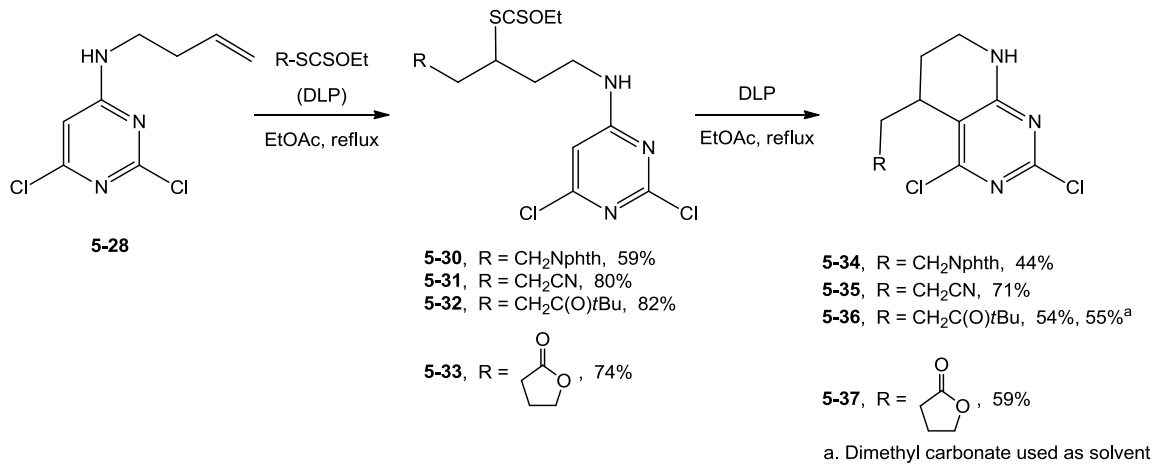
Based on the analysis above, the homologous series was explored with cyclizations leading to fused six- and seven-membered rings. The starting olefins were obtained by reaction of the corresponding primary amines with 2,4,6-trichloropyrimidine. The req.uisite but-3-en-1-amine and pent-4-en-1-amine could be obtained through the classical Gabriel synthesis of primary amines,[231] which were transformed into the corresponding hydrochloride salts for the convenience of storage. The req.uired olefin precursors **5-28** and **5-29** were formed by mixing 2,4,6-trichloropyrimidine and the corresponding amine hydrochloride salts in ethanol in the presence of TEA. For example, substitution of one chlorine with pent-4-en-1-amine furnished an easily separable mixture of the desired 2,6-dichloro-*N*-(pent-4-en-1-yl)pyrimidin-4-amine **5-29** and its regioisomer **5-29'**[232] (Scheme 5.40).



Scheme 5.40 Synthesis of the olefinic precursors

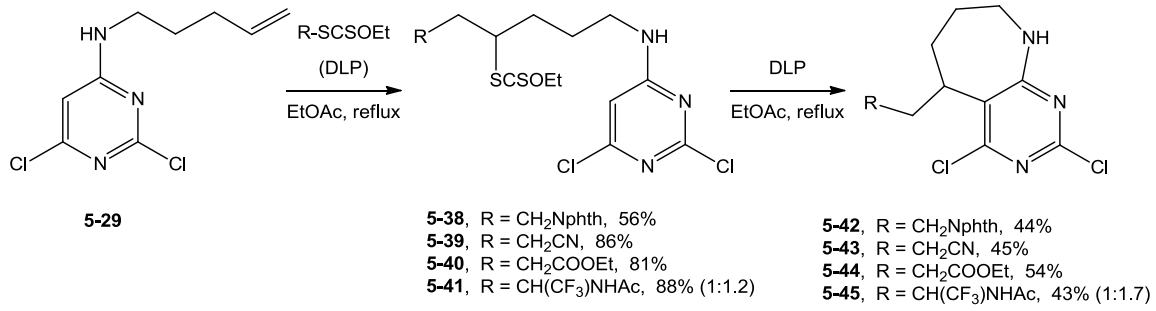
A similar radical seq.uence with the unprotected *N*-butenylamino-dichloropyrimidine furnished the desired cyclized products in much better yield. As shown in Scheme 5.41, addition of various xanthates to **5-28** afforded the corresponding adducts **5-30** to **5-33** in good yield. Further treatment with stoichiometric amounts of lauroyl peroxide gave the desired 5-substituted-piperido[2,3-d]pyrimidine **5-34** to **5-37** in synthetically useful yields.

[231] Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670-9685.
[232] Koga, M.; Schneller, S. W. *J. Heterocycl. Chem.* **1992**, *29*, 1741-1747.



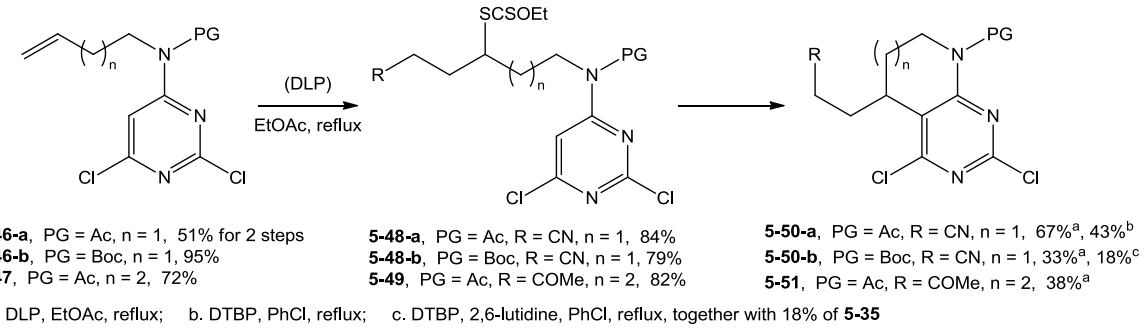
Scheme 5.41 Radical addition-cyclization seq.uence leading to piperidopyrimidines

Furthermore, bicyclic 5-substituted-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepane **5-42** to **5-45** could also be readily generated by subjecting *N*-pentenylamino-dichloro-pyrimidine **5-29** to the same seq.uence (Scheme 5.42).



Scheme 5.42 Radical addition-cyclization seq.uence leading to pyrimidoazepines

As shown in Scheme 5.43, cyclization of the analogs with the protecting groups in the extranulear nitrogen afforded similar or even lower yields. If the protecting group is replaced by Boc, the corresponding yields for the radical cyclization decreased to 33% and 18% respectively. Enhanced hydrogen bonding between the aromatic hydrogen and the protecting groups could also explain this phenomenon via the disfavored conformation. The use of unprotected precursors is not only of importance to the reaction mechanism, but also important to the convenience of this methodology.



5-46-a, PG = Ac, n = 1, 51% for 2 steps
5-46-b, PG = Boc, n = 1, 95%
5-47, PG = Ac, n = 2, 72%

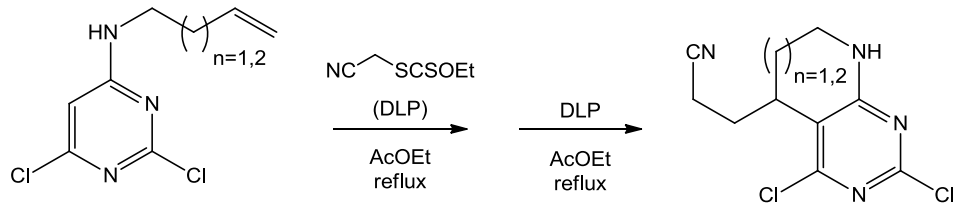
5-48-a, PG = Ac, R = CN, n = 1, 84%
5-48-b, PG = Boc, R = CN, n = 1, 79%
5-49, PG = Ac, R = COMe, n = 2, 82%

5-50-a, PG = Ac, R = CN, n = 1, 67%[a], 43%[b]
5-50-b, PG = Boc, R = CN, n = 1, 33%[a], 18%[c]
5-51, PG = Ac, R = COMe, n = 2, 38%[a]

a. DLP, EtOAc, reflux; b. DTBP, PhCl, reflux; c. DTBP, 2,6-lutidine, PhCl, reflux, together with 18% of **5-35**

Scheme 5.43 Comparison of the corresponding cyclizations with protection of the nitrogen

Another point to emphasize is that, since the solvent and the initiator are same in both the radical addition and the cyclization, we combined these two steps into a one-pot process by just changing the reaction concentration: once TLC showed that the intermolecular addition of the xanthates to the olefin was almost finished, the reaction mixture was diluted and a stoichiometric amount of lauroyl peroxide was added portionwise to complete the cyclization. Thus **5-35** and **5-43** can be synthesized using this strategy in comparable overall yields for the two steps, 41% and 34% respectively.



5-28, n=1
5-29, n=2

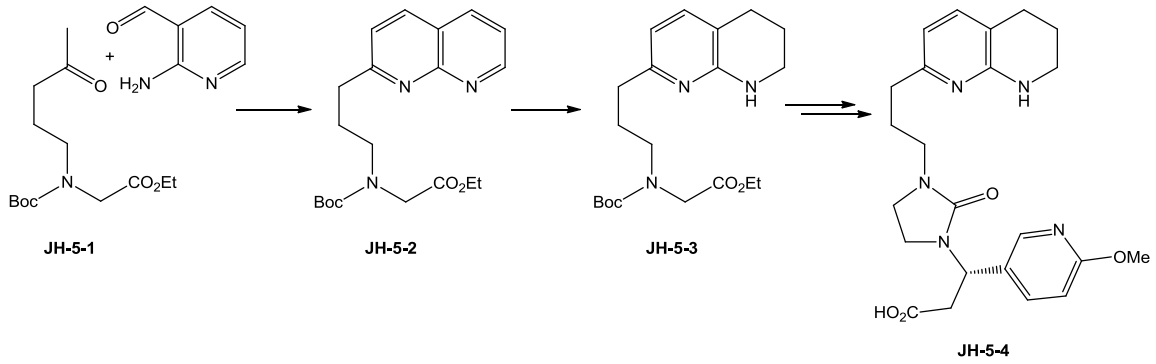
5-35, n=1, 41%
5-43, n=2, 34%

Scheme 5.44 One-pot synthesis of bicyclic aza-pyrimidines

c. Parallel study of the substrates based on pyridine ring

Bicyclic pyridine derivatives are an important class of heterocyclic structures, widely used in industry in pharmaceuticals, agrochemicals, vitamins, food flavorings, paints, dyes, rubber products, and adhesives, etc. Therefore, their preparation has garnered much attention both in academia and in industry.

For example, Merck has developed the processes to produce both six and seven membered ring fused pyridines. As shown in Scheme 5.45, compound **JH-5-4** was identified as a potent $\alpha_v\beta_3$ antagonist for the prevention and treatment of osteoporosis.[233] The synthesis starts with the glycine derivative **JH-5-1**, which is obtained from 3-(2-methyl-1,3-dioxolan-2-yl)propanal via a three step procedure (reductive amination, protection, and deketalization). Then Friedlander condensation between the methyl ketone moiety of **JH-5-1** and 2-amino-3-formylpyridine affords naphthyridine **JH-5-2**, which is then regioselectively hydrogenated in the presence of Pt_2O and H_2 gas to give the key tetrahydronaphthyridine structure **JH-5-3**.

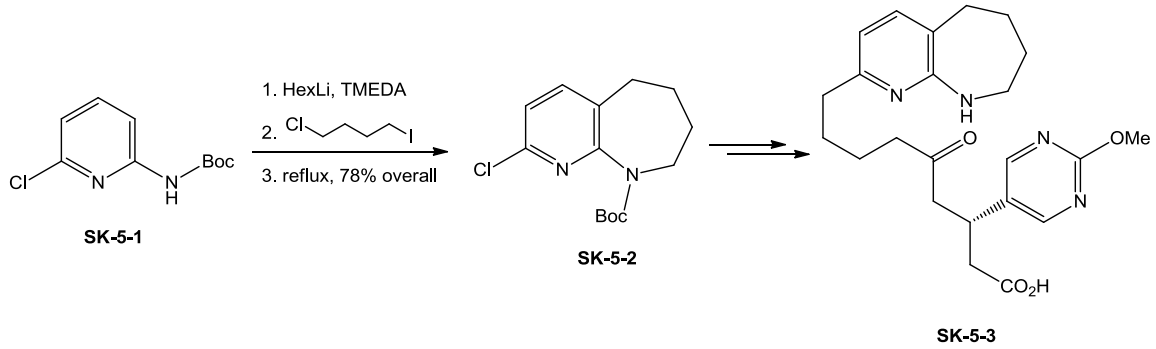


Scheme 5.45 Synthetic route to tetrahydronaphthyridine by Merck

Also selected as a nonpeptidic $\alpha_v\beta_3$ antagonist, the drug candidate **SK-5-3** was prepared by Merck in kilogram quantities (~2kg scale) using a convergent seq.uence.[234] Highlights of this synthesis include a one-pot alkylation-cyclization process to construct the seven-

[233] Hutchinson, J. H.; Duggan, M. E. *J. Med. Chem.* **2003**, *46*, 4790-4798.
[234] Keen, S. P.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771-1779.

membered ring of the tetrahydropyrido[2,3-*b*]azepane **SK-5-2**. As depicted in Scheme 5.46, dilithiation of *N*-Boc aminopyridine **SK-5-1** with hexyllithium/TMEDA at -78°C, followed by addition of 1-chloro-4-iodobutane and warming to room temperature results in a clean conversion to the chlorobutyl intermediate. Then upon refluxing the resulting reaction mixture, the desired pyridoazepine structure is generated in a good yield.

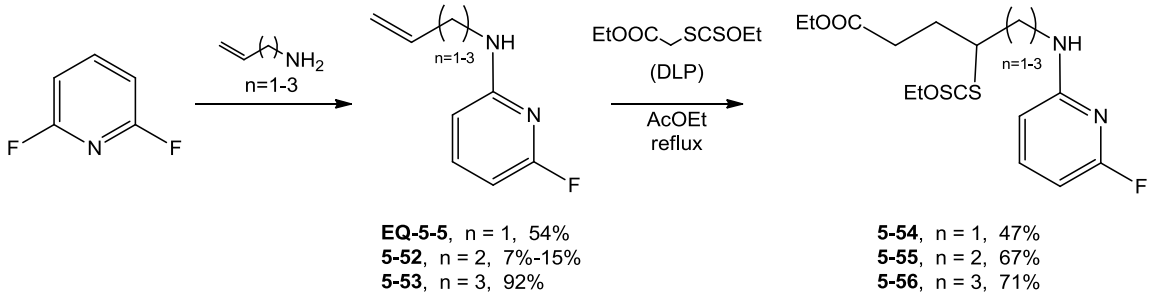


Scheme 5.46 Synthetic route to a tetrahydropyrido[2,3-b]azepane by Merck

Based on the xanthates technology, the synthesis of bicyclic pyridines has been well investigated in our laboratory over the past decade. All the substrates had a protecting group on the extranuclear nitrogen, due to the feared nucleophilicity as mentioned above. However, following the synthesis of *N*-unprotected bicyclic pyrimidine structures, a similar strategy would also be valuable in the pyridine series. If the protection could be avoided, the synthetic seq.uence would be significantly simplified. Conseq.uently, heterocyclic substrates fused on the fluoropyridine motif were tested with the established seq.uence. This work could also serve as an ancillary study to better understand the related pyrimidine system.

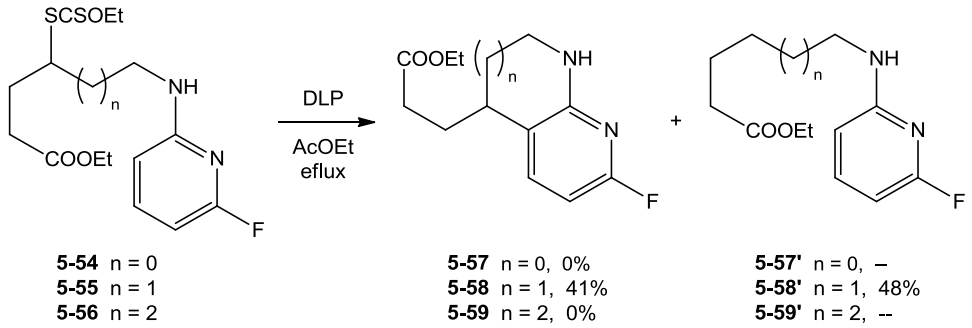
As shown in Scheme 5.47, *N*-alkenyl-fluoropyridine-2-amines were prepared through reaction of the corresponding primary amines with 2,6-difluoropyridine. Allyl-(6-fluoro-pyridin-2-yl)-amine (n=1) was prepared by refluxing for 7 hours a mixture of 2,6-difluoropyridine and 2 eq.alents of *N*-allylamine in distilled THF. But this procedure only afforded 7% yield of *N*-(but-3-enyl)-6-fluoropyridin-2-amine (n=2). A moderately improved yield of 15% could be achieved with the reaction in DMF at 95°C for 18 hours.

Although fluorine is preferred in nucleophilic aromatic substitutions due to its strong inductive effect and small size, reactions of 2,6-difluoropyridine with 4-butenylamine or 5-pentenylamine did not proceed as efficiently as expected. However, reaction under high pressure overcame this setback. For example, we obtained a yield of 92% in the preparation of 6-fluoro-*N*-(pent-4-enyl)pyridin-2-amine (n=3) when a mixture of 2,6-difluoropyridine, 5-pentenylamine hydrochloride and 2 eq.alent of DIPEA were heated in a sealed tube under 110°C for 40 hours.



Scheme 5.47 Synthesis of xanthate precursors with pyridine ring

With the *N*-alkenyl fluoropyridine-2-amines in hand, the subseq.uent intermolecular addition proceeded in reasonable yield, albeit somewhat less efficiently (Scheme 5.47). However, cyclization of the resulting adducts **5-54** ~ **5-56** occurred only when a six-membered fused ring is generated. Two products were formed when **5-55** was subjected to the action of lauroyl peroxide in refluxing ethyl acetate. The first product, isolated in 41% yield, was the desired cyclized compound **5-58**. The second product turned out to be the prematurely reduced xanthate **5-58'**, obtained in 48% yield (Scheme 5.48).

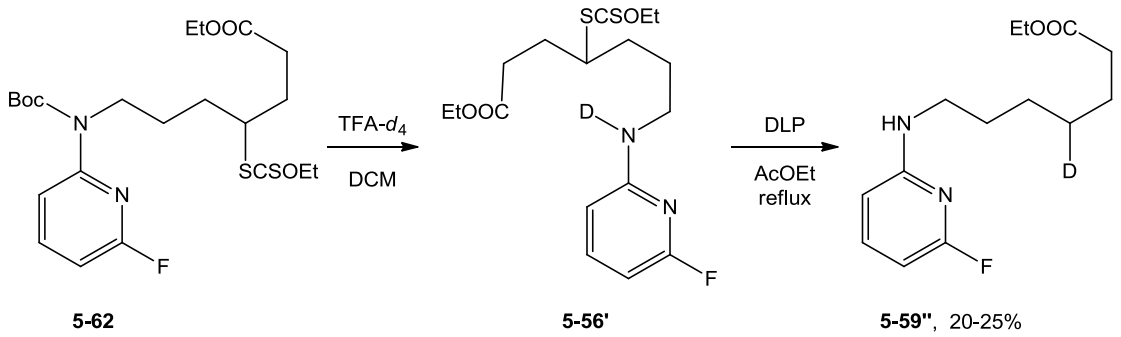


Scheme 5.48 Radical cyclization of xanthates based on a pyridine ring

Treatment of xanthates **5-54** and **5-56** with a stoichiometric amount of lauroyl peroxide in the usual manner did not produce any of the corresponding azaindoline **5-57** or pyridoazepine **5-59**. Prematurely reduced compounds (**5-57'** and **5-59'**) were observed as the sole products but were not isolated.

We were not so surprised that five-membered rings were not formed in this radical cyclization. Although the reasons are not clear yet, this is probably the result of the unfavorable bond angle as discussed above. However, the absence of seven-membered ring fused pyridine is puzzling in this study. Since formation of the prematurely reduced compound is faster than attack on the pyridine ring by the intermediate radical, this raised the question of which hydrogen atom is abstracted by the intermediate radical, from the solvent or from the substrate itself?

Although the undesired 1,5-hydrogen atom shift did not materialize to any significant level in the previous dichloropyrimidine substrates, it could nevertheless be problematic with the less electrophilic fluoropyridine ring. Polar effects are known to influence considerably the rate of hydrogen atom abstraction.[235] We therefore performed the cyclization on deuterated xanthate **5-56'** and indeed observed partial intramolecular deuterium abstraction.

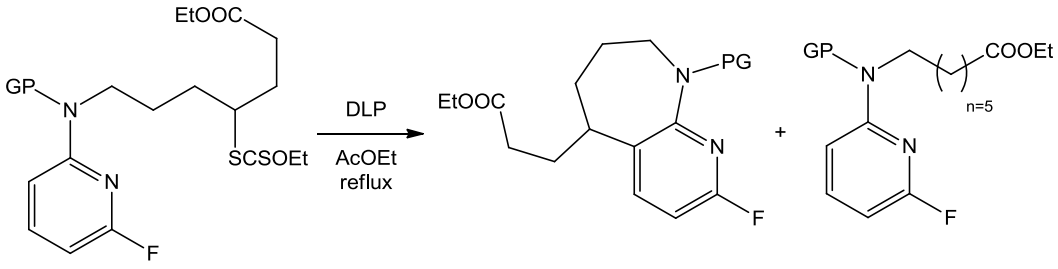


Scheme 5.49 Mechanism study based on deuterated substrate **5-56'**

[235] Tedder, J. M. *Angew.Chem.Int.Ed.* **1982**, *21*, 401-410.

As shown in Scheme 5.49, about 20-25% (by MS) of **5-59"** was isolated.[236] The proportion of intramolecular abstraction in the case of the hydrogen analog must be higher because of the kinetic isotope effect.[237]

Hence, experiments with protected substrates **5-62** and **5-63** were launched in the usual manner, but none of the desired bicyclic compounds were obtained. Only prematurely reduced products **5-64'** and **5-65'** were isolated as major products or observed on TLC as the sole products. In this case, the radical intermediate must abstract the hydrogen atom from the solvent.



5-62, PG = Boc, 45%
5-63, PG = Ac, 48%

5-64, PG = Boc, 0%
5-65, PG = Ac, 0%

5-64', PG = Boc, 58%
5-65', PG = Ac, --

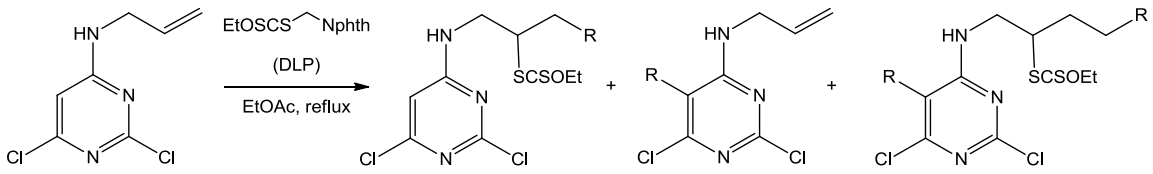
Scheme 5.50 Unsuccessful cyclization to form the seven-membered ring

Apparently, the radical cyclization onto the fluoropyridine ring is significantly slower as compared with the corresponding dichloropyrimidine ring under similar conditions. Since the fluoropyridine nucleus is more aromatic and less electrophilic than the dichloropyrimidine nucleus, reduced reactivity towards the mildly nucleophilic carbon radicals might explain this failure.

[236] See experimental part for details.
[237] An N-H bond is slightly weaker than an N-D bond.

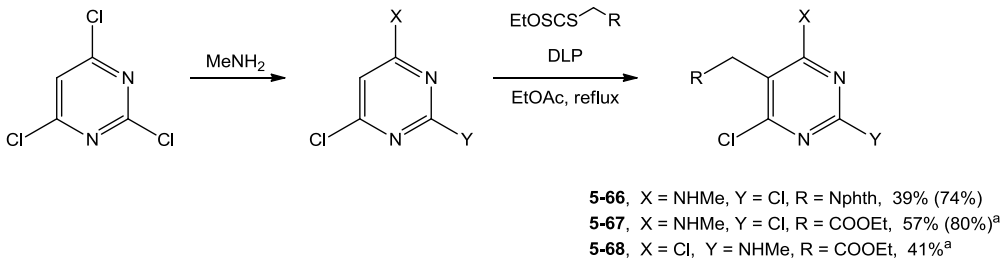
d. C-C bond formation via intermolecular radical addition to aromatic ring

Intermolecular addition of a radical to an aromatic ring followed by oxidation of the new resonance stabilized radical to produce back the aromatic system is a process which has considerably synthetic utility. During our study in preparing unprotected bicyclic aza-pyrimidines, we observed the oxidative intermolecular addition of certain xanthates to the pyrimidine ring (Scheme 5.51). Similar phenomenon was also observed when using the same xanthate to add to olefin **5-29** (not depicted here).



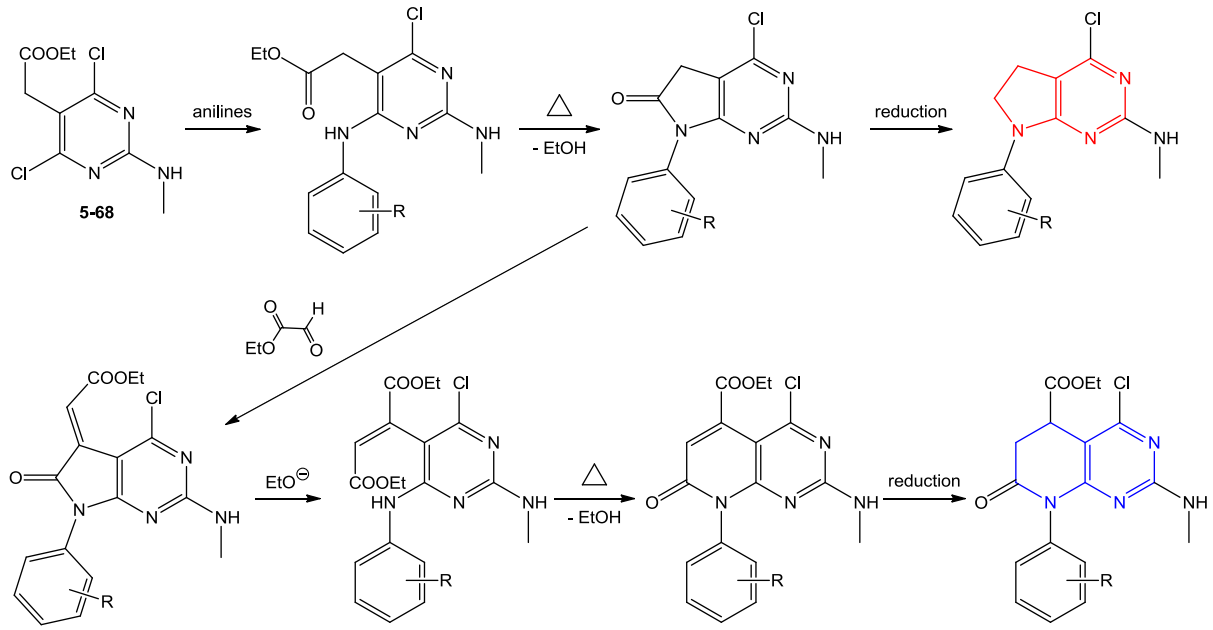
Scheme 5.51 Preparation of the cyclization precursors

Although the yields of **5-24'** and **5-24"** were not comparable with the normal addition product **5-24**, this observation was still encouraging since it opened another door to form a C-C bond onto the pyrimidine ring. A modification was then made to the substrate in order to remove the addition to an olefin. As shown in Scheme 5.52, 2,6-dichloro-4-*N*-methylamino pyrimidine and 4,6-dichloro-2-*N*-methylamino pyrimidine were readily obtained in 61% and 36% yield by substitution of trichloropyrimidine with methylamine. Treatment with various xanthates in the presence of stoichiometric DLP in refluxing AcOEt furnished the desired addition products in moderate yields. Although the yields were not quite satisfactory, it should be noted that this intermolecular addition is normally more difficult than the corresponding intramolecular process.



Scheme 5.52 Intermolecular addition of xanthates to the pyrimidine ring

Combined with more traditional reactions, these compounds could serve as universal building blocks to construct various structures based on the pyrimidine moiety. For example, diazaindolines and pyrido[2,3-*d*]pyrimidines could be prepared from **5-68** following the synthetic route depicted in Scheme 5.53. Moreover, the presence of halogen containing aromatic system allowed the further functionalization employing cross coupling technologies.



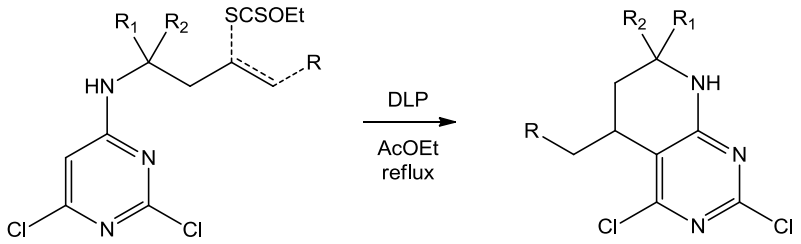
Scheme 5.53 Synthesis of five and six-membered ring fused pyrimidine by **5-68**

3. Expansion of the reaction scope

As discussed above, we now have in hand a modular, flexible and concise route to bicyclic pyrimidines. We next investigated the scope of this approach in order to delineate its applicability to more complex structures. First, functional groups on the side chain between the nitrogen and the xanthate were introduced; second, an alternative synthetic route was designed for generating the seven-membered ring fused pyrimidine; and last, ionic inter- and intra-molecular substitutions on the dichloropyrimidine moiety were explored and found to lead to numerous interesting structures, including novel polycyclic pyrimidines.

a. Synthesis of 7,7-disubstituted piperido[2,3-d]pyrimidines

As shown in Scheme 5.54, functional groups were installed on the side chain of **5-VIII** between the nitrogen and the xanthate group. In principle, the radical cyclization of these precursors should lead to the formation of 7,7-disubstituted piperido[2,3-*d*]pyrimidine **5-IX**.

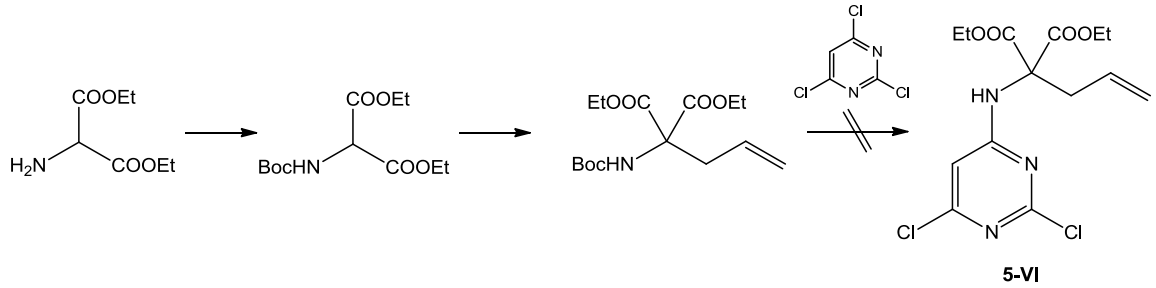


5-VIII **5-IX**

Scheme 5.54 Expended synthesis to generate bicyclic compound **5-IX**

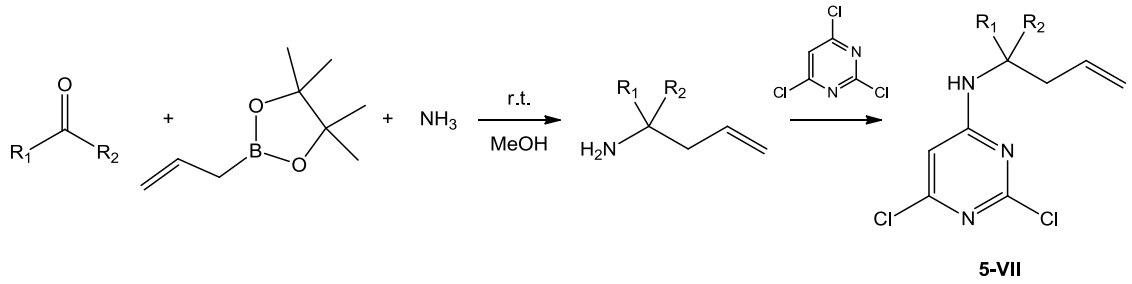
In the first attempt, diethyl 2-allyl-2-((*tert*-butoxycarbonyl)amino)malonate was obtained in two steps from diethyl aminomalonate. Unfortunately, the following substitution reaction to the trichloropyrimidine was unsuccessful, probably due to the steric bulk of the liberated primary amine, as well as its weak nucleophilicity caused by two adjacent electron-withdrawing ester functionalities.[238]

[238] A reaction in a sealed tube was not tested.



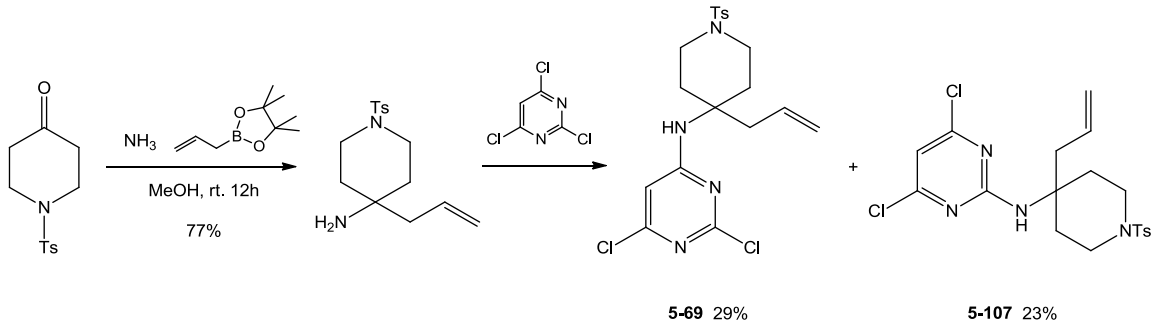
Scheme 5.55 Attempts to prepare the olefinic precursor **5-VI**

We therefore adopted another strategy[239] based on a three-component reaction of a ketone with excess ammonia and allylboronate. This method proved to be more convenient in providing the desired homoallylic amine **5-VII**.



Scheme 5.56 Synthesis of the olefinic precursor **5-VII**

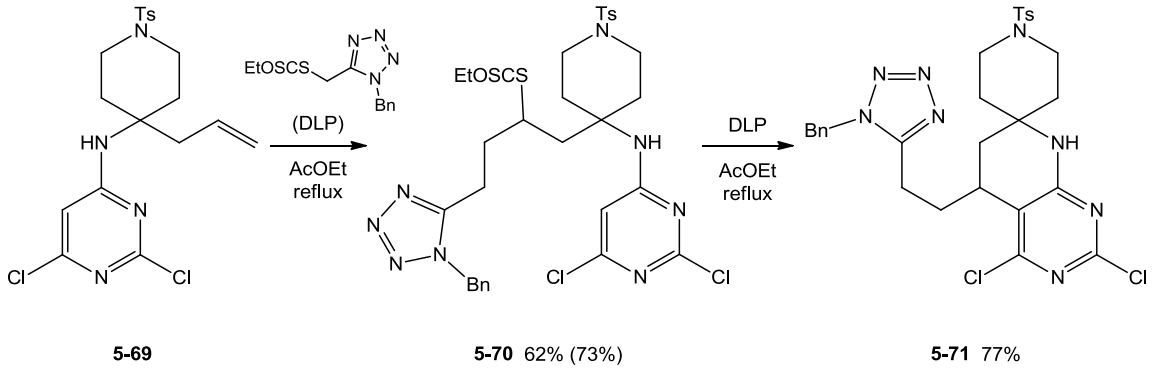
A diverse range of ketones could be used in this allylation of *N*-unsubstituted imines. We chose 1-tosylpiperidin-4-one to illustrate this synthetic strategy. As shown in Scheme 5.57, 4-allyl-1-tosylpiperidin-4-amine was readily obtained by this reaction. Nucleophilic substitution with trichloropyrimidine afforded the desired alkene in a modest yield, due to the competing substitution at C-2.[240]



Scheme 5.57 Synthesis of the olefinic precursor **5-69**

[239] (a) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182-7183.(b) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551-5553.
[240] The regioisomer **5-107** was even more useful in another reaction, see page 205.

With this olefin in hand, radical addition of tetrazole xanthate followed by intramolecular cyclization afforded a highly functionalized spiro derivative **5-71**. It is very difficult to access such structures using conventional ionic and organometallic reactions. As far as we know, this is the first synthesis of this tricyclic skeleton. It is also worth noting that the radical cyclization of the side chain substituted xanthate **5-70** is more effective than that with a naked chain, probably due to the conformational proximity of the generated radical to the aromatic ring. The protected piperidine ring further compresses the radical terminus toward the pyrimidine nucleus and thus promotes the cyclization (Thorpe-Ingold effect).



5-69 **5-70** 62% (73%) **5-71** 77%

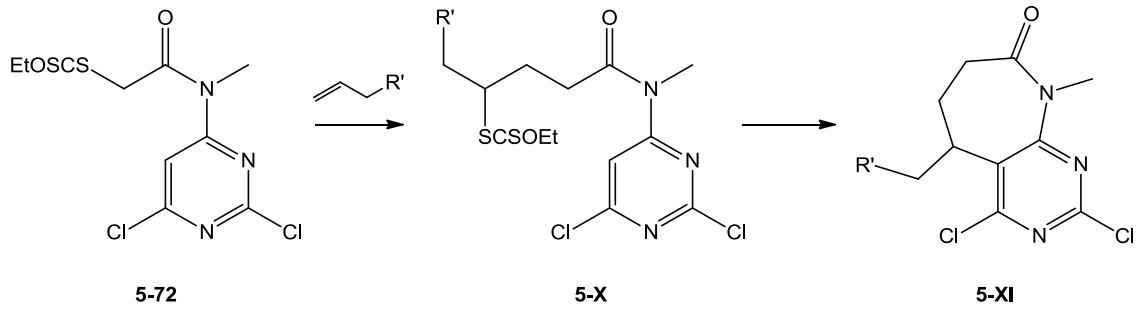
Scheme 5.58 Synthesis of highly functionalized spiro derivative **5-71**

The tetrazole ring introduced by the xanthate part is also of interest. Since this unit is not only comparable to a carboxylic acid moiety, both in size and in acidity, but is also metabolically more stables. It has been used as a carboxylic acid mimic in a wide number of compounds of biological importance, especially in relation to antagonists of angiotensin II. [241] The radical seq.uence above provides a particularly convenient installation of this functional group and this should prove useful in designing other bioactive derivatives. Furthermore, the benzyl group on the tetrazole moiety could be in principle removed later if a naked tetrazole is needed in the final product.

[241] Biadatti, T.; Quiclet-Sire, B.; Saunier, J. B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 19-22. and reference cited therein.

b. Alternative strategy for preparing pyrimidoazepines

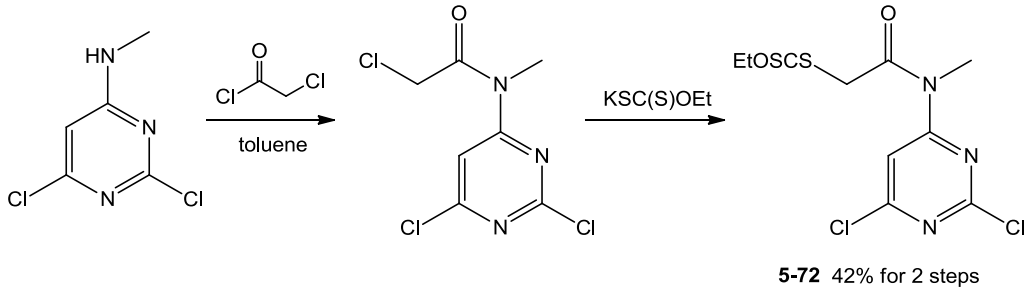
An alternative strategy could also be applied for the synthesis of pyrimidoazepines, as depicted in Scheme 5.59. This synthetic route uses a different radical addition, whereby the aromatic ring now bears the xanthate group as in compound **5-72**. This xanthate readily adds to various olefinic partners to generate the adducts **5-X**, which can then undergo ring closure to create the bicyclic products **5-XI**. One advantage of this method is that the R' group introduced through olefinic partners enriches the functionalities contained in the pyrimidoazepines. The additional carbonyl group in the saturated seven-membered ring provides the possibility of further modifying these derivatives. Conseq.uently, together with the former method, a broad range of bicyclic pyrimidoazepines can be obtained by short synthetic routes.



5-72 **5-X** **5-XI**

Scheme 5.59 An alternative strategy to synthesize pyrimidoazepines

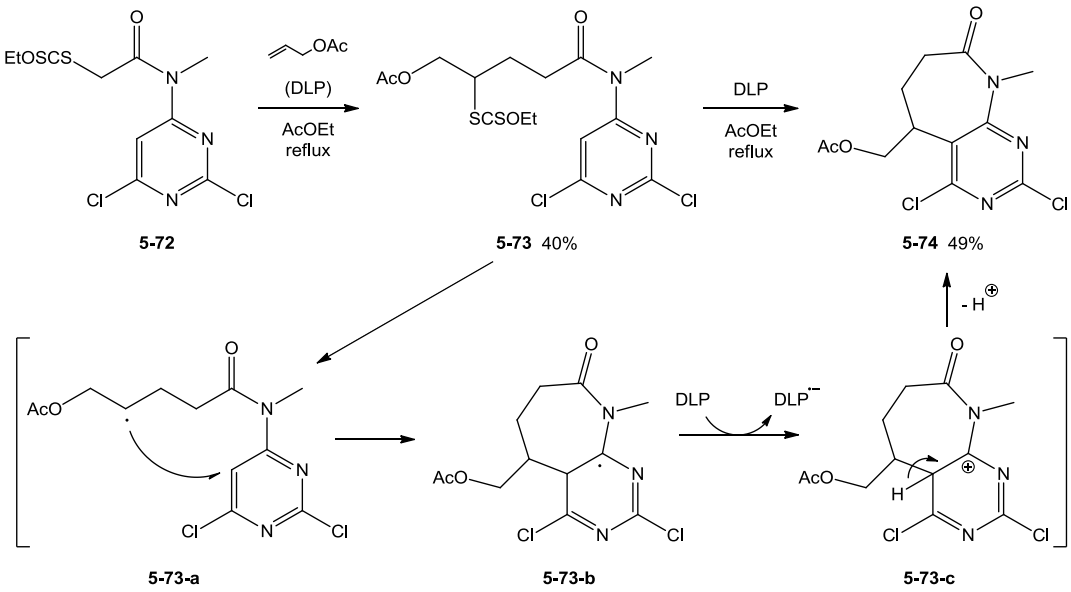
Xanthate **5-72** is prepared from 2,6-dichloro-4-*N*-methylamino pyrimidine by reaction with chloroacetyl chloride to give 2-chloro-*N*-(2,6-dichloropyrimidin-4-yl)-*N*-methyl-acetamide, followed by displacement of the chlorine atom with potassium *O*-ethyldithiocarbonate (Scheme 5.60).



5-72 42% for 2 steps

Scheme 5.60 Synthesis of precursor xanthate **5-72**

Xanthate **5-72** readily adds to allylacetate following initiation with DLP in refluxing ethyl acetate to give the corresponding addition product **5-73**. Treatment of **5-73** with stoichiometric amount of DLP results in ring-closure onto the pyrimidine to form a new radical species **5-73-b**, which is oxidized to cation **5-73-c** by electron transfer to the peroxide and finally aromatized by loss of a proton into the desired compound **5-74** (Scheme 5.61).

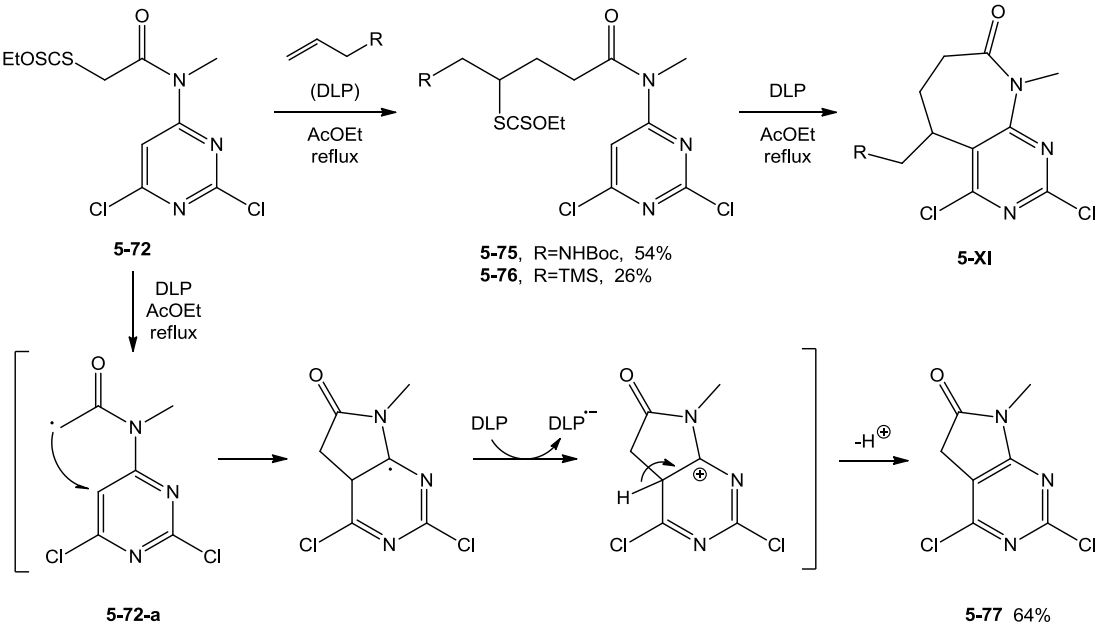


Scheme 5.61 Alternative strategy for the synthesis of pyrimidoazepines **5-74**

Our efforts at improving the yield of **5-73** were not successful: the radical addition of **5-72** to allyl acetate was repeated very carefully but gave the same modest yield, i.e. 40%. However, we noticed that the color of xanthate **5-72**, which is light yellow just after purification, changes to deep yellow after a few weeks of storage, even when covered with aluminum foil and kept in refrigerator. This phenomenon is rather uncommon in comparison with other freq.uently used xanthates in our laboratory.

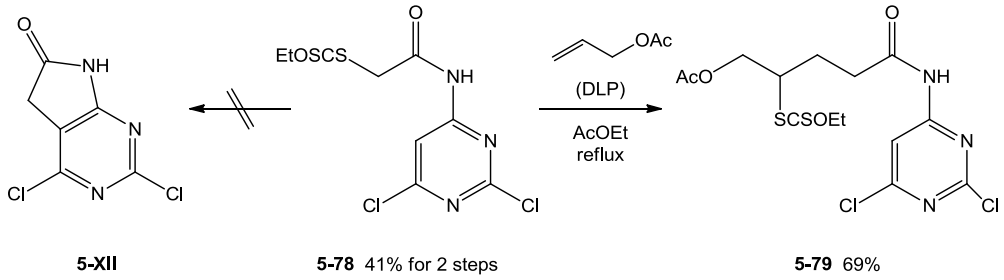
Furthermore, attempts at preparing related analogous **5-75** and **5-76** afforded unreliable results. For example, when newly purified **5-72** was reacted with Boc-protected allylamine, the addition product **5-75** could be generated in a somewhat better yield as compared to the first example **5-73**; but if the xanthate was kept several days in refrigerator and was not repurified before using, only 26% of the addition product **5-76** was generated (Scheme 5.62).

One possible explanation for the variability and generally modest yields is the direct cyclization of **5-72** via radical species **5-72-a** to give the diazaoxindole **5-77**. This hypothesis was confirmed by obtaining this bicyclic compound in good yield after treatment of **5-72** with a stoichiometric amount of DLP in refluxing ethyl acetate.



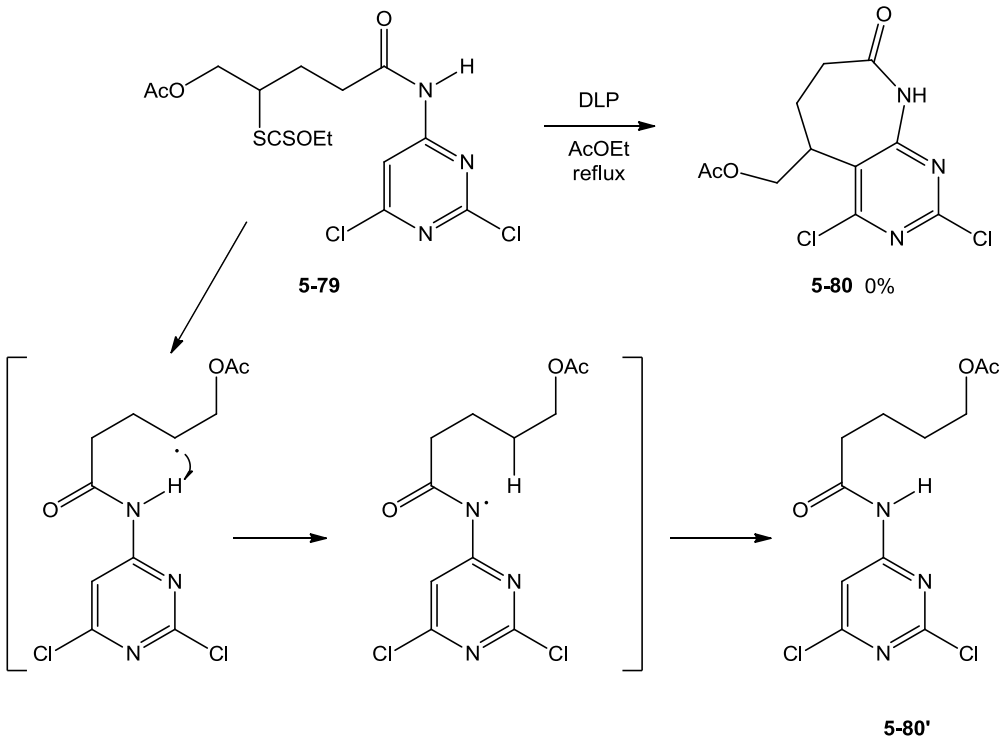
Scheme 5.62 Modest yields of radical addition of **5-72** caused by its self-cyclization

Although we could limit this side-reaction by playing with the reaction conditions such as adding an excess of olefin, this inherent defect still made this synthetic strategy less efficient. However, since we had shown that protection of extranuclear nitrogen was unnecessary and that five-membered ring formation was unfavored in the absence of a substituent on the nitrogen, a simple modification involving an unprotected xanthate precursor **5-78** could be envisaged to avoid the competitive oxindole formation.



Scheme 5.63 Radical addition of the unprotected xanthate **5-78**

As expected, direct ring-closure of xanthate **5-78** under usual conditions did not happen, and this opened the possibility of intermolecular addition to an olefinic partner, such as allyl acetate. As indicated in Scheme 5.63, the radical addition was accomplished efficiently to give the xanthate precursor **5-79**. However, the following cyclization did not proceed as expected and only prematurely reduced compound was isolated (Scheme 5.64).

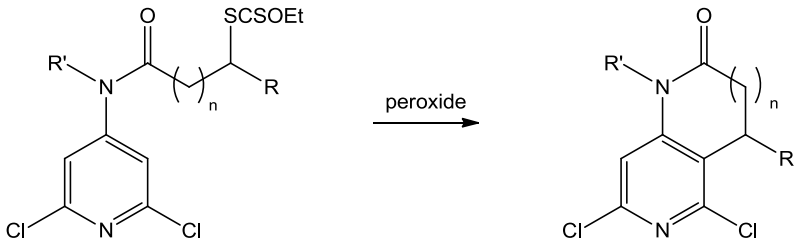


Scheme 5.64 Unsuccessful cyclization of **5-79** because of a possible intrmolecular hydrogen abstraction

A similar trend in lactam formation by radical cyclization has been documented in a recent review.[242] For example, treatment of xanthate **SZ-5-3** with peroxide furnished the desired azepinone **SZ-5-6** in 60% yield, whereas only prematurely reduced material was obtained from the *N*-unsubstituted analog **SZ-5-2**. Thus even a small methyl group is sufficient to promote the desired cyclization, which is in any case a difficult process that cannot usually be accomplished by other radical methods. However, the related six-membered ring-closure exhibited a very different picture: the presence of a substituent on

[242] Zard, S. Z. *J. Phys. Org. Chem.* **2012**, 25, 953-964.

the extranuclear nitrogen was not necessary for the cyclization to take place. For example, dihydroazaquinolone **SZ-5-4** could be obtained by the radical cyclization of the corresponding xanthate precursor in a reasonable yield.



SZ-5-1, R' = H, n = 1, R = CH_2CH_2COOEt
SZ-5-2, R' = H, n = 2, R = $CH(OEt)_2$
SZ-5-3, R' = Me, n = 2, R = CH_2CH_2COMe

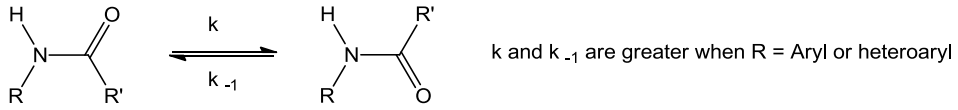
SZ-5-4, R' = H, n = 1, R = CH_2CH_2COOEt, 51%
SZ-5-5, R' = H, n = 2, R = $CH(OEt)_2$, 0%
SZ-5-6, R' = Me, n = 2, R = CH_2CH_2COMe, 60%

Scheme 5.65 Curious aspects of lactam formation

Although the underlying causes are not yet clear, we suspected that this phenomenon is probably due to a combination of several factors.

In the case of the azaoxindoles, the substituent is needed on the nitrogen to compress the side chain (and bring the radical closer to the aromatic nucleus) and to modify the rotamer population toward the rotamer with geometry favorable for cyclization. It must be remembered that fusing a five-membered lactam to a six-membered aromatic or heteroaromatic ring introduces some strain into the structure.

In the case of a six-membered lactam, the cyclization process does not introduce a significant strain and the rotamer population, even if it is tilted towards the ones with an unfavorable geometry, is in a dynamic eq.uilibrium. The rate of rotation around the amide bond is greater when the nitrogen is substituted by an aryl or heteroaryl group, because of the diminished π-bond character between the nitrogen and the carbonyl carbon:



Scheme 5.66 Rotation around the amide bond

In the case of seven-membered ring lactams, the problem now is not due to strain or rotamer population, but to an unfavorable entropy term due to the longer distance between the radical located on a floppy side-chain and the aromatic ring. The slower ring-closure opens up a greater probability of a premature hydrogen atom abstraction from the solvent. Furthermore, the intermediate carbon radical can also abstract the hydrogen on the amide nitrogen as it is now within an ideal distance. Thus the simple introduction of a methyl group on the nitrogen removes this possibility and compensates for the floppiness of the side-chain by modifying the rotamer population in a more favorable direction.

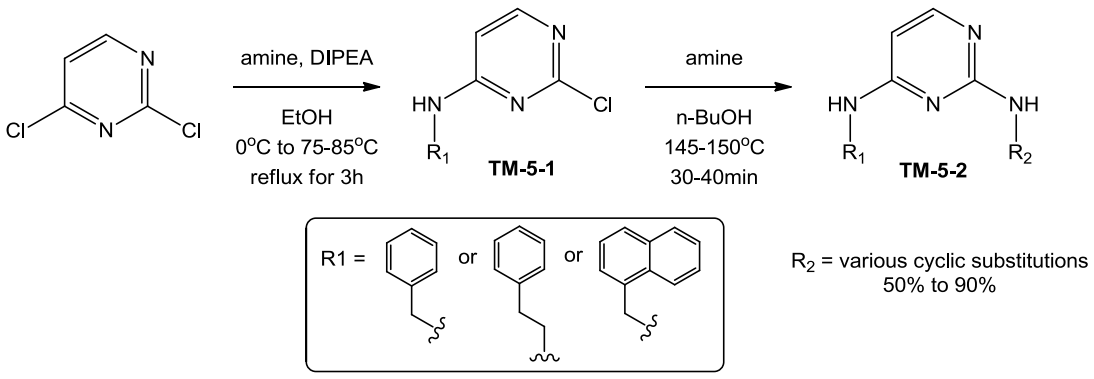
While all these factors are individually energetically of a small magnitude in absolute terms, they can dramatically affect the outcome of the radical process.

c. Functionalization of the bicyclic aza-pyrimidine derivatives

The presence of halogen atoms on the bicyclic aza-pyrimidines allows the potential modification of these structures. In order to diversify the products within our subject, further substitutions in either intermolecular or intramolecular fashion were investigated. A number of interesting fused pyrimidines with various substituents and related polycyclic compounds were thus generated. Many of these structures are not readily prepared by more classical methods.

1) Intermolecular substitution

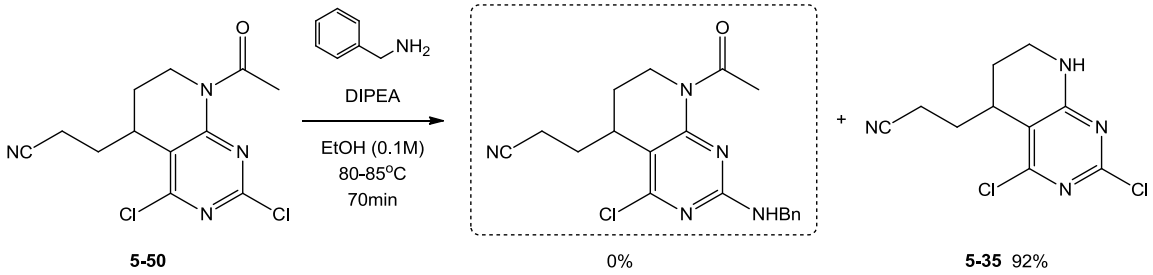
An earlier work by Mohamed [243] describes the selective synthesis of differentially substituted 2,4-diamino pyrimidines. As depicted in Scheme 5.67, derivatives **TM-5-2** were obtained in two steps from 2,4-dichloropyrimidine. In the first step, nucleophilic aromatic substitution was accomplished at C-4 using primary amines with a base such as DIPEA. The second more difficult substitution of **TM-5-1** afforded moderate to good yields ranging from 60% to 75%. In the second step, the C-2 chlorine was replaced by various cyclic amines under vigorous conditions in a sealed tube.



Scheme 5.67 Selective substitution of 2,4-dichloropyrimidine

[243] Mohamed, T.; Zhao, X. B.; Habib, L. K.; Yang, J. R.; Rao, P. P. N. *Bioorg. Med. Chem.* **2011**, *19*, 2269-2281.

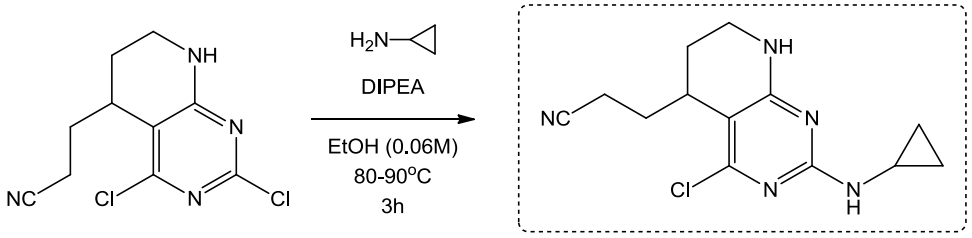
In view of the similarity of 2,4-dichloropyrimidine with the bicyclic compounds in our study, we decided to employ these conditions in our synthesis. The first attempt was performed with adduct **5-50**, which was heated with 1eq. of benzylamine and 1.1eq. DIPEA in ethanol. But no substitution took place and the sole product generated was the deprotected product **5-35**.



5-50 0% **5-35** 92%

Scheme 5.68 Unsuccessful substitution of acetylated substrate

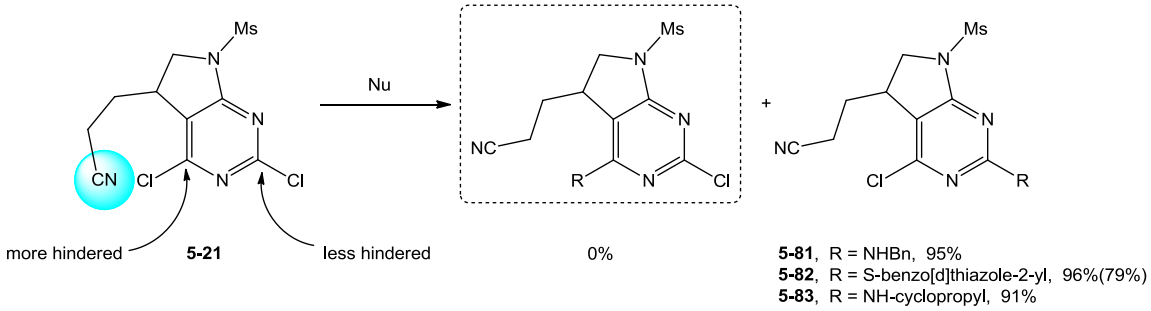
Further treatment of **5-35** with 7eq. of the smaller cyclopropylamine and 10eq. DIPEA in ethanol still gave no desired substitution, with only recovery of the starting material.



5-35 0%

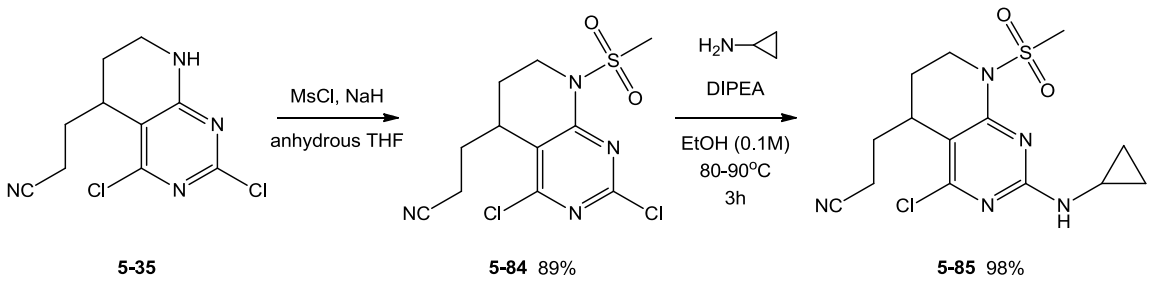
Scheme 5.69 Unsuccessful substitution of unprotected piperidopyrimidine

Since similar structures (diazaindolines) were prepared earlier on a relatively large scale, we decided to try the substitution with analog **5-21**. According to the literature, both of the chlorine atoms in the pyrimidine ring can be replaced by a proper nucleophile. However, due to the presence of the side chain, only the chlorine at the less hindered position should be attacked under the conditions used. Primary amines and thiol were used as the nucleophiles to illustrate this substitution. Good yields were obtained as shown by the results depicted in Scheme 5.70.



Scheme 5.70 Nucleophilic substitutions of diazaindoline **5-21**

Compound **5-21**, with an electrophilic mesyl protecting group, improves the reactivity of the pyrimidine ring towards nucleophilic substitution. We therefore introduced this protecting group to the previous substrate **5-35** and obtained the desired product **5-85** in excellent yield (Scheme 5.71).



5-35 **5-84** 89% **5-85** 98%

Scheme 5.71 Nucleophilic substitution to mesyl protected piperidopyrimidine

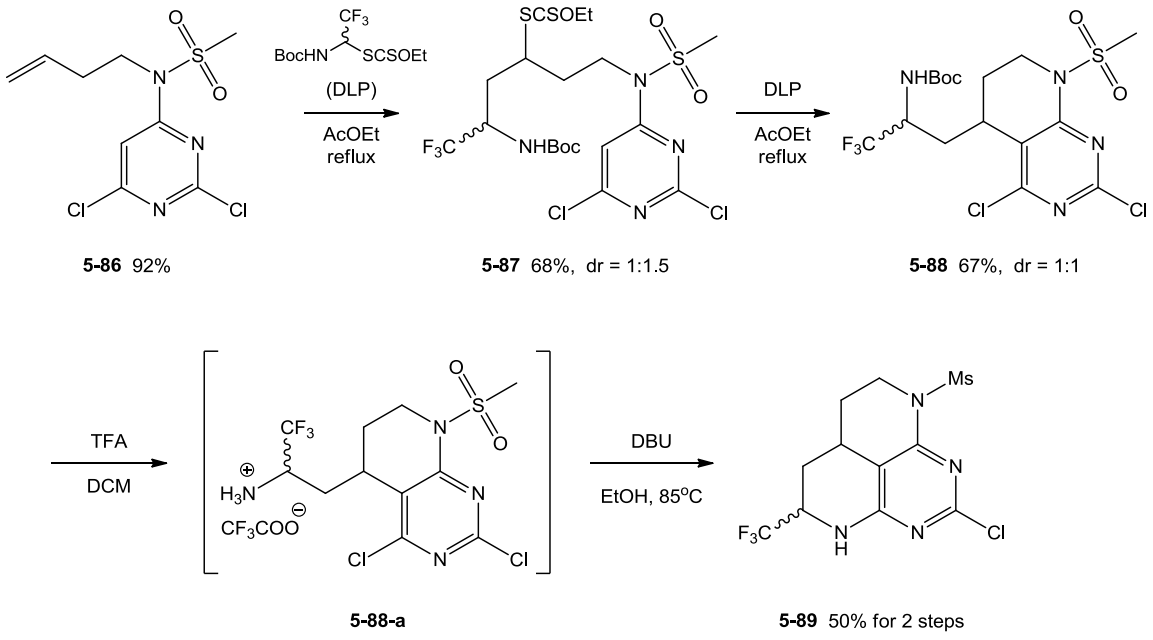
Since we mainly concentrated on illustrating the feasibility of the substitution, we did not investigate the utility of other solvents, such as DMF. Nor did we attempt a second intermolecular substitution of C-4 chlorine.[244] We rather directed our attention on investigating the synthetic potential of an intramolecular substitution.

[244] Theoretically this could be achieved using somewhat vigorous conditions.

2) Intermolecular substitution: a convenient way to tricycles

As mentioned above, the incorporation of various xanthate partners provides the ability to introduce various functional groups into the products. Thus, a latent nucleophile can be installed via the xanthate on the bicyclic structure, allowing a third ring to be constructed by simple application of an ionic process.

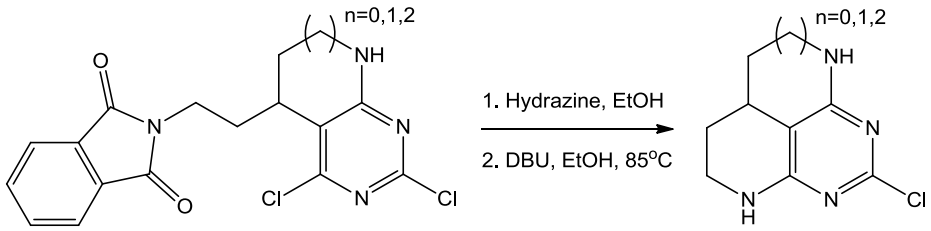
As shown in Scheme 5.72, the mesyl protected olefin **5-86** readily obtained by deprotonation and mesylation of the parent amine, undergoes radical addition to give product **5-87**. This compound is obtained as two separable diastereoisomers in a good yield. Treatment of these two diastereoisomers with stoichiometric amounts of lauroyl peroxide in the usual manner furnished the bicyclic compounds **5-88** in exactly the same yield.



Scheme 5.72 Preparation of the novel tricyclic compound **5-89**

Bicyclic product **5-88** was converted into intermediate **5-88-a** by removal of the Boc group with TFA, and induced to cyclize by exposure to a moderate base in ethanol to give the novel tricyclic compound **5-89**.

In the similar way, bicyclic products **5-34** and **5-42** could be transformed into the tricyclic compounds **5-91** and **5-92** by cleavage of the phthalimido group with hydrazine and treatment with base. Interestingly, the same seq.uence failed with compound **5-26**, presumably because of the strain introduced in to the structure **5-90** (Scheme 5.73).

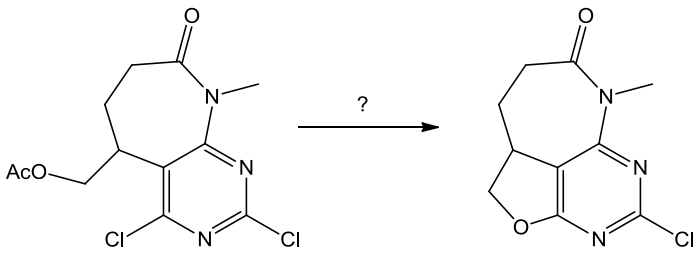


5-26 n = 0
5-34 n = 1
5-42 n = 2

5-90 n = 0, 0%
5-91 n = 1, 91%
5-92 n = 2, 75%

Scheme 5.73 Synthesis of novel tricyclic compounds

The presence of a larger seven-membered ring in compound **5-80** could allow the formation of a five-membered ring leading to the tricyclic structure in Scheme 5.74. This synthesis has not yet been attempted.



5-80

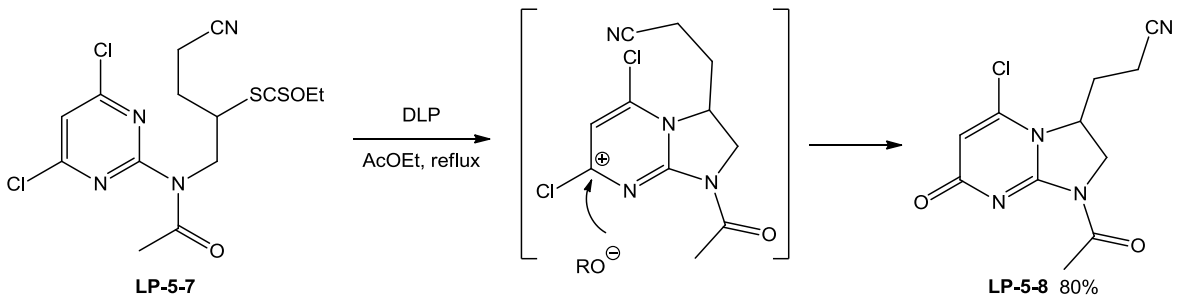
Scheme 5.74 Possible access to an oxygen-containing tricycle

It should be noted that all these tricycles, which may have some interest in medicinal chemistry or as ligands in organometallic processes, would not be easy to make by more traditional routes.

4. Synthesis of bicyclic aza-pyrimidones via C-N bond formation

a. Preliminary study in synthesizing tricyclic aza-pyrimidones

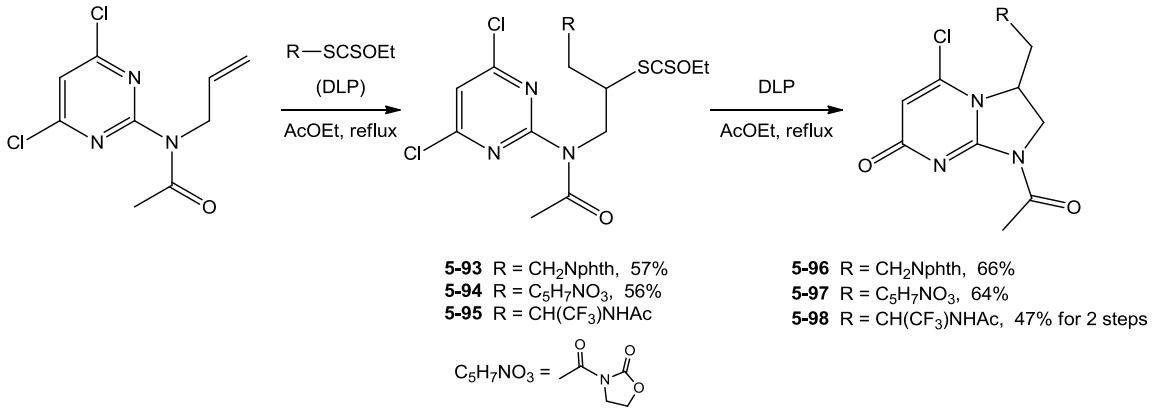
In parallel to investigating the "carbamate puzzle", we examined another series of radical cyclizations. As shown in Scheme 5.75, because of the symmetry, the radical derived from **LP-5-7** has no choice but to cyclize on either of the two heteroaromatic nitrogen to furnish pyrimidinone **LP-5-8**.



LP-5-7 **LP-5-8** 80%

Scheme 5.75 Related *N*-cyclization with regioisomeric precursor **LP-5-4**

Diversity was introduced by using different xanthate partners.[245] We repeated three of these reactions with the initial purpose of cyclizing the nucleophilic nitrogen terminus by substitution of the adjacent chlorine atom and then create tricyclic compounds (Scheme 5.76).



5-93 R = CH_2Nphth, 57%
5-94 R = $C_5H_7NO_3$, 56%
5-95 R = $CH(CF_3)NHAc$

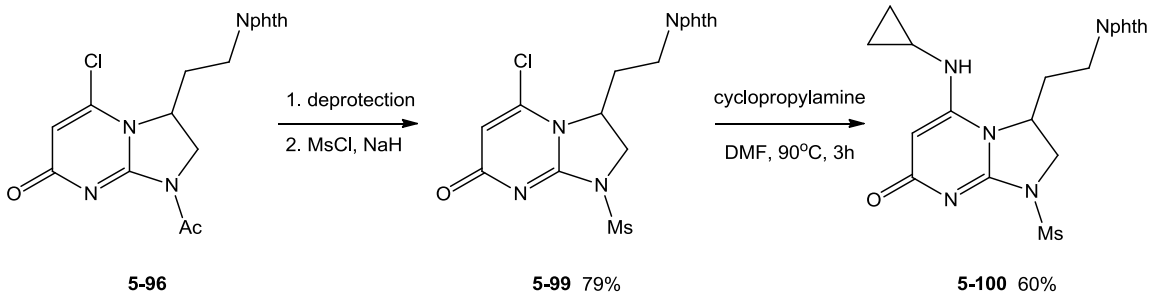
$C_5H_7NO_3$ =

5-96 R = CH_2Nphth, 66%
5-97 R = $C_5H_7NO_3$, 64%
5-98 R = $CH(CF_3)NHAc$, 47% for 2 steps

Scheme 5.76 Related *N*-cyclization with regioisomeric precursors

[245] (a) Laot, Y.; Petit, L.; Ngoc, D. M. T.; Zard, S. Z. *Aust. J. Chem.* **2011**, *64*, 416-425; (b) Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 3426-3429.

However, the original purpose for synthesizing the tricyclic compounds was not achieved, no matter the size of the third ring (six-membered ring for **5-96** and seven-membered ring for **5-97**). In order to investigate the reactivity of the chlorine, we decided to study the intramolecular substitution, by analogy with our previous experiments.



5-96 **5-99** 79% **5-100** 60%

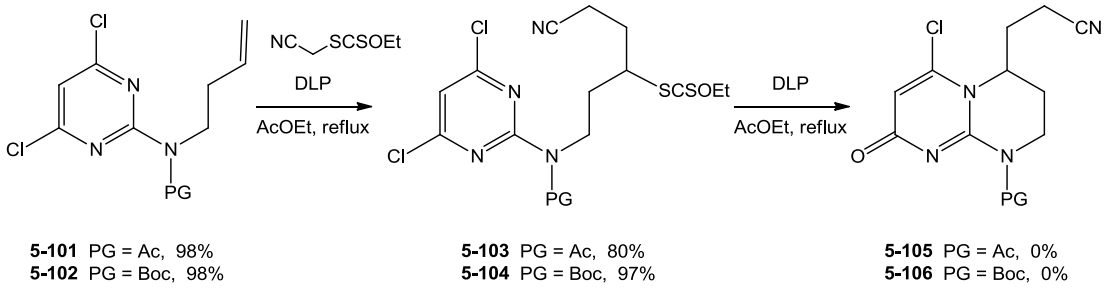
Scheme 5.77 Substitution of the chlorine in bicycle **5-96**

As illustrated in Scheme 5.77, substitution indeed readily proceeded with the mesyl protected substrate **5-99** by heating with cyclopropylamine in DMF. However, surprisingly, the liberated primary amine from the phthalimido group did not furnish the desired cyclized product under the same conditions. Again, this could be due to the strain inherent to the structure as in the case of compound **5-26** (Scheme 5.73).

Could we however start with a six-membered ring fused pyrimidone? The radical cyclization to the aromatic nitrogen to create a six-membered ring is a much more interesting and challenging problem and was therefore studied next.

b. Six-membered ring closure on heteroaromatic nitrogen

Starting from olefin **5-28'**, two olefinic precursors **5-101** and **5-102** were readily prepared following the common protection procedure. While the radical addition proceeded well as usual, the final ring closure step gave none of the desired cyclization to the heteroaromatic nitrogen (Scheme 5.78). For both of the two reactions, only prematurely reduced materials were identified from the complex reaction mixtures. Other compounds observed by TLC plate were not identified.



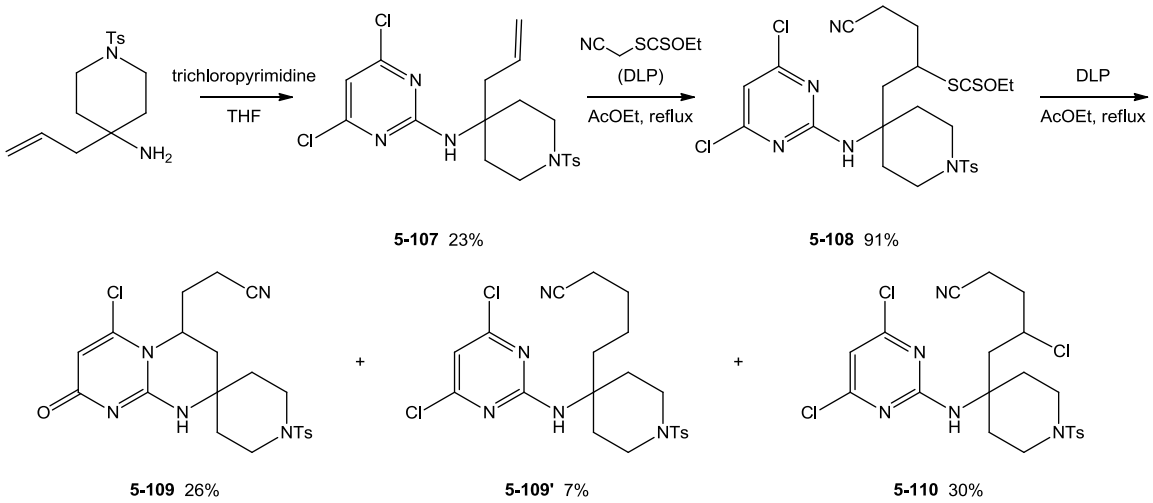
5-101 PG = Ac, 98%
5-102 PG = Boc, 98%

5-103 PG = Ac, 80%
5-104 PG = Boc, 97%

5-105 PG = Ac, 0%
5-106 PG = Boc, 0%

Scheme 5.78 Failed cyclizations on the nitrogen atom of pyrimidines

This failure reminded us of the difficulty inherent in such a process. However, during the previous study, the side-chain substituent proved to be useful in promoting the radical cyclization. As the regioisomer **5-107** of **5-69** was already in hand, we converted it into adduct **5-108** and tested again the cyclization on the nitrogen. Surprisingly, this time we obtained the desired spiro derivative **5-109,** together with the prematurely reduced material **5-109"**, and a chloro-substituted compound **5-110**.



5-107 23%

5-108 91%

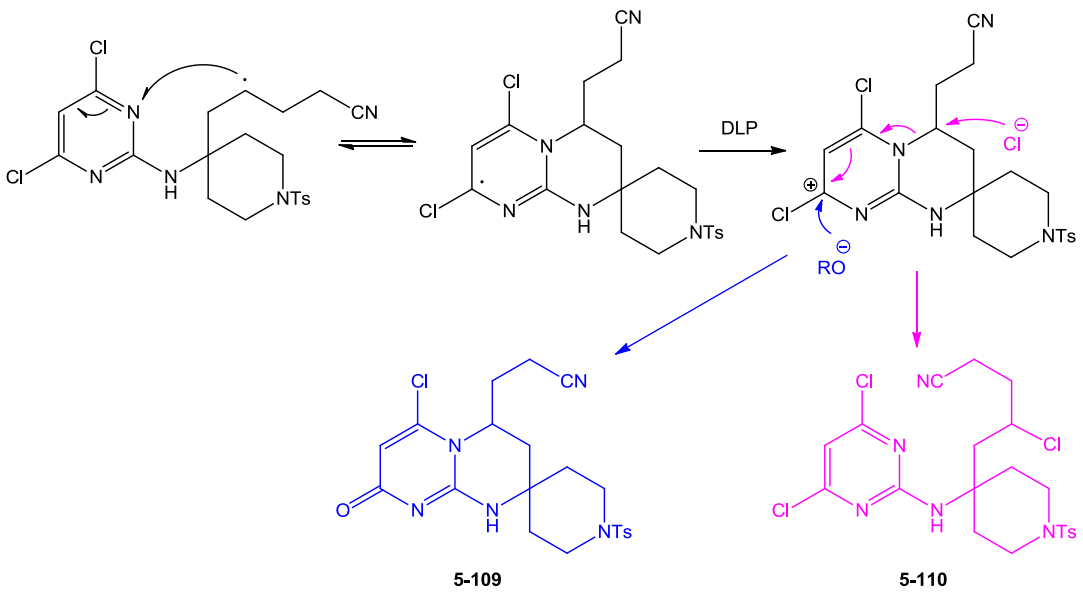
5-109 26%

5-109' 7%

5-110 30%

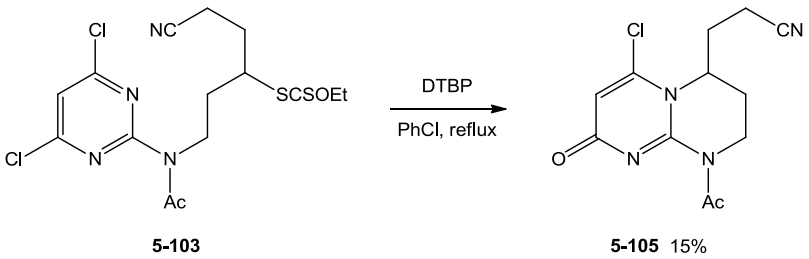
Scheme 5.79 *N*-Cyclization on the nitrogen of pyrimidines

Chloride **5-110** is possibly derived through substitution by the chlorine anion on the cyclized intermediate, as shown in Scheme 5.80. Since its spot on the TLC plate is very close to that of the prematurely reduced material, it is easily overlooked in a complex reaction mixture. It is worth mentioning that we found that tricyclic structures like **5-109** are readily identified as strong clear yellow spots on the TLC plate when revealed with hot acidic vanillin solution. This observation simplified our subseq.uent study.



Scheme 5.80 Related *N*-cyclization with regioisomeric precursors

The formation of chloro compound **5-110** is quite important, since it helps to explain some of the previous unclear results, such as the variable cyclization yields. With the knowledge that the chlorine anion is detrimental to this radical process, we attempted to remove it from the reaction medium. We first employed high temperature (refluxing chlorobenzene) and a different initiator/oxidant (DTBP).

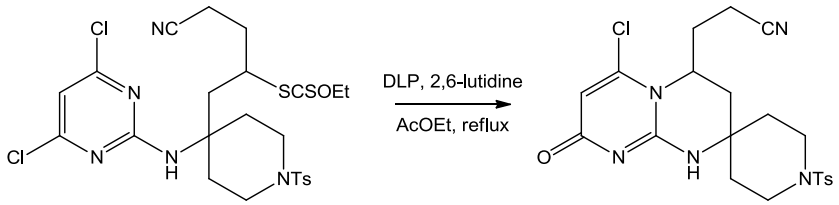


Scheme 5.81 Radical cyclization of **5-103** in a high boiling solvent

We were pleased to find that, even without the spiro substitution, the radical cyclization could happen to some extent when the problematic chlorine anion was removed (Scheme 5.81).

Camphorsulfonic acid and 2,6-lutidine were also used as adjuvants. Addition of a solid acid was supposed to facilitate the evaporation of HCl and activate the pyrimidine ring through protonation. However, no significant cyclization was observed under these

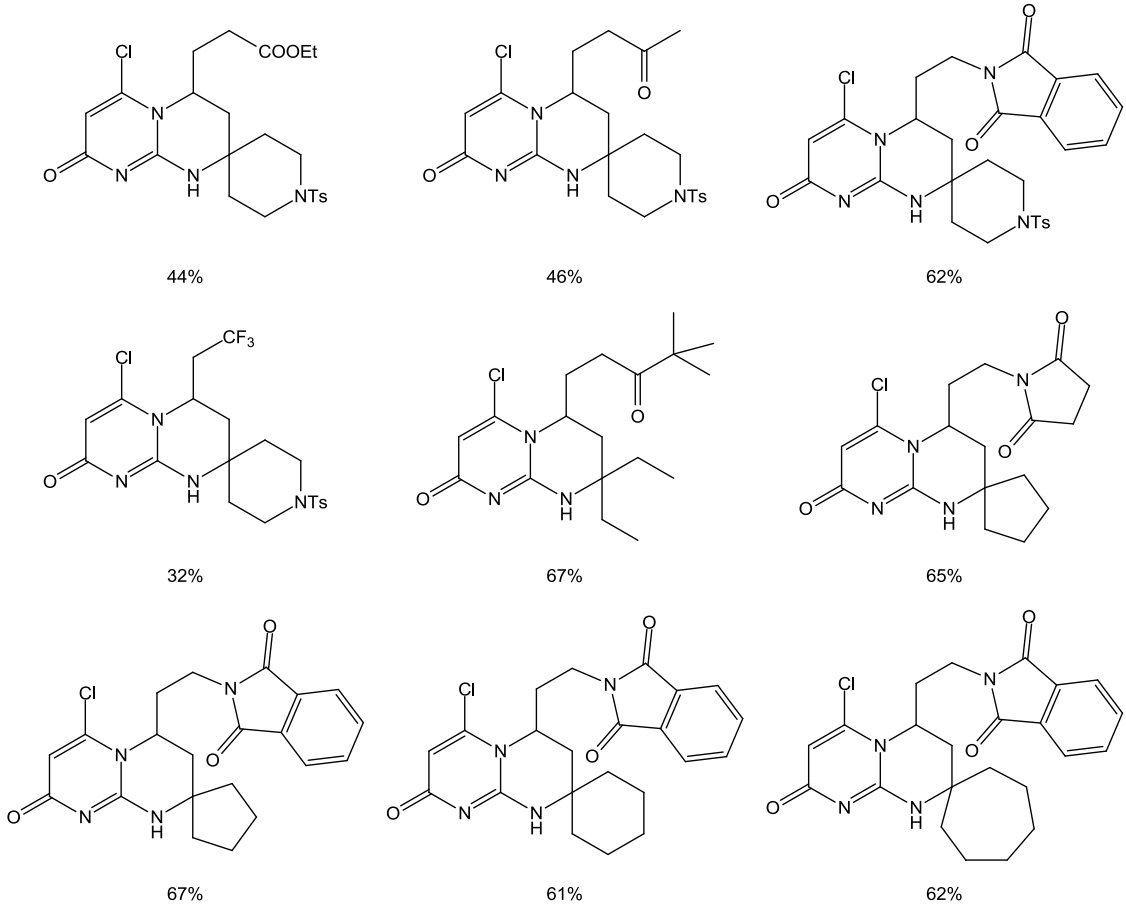
conditions. In contrast, addition of 2,6-lutidine as a non-nucleophilic HCl scavenger proved more promising, as indicated by the transformations displayed in Scheme 5.82.



5-108 **5-109** 53%

Scheme 5.82 Radical cyclization of **5-108** with 2,6-lutidine as HCl scavenger

Same conditions for the cyclization were then applied to prepare a number of six-membered ring fused pyrimidones with various functional groups[246] (Scheme 5.83).



Scheme 5.83 Preparation of six-membered ring fused pyrimidones

[246] These results are taken from the work of Mr. Ling QIN, who has pursued this study.

Conclusion

In summary, compounds containing a pyrimidine nucleus fused to a saturated *N*-containing ring were prepared in modest to good yield starting from 2,4,6-trichloropyrimidine. Various new tricyclic compounds were also constructed by S_NAr reactions of a nucleophilic terminus and displacement of the chlorine of the pyrimidine ring. Diversity could be introduced by modifying the starting xanthate or by further transformation of the functional groups present in the xanthate component, or by exploiting the presence of the chlorine atom in the final products. The resulting polycyclic aza-pyrimidines could serve as novel templates for potential drug discovery programs.

In the course of this study, we have also investigated the uncommon regioselectivity caused by the protecting group on the extranuclear nitrogen. This unusual phenomenon has confused us for quite a while. We hope this work will contribute to a satisfactory solution of this puzzle in the future.

Finally, we have discovered an unprecedented radical cyclization to heteroaromatic nitrogen to form a six-membered ring. This again opens the way to numerous novel nitrogen heterocycles.

Experimental Part

General Experimental Methods

Anhydrous solvents were obtained by distillation under nitrogen, and from the solvent drying columns. Other solvents were used as supplied by commercial sources. Petroleum ether refers to the fraction of light petroleum ether, boiling between 40-60°C.

Purification procedures were in accordance with the instructions in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Fourth Edition, The Bath Press, Bath, 2002. All reactions were carried out under dry, oxygen free nitrogen.

Recrystallization was performed following the procedure of dissolving the impure substance in hot ethyl acetate with the minimum volume, cooling down the hot solution by adding cold petroleum ether which causing the dissolved substance to crystallise out, then separating the crystals from the supernatant solution.

Flash chromatography was performed on silica gel (SDS, 60 Å C. C. 40-63 μm) as the stationary phase. Thin Layer Chromatography (TLC) was performed on alumina plates pre-coated with silica gel (Merck silica gel, 60 F_{254}), which were visualized by the quenching of UV fluorescence (λ_{max} = 254 nm and/or 366 nm) and/or by staining with anisaldehyde in acidic ethanol and/or $KMnO_4$ in basic water followed by heating.

Melting points were recorded by heating on Reichert plates under a microscope and are uncorrected. For the substances whose melting points were higher than 230°C, they were recorded by Automatic Melting Point Apparatus Model SMP40.

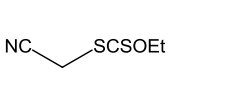
Infrared spectra were recorded as solutions in CCl_4 or $CDCl_3$ using CaF_2 cells or as solids in Nujol using KBr cells, on a Perkin-Elmer FT 1600. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported.

Nuclear magnetic resonance spectra were recorded at ambient temperature on a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz and coupling constants (*J*) are reported to ± 0.5 Hz. The following

abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100.6 MHz. Chemical shifts (δ_H, δ_C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: δ_H = 7.26 and δ_C = 77.0 ; DMSO: δ_H = 2.50 and δ_C = 39.43 ; Acetone-d6: δ_H = 2.05 and δ_C = 30.83 ; CD_3OD: δ_H = 3.31 and δ_C = 49.05).

High-resolution mass spectra were recorded by positive electron impact ionization (EI+) at 70 eV on a JEOL JMS-GCmate II mass spectrometer. The quoted masses are accurate to ± 4 ppm.

Xanthates cited in the work



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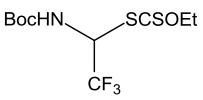

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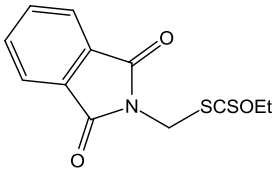

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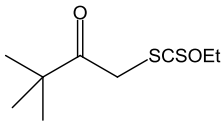

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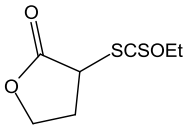

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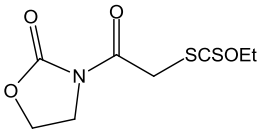

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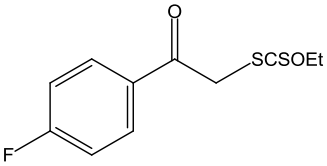

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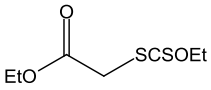

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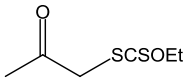

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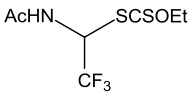

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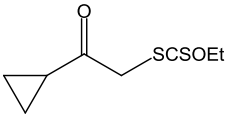

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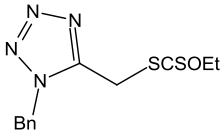
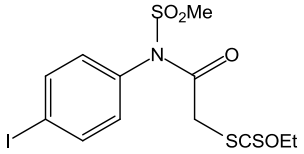


Xa-m

Molecules cited in the experimental part

Molecules of chapter 3



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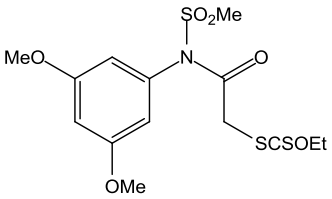

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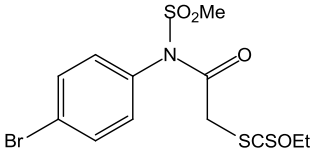

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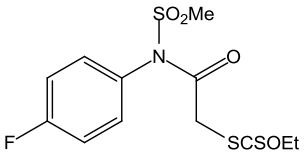

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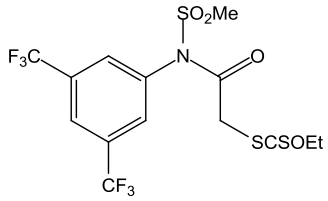

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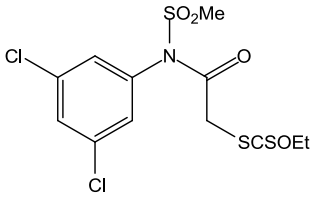

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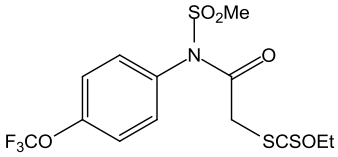

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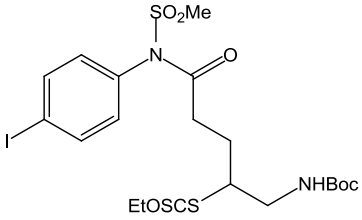

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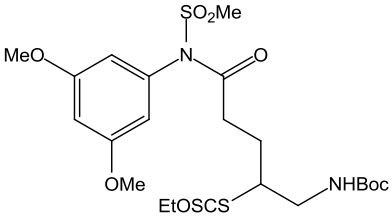

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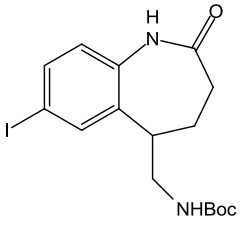

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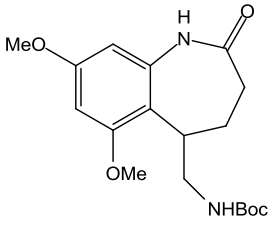

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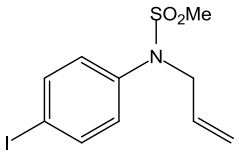

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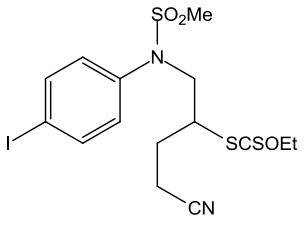

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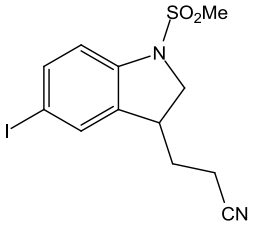

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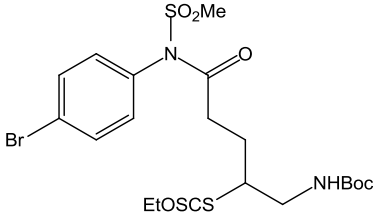

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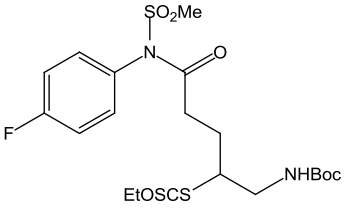

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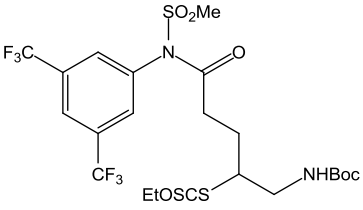

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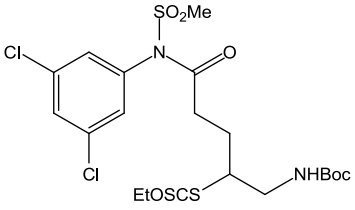

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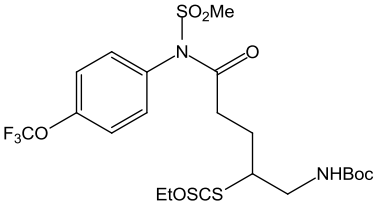

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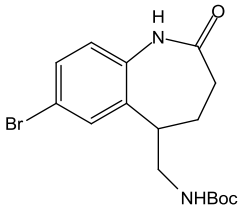

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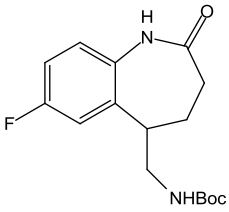

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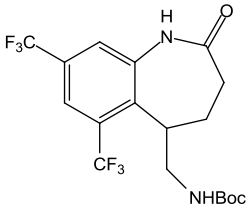

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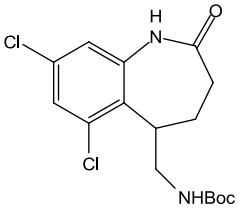

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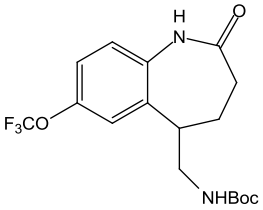

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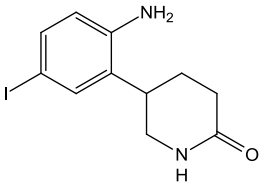

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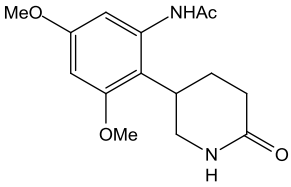

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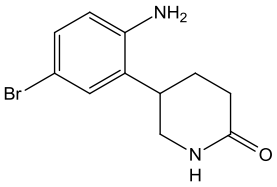

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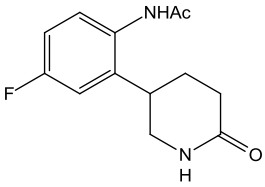

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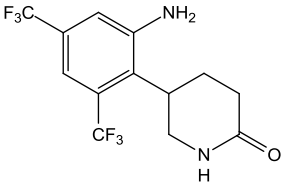

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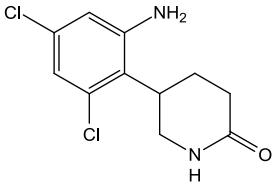

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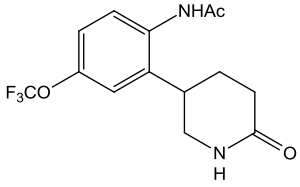

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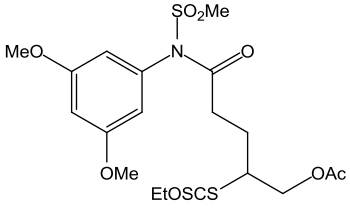

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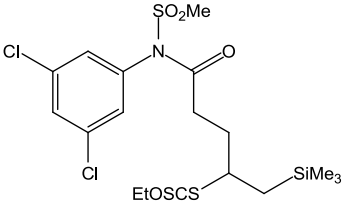

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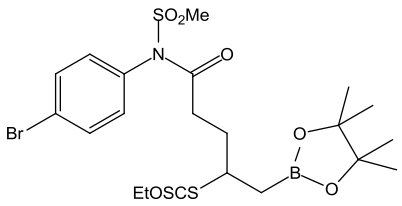

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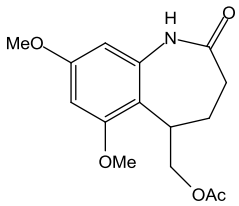

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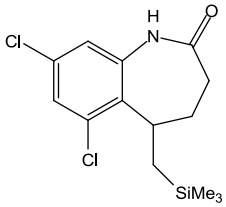

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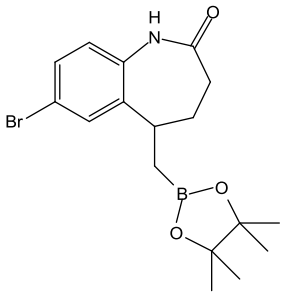

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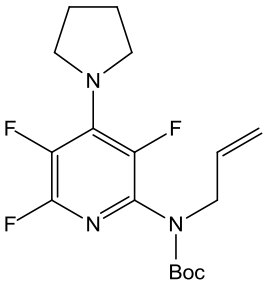
Molecules of chapter 4



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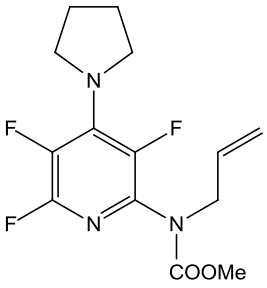

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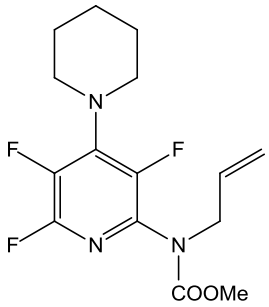

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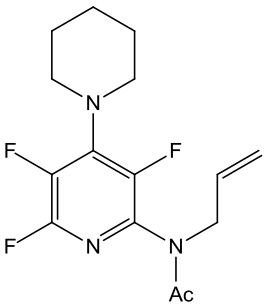

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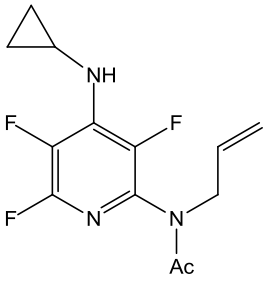

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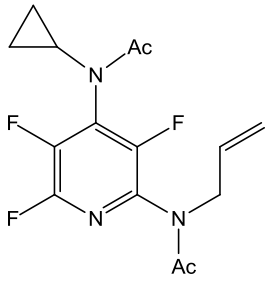

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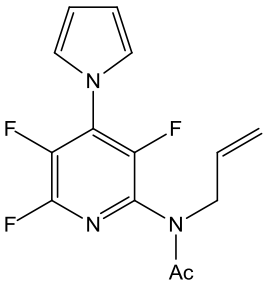

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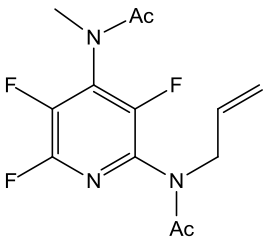

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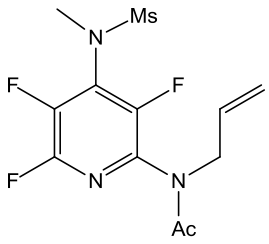

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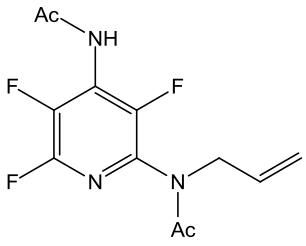

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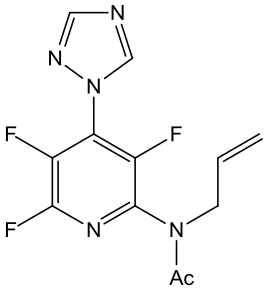

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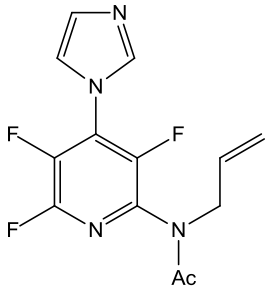

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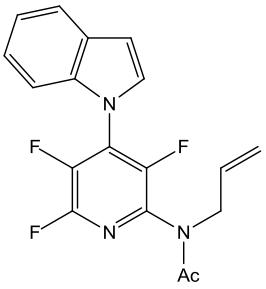

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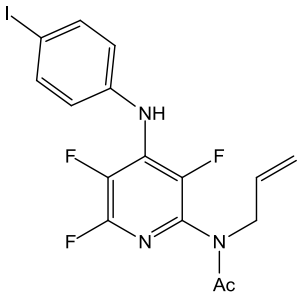

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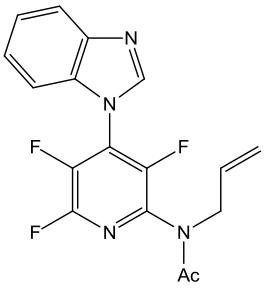

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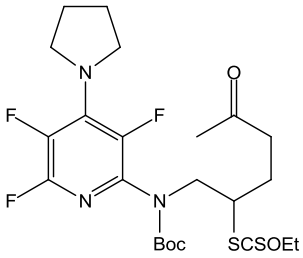

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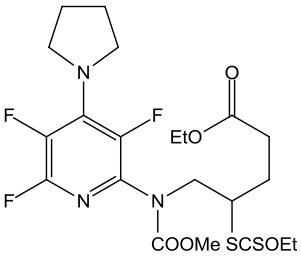

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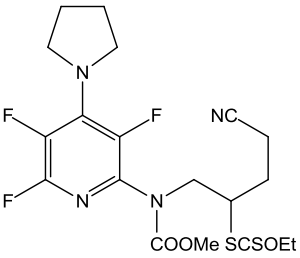

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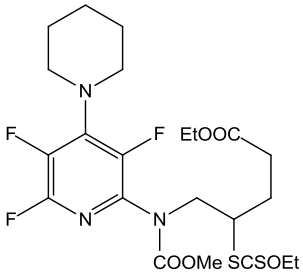

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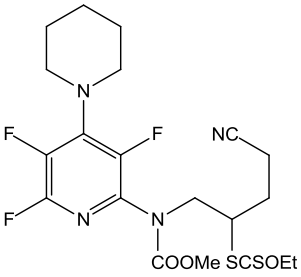

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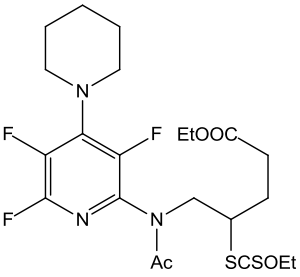

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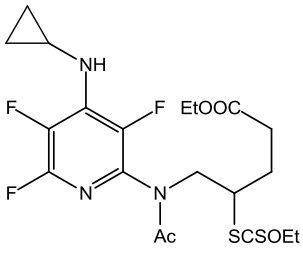

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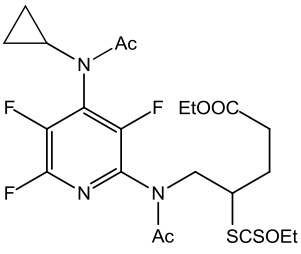

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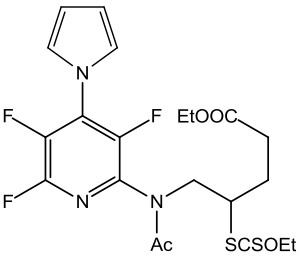

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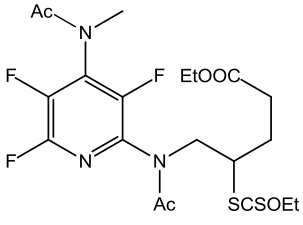

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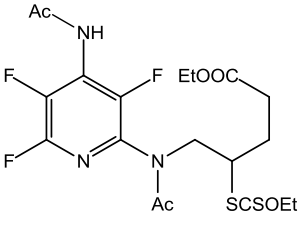

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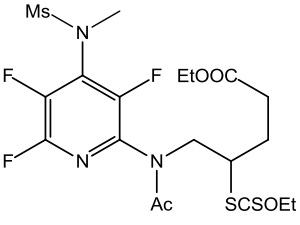

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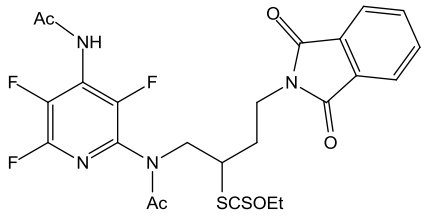

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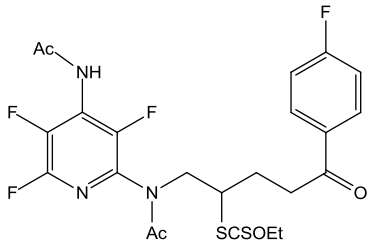

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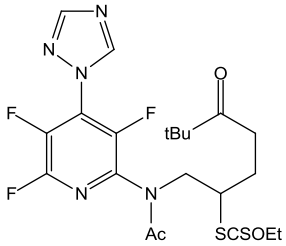

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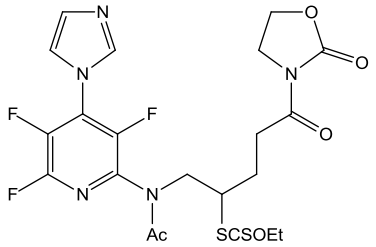

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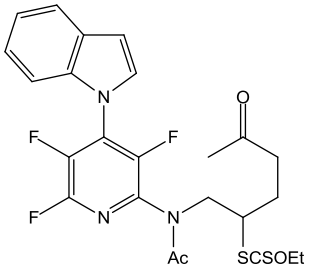

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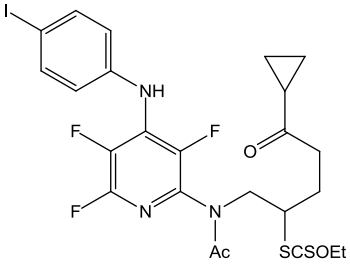

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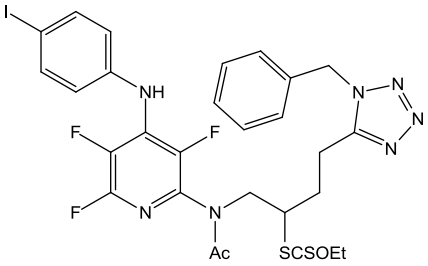

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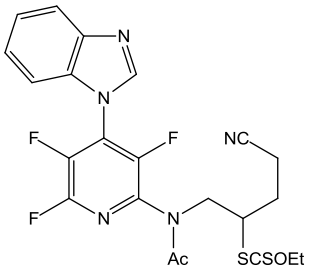

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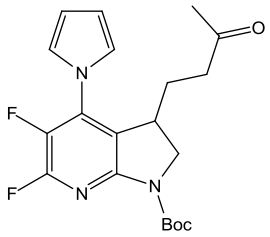

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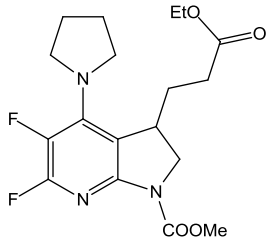

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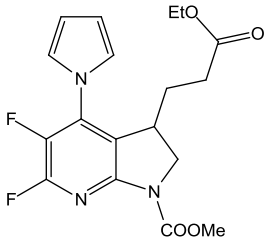

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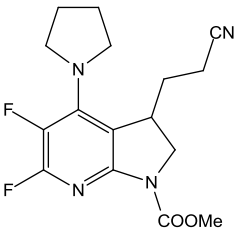

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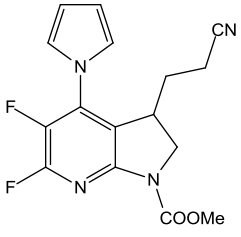

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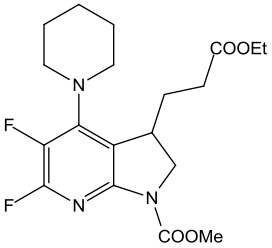

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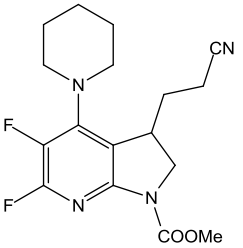

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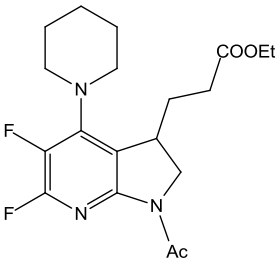

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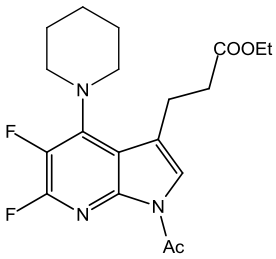

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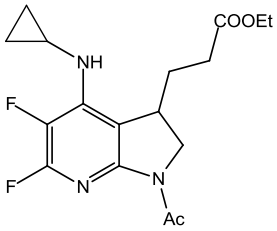

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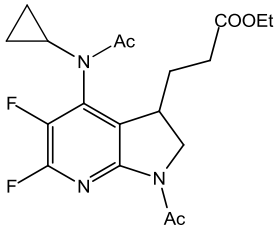

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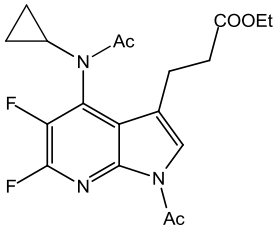

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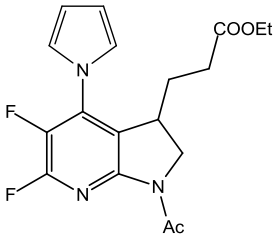

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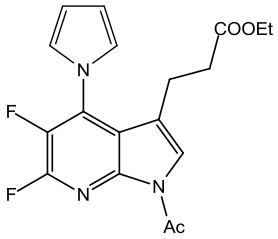

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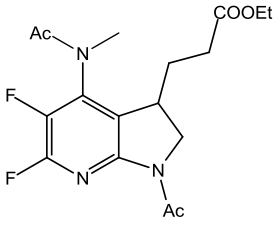

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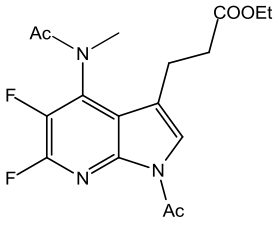

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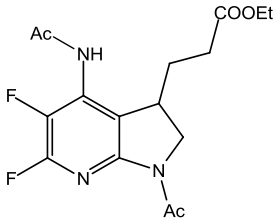

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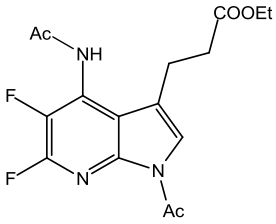

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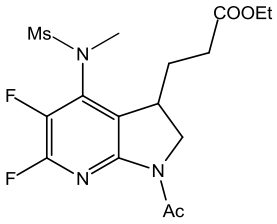

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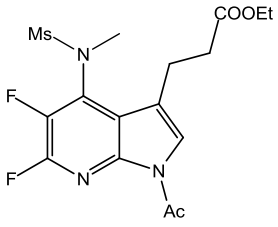

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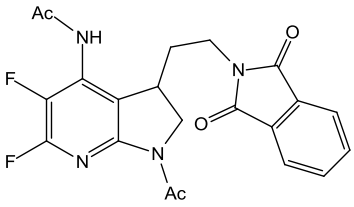

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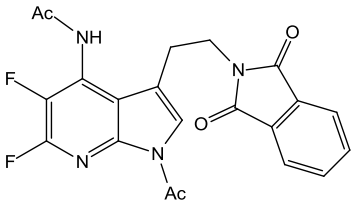

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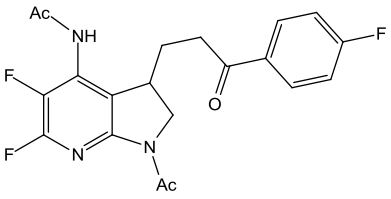

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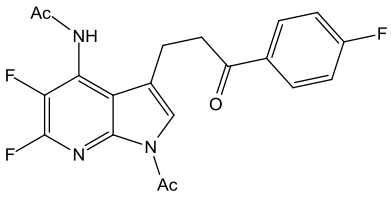

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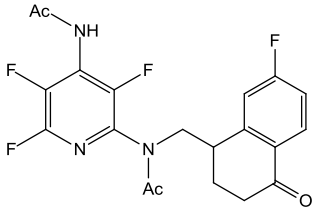

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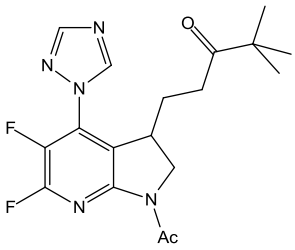

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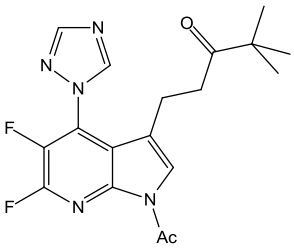

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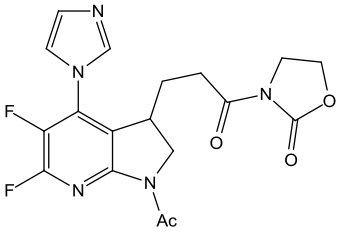

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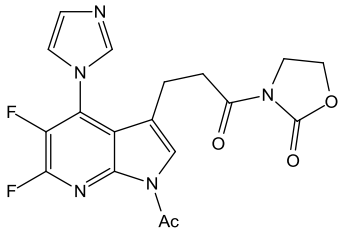

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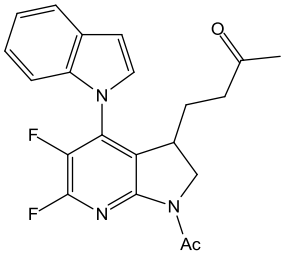

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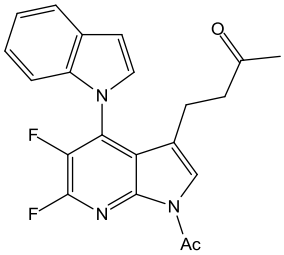

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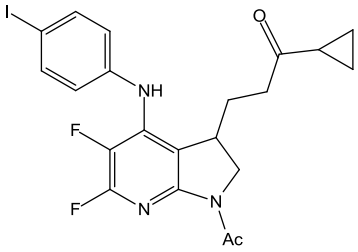

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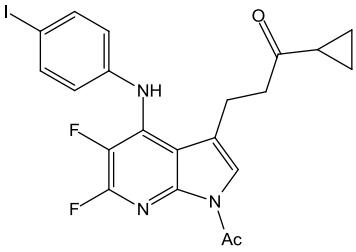

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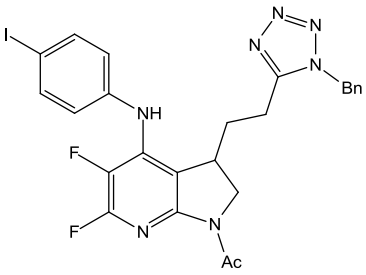

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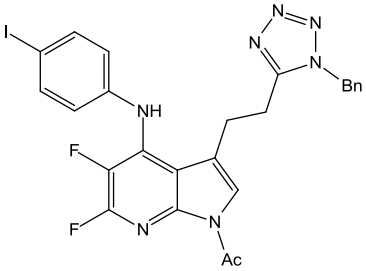

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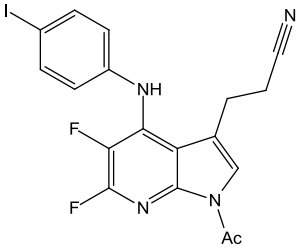

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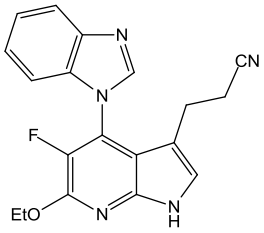

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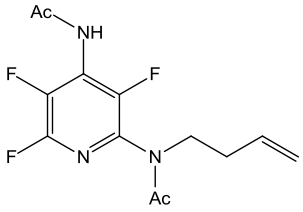

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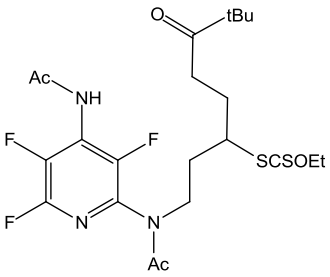

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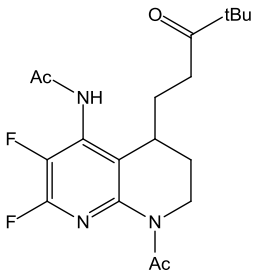

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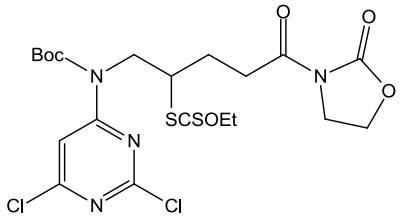

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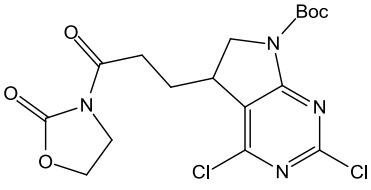

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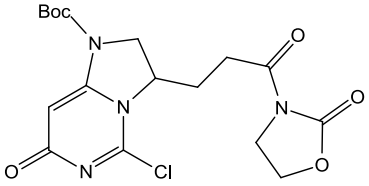

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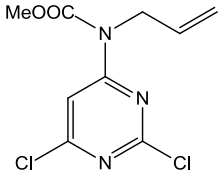

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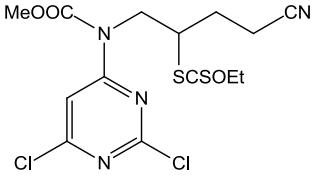

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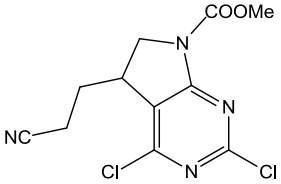

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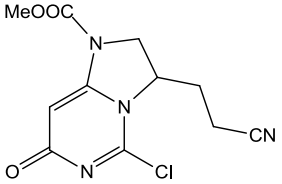

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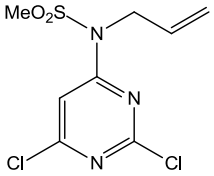

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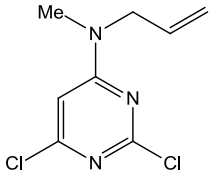

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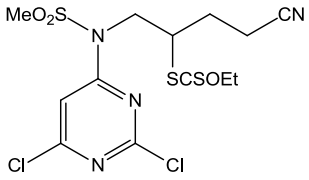

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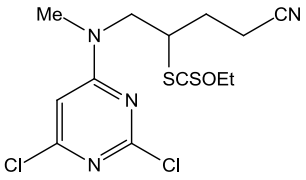

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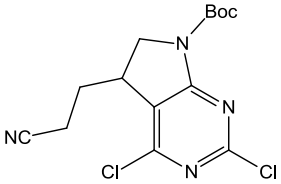

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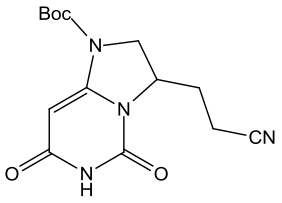

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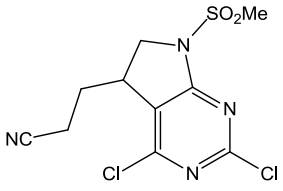

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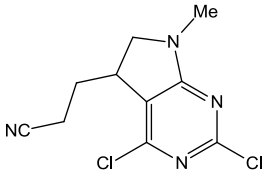

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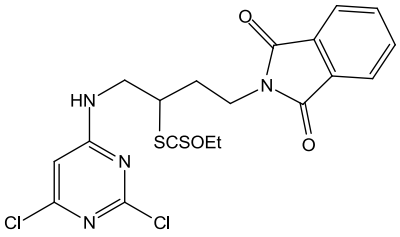

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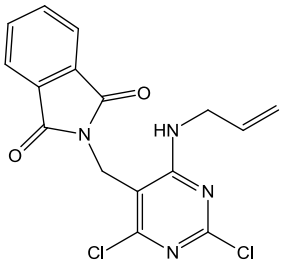

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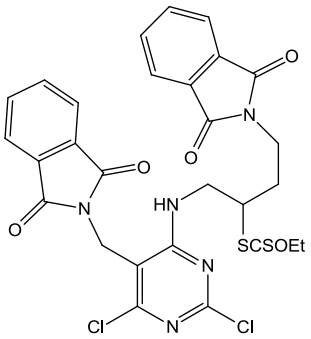

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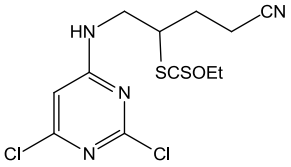

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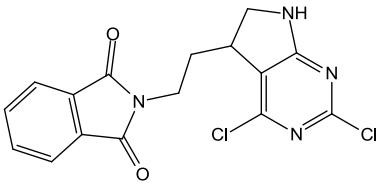

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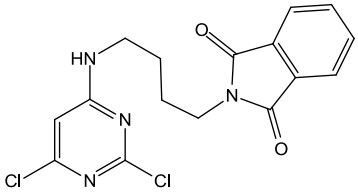

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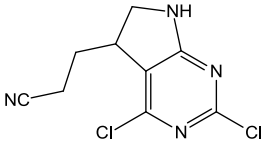

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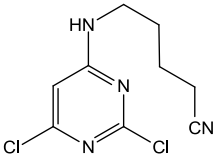

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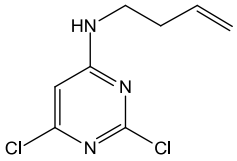

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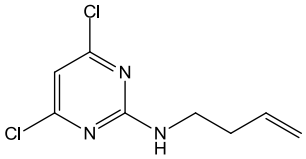

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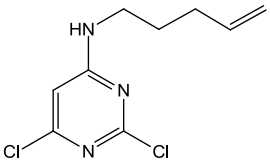

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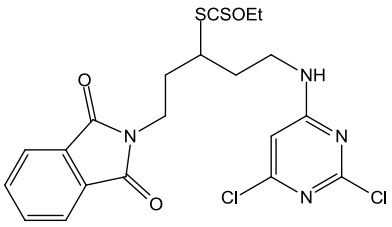

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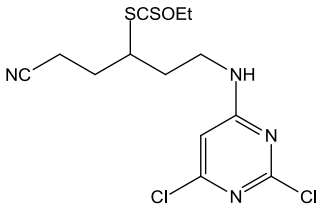

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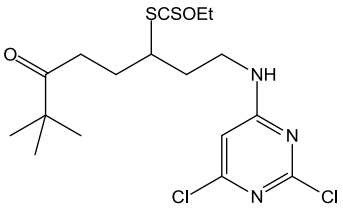

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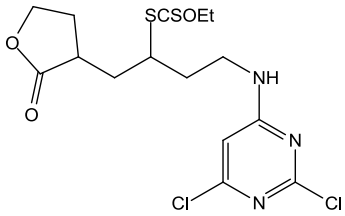

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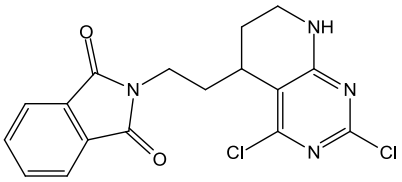

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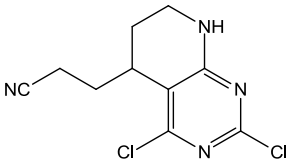

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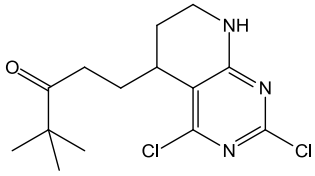

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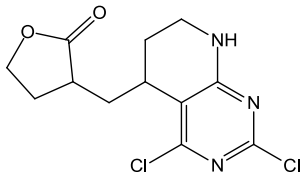

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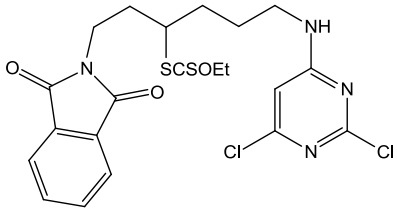

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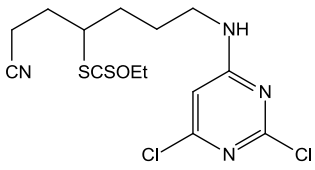

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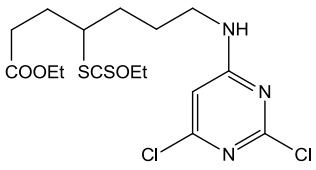

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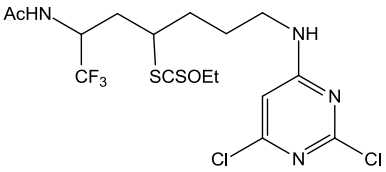

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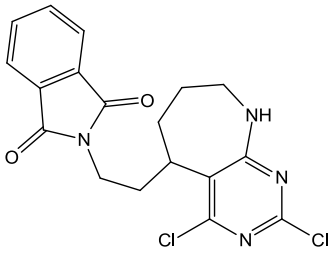

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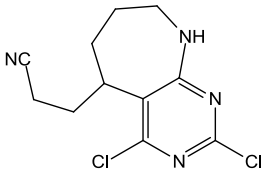

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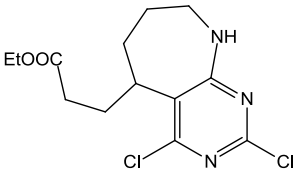

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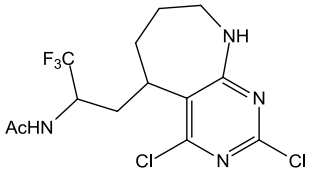

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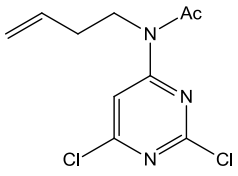

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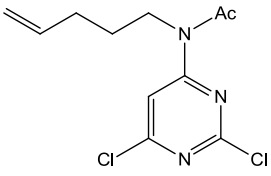

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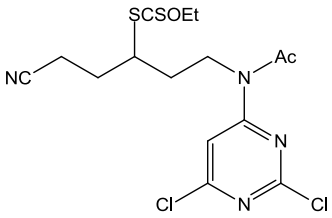

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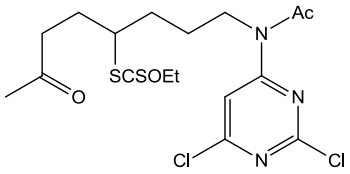

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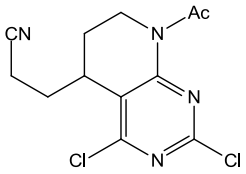

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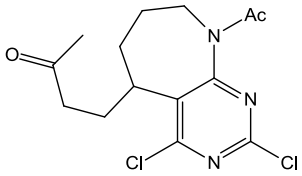

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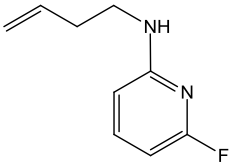

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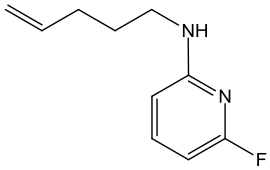

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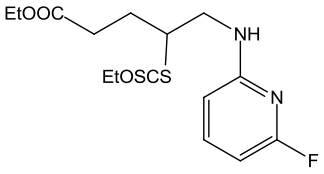

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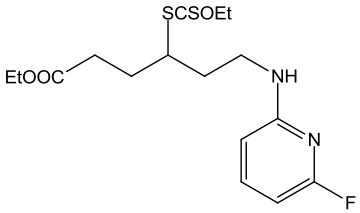

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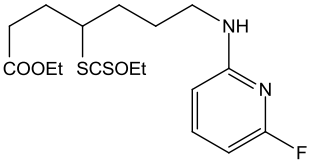

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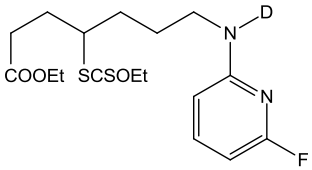

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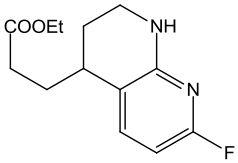

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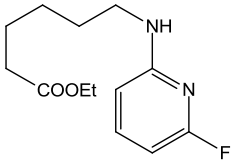

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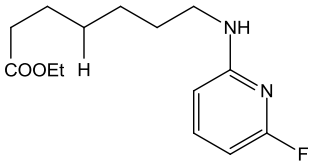

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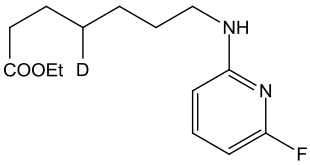

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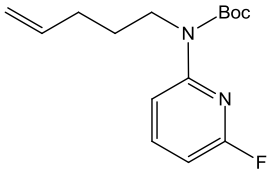

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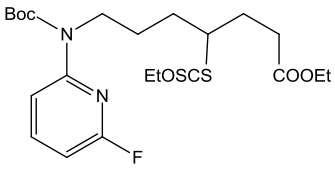

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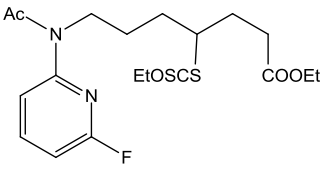

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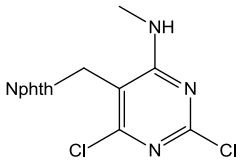

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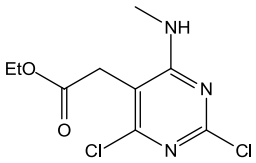

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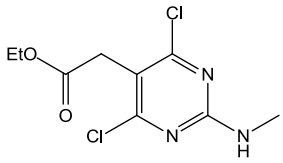

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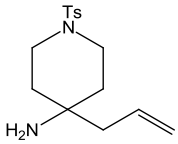

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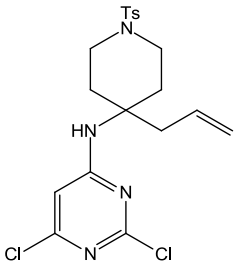

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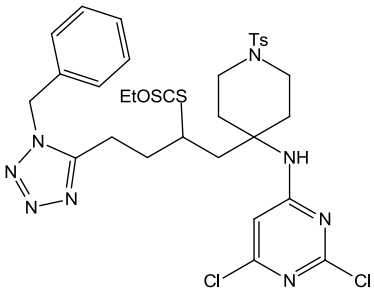

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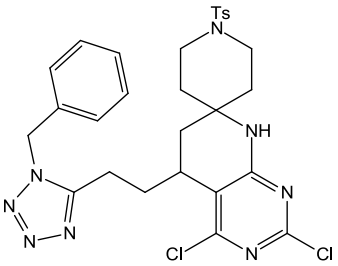

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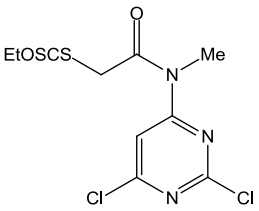

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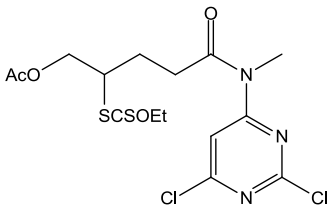

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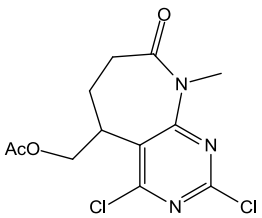

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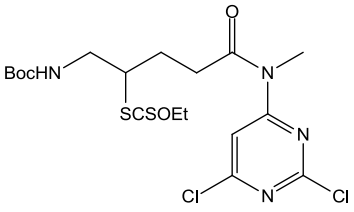

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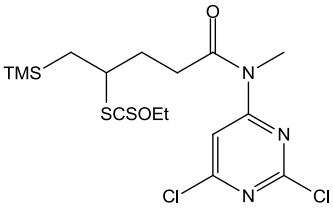

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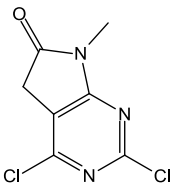

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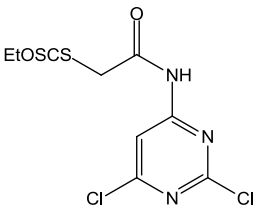

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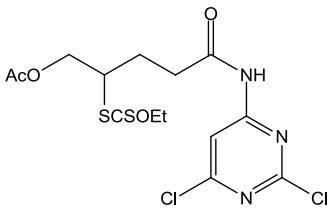

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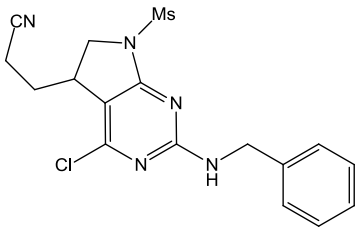

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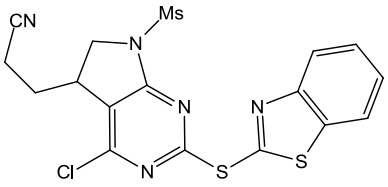

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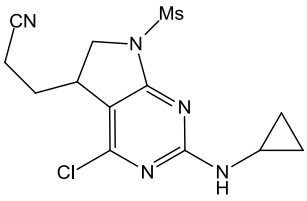

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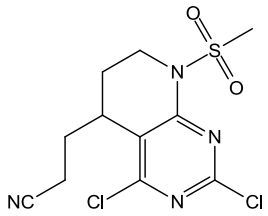

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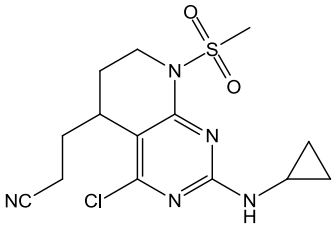

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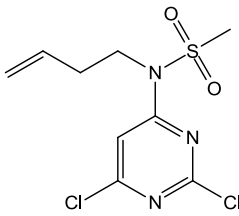

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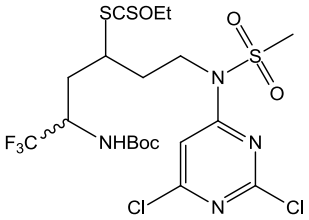

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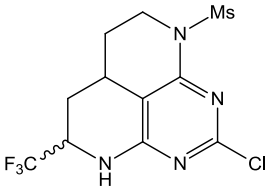

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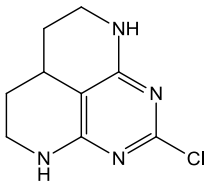

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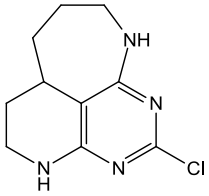

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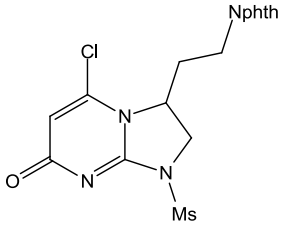

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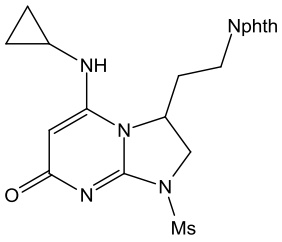

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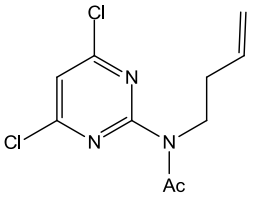

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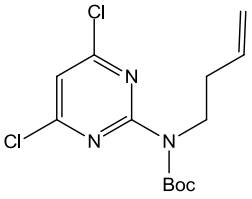

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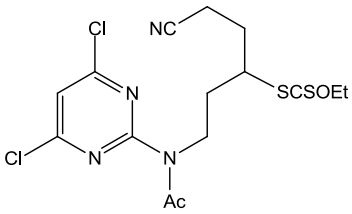

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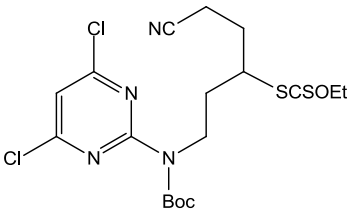

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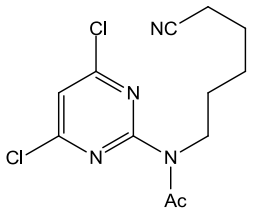

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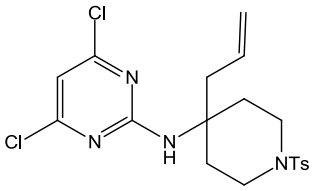

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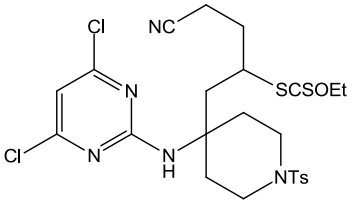

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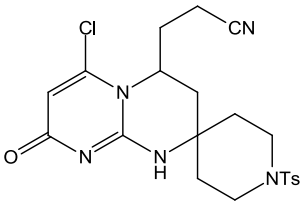

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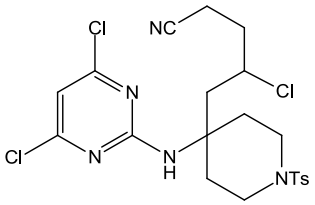

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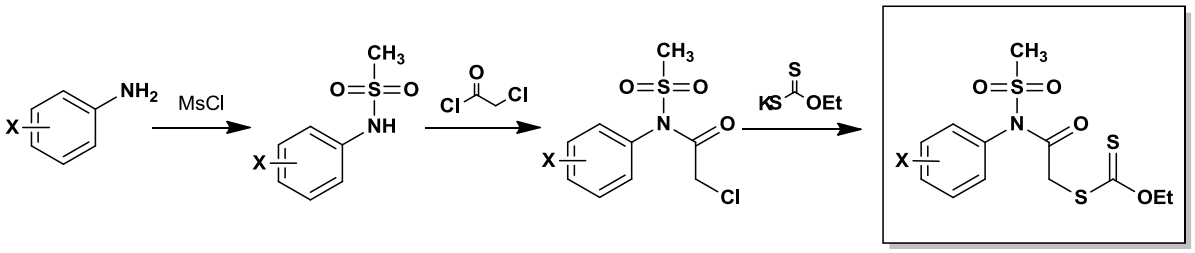
Chapter 3

General procedure 3-I for preparing the xanthates of 3-1 to 3-7

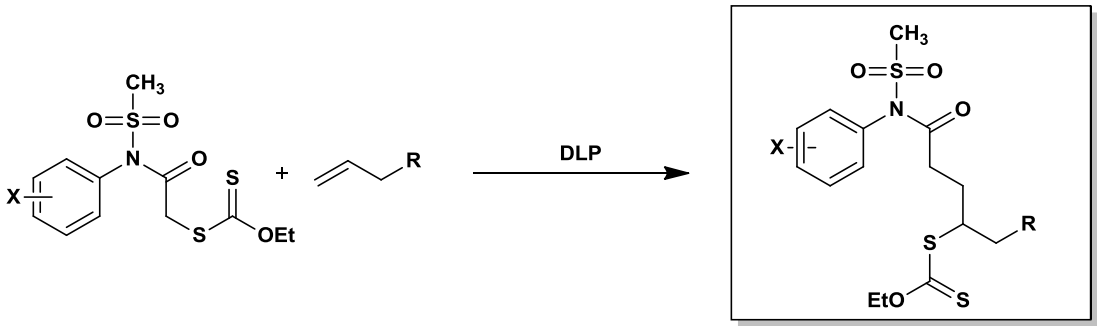


A magnetically stirred solution of substituted aniline (1 eq.) in distillated 1,2-dichloroethane (1.2-1.6M of corresponding aniline) was cooled to 0°C. Methanesulfonyl-chloride (1.1 eq.) was then added prior to a dropwise addition of pyridine (1.1-2.2 eq.). The mixture was warmed to room temperature and stirred for 2-3 hours. Then normal 1,2-dichloroethane was added and the organic phase was washed once with solution of 2N hydrochloric acid, twice with a saturated solution of sodium hydrogenocarbonate, twice with water, and once with brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The crude product was recrystallized by AcOEt / EP to yield the desired protected anilines.

Then to a magnetically stirred solution of the protected aniline (1 eq.) in dry DMF (0.4-0.6M of the protected aniline) under nitrogen in an ice bain, was added sodium hydride (60% in mineral oil, 1.2 eq.) little by little. The resulting mixture was warmed to room temperature for about 10-20min. Chloroacetylchloride (1.5 eq.) was then added and the solution was stirred for 2-3 hours. Ethyl acetate was added and the solution was washed with water 3 times and once with brine. The organic phase was dried over anhydrous magnesium sulfate and filtered. Then the solvent was removed under reduced pressure. The crude product was recrystallized with AcOEt or AcOEt / EP to yield the desired halogenides.

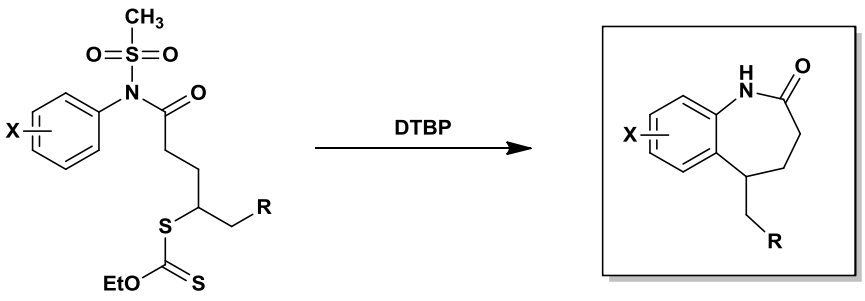
Then to a magnetically stirred solution of the halogenide (1 eq.) in acetone (0.2-0.4M of halogenide) under nitrogen at room temperature, was added potassium *O*-ethylxanthogenate (1.1 eq.). The resulting mixture was stirred at room temperature for 2-3 hour. The solvent was then removed under reduce pressure and the residue was dissolved in AcOEt. The organic phase was washed by water and brine, dried over anhydrous magnesium sulfate and filtered. Then the solvent was removed under reduced pressure. The crude product was recrystallized with AcOEt / EP or purified by flash chromatography on silica gel to yield the desired xanthates **3-1** to **3-7**.

General procedure 3-II for the radical addition to olefin



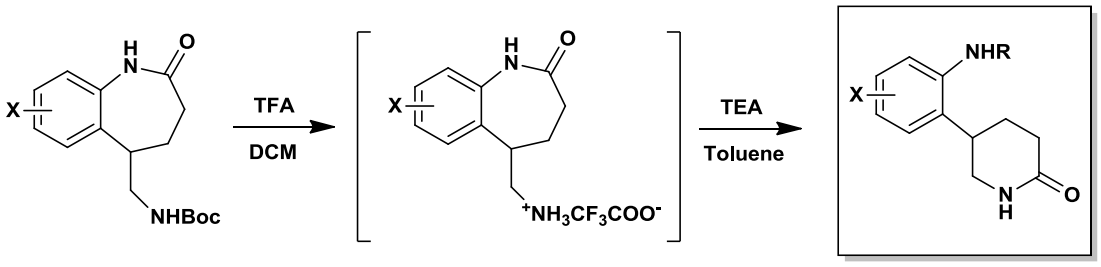
A magnetically stirred solution of the corresponding xanthates (1 eq.) and the desired olefin (1.5-2 eq.) in AcOEt (0.7-1.0M of xanthate) was refluxed for about 15-30min under nitrogen. Lauroyl peroxide (DLP) (5%mol) was then added to the refluxing solution, followed by additional portions (5%mol) every 60min until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

General procedure 3-III for the radical cyclization using DTBP



A magnetically stirred solution of the corresponding addition products from xanthates (1 eq.) in chlorobenzene (0.02M of xanthate) together with 2,6-lutidine (1 eq.) were refluxed for about 15min under nitrogen. Di-*tert*-butylperoxide (DTBP) (5 eq.) was then added to the refluxing solution. The reaction was monitored by TLC every hour until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

General procedure 3-IV for the preparation of piperidin-2-ones

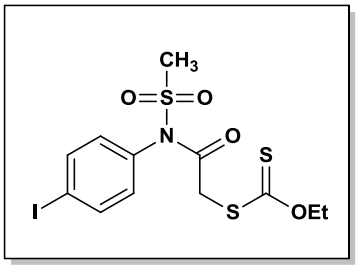


To a round-bottomed flask which contained the corresponding *N*-Boc protected bicycles (1 eq.) was added trifluoroacetic acid (TFA) (8 eq.), in the form of a solution of 30% TFA in DCM. The mixture was stirring at room temperature under nitrogen for about 1 hour to complete the reaction. Then the solvent was removed under reduced pressure and to the residue was added directly toluene (0.05M of the starting material) and triethylamine (TEA)

(12 eq.). The resulting mixture was stirred at 70~90°C for about 1~2 hours to complete the reaction. Then for the products of **3-10**, **3-20**, **3-22** and **3-23**, the precipitation was separated by centrifuge and washed by cold acetone to yield the desired compounds **3-25**, **3-27**, **3-29** and **3-30**.

For the series of **3-11**, **3-21**, and **3-24**, acetic anhydride (Ac_2O) (8 eq.) was added directly and the mixture was kept stirring at ~90°C for about 30 minutes to complete the reaction. Then the precipitation was seperated by centrifuge, and washed by cold AcOEt to yield the desired compounds **3-26**, **3-28**, and **3-31**.

Dithiocarbonic acid S-{2-[(4-iodo-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-1)

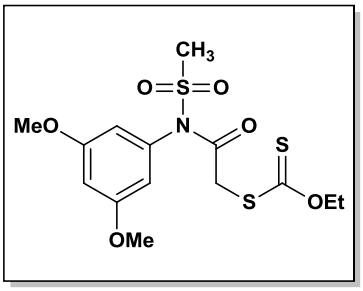


Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 4-iodoaniline (3.24g, 14.8mmol) in distillated 1,2-dichloroethane (10ml, 1.5M), methanesulfonylchloride (1.3mL, 16.3mmol) and pyridine (1.3ml, 16.3mmol). Recrystallization with AcOEt / EP afforded the protected 4-iodoaniline (3.93 g, 89%) as a light violet solid. Then the chloroacetylation was carried out with the solution of the above solid (2.96g, 9.96mmol) in dry DMF (26.5ml, 0.4M), chloroacetylchloride (1.19mL, 14.9mmol) and sodium hydride (60% in mineral oil, 478mg, 12.0mmol). Recrystallization with AcOEt / EP afforded the halogenide (3.06g, 51%) as a white solid. Then the reaction was carried out with the solution of the halogenide (1.04g, 2.77mmol) in acetone (10.5ml, 0.3M) and potassium *O*-ethylxanthogenate (0.49g, 3.05mmol).

Flash chromatography on silica gel with CH_2Cl_2 / EP / AcOEt / = 70 / 25 / 5 afforded **3-1** (1.05g, 82%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.87 (d, 2H, J=8.1Hz, I-C-C*H*), 7.18 (d, 2H, J=8.0Hz, CN-C*H*), 4.62 (q, 2H, J=7.1Hz, C*H*$_2$CH$_3$), 3.76 (s, 2H, CO-C*H*$_2$), 3.47 (s, 3H, SO_2-C*H*$_3$), 1.41 (t, 3H, J=7.1Hz, CH_2C*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 167.2 (O=*C*), 139.5 (s, 2 I-C-*C*), 134.4 (s, N-*C*), 131.7 (s, 2 N-C-*C*), 96.9 (s, I-*C*), 71.3 (*C*H$_2$CH$_3$), 42.2 (S-*C*), 41.3 (CO-*C*), 13.7 (CH_2*C*H$_3$)
IR (ν, cm^{-1}, $CDCl_3$) 2985, 2937, 1725, 1479, 1365, 1300, 1239, 1155, 1113, 1050
HRMS (EI+) Calcd. for $C_{12}H_{14}INO_4S_3$: 458.9130 Found : 458.9146

Dithiocarbonic acid S-{2-[(3,5-dimethoxy-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-2)



Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 3,5-dimethoxyaniline (3.80g, 24.8mmol) in distillated 1,2-dichloroethane (20ml, 1.2M), methanesulfonylchloride (2.1mL, 27.3mmol) and pyridine (4.4ml, 54.5mmol). Recrystallization with AcOEt / EP afforded the protected 3,5-dimethoxyaniline (5.23 g, 91%) as a grey solid. Then the chloroacetylation was carried out with the solution of the above solid (2.86g, 12.4mmol) in dry DMF (29ml, 0.4M), chloroacetylchloride (1.82mL, 22.9mmol) and sodium hydride (60% in mineral oil, 713mg, 17.8mmol). Recrystallization with AcOEt afforded the halogenide (2.74g, 72%) as a white

solid. Then the reaction was carried out with the solution of the halogenide (1.63g, 5.28mmol) in acetone (23ml, 0.2M) and potassium *O*-ethylxanthogenate (0.951g, 5.9mmol). Recrystallization with AcOEt / EP afforded **3-2** (1.78g, 86%) as a pale pink solid.

m.p. : 131-134°C

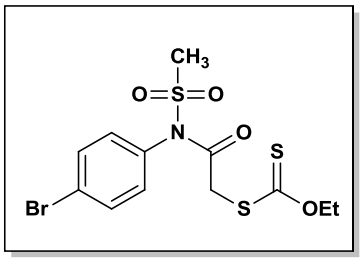
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.62 (m, 3H, aromatic H), 4.67 (q, 2H, J=7.1Hz, C*H*$_2$CH$_3$), 3.90 (s, 2H, CO-C*H*$_2$), 3.88 (s, 6H, 2 OC*H*$_3$), 3.52 (s, 3H, S-C*H*$_3$), 1.47 (t, 3H, J=7.1Hz, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 167.5 (O=*C*), 161.6 (2 MeO-*C*), 136.1 (N-*C*), 108.3 (2 N-C-*C*H), 102.5 (MeOC-*C*H-COMe), 71.1 (*C*H$_2$CH$_3$), 55.7 (2 O*C*H$_3$), 42.1 (CO-*C*), 40.9 (SO$_2$-*C*H$_3$), 13.7 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2966, 2942, 2842, 1715, 1609, 1473, 1429, 1364, 1292, 1238, 1207, 1159, 1113, 1050

HRMS (EI+) Calcd. for $C_{14}H_{19}NO_6S_3$: 393.0375 Found : 393.0374

Dithiocarbonic acid S-{2-[(4-bromo-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-3)

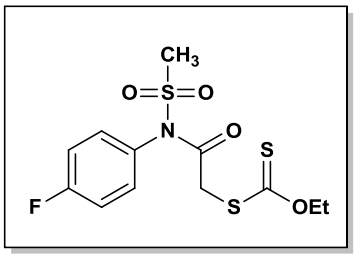


Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 4-bromoaniline (6.00g, 34.9mmol) in distillated 1,2-dichloroethane (25ml, 1.4M), methanesulfonylchloride (3.0mL, 38.8mmol) and pyridine (3.2ml, 39.6mmol). Recrystallization with AcOEt / EP ether afforded the protected 4-bromoaniline (8.36 g, 95%) as a pale white solid. Then the chloroacetylation was carried out with the solution of the above solid (4.70g, 18.8mmol) in dry DMF (41ml, 0.5M),

chloroacetylchloride (2.2mL, 27.7mmol) and sodium hydride (60% in mineral oil, 900mg, 22.5mmol). Recrystallization with AcOEt / EP afforded the halogenide (4.82g, 78%) as a white solid. Then the reaction was carried out with the solution of the halogenide (2.67g, 8.2mmol) in acetone (27ml, 0.3M) and potassium *O*-ethylxanthogenate (1.44g, 9.0mmol). Flash chromatography on silica gel with AcOEt / EP = 15 /85 ~ 20 / 80 afforded **3-3** (2.70g, 80%) as a yellow foam.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.67 (d, 2H, J=8.6Hz, Br-C-C*H*), 7.32 (d, 2H, J=8.6Hz, C*H*-CN), 4.62 (q, 2H, J=7.1Hz, CH_2CH$_3$), 3.76 (s, 2H, CO-CH_2), 3.48 (s, 3H, SO_2-CH_3), 1.42 (t, 1H, J=7.1Hz, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 213.2 (S=*C*), 167.2 (O=*C*), 133.7 (N-*C*), 133.5 (2 Br-C-*C*), 131.6 (2 N-C-*C*), 125.1 (Br-*C*), 71.3 (*C*H_2CH$_3$), 42.2 (S-*C*), 41.3 (CO-*C*), 13.7 (CH_2*C*H$_3$)
IR (ν, cm^{-1}, $CDCl_3$) 2987, 2938, 1714, 1488, 1365, 1300, 1239, 1155, 1112, 1050
HRMS (EI) Calcd. for $C_{12}H_{14}NO_4S_3Br$: 410.9268 Found : 410.9265

Dithiocarbonic acid S-{2-[(4-fluoro-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-4)

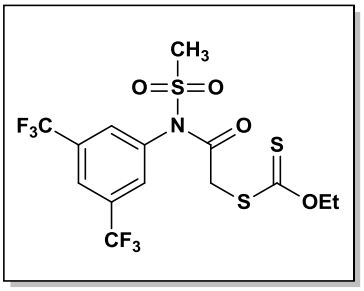


Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 4-fluoroaniline (5.45g, 49mmol) in distillated 1,2-dichloroethane (34ml, 1.4M), methanesulfonylchloride (4.2mL, 54.3mmol) and pyridine (4.4ml, 54.5mmol). Recrystallization with AcOEt / EP afforded the protected 4-fluoroaniline (7.32 g, 79%) as a light brown solid. Then the chloroacetylation was carried out

with the solution of the above solid (2.73g, 14.4mmol) in dry DMF (25ml, 0.6M), chloroacetylchloride (1.72mL, 21.6mmol) and sodium hydride (60% in mineral oil, 694mg, 17.4mmol). Recrystallization with AcOEt / EP afforded the halogenide (2.82g, 74%) as a pale white solid. Then the reaction was carried out with the solution of the halogenide (1.10g, 4.14mmol) in acetone (11ml, 0.4M) and potassium *O*-ethylxanthogenate (0.73g, 4.55mmol). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **3-4** (1.18g, 81%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.43 (m, 2H, C*H*-CN), 7.22 (m, 2H, F-C-C*H*), 4.62 (q, 2H, J=7.1Hz, CH_2CH_3), 3.76 (s, 2H, CO-CH_2), 3.48 (s, 3H, SO_2-CH_3), 1.41 (t, 1H, J=7.1Hz, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 167.4 (O=*C*), 163.5 (d, J=252.3Hz, F-*C*), 132.0 (d, J=9.1Hz, 2 N-C-*C*), 130.6 (d, J=3.5Hz, N-*C*), 117.3 (d, J=23.1Hz, 2F-C-*C*), 71.3 (CH_2CH_3), 42.1 (S-*C*), 41.3 (CO-*C*), 13.7 (CH_2CH_3)
IR (ν, cm^{-1}, $CDCl_3$) 2987, 2937, 1716, 1601, 1506, 1364, 1302, 1155, 1113, 1050
HRMS (EI+) Calcd. for $C_{12}H_{14}FNO_4S_3$: 351.0069 Found : 351.0066

Dithiocarbonic acid S-{2-[(3,5-bis(trifluoromethyl)-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-5)



Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 3,5-bis(trifluoromethyl)aniline (7.46g, 32.5mmol) in distillated 1,2-dichloroethane (20ml, 1.6M), methanesulfonylchloride

(2.8mL, 36.2mmol) and pyridine (2.9ml, 35.9mmol). Recrystallization with AcOEt / EP afforded the protected 3,5-bis(trifluoromethyl)aniline (9.19 g, 92%) as a white solid. Then the chloroacetylation was carried out with the solution of the above solid (4.03g, 13.1mmol) in dry DMF (24ml, 0.6M), chloroacetylchloride (1.6mL, 19.7mmol) and sodium hydride (60% in mineral oil, 629mg, 15.7mmol). Recrystallization with AcOEt / EP afforded the halogenide (3.47g, 69%) as a white crystal. Then the reaction was carried out with the solution of the halogenide (3.10g, 8.1mmol) in acetone (31ml, 0.3M) and potassium *O*-ethylxanthogenate (1.42g, 8.9mmol). Flash chromatography on silica gel with AcOEt / EP = 5 / 95 afforded **3-5** (2.70g, 71%) as a light yellow crystal.

m.p. : 116-120°C

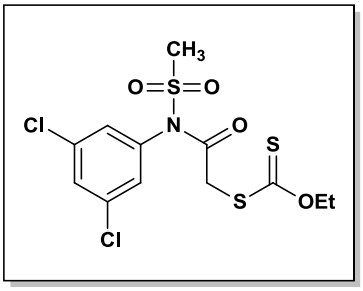
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.04 (s, 1H, CF_3C-C*H*-CCF_3), 7.91 (s, 2H, CF_3C-C*H*-CN), 4.62 (q, 2H, J=7.1Hz, C*H*$_2$$CH_3$), 3.81 (s, 2H, CO-C*H*$_2$), 3.54 (s, 3H, S-C*H*$_3$), 1.42 (t, 1H, J=7.1Hz, CH_2C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.4 (S=*C*), 166.9 (O=*C*), 136.4 (N-*C*), 133.7 (q, J=34.5Hz, 2 CF_3-*C*), 130.7 (2 N-C-*C*), 124.5 (CF_3-C-*C*-C-CF_3), 122.4 (q, J=273.0Hz, 2 *C*F_3), 71.7 (*C*H_2CH_3), 42.6 (S-*C*), 41.4 (CO-*C*), 13.7 (CH_2*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2989, 2935, 1719, 1622, 1468, 1375, 1279, 1186, 1147, 1112, 1049

HRMS (EI+) Calcd. for $C_{14}H_{13}F_6NO_4S_3$: 468.9911 Found : 468.9917

Dithiocarbonic acid S-{2-[(3,5-dichloro-phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-6)



Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 3,5-dichloroaniline (7.20g, 44.4mmol) in distillated 1,2-dichloroethane (27ml, 1.6M), methanesulfonylchloride (3.8mL, 49.1mmol) and pyridine (4.0ml, 49.6mmol). Recrystallization with AcOEt / EP afforded the protected 3,5-dichloroaniline (10.1 g, 95%) as a violet solid. Then the chloroacetylation was carried out with the solution of the above solid (5.10g, 21.2mmol) in dry DMF (50ml, 0.4M), chloroacetylchloride (2.5mL, 31.4mmol) and sodium hydride (60% in mineral oil, 1.02g, 25.5mmol). Recrystallization with AcOEt / EP afforded the halogenide (5.21g, 77%) as a white solid. Then the reaction was carried out with the solution of the halogenide (2.61g, 8.2mmol) in acetone (26ml, 0.3M) and potassium *O*-ethylxanthogenate (1.45g, 9.1mmol). Recrystallization with AcOEt / EP afforded **3-6** (2.69g, 81%) as a light brown powder.

m.p. : 144-147°C

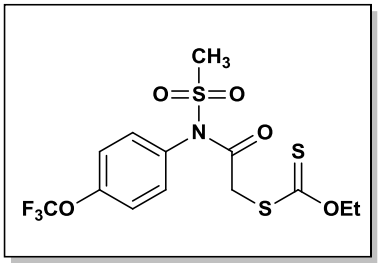
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.53 (t, 1H, J=1.7Hz, ClC-C*H*-CCl), 7.37 (d, 2H, J=1.7Hz, ClC-C*H*-CN), 4.63 (q, 2H, J=7.1Hz, CH_2CH$_3$), 3.81 (s, 2H, CO-CH_2), 3.49 (s, 3H, S-CH_3), 1.42 (t, 1H, J=7.1Hz, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 167.0 (O=*C*), 136.5 (N-*C*), 136.3 (2 Cl-*C*), 131.1 (Cl-C-*C*-C-Cl), 128.9 (2 N-C-*C*), 71.5 (*C*H$_2$CH$_3$) 42.5 (S-*C*), 41.2 (CO-*C*), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2987, 2938, 1718, 1574, 1366, 1299, 1158, 1113, 1050

HRMS (EI+) Calcd. for $C_{12}H_{13}NO_4S_3Cl_2$: 400.9384 Found : 400.9389

Dithiocarbonic acid S-{2-[(4-trifluoromethoxy -phenyl)-methanesulfonyl-amino]-2-oxo-ethyl} ester *O*-ethyl ester (3-7)



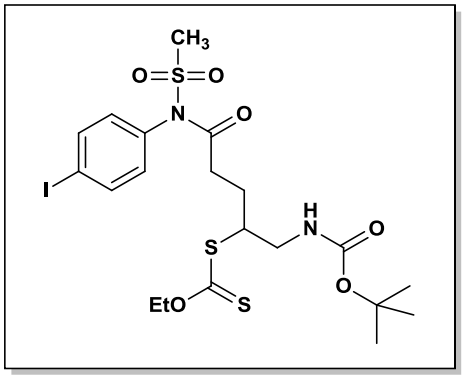
Following the general procedure **3-I** for the preparation of the corresponding xanthate, the reaction was started with the mesylation of a solution of 4-(trifluoromethoxy)aniline (8.09g, 45.7mmol) in distillated 1,2-dichloroethane (33ml, 1.4M), methanesulfonylchloride (3.9mL, 50.2mmol) and pyridine (4.2ml, 52.0mmol). Recrystallization with AcOEt / EP afforded the protected 4-(trifluoromethoxy)aniline (10.2 g, 87%) as a pale white solid.

Then the chloroacetylation was carried out with the solution of the above solid (4.88g, 19.1mmol) in dry DMF (25ml, 0.6M), chloroacetylchloride (3.27mL, 28.9mmol) and sodium hydride (60% in mineral oil, 916mg, 22.9mmol). Recrystallization with AcOEt / EP afforded the halogenide (4.68g, 74%) as a pale white solid.

Then the reaction was carried out with the solution of the halogenide (2.52g, 7.60mmol) in acetone (25ml, 0.3M) and potassium *O*-ethylxanthogenate (1.34g, 8.36mmol). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **3-7** (2.70g, 85%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.49 (m, 2H, C*H*-CN), 7.37 (d, 2H, J=8.7Hz, CF_3OC-C*H*), 4.62 (q, 2H, J=7.1Hz, C*H*$_2$$CH_3$), 3.76 (s, 2H, CO-C*H*$_2$), 3.49 (s, 3H, SO_2-C*H*$_3$), 1.41 (t, 1H, J=7.1Hz, CH_2C*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 167.3 (O=*C*), 150.5 (d, J=1.6Hz, CF_3O-*C*), 132.9 (s, N-*C*), 131.8 (s, 2 N-C-*C*), 122.2 (s, 2CF_3O-C-*C*), 120.2 (q, J=258.9Hz, *C*F_3), 71.3 (*C*H_2CH_3), 42.2 (S-*C*), 41.3 (CO-*C*), 13.7 (CH_2*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 2988, 2937, 1717, 1507, 1364, 1263, 1112, 1050
HRMS (EI+) Calcd. for $C_{13}H_{14}O_5NF_3S_3$: 416.9986 Found : 416.9981

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(4-iodo-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-8)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-1** (1.05g, 2.28mmol) and *N*-Boc-allylamine (0.54g, 3.44mmol) in AcOEt (2.5ml, 0.9M), with 10%mol of DLP. Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 afforded **3-8** (1.11g, 79%) as a light yellow foam.

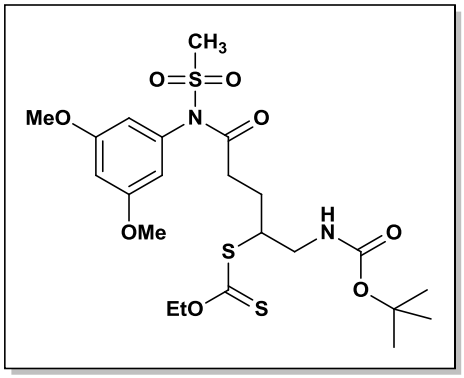
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.80 (d, 2H, J=8.5Hz, I-C-C*H*), 7.01 (d, 2H, J=8.4Hz, C*H*-CN), 4.81 (br s, 1H, N*H*), 4.62 (m, 2H, CH_2CH$_3$), 3.82-3.76 (m, 1H, C*H*S), 3.45 (s, 3H, SO_2-CH_3), 3.43-3.38 (m, 1H, CH_2NHBoc), 3.32-3.25 (m, 1H, CH_2NHBoc), 2.35-2.22 (m, 2H, CO-CH_2), 2.17-2.08 (m, 1H, CH_2-CH$_2$CO), 1.85-1.75 (m, 1H, CH_2-CH$_2$CO), 1.42 (s, 9H, C(CH_3)$_3$), 1.41 (t, 3H, J=7.1Hz, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (S=*C*), 172.7 (O=*C*-NMs), 155.8 (O=*C*-NH), 139.3 (2 I-C-*C*), 134.8 (N-*C*), 131.6 (2 N-C-*C*), 96.4 (I-*C*), 79.7 (*C*(CH$_3$)$_3$), 70.5 (*C*H$_2$CH$_3$), 51.0 (*C*HS), 43.6 (*C*H$_2$-NH), 42.2 (SO_2-*C*), 33.8 (*C*H$_2$-CO), 28.3 (C(*C*H$_3$)$_3$), 26.0 (*C*H$_2$-CH$_2$CO), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3451, 2982, 2936, 1698, 1505, 1367, 1235, 1156, 1112, 1050

HRMS (EI+) Calcd. for $C_{20}H_{29}N_2O_6S_3I$: 616.0232 Found : 616.0247

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(3,5-dimethoxy-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-9)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-2** (1.00g, 2.54mmol) and *N*-Boc-allylamine (0.80g, 5.11mmol) in AcOEt (3.5ml, 0.7M), with 15%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 35 / 65 ~ 40 / 60 afforded **3-9** (1.18g, 84%) as a light yellow oil.

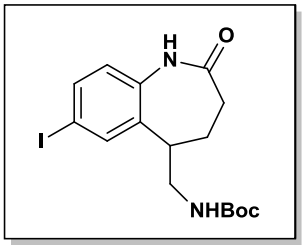
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.54 (t, 1H, J=1.9Hz, MeOC-C*H*-COMe), 6.40 (d, 2H, J=1.7Hz, 2C*H*-CN), 4.81 (br s, 1H, N*H*), 4.61 (dq, 2H, J=1.8Hz, J=7.1Hz, CH_2-CH_3), 3.84-3.77 (m+s, 7H, C*H*S + 2OCH_3), 3.45 (s, 3H, SO_2CH_3), 3.44-3.38 (m, 1H, CH_2NHBoc), 3.32-3.27 (m, 1H, CH_2NHBoc), 2.45-2.31 (m, 2H, CH_2CO), 2.17-2.08 (m, 1H, CH_2), 1.84-1.75 (m, 1H, CH_2), 1.41 (s, 9H, C(CH_3)$_3$), 1.40 (t, 3H, J=7.2Hz, CH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (S=*C*), 173.1 (O=*C*-NMs), 161.4 (2 MeO-*C*), 155.8 (O=*C*-NH), 136.5 (N-*C*), 108.1 (2 N-C-*C*), 102.1 (MeOC-*C*-COMe), 79.6 (*C*(CH$_3$)$_3$), 70.4 (*C*H_2CH$_3$), 55.6 (2 O-*C*H$_3$), 50.9 (*C*HS), 43.6 (*C*H$_2$-NH), 42.0 (SO_2-*C*), 33.3 (*C*H$_2$-CO), 28.3 (C(*C*H$_3$)$_3$), 26.0 (*C*H$_2$-CH$_2$CO), 13.7 (CH_2CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 3451, 2982, 2939, 2842, 1709, 1610, 1505, 1473, 1429, 1367, 1208, 1159, 1064

HRMS (EI+) Calcd. for $C_{22}H_{34}N_2O_8S_3$: 550.1477 Found : 550.1490

(7-iodo-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-10)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-8** (568mg, 0.92mmol) and 2,6-lutidine (0.11ml, 0.92mmol) in chlorobenzene (46ml, 0.02mmol/ml), with DTBP (0.85ml, 4.60mmol) for 70min. Flash chromatography on silica gel with AcOEt / EP = 60 / 40 afforded **3-10** (289mg, 75%) as a white powder.

m.p. : 142-145°C

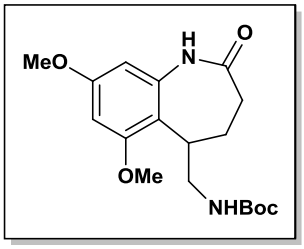
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.75 (br s, 1H, CO-N*H*), 7.59-7.57 (m, 2H, C*H*-C-I), 6.75 (d, 1H, J=8.1Hz, I-C-CH-C*H*), 4.63 (br s, 1H, N*H*Boc), 3.63-3.56 (m, 1H, CH_2NHBoc), 3.45-3.39 (m, 1H, CH_2NHBoc), 3.14-3.06 (m, 1H, C*H*), 2.44-2.25 (m, 3H, CH*H*-CH_2CO + CH_2CO), 1.83-1.75 (m, 1H, C*H*H-CH_2CO), 1.43 (s, 9H, C(CH_3)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.5 (O=*C*-NH), 155.7 (O=*C*-NHBoc), 137.6 (s, N-*C*), 136.7 (s, NC-C-*C*H), 136.6 (s, NC-*C*), 136.1 (s, NC-CH-*C*H), 124.1 (s, NC-*C*H), 90.2 (s, I-*C*), 79.7 (*C*(CH_3)$_3$), 42.3 (*C*H_2-NHBoc), 39.8 (*C*H-CH_2NHBoc), 32.2 (*C*H_2-CH_2CO), 32.1 (*C*H_2-CONH), 28.4 (3 C(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 3393, 2981, 2935, 1676, 1509, 1393, 1249, 1165

HRMS (EI+) Calcd. for $C_{16}H_{21}N_2O_3I$: 416.0597 Found : 416.0590

(6,8-dimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-11)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-9** (251mg, 0.46mmol) and 2,6-lutidine (0.05ml, 0.46mmol) in chlorobenzene (23ml, 0.02mmol/ml), with DTBP (0.42ml, 2.28mmol) for 70min. Flash chromatography on silica gel with AcOEt / DCM = 33 / 67 afforded **3-11** (130mg, 81%) as a light yellow oil.

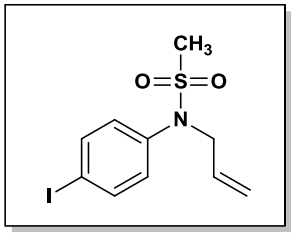
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.34 (br s, 1H, CO-N*H*), 6.31 (d, 1H, J=2.3Hz, MeO-C-C*H*-C-OMe), 6.09 (d, 1H, J=2.3Hz, MeO-C-C*H*-C-N), 4.40 (br s, 1H, N*H*Boc), 3.79 (s, 3H, -OCH_3), 3.78 (s, 3H, -OCH_3), 3.76-3.71 (m, 1H, C*H*), 3.47-3.40 (m, 1H, CH_2NHBoc), 3.38-3.31 (m, 1H, CH_2NHBoc), 2.50-2.42 (m, 1H, C*H*H-CH_2CO), 2.34-2.26 (m, 2H, CH*H*-CH_2CO + CH*H*CO), 2.07-2.00 (m, 1H, CH*H*CO), 1.42 (s, 2H, C(CH_3)$_3$), 1.35 (s, 7H, C(CH_3)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 175.2 (O=*C*-NH), 159.5 (2 *C*-OMe), 155.8 (O=*C*-NHBoc), 139.0 (s, N-*C*), 114.6 (s, *C*-C-N), 99.6 (s, *C*H-C-N), 95.9 (s, MeO-C-*C*-C-OMe), 78.9 (*C*(CH_3)$_3$), 55.9 (O*C*H_3), 55.4 (O*C*H_3), 43.8 (*C*H_2-NH), 32.9 (*C*H-CH_2NHBoc), 32.5 (*C*H_2-CH_2CO), 30.0 (*C*H_2-CONH), 28.3 (3 C(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3453, 3394, 2979, 2937, 1674, 1613, 1504, 1459, 1368, 1155

HRMS (EI+) Calcd. for $C_{18}H_{26}N_2O_5$: 350.1842 Found : 350.1837

_N_-allyl-_N_-(4-iodophenyl)-methanesulfonamide (3-12)



To a magnetically stirred solution of the protected 4-iodoaniline (388mg, 1.31mmol) in anhydrous DMF (13ml, 0.1M) under nitrogen in an ice bain, was added sodium hydride (78mg, 1.96mmol, 60% in mineral oil) little by little. The resulting mixture was warmed to room temperature for about 10min. Allylbromide (0.17ml, 1.96mmol) was then added and the solution was stirred for 2 hours. Ethyl acetate was added and the solution was washed with water 3 times and once with brine. The organic phase was dried over anhydrous magnesium sulfate and filtered. Then the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel with AcOEt / EP = 15 / 85 ~ 20 / 80 to afford **3-12** (436mg, 99%) as a colourless oil.

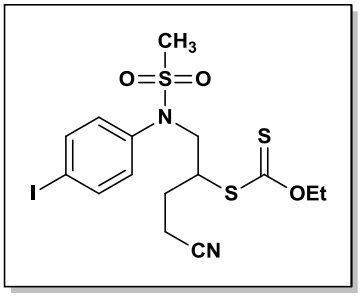
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.71 (d, 2H, J=8.6Hz, IC-C*H*), 7.08 (d, 2H, J=8.6Hz, CH-CN), 5.85-5.75 (m, 1H, $CH=CH_2$), 5.16 (dd, 2H, J=6.4Hz, J=13.1Hz, $CH=CH_2$), 4.26 (d, 2H, J=6.3Hz, N-CH_2), 2.90(s, 3H, S-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 139.0 (N-*C*), 138.5 (2 I-C-*C*), 132.5 (*C*H=CH_2), 130.1 (2 N-C-*C*), 119.5 (CH=*C*H_2), 93.3 (I-*C*), 53.5 (N-*C*H_2), 38.1 (S-*C*)

IR (ν, cm^{-1}, $CDCl_3$) 3088, 2933, 1645, 1486, 1420, 1345, 1217, 1159, 1070, 1009, 958

HRMS (EI+) Calcd. for $C_{10}H_{12}INO_2S$: 336.9633 Found : 336.9638

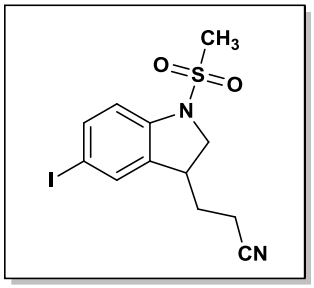
S-1-(4-iodophenyl-methanesulfonyl-amino)-4-cyanobutan-2-yl O-ethyl carbonodithioate (3-13)



A magnetically stirred solution of S-cyanomethyl *O*-ethyl carbonodithioate (204mg, 1.27mmol) and the olefin **3-12** (212mg, 0.63mmol) in AcOEt (1.3ml, 1.0M of the xanthate) were refluxed for about 30min under nitrogen. DLP (51mg, 10%mol) was then added to the refluxing solution, followed by the addition of DLP (26mg, 5%mol) after 60min. 1 hour later the reaction was completed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel with AcOEt / EP = 20 / 80 ~ 30 / 70 to yield the desired compounds **3-13** (279mg, 89%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.79 (d, 2H, J=8.7Hz, I-C-C*H*), 7.14 (d, 2H, J=8.7Hz, C*H*-CN), 4.58 (q, 2H, J=7.1Hz, CH_2CH$_3$), 3.99-3.88 (m, 2H, CH_2NMs), 3.76-3.68 (m, 1H, C*H*S), 2.88 (s, 3H, SO_2-CH_3), 2.63-2.55 (m, 1H, C*H*H-CN), 2.51-2.34 (m, 2H, CH*H*-CN + C*H*H-CH_2CN), 1.97-1.87 (m, 1H, CH*H*-CH_2CN), 1.36 (t, 3H, J=7.1Hz, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.2 (S=*C*), 139.0 (2 I-C-*C*), 137.9 (N-*C*), 130.4 (2 N-C-*C*), 118.6 (I-*C*), 94.4 (*C*N), 70.7 (*C*H_2CH$_3$), 53.0 (*C*H_2-NMs), 47.7 (*C*HS), 43.6 (*C*H_2-NH), 37.2 (SO_2-*C*), 26.4 (*C*H_2-CH_2CN), 14.9 (*C*H_2CN), 13.6 (CH_2*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3690, 2986, 2933, 1483, 1444, 1348, 1230, 1159, 1111, 1050, 1009, 963
HRMS (EI+) Calcd. for $C_{15}H_{19}IN_2O_3S_3$: 497.9602 Found : 497.9607

3-(1-methanesulfonyl-5-iodoindolin-3-yl)propanenitrile (3-14)



A magnetically stirred solution of the xanthate **3-13** (121mg, 0.24mmol) in chlorobenzene (15ml, 0.02M of xanthate) together with 2,6-lutidine (0.04ml, 0.34mmol) were refluxed for about 30min under nitrogen. Di-*tert*-butylperoxide (DTBP) (0.28ml, 1.5mmol) was then added to the refluxing solution. The reaction was monitored by TLC until 3 hours when the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel with AcOEt / DCM = 1 / 99 ~ 2 / 98 to afford **3-14** (60mg, 66%) as a light yellow oil.

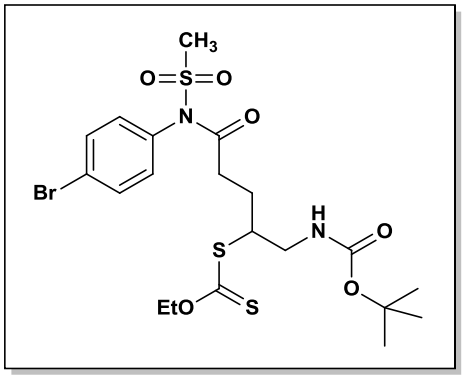
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.57 (dd, 1H, J=1.6Hz, J=8.5Hz, I-C-C*H*-CH), 7.52 (s, 1H, I-C-C*H*-C), 7.19 (d, 1H, J=8.5Hz, I-C-CH-C*H*), 4.04 (dd, 1H, J=9.0Hz, J=10.4Hz, C*H*HNMs), 3.73 (dd, 1H, J=4.9Hz, J=10.4Hz, CH*H*NMs), 3.55-3.49 (m, 1H, C*H*), 2.91 (s, 3H, SO_2-CH_3), 2.45 (t, 2H, J=7.2Hz,CH_2-CN), 2.14-2.04 (m, H, C*H*H-CH_2CN), 2.00-1.91 (m, 1H, CH*H*-CH_2CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 141.6 (N-*C*), 138.0 (I-C-*C*H-CH), 135.1 (N-C-*C*), 133.7 (I-C-*C*H-C), 118.5 (I-*C*), 115.5 (NC-*C*H), 86.5 (*C*N), 55.4 (*C*H_2-N), 38.4 (*C*H), 34.9 (SO_2-*C*), 30.1 (*C*H_2-CH_2CN), 14.8 (*C*H_2CN)

IR (ν, cm^{-1}, $CDCl_3$) 2934, 2880, 1593, 1476, 1357, 1247, 1165, 1121, 1069, 994, 955

HRMS (EI+) Calcd. for $C_{12}H_{13}IN_2O_2S$: 375.9742 Found : 375.9743

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(4-bromo-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-15)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-3** (1.06g, 2.6mmol) and *N*-Boc-allylamine (0.82g, 5.2mmol) in AcOEt (3ml, 0.9M), with 10%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **3-15** (1.27g, 86%) as a white powder.

m.p. : 126-129°C

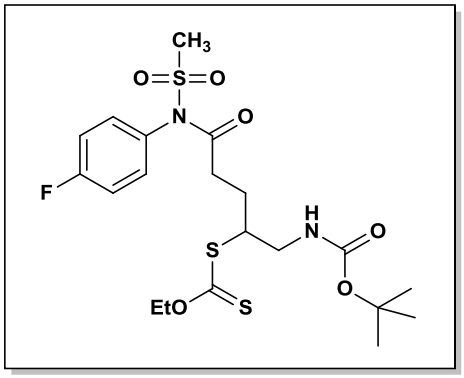
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.61 (d, 2H, J=8.5Hz, Br-C-C*H*), 7.15 (d, 2H, J=8.5Hz, C*H*-CN), 4.79 (br s, 1H, N*H*), 4.62 (m, 2H, CH_2CH$_3$), 3.80 (dt, 1H, J=5.8Hz, J=11.1Hz, C*H*S), 3.46 (s, 3H, SO_2-CH_3), 3.43-3.38 (m, 1H, CH_2NHBoc), 3.33-3.26 (m, 1H, CH_2NHBoc), 2.34-2.23 (m, 2H, CO-CH_2), 2.17-2.09 (m, 1H, CH_2-CH$_2$CO), 1.85-1.76 (m, 1H, CH_2-CH$_2$CO), 1.42 (s, 9H, C(CH_3)$_3$), 1.42 (t, 3H, J=7.1Hz, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (S=*C*), 172.8 (O=*C*-NMs), 155.8 (O=*C*-NH), 134.1 (N-*C*), 133.3 (2 Br-C-*C*), 131.4 (2 N-C-*C*), 124.6 (Br-*C*), 79.7 (*C*(CH$_3$)$_3$), 70.5 (*C*H$_2$CH$_3$), 51.0 (*C*HS), 43.6 (*C*H$_2$-NH), 42.2 (SO_2-*C*), 33.8 (*C*H$_2$-CO), 28.3 (C(*C*H$_3$)$_3$), 26.0 (*C*H$_2$-CH$_2$CO), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3451, 2982, 2936, 1710, 1505, 1367, 1230, 1157, 1112, 1050

HRMS (EI+) Calcd. for $C_{20}H_{29}N_2O_6S_3Br$: 568.0371 Found : 568.0358

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(4-fluoro-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-16)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-4** (1.16g, 3.3mmol) and *N*-Boc-allylamine (0.78g, 5.0mmol) in AcOEt (4ml, 0.8M), with 10%mol of DLP. Flash chromatography on silica gel with Et_2O / EP = 1 / 1 afforded **3-16** (1.20g, 72%) as a light yellow oil.

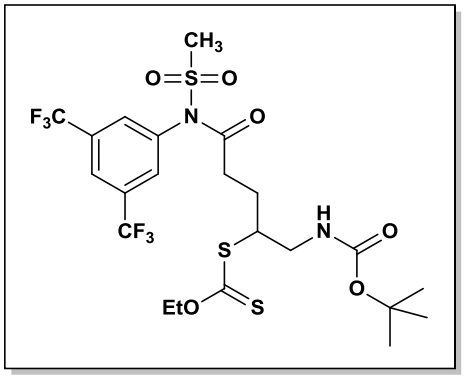
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.24 (m, 2H, C*H*-CN), 7.13 (m, 2H, CF-C*H*), 4.87 (br s, 1H, N*H*), 4.58 (m, 2H, CH_2CH_3), 3.76 (dt, 1H, J=5.9Hz, J=11.1Hz, C*H*S), 3.43 (s, 3H, SO_2-CH_3), 3.40-3.33 (m, 1H, CH_2NHBoc), 3.29-3.22 (m, 1H, CH_2NHBoc), 2.27-2.24 (m, 2H, CO-CH_2), 2.14-2.05 (m, 1H, CH_2-CH_2CO), 1.82-1.73 (m, 1H, CH_2-CH_2CO), 1.39 (s, 9H, $C(CH_3)_3$), 1.37 (t, 3H, J=7.1Hz, CH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.1 (S=*C*), 172.9 (O=*C*-NMs), 163.1 (d, J=251.4Hz, F-*C*), 155.7 (O=*C*-NH), 131.6 (d, J=9.0Hz, 2 N-C-*C*), 131.0 (d, J=3.4Hz, N-*C*), 117.0 (d, J=23.0Hz, 2 F-C-*C*), 79.5 ($C(CH_3)_3$), 70.3 (CH_2CH_3), 50.8 (*C*HS), 43.4 (CH_2-NH), 41.9 (SO_2-*C*), 33.7 (CH_2-CO), 28.2 (3 $C(CH_3)_3$), 25.8 (CH_2-CH_2CO), 13.6 (CH_2CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 3451, 2982, 2935, 1710, 1602, 1506, 1366, 1223, 1158, 1050

HRMS (EI+) Calcd. for $C_{20}H_{29}N_2O_6FS_3$: 508.1172 Found : 508.1158

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(3,5-bis(trifluoromethyl) -phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-17)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-5** (1.64g, 3.5mmol) and *N*-Boc-allylamine (0.82g, 5.2mmol) in AcOEt (3.5ml, 1.0M), with 15%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 15 / 85 afforded **3-17** (1.77g, 81%) as a yellow oil.

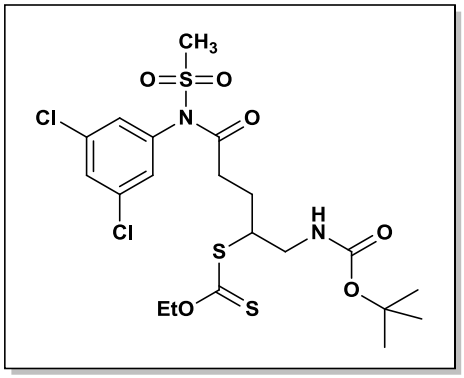
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.99 (s, 1H, CF_3C-C*H*-CCF_3), 7.77 (s, 2H, CF_3C-C*H*-CN), 4.83 (br s, 1H, N*H*), 4.60 (m, 2H, C*H*$_2$$CH_3$), 3.88-3.84 (m, 1H, C*H*S), 3.53 (s, 3H, SO_2-C*H*$_3$), 3.46-3.39 (m, 1H, C*H*$_2$NHBoc), 3.32-3.26 (m, 1H, C*H*$_2$NHBoc), 2.38-2.26 (m, 2H, CO-C*H*$_2$), 2.22-2.16 (m, 1H, C*H*$_2$-CH_2CO), 1.85-1.76 (m, 1H, C*H*$_2$-CH_2CO), 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.40 (t, 3H, CH_2C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 213.8 (S=*C*), 172.0 (O=*C*-NMs), 155.8 (O=*C*-NH), 136.8 (N-*C*), 133.8 (q, J=34.4Hz, 2 CF_3-*C*), 130.5 (d, J=3.0Hz, 2 N-C-*C*), 124.0 (m, CF_3-C-*C*-C-CF_3), 122.3 (q, J=273.2Hz, 2 *C*F_3), 79.6 (*C*(CH_3)$_3$), 70.6 (*C*$H_2$$CH_3$), 51.2 (*C*HS), 43.5 (*C*H_2-NH), 42.4 (SO_2-*C*), 33.9 (*C*H_2-CO), 28.2 (C(*C*H_3)$_3$), 26.0 (*C*H_2-CH_2CO), 13.5 (CH_2*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 2982, 2933, 1713, 1505, 1462, 1371, 1279, 1230, 1151, 1110, 1050

HRMS (EI+) Calcd. for $C_{22}H_{28}F_6N_2O_6S_3$: 626.1014 Found : 626.0987

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(3,5-dichloro-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-18)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-6** (1.11g, 2.8mmol) and *N*-Boc-allylamine (0.87g, 5.5mmol) in AcOEt (3ml, 0.9M), with 10%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **3-18** (1.27g, 81%) as a yellow foam.

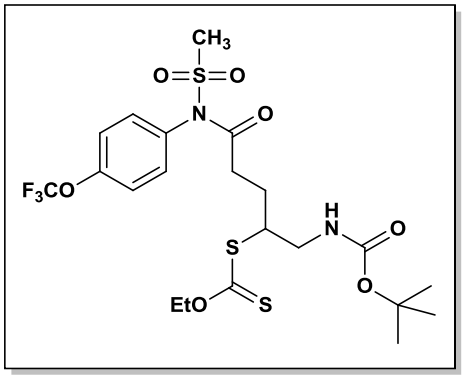
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.49 (t, 1H, J=1.68Hz, ClC-C*H*-CCl), 7.21 (d, 2H, ClC-C*H*-CN), 4.80 (br s, 1H, N*H*), 4.65 (q, 2H, *J* = 7.1Hz, CH_2CH$_3$), 3.87-3.83 (m, 1H, C*H*S), 3.49 (s, 3H, SO_2-CH_3), 3.46-3.41 (m, 1H, CH_2NHBoc), 3.34-3.28 (m, 1H, CH_2NHBoc), 2.40-2.26 (m, 2H, CO-CH_2), 2.22-2.11 (m, 1H, CH_2-CH$_2$CO), 1.85-1.74 (m, 1H, CH_2-CH$_2$CO), 1.42 (s, 9H, C(CH_3)$_3$), 1.42 (t, 3H, *J* = 7.0Hz, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 213.6 (S=*C*), 172.3 (O=*C*-NMs), 155.9 (O=*C*-NH), 136.8 (N-*C*), 136.1 (2 Cl-*C*), 130.7 (Cl-C-*C*-C-Cl), 128.8 (2 N-C-*C*), 79.7 (*C*(CH$_3$)$_3$), 70.7 (*C*H$_2$CH$_3$), 51.3 (*C*HS), 43.7 (*C*H$_2$-NH), 42.4 (SO_2-*C*), 33.8 (*C*H$_2$-CO), 28.3 (C(*C*H$_3$)$_3$), 26.1 (*C*H$_2$-CH$_2$CO), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 2982, 2932, 1712, 1574, 1506, 1367, 1227, 1169, 1050

HRMS (EI+) Calcd. for $C_{20}H_{28}Cl_2N_2O_6S_3$: 558.0487 Found : 558.0510

Dithiocarbonic acid S-{1-(*tert*-butoxycarbonylamino-methyl)-4-[(4-trifluoromethoxy-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-19)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-7** (0.89g, 2.1mmol) and *N*-Boc-allylamine (0.52g, 3.2mmol) in AcOEt (2.5ml, 0.8m), with 10%mol of DLP. Recrystallization with AcOEt / EP afforded **3-19** (0.99g, 82%) as a white powder.

m.p. : 122-125°C

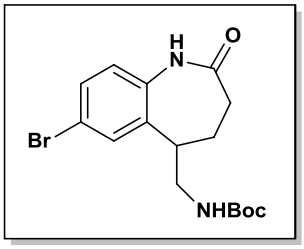
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.32 (m, 4H, *H*-Ar), 4.80 (br s, 1H, N*H*), 4.61 (m, 2H, J=1.0Hz, J=7.1Hz, CH_2CH$_3$), 3.80 (dt, 1H, J=5.6Hz, J=11.1Hz, C*H*S), 3.48 (s, 3H, SO_2-CH_3), 3.46-3.39 (m, 1H, CH_2NHBoc), 3.32-3.26 (m, 1H, CH_2NHBoc), 2.32-2.28 (m, 2H, CO-CH_2), 2.18-2.10 (m, 1H, CH_2-CH$_2$CO), 1.87-1.76 (m, 1H, CH_2-CH$_2$CO), 1.42 (s, 9H, C(CH_3)$_3$), 1.41 (t, 3H, J=7.1Hz, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (S=*C*), 172.8 (O=*C*-NMs), 155.8 (O=*C*-NH), 150.2 (d, J=1.9Hz, CF_3O-*C*), 133.4 (s, N-*C*), 131.5 (s, 2 N-C-*C*), 122.0 (s, 2 CF_3O-C-*C*), 120.3 (q, J=258.6Hz, O*C*F$_3$), 79.7 (*C*(CH$_3$)$_3$), 70.5 (*C*H$_2$CH$_3$), 51.0 (*C*HS), 43.6 (*C*H$_2$-NH), 42.2 (SO_2-*C*), 33.9 (*C*H$_2$-CO), 28.3 (3 C(*C*H$_3$)$_3$), 26.0 (*C*H$_2$-CH$_2$CO), 13.7 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3451, 2982, 2936, 1712, 1507, 1367, 1258, 1221, 1169, 1112, 1050

HRMS (EI+) Calcd. for $C_{21}H_{29}N_2O_7F_3S_3$: 574.1089 Found : 574.1099

(7-bromo-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-20)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-15** (273mg, 0.48mmol) and 2,6-lutidine (0.03ml, 0.24mmol) in chlorobenzene (24ml, 0.02mmol/ml), with DTBP (0.44ml, 2.40mmol) for 120min. Flash chromatography on silica gel with AcOEt / EP = 50 / 50 ~ 67 / 33 afforded **3-20** (98mg, 56%) as a white powder.

m.p. : 126-129°C

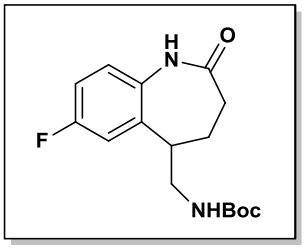
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.16 (br s, 1H, CO-N*H*), 7.40-7.38 (m, 2H, *H*-Ar), 6.90 (d, 1H, J=8.7Hz, , Br-C-CH-C*H*), 4.78 (br s, 1H, N*H*Boc), 3.65-3.57 (m, 1H, C*H*$_2$-NHBoc), 3.43-3.37 (m, 1H, C*H*$_2$NHBoc), 3.14-3.09 (m, 1H, C*H*), 2.35-2.27 (m, 3H, CH*H*-CH_2CO + C*H*$_2$CO), 1.79-1.75 (m, 1H, C*H*H-CH_2CO), 1.42 (s, 9H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.8 (O=*C*-NH), 155.7 (O=*C*-NHBoc), 136.9 (s, N-*C*), 136.4 (s, N-C-*C*), 130.6 (s, Br-C-*C*H-C), 130.2 (s, Br-C-*C*H-CH), 123.8 (s, N-C-*C*H), 119.2 (s, Br-*C*), 79.7 (*C*(CH_3)$_3$), 42.2 (*C*H_2-NH), 39.8 (*C*H-CH_2NHBoc), 32.2 (*C*H_2-CH_2CO), 32.1 (*C*H_2-CONH), 28.4 (3 C(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 3394, 2981, 2931, 1675, 1508, 1455, 1368, 1249, 1165

HRMS (EI+) Calcd. for $C_{16}H_{21}N_2O_3Br$: 368.0736 Found : 368.0737

(7-fluoro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-21)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-16** (233mg, 0.46mmol) and 2,6-lutidine (0.05ml, 0.46mmol) in chlorobenzene (30ml, 0.02mmol/ml), with DTBP (0.42ml, 2.29mmol) for 120min. Flash chromatography on silica gel with AcOEt / EP = 50 / 50 ~ 60 / 40 afforded **3-21** (81mg, 57%) as a white powder.

m.p. : 154-157°C

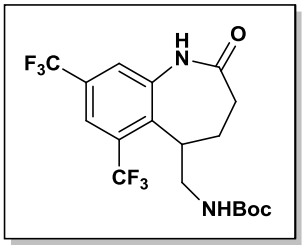
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.67 (br s, 1H, CO-N*H*), 7.01-6.94 (m, 3H, *H*-Ar), 4.65 (br s, 1H, N*H*), 3.62-3.55 (m, 1H, C*H*$_2$NHBoc), 3.48-3.42 (m, 1H, C*H*$_2$NHBoc), 3.17-3.09 (m, 1H, C*H*), 2.43-2.24 (m, 3H, CH*H*-CH_2CO + C*H*$_2$CO), 1.81-1.73 (m, 1H, C*H*H-CH_2CO), 1.42 (s, 9H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.5 (O=*C*-NH), 160.7 (d, J=245.6Hz, F-*C*), 155.7 (O=*C*-NHBoc), 136.6 (s, N-*C*), 133.7 (d, J=3.0Hz, N-C-*C*), 123.9 (d, J=8.5Hz, N-C-*C*H), 114.23 (d, J=22.8Hz, F-C-*C*H-C), 113.96 (d, J=23.8Hz, F-C-*C*H-CH), 79.7 (*C*$(CH_3)_3$), 42.3 (*C*H_2-NH), 39.8 (*C*H-CH_2NHBoc), 32.2 (*C*H_2-CH_2CO), 32.0 (*C*H_2-CONH), 28.3 (3 C(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 3396, 2930, 1674, 1500, 1456, 1368, 1249, 1170

HRMS (EI+) Calcd. for $C_{16}H_{21}FN_2O_3$: 308.1536 Found : 308.1539

[6,8-bis(trifluoromethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl]-carbamic acid *tert*-butyl ester (3-22)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-17** (526mg, 0.84mmol) and 2,6-lutidine (0.10ml, 0.84mmol) in chlorobenzene (42ml, 0.02mmol/ml), with DTBP (0.77ml, 4.20mmol) for 60min. Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded **3-22** (94mg, 26%) as a colourless oil.

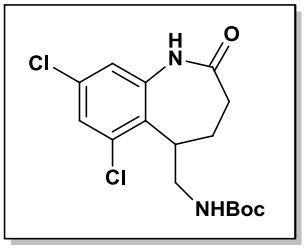
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.30 (br s, 1H, CO-N*H*), 7.75 (s, 1H, CF_3-C-C*H*-C-CF_3), 7.44 (s, 1H, CF_3-C-C*H*-C-N), 4.49 (br s, 1H, N*H*Boc), 4.06-3.98 (m, 1H, C*H*$_2$NHBoc), 3.65-3.59 (m, 1H, C*H*), 3.33-3.26 (m, 1H, C*H*$_2$NHBoc), 2.46-2.20 (m, 4H, CH*H*-CH_2CO + C*H*$_2$CO), 1.25 (s, 2H, C(C*H*$_3$)$_3$), 1.22 (s, 7H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.2 (O=*C*-NH), 155.6 (O=*C*-NHBoc), 140.9 (N-*C*), 137.3 (CF_3-C-*C*), 132.8 (d, J=30.1Hz, CF_3-*C*-CH-CN) 130.6 (d, J=31.4Hz, CF_3-*C*-C-CN), 123.8 (N-C-*C*H-C-CF_3), 123.4 (d, J=275.1Hz, NC-CH-C-*C*F_3), 122.9 (d, J=274.8Hz, NC-C-C-*C*F_3), 119.8 (CF_3-C-*C*H-C-CF_3), 79.4 (*C*(CH_3)$_3$), 42.4 (*C*H_2-NHBoc), 38.8 (*C*H-CH_2-NHBoc), 31.6 (*C*H_2-CONH), 30.5 (*C*H_2-CH_2CO), 28.1 (3 C(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3456, 3386, 2930, 1698, 1509, 1460, 1355, 1274, 1189, 1142

HRMS (EI+) Calcd. for $C_{18}H_{20}F_6N_2O_3$: 426.1378 Found : 426.1384

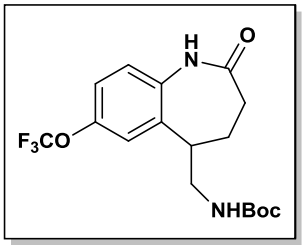
(6,8-dichloro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-23)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-18** (342mg, 0.61mmol) and 2,6-lutidine (0.08ml, 0.61mmol) in chlorobenzene (31ml, 0.02mmol/ml), with DTBP (0.57ml, 3.06mmol) for 60min. Flash chromatography on silica gel with AcOEt / DCM = 45 / 55 afforded **3-23** (129mg, 59%) as a light yellow foam.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 9.00 (br s, 1H, CO-N*H*), 7.23 (s, 1H, Cl-C-C*H*-C-Cl), 6.96 (s, 1H, Cl-C-C*H*-C-N), 4.63 (br s, 1H, N*H*Boc), 3.98-3.96 (m, 1H, C*H*), 3.55-3.47 (m, 1H, C*H*$_2$NHBoc), 3.39-3.33 (m, 1H, C*H*$_2$NHBoc), 2.46-2.27 (m, 3H, CH*H*-CH_2CO + C*H*$_2$CO), 2.18-2.13 (m, 1H, C*H*H-CH_2CO), 1.40 (s, 2H, C(C*H*$_3$)$_3$), 1.32 (s, 7H, C(C*H*$_3$)$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 175.5 (O=*C*-NH), 155.7 (O=*C*-NHBoc), 140.0 (s, N-*C*), 137.0 (s, Cl-*C*-C), 133.3 (s, Cl-*C*-CH), 130.4 (s, N-C-*C*-C-Cl), 126.3 (s, Cl-C-*C*H-C-Cl), 122.0 (s, N-C-*C*H-C-Cl), 79.3 (*C*(CH_3)$_3$), 43.0 (*C*H_2-NH), 37.7 (*C*H-CH_2NHBoc), 32.1 (*C*H_2-CONH), 29.5 (*C*H_2-CH_2CO), 28.2 (3 C(*C*H_3)$_3$)
IR (ν, cm^{-1}, $CDCl_3$) 3455, 3389, 2981, 1683, 1590, 1508, 1457, 1369, 1251, 1164
HRMS (EI+) Calcd. for $C_{16}H_{20}Cl_2N_2O_3$: 358.0851 Found : 358.0856

(7-trifluoromethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylmethyl)-carbamic acid *tert*-butyl ester (3-24)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-19** (649mg, 1.13mmol) and 2,6-lutidine (0.13ml, 1.13mmol) in chlorobenzene (56.5ml, 0.02mmol/ml), with DTBP (1.04ml, 5.65mmol) for 60min. Flash chromatography on silica gel with AcOEt / DCM = 45 / 55 afforded **3-24** (161mg, 38%) as a white powder.

m.p. : 120-123°C

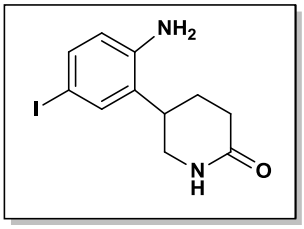
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.53 (br s, 1H, CO-N*H*), 7.16-7.05 (m, 3H, *H*-Ar), 4.94 (br s, 1H, N*H*Boc), 3.68-3.60 (m, 1H, C*H*$_2$NHBoc), 3.39-3.33 (m, 1H, C*H*$_2$NHBoc), 3.15-3.06 (m, 1H, C*H*), 2.35-2.12 (m, 3H, CH*H*-CH_2CO + C*H*$_2$CO), 1.78-1.72 (m, 1H, C*H*H-CH_2CO), 1.40 (s, 9H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 175.1 (O=*C*-NH), 155.7 (O=*C*-NHBoc), 146.9 (d, J=1.7Hz, CF_3O-*C*), 136.4 (s, N-C-*C*), 136.2 (s, N-*C*), 123.4 (s, N-C-*C*H), 120.4 (q, J=258.2, O*C*F$_3$), 120.2 (s, OCF_3-C-*C*H-C), 120.1 (s, OCF_3-C-*C*H-CH), 79.6 (*C*(CH$_3$)$_3$), 42.2 *C*H$_2$-NH), 39.7 (*C*H-CH_2NHBoc), 32.15 (*C*H$_2$-CH_2CO), 32.05 (*C*H$_2$-CONH), 28.3 (3 C(*C*H$_3$)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3452, 3395, 2931, 1680, 1504, 1456, 1369, 1262, 1171

HRMS (EI+) Calcd. for $C_{17}H_{21}F_3N_2O_4$: 374.1453 Found : 374.1458

5-(2-amino-5-iodo-phenyl)-piperidin-2-one (3-25)



Following the general procedure **3-IV**, the reaction was carried out with 25mg of **3-10** (0.06mmol) and 0.14ml of the solution of 30% TFA (0.57mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 1.4ml toluene (0.05M) and 0.12ml TEA (0.85mmol). The mixture was kept stirring at 90°C for about 1 hour, and then the precipitation was seperated by centrifuge and washed by cold acetone to afford **3-25** (11mg, 55%) as a white powder.

m.p. : 207-210 °C

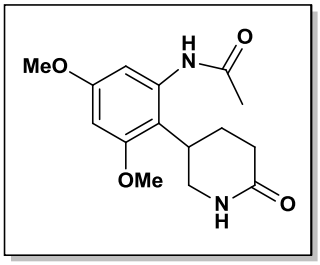
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.53 (d, 1H, J=2.9Hz, CO-N*H*), 7.19 (d, 2H, J=9.1Hz, C*H*-C-I), 6.47 (d, 1H, J=8.0Hz, I-C-CH-C*H*), 5.26 (s, 2H, NH_2), 3.26-3.24 (m, 1H, CH*H*-NHCO), 3.08-2.97 (m, 2H, C*H*H-NHCO + C*H*), 2.37-2.18 (m, 2H, CH_2CO), 1.94-1.78 (m, 2H, CH_2-CH_2CO)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 169.7 (O=*C*-NH), 145.9 (NH_2-*C*), 135.2 (NC-C-*C*H), 133.8 (NC-CH-*C*H), 128.4 (NC-*C*), 117.4 (NC-*C*H), 76.9 (I-*C*), 45.6 (*C*H_2-NHCO), 32.4 (*C*H-CH_2NHCO), 31.3 (*C*H_2-CONH), 26.2 (*C*H_2-CH_2CO)

IR (ν, cm^{-1}, Nujol) 3343, 3211, 2950, 1633, 1460, 1377, 1261, 1211

HRMS (EI+) Calcd. for $C_{11}H_{13}N_2OI$: 316.0073 Found : 316.0072

5-(2-acetyl-amino-4,6-dimethoxy-phenyl)-piperidin-2-one (3-26)



Following the general procedure **3-IV**, the reaction was carried out with 34mg of **3-11** (0.10mmol) and 0.20ml of the solution of 30% TFA (0.78mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 1.9ml toluene (0.05M) and 0.16ml TEA (1.16mmol). The mixture was kept stirring at 90°C for about 1 hour and then 0.07ml Ac_2O (0.78mmol) was added directly. The mixture was kept stirring at 90°C for about 30 minutes, and then the precipitation was seperated by centrifuge and washed by cold AcOEt to afford **3-26** (27mg, 95%) as a white powder.

m.p. : 227-231°C

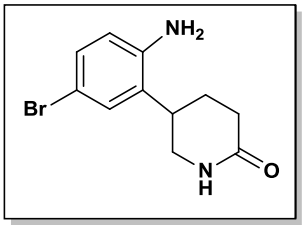
^{1}H-NMR (δ, ppm) (MeOD, 400 MHz) 6.48 (s, 1H, MeO-C-C*H*-C-OMe), 6.38 (s, 1H, C*H*-CN), 3.80 (s, 3H, NC-CH-C-OCH_3), 3.75 (s, 3H, NC-C-C-OCH_3), 3.77-3.72 (m, 1H, CH*H*-NHCO), 3.18-3.12 (m, 2H, CH*H*-NHCO + C*H*-CH_2-NHCO), 2.58-2.47 (m, 1H, CH*H*-CH_2CO), 2.43-2.28 (m, 2H, CO-CH_2), 2.12 (s, 3H, CO-CH_3) 1.76-1.72 (m, 1H, CH*H*-CH_2CO)

^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 175.3 (O=*C*-NH), 173.1 (O=*C*-CH_3), 161.3 (MeO-*C*-CH-CN), 161.0 (MeO-*C*-C-CN), 138.1 (*C*-N), 119.7 (*C*-CN), 105.8 (*C*H-CN), 99.4 (MeO-C-*C*H-C-OMe), 56.0 (CN-CH-C-O*C*H_3), 55.9 (CN-C-C-O*C*H_3), 45.0 (*C*H_2-NHCO), 35.0 (*C*H-CH_2NH), 32.7 (*C*H_2-CO), 25.6 (*C*H_2-CH_2CO), 22.9 (CO-*C*H_3)

IR (ν, cm^{-1}, Nujol) 3260, 2923, 2855, 1671, 1583, 1466, 1276, 1150, 1110

HRMS (EI+) Calcd. for $C_{15}H_{20}N_2O_4$: 292.1423 Found : 292.1416

5-(2-amino-5-bromo-phenyl)-piperidin-2-one (3-27)



Following the general procedure **3-IV**, the reaction was carried out with 126mg of **3-20** (0.34mmol) and 0.7ml of the solution of 30% TFA (2.74mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 6.8ml toluene (0.05M) and 0.57ml TEA (4.10mmol). The mixture was kept stirring at 70-90°C for about 2 hours, and then the precipitation was seperated by centrifuge and washed by cold acetone to afford **3-27** (76mg, 83%) as a very light yellow powder.

m.p. : 263-266°C

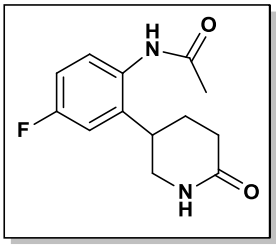
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.54 (d, 1H, J=3.4Hz, NHCO), 7.07 (d, 1H, J=2.3Hz, BrC-C*H*-CH), 7.04 (dd, 1H, J=2.4Hz, J=8.4Hz, BrC-C*H*-C), 6.58 (d, 1H, J=8.5Hz, C*H*-CN), 5.26 (s, 2H, NH_2), 3.29-3.24 (m, 1H, CH_2NHCO), 3.09-2.99 (m, 2H, C*H*S + CH_2NHCO), 2.37-2.18 (m, 2H, CO-CH_2), 1.96-1.78 (m, 2H, CH_2-CH_2CO)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 169.7 (O=*C*-NH), 145.4 (NH_2-*C*), 129.4 (Br-C-*C*H-C), 128.2 (Br-C-*C*H-CH), 127.8 (*C*-C-NH_2), 116.7 (*C*H-C-NH_2), 106.9 (*C*-Br), 45.6 (CH_2-NHCO), 32.5 (*C*H-CH_2NH), 31.3 (CH_2-CO), 26.2 (CH_2-CH_2CO)

IR (ν, cm^{-1}, Nujol) 3340, 3174, 2964, 2864, 1633, 1464, 1377, 1260, 1211

HRMS (EI+) Calcd. for $C_{11}H_{13}BrN_2O$: 268.0211 Found : 268.0221

5-(2-acetyl-amino-5-fluoro-phenyl)-piperidin-2-one (3-28)



Following the general procedure **3-IV**, the reaction was carried out with 43mg of **3-21** (0.14mmol) and 0.28ml of the solution of 30% TFA (1.12mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 2.8ml toluene (0.05M) and 0.23ml TEA (1.67mmol). The mixture was kept stirring at 90°C for about 1 hour and then 0.11ml Ac_2O (1.12mmol) was added directly. The mixture was kept stirring at 90°C for about 30 minutes, and then the precipitation was seperated by centrifuge and washed by cold AcOEt to afford **3-28** (21mg, 60%) as a pale white powder.

m.p. : 238-242 °C

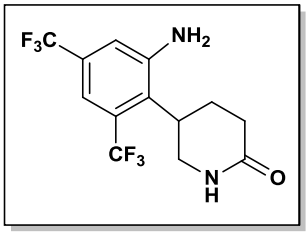
^{1}H-NMR (δ, ppm) (MeOD, 400 MHz) 7.25 (dd, 1H, J=5.5Hz, J=8.8Hz, N-C-C*H*), 7.15 (dd, 1H, J=2.8Hz, J=10.0Hz, F-C-C*H*-CH), 7.01 (dt, 1H, J=2.9Hz, J=8.4Hz, F-C-C*H*-C), 3.41-3.36 (m, 1H, CH*H*-NHCO), 3.25-3.19 (m, 2H, C*H*H-NHCO + C*H*-CH_2NH), 2.48-2.45 (m, 2H, C*H*$_2$CO), 2.16 (s, 3H, O=C-C*H*$_3$), 2.12-1.94 (m, 2H, C*H*$_2$-CH_2CO)

^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 174.4 (O=*C*-NH), 173.3 (O=*C*-CH_3), 163.1 (d, J=244.8Hz, F-*C*), 142.3 (d, J=7.6Hz, N-C-*C*), 132.5 (d, J=2.8Hz, N-*C*), 131.0 (d, J=8.7Hz, N-C-*C*H), 115.2 (d, J=22.5Hz, F-C-*C*H-C), 114.6 (d, J=23.4Hz, F-C-*C*H-CH), 48.3 (*C*H_2-NHCO), 35.6 (*C*H-CH_2-NHCO), 32.1 (*C*H_2-CONH), 28.2 (*C*H_2-CH_2CO), 22.9 (O=C-*C*H_3)

IR (ν, cm^{-1}, Nujol) 3242, 1670, 1637, 1535, 1491, 1294, 1249, 1193

HRMS (EI+) Calcd. for $C_{13}H_{15}N_2O_2F$: 250.1118 Found : 250.1119

5-[2-amino-4,6-bis(trifluoromethyl)-phenyl]-piperidin-2-one (3-29)



Following the general procedure **3-IV**, the reaction was carried out with 71mg of **3-22** (0.17mmol) and 0.34ml of the solution of 30% TFA (1.34mmol) in DCM. After finishing the first step, which took 70min stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 3.3ml toluene (0.05M) and 0.28ml TEA (2.0mmol). The mixture was kept stirring at 80°C for about 1.5 hours, and then the precipitation was seperated by centrifuge and washed by cold acetone to afford **3-29** (31mg, 56%) as a white powder.

m.p. : 270-273 °C

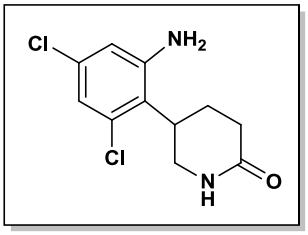
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.57 (s, 1H, CO-N*H*), 7.28 (s, 1H, NH_2-C-C*H*), 7.07 (s, 1H, CF_3C-C*H*-CCF_3), 5.89 (s, 2H, NH_2), 3.78-3.73 (m, 1H, CH*H*-NHCO), 3.40-3.26 (m, 1H, C*H*), 3.07-3.05 (m, 1H, C*H*H-NHCO), 2.61-2.58 (m, 1H, C*H*H-CH_2CO), 2.33-2.21 (m, 2H, CH_2CO), 1.65-1.61 (m, 1H, CH*H*-CH_2CO)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 170.3 (O=*C*-NH), 148.9 (NH_2-*C*), 129.7 (q, J=27.7Hz, *C*F_3-C-CH-CN), 128.1 (q, J=31.5Hz, *C*F_3-C-C-CN), 124.1 (q, J=275.0Hz, CF_3-*C*-CH-CN), 125.2 (NC-*C*), 123.5 (q, J=271.8Hz, CF_3-*C*-C-CN), 116.3 (NC-*C*H), 108.9 (CF_3-C-*C*H-C-CF_3), 40.3 (*C*H_2-NHCO), 34.7 (*C*H-CH_2NHCO), 31.4 (*C*H_2-CONH), 21.2 (*C*H_2-CH_2CO)

IR (ν, cm^{-1}, Nujol) 3453, 3368, 2972, 1644, 1461, 1377, 1269, 1213, 1169, 1119

HRMS (EI+) Calcd. for $C_{13}H_{12}N_2OF_6$: 326.0854 Found : 326.0852

5-(2-amino-4,6-dichloro-phenyl)-piperidin-2-one (3-30)



Following the general procedure **3-IV**, the reaction was carried out with 129mg of **3-23** (0.36mmol) and 0.73ml of the solution of 30% TFA (2.86mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 7.2ml toluene (0.05M) and 0.60ml TEA (4.29mmol). The mixture was kept stirring at 80°C for about 30min, and then the precipitation was seperated by centrifuge and washed by cold acetone to afford **3-30** (76mg, 81%) as a white powder.

m.p. : 276-280 °C

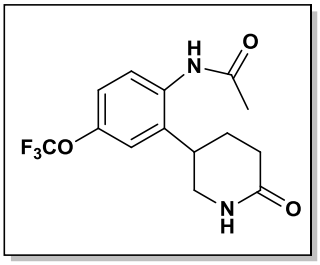
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.52 (s, 1H, CO-N*H*), 6.67 (s, 1H, NH_2-C-C*H*), 6.63 (s, 1H, ClC-C*H*-CCl), 5.65 (s, 2H, NH_2), 3.66 (t, 1H, J=11.5Hz, CH*H*-NHCO), 3.52-3.42 (m, 1H, C*H*), 3.03-2.99 (m, 1H, C*H*H-NHCO), 2.61-2.44 (m, 1H, C*H*H-CH_2CO), 2.34-2.21 (m, 2H, CH_2CO), 1.63 (d, 1H, J=12.0Hz, CH*H*-CH_2CO)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 170.2 (O=*C*-NH), 149.6 (NH_2-*C*), 134.4 (Cl-*C*-C-CN), 131.6 (Cl-*C*-CH-CN), 120.4 (NC-*C*), 116.6 (Cl-C-*C*H-C-Cl), 113.8 (NC-*C*H), 41.4 (*C*H_2-NHCO), 33.7 (*C*H-CH_2NHCO), 31.7 (*C*H_2-CONH), 22.9 (*C*H_2-CH_2CO)

IR (ν, cm^{-1}, Nujol) 3449, 3362, 3261, 1644, 1561, 1403, 1203, 1130

HRMS (EI+) Calcd. for $C_{11}H_{12}Cl_2N_2O$: 258.0327 Found : 258.0324

5-(2-acetyl-amino-5-trifluoromethoxy-phenyl)-piperidin-2-one (3-31)



Following the general procedure **3-IV**, the reaction was carried out with 18mg of **3-24** (0.05mmol) and 0.1ml of the solution of 30% TFA (0.39mmol) in DCM. After finishing the first step, which took 1 hour stirring at room temperature, the solvent was removed under reduced pressure. Then the reaction was carried out with 1.0ml toluene (0.05M) and 0.08ml TEA (0.58mmol). The mixture was kept stirring at 90°C for about 1 hour and then 0.04ml Ac_2O (0.38mmol) was added directly. The mixture was kept stirring at 90°C for about 30 minutes, and then the precipitation was seperated by centrifuge and washed by cold AcOEt to afford **3-31** (11mg, 75%) as a white powder.

m.p. : 222-225 °C

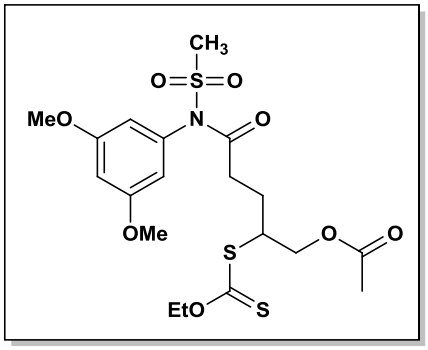
^{1}H-NMR (δ, ppm) (MeOD, 400 MHz) 7.37 (dd, 1H, J=3.8Hz, J=8.7Hz, N-C-C*H*), 7.29 (d, 1H, J=2.9Hz, CF_3O-C-C*H*-C), 7.19 (d, 1H, J=7.9Hz, CF_3O-C-C*H*-CH), 3.41-3.36 (m, 1H, CH*H*-NHCO), 3.28-3.21 (m, 2H, C*H*H-NHCO + C*H*-CH_2NH), 2.48-2.44 (m, 2H, CH_2CO), 2.17 (s, 3H, O=C-CH_3), 2.12-1.94 (m, 2H, CH_2-CH_2CO)

^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 174.3 (O=*C*-NH), 173.2 (O=*C*-CH_3), 149.2 (d, J=1.6Hz, CF_3O-*C*), 141.8 (N-C-*C*), 135.5 (N-*C*), 130.5 (N-C-*C*H), 121.9 (q, J=255.8Hz, *C*F_3O), 121.0 (CF_3O-C-*C*H-CH), 120.8 (CF_3O-C-*C*H-C), 48.2 (*C*H_2-NHCO), 35.4 (*C*H-CH_2-NHCO), 32.0 (*C*H_2-CONH), 28.2 (*C*H_2-CH_2CO), 23.0 (O=C-*C*H_3)

IR (ν, cm^{-1}, Nujol) 3261, 1634, 1538, 1494, 1342, 1268, 1220, 1151

HRMS (EI+) Calcd. for $C_{14}H_{15}N_2O_3F_3$: 316.1035 Found : 316.1030

Dithiocarbonic acid S-{1-(acetoxy-methyl)-4-[(3,5-dimethoxy-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-32)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-2** (98mg, 0.25mmol) and allyl acetate (50mg, 0.50mmol) in AcOEt (0.3ml, 0.8M), with 5%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 30/70 ~ 40/60 afforded **3-32** (85.4mg, 70%) as a light yellow oil.

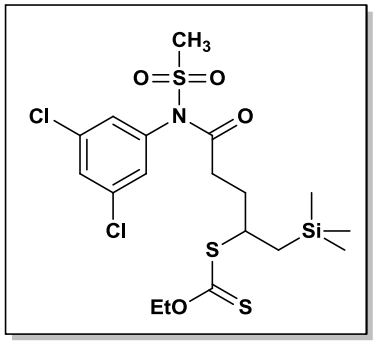
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.55 (t, 1H, J=2.2Hz, MeOC-C*H*-COMe), 6.39 (d, 2H, J=2.2Hz, 2C*H*-CN), 4.62 (dq, 2H, J=1.8Hz, J=7.1Hz, CH_2-CH_3), 4.28-4.15 (m, 2H, CH_2OAc), 4.00-3.94 (m, 1H, C*H*S), 3.80 (s, 6H, 2OCH_3), 3.46 (s, 3H, SO_2CH_3), 3.41-3.36 (m, 2H, CH_2CO), 2.23-2.15 (m, 1H, CH_2), 2.05 (s, 3H, COCH_3), 1.90-1.80 (m, 1H, CH_2), 1.41 (t, 3H, J=7.1Hz, CH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (S=*C*), 172.9 (O=*C*-NMs), 170.5 (*C*OCH_3), 161.4 (2 MeO-*C*), 136.5 (N-*C*), 108.2 (2 N-C-*C*), 101.9 (MeOC-*C*-COMe), 70.5 (*C*H_2CH_3), 65.6 (*C*H_2-OAc), 55.6 (2 O-*C*H_3), 48.7 (*C*HS), 42.1 (SO_2-*C*), 33.2 (*C*H_2-CO), 25.7 (*C*H_2-CH_2CO), 20.7 ($COCH_3$), 13.7 (CH_2CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 2965, 2942, 2842, 1741, 1699, 1610, 1472, 1429, 1363, 1208, 1159, 1112, 1064

HRMS (EI+) Calcd. for $C_{19}H_{27}NO_8S_3$: 493.0899 Found : 493.0844

Dithiocarbonic acid S-{1-(trimethylsilyl-methyl)-4-[(3,5-dichloro-phenyl)-methane sulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-33)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-6** (420g, 1.04mmol) and allyltrimethylsilane (239g, 2.09mmol) in AcOEt (1.0ml, 1.0M), with 5%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 10 / 90 ~ 20 / 80 afforded **3-33** (519mg, 96%) as a light yellow oil.

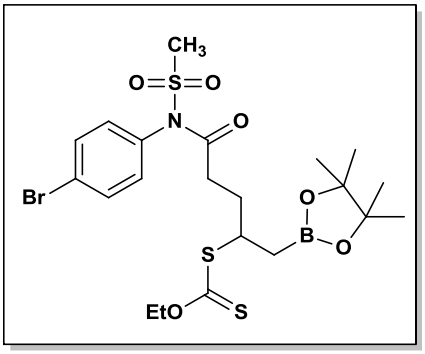
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.48 (t, 1H, J=1.9Hz, ClC-C*H*-CCl), 7.20 (d, 2H, J=1.9Hz, 2C*H*-CN), 4.69-4.58 (m, 2H, CH_2-CH_3), 3.94-3.87 (m, 1H, C*H*), 3.50 (s, 3H, SO_2CH_3), 2.34-2.18 (m, 3H, CH_2CO + C*H*H-CH_2CO), 1.78-1.67 (m, 1H, C*H*H-CH_2CO), 1.42 (t, 3H, J=7.1Hz, CH_2CH_3), 1.03 (ddd, 2H, J=7.6Hz, J=14.9Hz, J=23.1Hz, TMS-CH_2), 0.08 (s, 9H, $Si(CH_3)_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 215.1 (S=*C*), 172.4 (O=*C*-NMs), 136.9 (N-*C*), 136.0 (2 Cl-*C*), 130.5 (ClC-*C*-CCl), 128.8 (2 N-C-*C*), 70.2 (*C*H_2CH_3), 48.5 (*C*HS), 42.4 (SO_2-*C*), 34.1 (*C*H_2-CO), 32.2 (*C*H_2-CH_2CO), 24.3 (*C*H_2-TMS), 13.8 (CH_2CH_3), -0.8 ($Si(CH_3)_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2927, 2855, 1723, 1582, 1574, 1427, 1362, 1251, 1214, 1169, 1112, 1051, 967

HRMS (EI+) Calcd. for $C_{18}H_{27}Cl_2NO_4S_3Si$: 515.0249 Found : 515.0241

Dithiocarbonic acid S-{1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-methyl)-4-[(4-bromo-phenyl)-methanesulfonyl-amino]-4-oxo-butyl} ester *O*-ethyl ester (3-34)



Following the general procedure **3-II** for the addition of xanthate to olefin, the reaction was carried out with the solution of **3-3** (229mg, 0.556mmol) and allylboronic acid pinacolester (187mg, 1.11mmol) in AcOEt (0.6ml, 0.9M), with 10%mol of DLP. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **3-34** (208mg, 84%) as a light yellow oil.

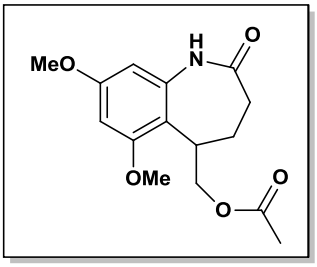
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.59 (dd, 2H, J=1.6Hz, J=8.4Hz, Br-C-C*H*), 7.14 (dd, 2H, J=1.7Hz, J=8.5Hz, C*H*-CN), 4.65-4.52 (m, 2H, CH_2CH$_3$), 3.90-3.83 (m, 1H, C*H*S), 3.46 (s, 3H, SO_2-CH_3), 2.28-2.21 (m, 2H, CO-CH_2), 2.18-2.07 (m, 1H, C*H*H-CH_2CO), 1.96-1.87 (m, 1H, C*H*H-CH_2CO), 1.39 (t, 3H, J=7.1Hz, CH_2CH_3), 1.27-1.22 (m, 2H, CH_2B), 1.22 (s, 6H, 2CCH_3), 1.21 (s, 6H, 2CCH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.2 (S=*C*), 173.0 (O=*C*-NMs), 134.2 (N-*C*), 133.3 (2 Br-C-*C*), 131.4 (2 N-C-*C*), 124.5 (Br-*C*), 83.6 (2*C*(CH_3)$_2$), 69.8 (*C*H_2CH$_3$), 47.0 (*C*HS), 42.2 (SO_2-*C*), 34.2 (*C*H_2-CO), 30.9 (*C*H_2-CH_2CO), 24.8 (2*C*H$_3$), 24.7 (2*C*H$_3$), 13.8 (CH_2*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2983, 2936, 1709, 1484, 1444, 1363, 1218, 1143, 1112, 1051, 1016, 966

HRMS (EI+) Calcd. for $C_{21}H_{31}BBrNO_6S_3$: 579.0590 Found : 589.0608

(2,3,4,5-tetrahydro-6,8-dimethoxy-2-oxo-1H-benzo[b]azepin-5-yl)methyl acetate (3-35)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-32** (70mg, 0.14mmol) and 2,6-lutidine (0.02ml, 0.14mmol) in chlorobenzene (7ml, 0.02mmol/ml), with DTBP (0.13ml, 0.71mmol) for 90min. Flash chromatography on silica gel with Acetone / DCM = 10 / 90 ~ 20 / 80 afforded **3-35** (27mg, 64%) as a colourless oil.

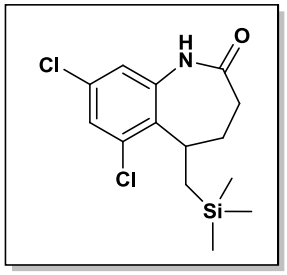
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.18 (br s, 1H, CO-N*H*), 6.30 (d, 1H, J=2.4Hz, MeO-C-C*H*-C-OMe), 6.07 (d, 1H, J=2.3Hz, MeO-C-C*H*-C-N), 4.25 (d, 2H, J=7.8Hz, CH_2OAc), 3.90-3.83 (m, 1H, C*H*), 3.80 (s, 3H, -OCH_3), 3.79 (s, 3H, -OCH_3), 2.53-2.43 (m, 1H, C*H*H-CH_2CO), 2.36-2.27 (m, 2H, CH*H*-CH_2CO + CH*H*CO), 2.19-2.11 (m, 1H, CH*H*CO), 1.97 (s, 3H, COCH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.9 (O=*C*-NH), 170.9 (O=*C*-Ac), 159.7 (*C*-OMe), 159.3 (*C*-OMe), 139.0 (s, N-*C*), 113.6 (s, *C*-C-N), 99.4 (s, *C*H-C-N), 95.8 (s, MeO-C-*C*-C-OMe), 66.2 (*C*H_2-OAc), 55.9 (O*C*H_3), 55.4 (O*C*H_3), 32.3 (*C*H_2-CH_2CO), 32.2 (*C*H-CH_2OAc), 28.9 (*C*H_2-CONH), 20.9 (CO*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3394, 2928, 2855, 1732, 1675, 1613, 1592, 1500, 1460, 1368, 1325, 1242, 1203, 1155, 1116, 1035

HRMS (EI+) Calcd. for $C_{15}H_{19}NO_5$: 293.1263 Found : 293.1257

6,8-dichloro-4,5-dihydro-5-((trimethylsilyl)methyl)-1H-benzo[b]azepin-2(3H)-one (3-36)



Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-33** (145mg, 0.281mmol) and 2,6-lutidine (0.05ml, 0.40mmol) in chlorobenzene (20ml, 0.02mmol/ml), with DTBP (0.37ml, 2.02mmol) for 60min. Flash chromatography on silica gel with AcOEt / DCM = 30 / 70 afforded **3-36** (60.3mg, 68%) as a white powder.

m.p. : 127-131°C

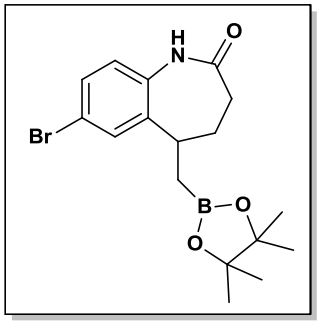
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.82 (br s, 1H, CO-N*H*), 7.23 (d, 1H, J=2.0Hz, Cl-C-C*H*-C-Cl), 6.89 (s, 1H, Cl-C-C*H*-C-N), 3.84 (q, 1H, J=7.4Hz, C*H*), 2.47-2.30 (m, 3H, CH*H*-CH_2CO + C*H*$_2$CO), 2.14-2.06 (m, 1H, C*H*H-CH_2CO), 1.11 (ddd, 1H, J=7.8Hz, J=14.9Hz, J=22.0Hz), -0.12 (s, 9H, Si(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 175.3 (O=*C*-NH), 139.6 (s, N-*C*), 135.1 (s, Cl-*C*-C), 135.0 (s, Cl-*C*-CH), 132.6 (s, N-C-*C*-C-Cl), 126.3 (s, Cl-C-*C*H-C-Cl), 121.8 (s, N-C-*C*H-C-Cl), 35.6 (*C*H_2-CH_2CO), 33.0 (*C*H), 32.0 (*C*H_2-CONH), 23.1 (*C*H_2-TMS), -1.3 (Si(*C*H_3)$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3690, 3393, 2955, 1677, 1589, 1562, 1456, 1440, 1375, 1249, 1181, 1097, 996

HRMS (EI+) Calcd. for $C_{14}H_{19}Cl_2NOSi$: 315.0613 Found : 315.0610

7-bromo-4,5-dihydro-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-1H-benzo[b]azepin-2(3H)-one (3-37)

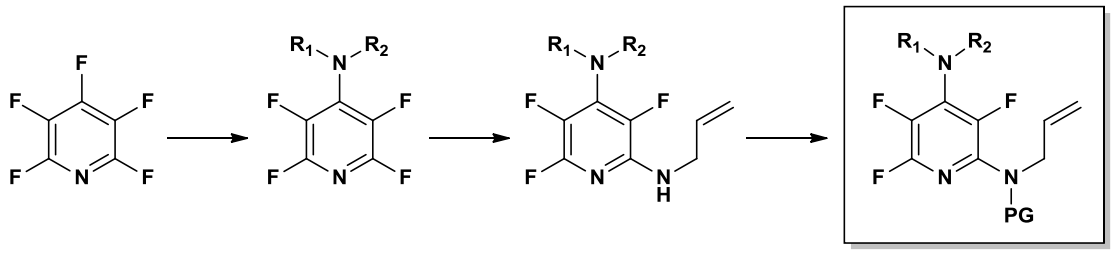


Following the general procedure **3-III** for the cyclization using DTBP, the reaction was carried out with the solution of **3-34** (54mg, 0.09mmol) and 2,6-lutidine (0.01ml, 0.11mmol) in chlorobenzene (4.7ml, 0.02mmol/ml), with DTBP (0.09ml, 0.46mmol) for 120min. Flash chromatography on silica gel with AcOEt / EP = 70 / 30 afforded **3-37** (16mg, 45%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.84 (br s, 1H, CO-N*H*),
7.42 (s, 1H, Br-C-C*H*-C), 7.33 (dd, 1H, J=2.0Hz, J=8.3Hz, Br-C-C*H*-CH), 6.84 (dd, 1H, J=3.6Hz, J=8.3Hz, Br-C-CH-C*H*), 3.32-3.23 (m, 1H, C*H*), 2.52-2.44 (m, 1H, C*H*H-CH_2CO), 2.30-2.26 (m, 2H, CH_2CO), 1.77-1.67 (m, 1H, CH*H*-CH_2CO), 1.29-1.20 (m, 2H, CH_2B), 1.20 (s, 6H, 2CCH_3), 1.14 (s, 6H, 2CCH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 174.7 (O=*C*-NH), 140.5 (s, N-*C*), 136.6 (s, N-C-*C*), 129.8 (2 Br-C-*C*H), 123.3 (s, N-C-*C*H), 119.0 (Br-*C*), 83.4 (2*C*(CH_3)$_2$), 37.1 (*C*H_2-CH_2CO), 34.8 (*C*H), 32.9 (*C*H_2-CO), 24.71 (2*C*H_3), 24.66 (2*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3631, 2982, 2943, 2253, 1674, 1480, 1375, 1328, 1265, 1143, 1016
HRMS (EI+) Calcd. for $C_{17}H_{23}BBrNO_3$: 379.0954 Found : 379.0955

Chapter 4

General procedure 4-I for preparing the olefinic precursors



Depending on the R_1 and R_2 groups of the amines, generally there were two methods for preparing 4-substituted tetrafluoropyridines. With a strong nucleophilic amine, a solution of the corresponding primary or secondary amine (2.1 eq.) was slowly added to a stirred solution of pentafluoropyridine (1 eq.) in ethanol (0.75M) at 0℃ under nitrogen. The reaction was stirred at room temperature for 10-30 minutes, then concentrated in vacuo and the residue was taken up in dichloromethane. The mixture was treated with a saturated sodium carbonate solution and the aqueous phase was extracted once with dichloromethane. Then the combined organic phase was dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. Normally it was pure enough to be involved in the next step without further purification.

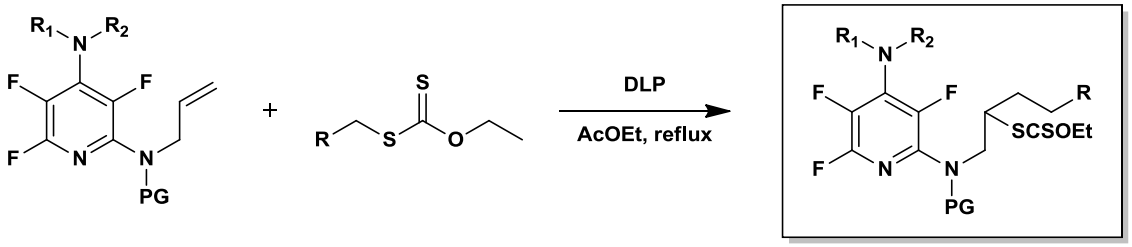
If the amines were not very strong nucleophiles, a solution of the corresponding secondary amine (1.1 eq.) was dissolved in anhydrous THF (1M), and then sodium hydride (1.2 eq.) was slowly added to this stirring solution in an ice-bain under nitrogen. The mixture was kept stirring for about 10 minutes followed by adding drop by drop to a solution of pentafluoropyridine (1.0 eq.) in anhydrous THF (1M) under nitrogen. The reaction mixture was then stirring at room temperature for 10-30 minutes. The reaction could not be monitored by TLC since the starting material was inactive to UV and other chromogenic reagent. Water was used to quench the reaction. The mixture was then taken up in dichloromethane and treated with a saturated sodium carbonate solution and the aqueous

phase was extracted once with dichloromethane. The combined organic phase was washed by water twice and dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. Normally it was pure enough to be involved in the next step without further purification.

Then 2-*N*-allylamine 4-substituted 3,5,6-trifluoropyridines were prepared following the protocol as: a mixture of allylamine (4 eq.) and the 4-substituted pentafluoropyridine (1 eq.) in THF (1.5M) under nitrogen was heated to reflux for several hours, during when more allylamine (13 eq. totally) was added several times, until the starting material was totally consumed. Then the mixture was concentrated in vacuo and the residue was taken up in dichloromethane and washed twice with a saturated sodium carbonate solution. Then the aqueous phase was extracted once with dichloromethane, and the combined organic phase was dried over magnesium sulphate, filtered and concentrated in vacuo. Normally the resulting crude product was pure enough for the following step, while it could also be purified by flash chromatography to give a pure product.

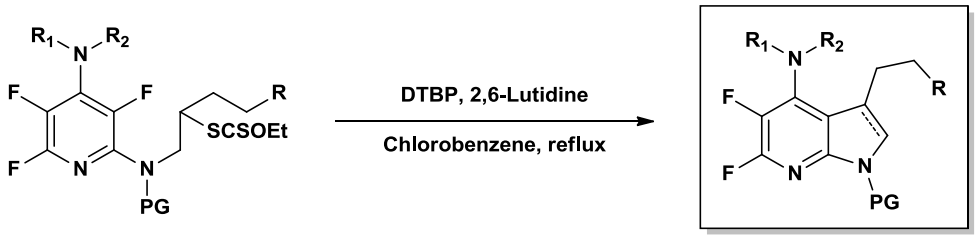
Finally, the mixture of the 2-*N*-allylamine 4-substituted 3,5,6-trifluoropyridine (1 eq.) and acetyl chloride (1.6, 4.1 eq.) in DCM (0.7M, 1M) under nitrogen was kept stirring at room temperature for several hours, during when more acetyl chloride (4.1 eq. totally) was added if necessary, until the starting material was totally consumed. Then the mixture was concentrated in vacuo and the residue was taken up in dichloromethane and washed twice with a saturated sodium carbonate solution. Then the aqueous phase was extracted once with dichloromethane, and the combined organic phase was dried over magnesium sulphate, filtered and concentrated in vacuo. The resulting crude product was then purified by flash chromatography on silica gel to yield the corresponding precursor for the radical addition.

General procedure 4-II for radical addition of xanthates



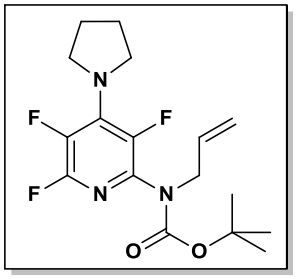
A magnetically stirred solution of the corresponding olefin (0.5-2.0 eq.) and the desired xanthates (1.0 eq.) in AcOEt (1.0M of xanthate) was refluxed for about 30min under nitrogen. Lauroyl peroxide (DLP) (10%mol) was then added to the refluxing solution, followed by additional portions (5%mol) every 90min until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

General procedure 4-III for radical cyclisation of the corresponding xanthates



A magnetically stirred solution of the corresponding xanthates (1.0 eq.) and 2,6-lutidine (1.2 eq.) in chlorobenzene (0.05M of xanthate) was refluxed for about 30min under nitrogen. Di-*t*-butyl-peroxide (DTBP) (5.0 eq.) was then added to the refluxing solution. The reaction was monitored by TLC every hour until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

tert-butyl allyl3,5,6-trifluoro-4-(pyrrolidin-1-yl)pyridin-2-ylcarbamate (4-1)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 1.43g pentafluoropyridine (8.45mmol, 1.0 eq.) and 1.50ml pyrrolidine (18.26 mmol, 2.1 eq.) in 12ml EtOH (0.75 mmol/ml) for 30 minutes. After work-up, the crude product, as white crystal, was used directly in the next step without further purification.

Then the reaction was carried out with 1.7g 4-substituted tetrafluoropyridine (7.7mmol, 1.0 eq.) and 8.5ml allylamine (111mmol, 14.4eq.) in 5.5ml THF (1.5 mmol/ml) refluxing for 3 days. After work-up, the crude product was purified by flash chromatography on silica gel with Et_2O / EP = 3 / 97 afforded the 2,4-substituted intermediate (937mg, 47%) as a colourless oil.

Finally, the protection was carried out with 760mg intermediate (2.95mmol, 1.0eq.) of last step and 5.66g di-tert-butyl-carbonate (25.9mmol, 8.8eq.) and 361mg DMAP (2.95mmol, 1.0eq.) in 22ml dichloromethane (0.2 mmol/ml) for about 36 hours at room temperature. Flash chromatography on silica gel with AcOEt / EP = 5 / 95 afforded **4-1** (924mg, 85% for 3 steps) as a colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.83 (qd, 1H, J=5.8Hz, J=11.0Hz, -C*H*=CH_2), 5.10 (ddd, 2H, J=1.5Hz, J=13.7Hz, J=35.9Hz, -CH=C*H*$_2$), 4.24 (d, 2H, J=4.6Hz, NH-C*H*$_2$), 3.72 (tt, 4H, J=2.8Hz, J=5.4Hz, -CH_2C*H*$_2$NC*H*$_2$$CH_2$-), 1.92 (tt, 4H, J=2.7Hz, J=6.6Hz, -C*H*$_2$$CH_2$$NCH_2$C*H*$_2$-), 1.43 (s, 9H, C(C*H*$_3$)$_3$)

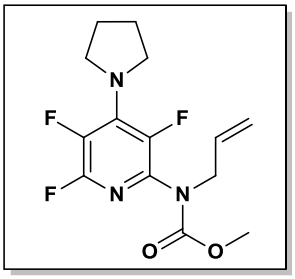
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 153.1 (*C*O), 147.4 (dd, J=15.6Hz, J=229.9Hz, N-*C*F), 141.5 (dt, J=3.2Hz, J=249.9Hz, *C*F-C-NBoc), 135.9 (td, J=5.0Hz, J=9.3Hz, N-*C*-NBoc),

134.2 (dt, J=3.2Hz, J=33.1Hz, N-*C*-CF), 133.6 (-*C*H=CH_2), 132.7 (ddd, J=4.7Hz, J=33.1Hz, J=218.0Hz, N-CF-*C*F), 116.8 (-CH=*C*H_2), 81.0 (*C*Me_3), 51.2 (t, J=6.2Hz, -*C*H_2-N-*C*H_2-), 50.1 (*C*H_2-NBoc), 28.1 (C(*C*H_3)$_3$), 25.6 (t, J=1.9Hz, -*C*H_2-CH_2-N-CH_2-*C*H_2-)

IR (ν, cm^{-1}, CCl_4) 2979, 2887, 1716, 1616, 1567, 1513, 1471, 1368, 1251, 1173, 1147, 1020

HRMS (EI+) Calcd. for $C_{17}H_{22}F_3N_3O_2$: 357.1664 Found : 357.1663

methyl allyl(3,5,6-trifluoro-4-(pyrrolidin-1-yl)pyridin-2-yl)carbamate (4-2)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 2.10g pentafluoropyridine (12.4mmol, 1.0eq.) and 2.14ml pyrrolidine (26.1mmol, 2.1 eq.) in 16.6ml EtOH (0.75 mmol/ml) for 10 minutes. After work-up, ~2.7g crude product, as white crystal, was used directly in the next step without further purification.

Then the reaction was carried out with 2.66g 4-substituted tetrafluoropyridine (12.1mmol, 1.0 eq.) and 14.5ml allylamine (193mmol, 16eq.) in 8ml THF (1.5 mmol/ml) refluxing for 112 hours. After work-up, ~3.0g crude product, as colourless oil, was used directly in the next step without further purification.

Finally, the protection was carried out with 1.39g intermediate (5.41mmol, 1.0eq.) of last step in 13.5ml methyl chloroformate (0.4mmol/ml) refluxing for about 12 hours. Flash chromatography on silica gel with AcOEt / DCM = 2 / 98 afforded **4-2** (1.49g, 85% for 3 steps) as white solid.

m.p. 78~81 ^{o}C

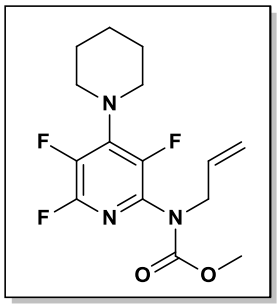
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.83 (qd, 1H, *J* = 11.0, 5.9 Hz, -C*H*=CH_2), 5.12 (dd, 2H, *J* = 33.8, 13.7 Hz, -CH=CH_2), 4.28 (d, 2H, *J* = 5.0 Hz, NH-CH_2), 3.76-3.69 (m + s, 7H, -CH_2CH_2NC$H_2$$CH_2$- + C$H_3$), 1.94-1.91 (m, 4H, -C$H_2$$CH_2NCH_2CH_2$-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 154.9 (*C*O), 147.7 (dd, *J* = 231.6, 15.2 Hz, N-*C*F), 141.9 (dt, *J* = 250.5 Hz, *C*F-C-NBoc), 136.3 (N-*C*-NBoc), 132.7 (dd, *J* = 177.4, 19.4 Hz, N-*C*-CF), 133.15 (-*C*H=CH_2), 117.4 (-CH=*C*H_2), 53.2 (*C*H_3), 51.3 (t, *J* = 6.18 Hz, -*C*H_2-N-*C*H_2-), 50.6 (*C*H_2-NBoc), 25.6 (-*C*H_2-CH_2-N-CH_2-*C*H_2-)

IR (ν, cm^{-1}, $CDCl_3$) 3695, 2980, 2975, 2889, 1715, 1616, 1564, 1519, 1473, 1449, 1422, 1368, 1355, 1309, 1277, 1252, 1198, 1179, 1139, 1116, 1022, 986

HRMS (EI+) Calcd. for $C_{14}H_{16}F_3N_3O_2$: 315.1195 Found : 315.1194

methyl allyl(3,5,6-trifluoro-4-(piperidin-1-yl)pyridin-2-yl)carbamate (4-3)



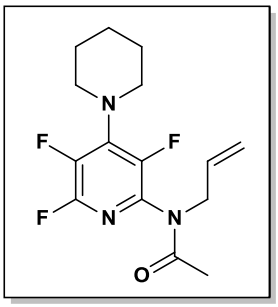
Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 1.22g pentafluoropyridine (7.22mmol, 1.0eq.) and 0.78ml piperidine (7.94mmol, 1.1eq.) in 10ml EtOH (0.75 mmol/ml) for 30 minutes. After work-up, the crude product was used directly in the next step without further purification

Then the reaction was carried out with the crude product of last step and 8.6ml allylamine (115mmol, 16eq.) in 4.8ml THF (1.5 mmol/ml) refluxing for 10 hours. After work-up, the crude product (~1.35g) was used directly in the next step without further purification.

Finally, the protection was carried out with 953mg intermediate (3.51mmol, 1.0eq.) of last step in 12.4ml methyl chloroformate (0.4mmol/ml) refluxing for about 12 hours. Flash chromatography on silica gel with Et_2O / DCM = 12 / 88 afforded **4-3** (905mg, 73% for 3 steps) as colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.83 (qd, 1H, *J* = 10.6, 5.8 Hz, C*H*=CH_2), 5.12 (ddd, 2H, *J* = 13.7, 11.6, 1.4 Hz, CH=CH_2), 4.29 (d, 2H, *J* = 5.8 Hz, CH_2-NCOOMe), 3.73 (s, 3H, COOCH_3), 3.35 (br s, 4H, CH_2-N-CH_2), 1.68 (br s, 6H, CH_2-CH_2-CH_2)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 154.7 (*C*O), 147.0 (dd, *J* = 234, 15 Hz, N-*C*F) 144.9 (d, *J* = 254 Hz, *C*F-C-NCO), 139.4-139.1 (m, N(piperidine)-*C*), 136.4 (dd, *J* = 256, 31 Hz, C-*C*F-CF), 133.5 (dt, *J* = 16, 3.9 Hz, N-*C*-N-CO), 133.0 (*C*H=CH_2), 117.3 (CH=*C*H_2), 53.3 (COO*C*H_3), 51.5 (t, *J* = 5.0 Hz, *C*H_2-N-*C*H_2), 50.5 (*C*H_2-NCOOMe), 26.3 (*C*H_2-CH_2-N-CH_2-*C*H_2), 24.0 (-N-CH_2-CH_2-*C*H_2)
IR (ν, cm^{-1}, $CDCl_3$) 3424 ,3086, 2988, 2943, 2857, 1714, 1618, 1570, 1512, 1444, 1365, 1331, 1246, 1190, 1155, 1123, 1104, 1071, 1027, 994
HRMS (EI+) Calcd. for $C_{15}H_{18}F_3N_3O_2$: 329.1351 Found : 329.1350

***N*-allyl-*N*-(3,5,6-trifluoro-4-(piperidin-1-yl)pyridin-2-yl)acetamide (4-4)**



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 3.02g pentafluoropyridine (17.88mmol, 1.0 eq.) and 3.7ml pyrrolidine (37.56 mmol, 2.1 eq.) in 24ml EtOH (0.75 mmol/ml) for 30 minutes. After work-up, the crude

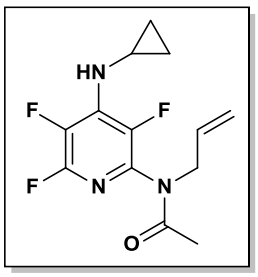
product was purified by flash chromatography on silica gel with DCM / EP = 5 / 95 to give the 4-substituted intermediate (3.91g, 94%) as a colourless oil.

Then the reaction was carried out with 3.91g 4-substituted tetrafluoropyridine (16.7mmol, 1.0 eq.) and 10ml allylamine (134mmol, 8 eq.) in 11ml THF (1.5 mmol/ml) refluxing for 40 hours. After work-up, the crude product was used directly in the next step without further purification.

Finally, the acetylation was carried out with 4.53g 2,4-substituted intermediate (16.7mmol, 1.0eq.) of last step in 20ml acetyl chloride (0.4 mmol/ml) for about 10 minutes at room temperature. After work-up, flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **4-4** (5.0g, 89% for 3 steps) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.80 (qd, 1H, J=6.1Hz, J=11.4Hz, C*H*=CH_2), 5.15-5.07 (m, 2H, CH=C*H*$_2$), 4.31 (d, 2H, J=5.8Hz, C*H*$_2$-NAc), 3.37 (s, 4H, C*H*$_2$-N-C*H*$_2$), 1.95 (s, 3H, COC*H*$_3$), 1.67 (s, 6H, C*H*$_2$-C*H*$_2$-C*H*$_2$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.7 (*C*OMe), 147.4 (dd, J=10.0Hz, J=232.2Hz, N-*C*F), 145.0 (d, J=253.6Hz, *C*F-C-NCO), 136.7 (dd, J=33.8Hz, J=258.0Hz, C-*C*F-CF), 139.4 (N(piperidine)-*C*), 134.6 (m, N-*C*-N-CO), 132.7 (*C*H=CH_2), 117.8 (CH=*C*H$_2$), 51.5 (t, J=4.1Hz, *C*H$_2$-N-*C*H$_2$), 49.5 (*C*H$_2$-NAc), 26.3 (*C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$), 23.9 (-N-CH$_2$-CH$_2$-*C*H$_2$), 21.9 (CO*C*H$_3$)

***N*-allyl-*N*-(4-(cyclopropylamino)-3,5,6-trifluoropyridin-2-yl)acetamide (4-5)**



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 3.10g pentafluoropyridine (18.32mmol, 1.0 eq.) and 1.4ml cyclopropylamine (20.15 mmol, 1.1 eq.) in 25ml EtOH (0.75 mmol/ml) for 30 minutes. After work-up, 2.68g crude product, as yellow oil, was used directly in the next step without further purification.

Then the reaction was carried out with 2.68g 4-substituted tetrafluoropyridine (13.0mmol, 1.0 eq.) and 19.6ml allylamine (261mmol, 20 eq.) in 9ml THF (1.5 mmol/ml) refluxing for 74 hours. After work-up, 3.53g crude product was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of last step and 10ml acetyl chloride (1.5mmol/ml) refluxing for about 20 hours. After work-up, flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **4-5** (364mg, 79% for 3steps) as light brown oil.

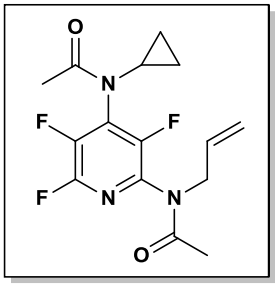
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.80 (qd, 1H, J=6.1Hz, J=11.5Hz, -C*H*=CH_2), 5.11 (dd, 2H, J=13.9Hz, J=21.0Hz, -CH=C*H*$_2$), 4.79 (s, 1H, N*H*), 4.32 (d, 2H, J=6.0Hz, N-C*H*$_2$), 2.98 (br s, 1H, N-C*H*), 1.95 (s, 3H, COC*H*$_3$), 0.87 (q, 2H, J=6.7Hz, -C*H*H-C*H*H-), 0.69 (m, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.7 (*C*OCH_3), 147.0 (ddd, J=1.7Hz, J=13.5Hz, J=233.9Hz, N-*C*F), 141.2 (dd, J=2.4Hz, J=251.2Hz, *C*F-C-NAc), 136.6 (td, J=6.7Hz, J=13.8Hz, NH-*C*-CF), 132.6 (-*C*H=CH_2), 132.5 (ddd, J=1.9Hz, J=34.1Hz, J=255.3Hz, N-CF-*C*F), 132.3 (N-*C*-NAc), 117.8 (-CH=*C*H$_2$), 49.5 (*C*H$_2$-NAc), 26.7 (dd, J=1.7Hz, J=4.1Hz, *C*H-NH), 21.9 (d, J=1.9Hz, CO*C*H$_3$), 8.7 (dd, J=1.3Hz, J=2.9Hz, -*C*H$_2$-*C*H$_2$-)

IR (ν, cm^{-1}, $CDCl_3$) 3428, 3016, 1669, 1625, 1527, 1477, 1455, 1419, 1361, 1259, 1226, 1182, 1103, 1030, 983

HRMS (EI+) Calcd. for $C_{13}H_{14}F_3N_3O$: 285.1089 Found : 285.1083

_N_-(4-(_N_-cyclopropyl-_N_-acetylamino)-3,5,6-trifluoropyridin-2-yl)-_N_-allylacetamide (4-6)



Following the procedure for preparing olefinic precursor **4-5**, final purification by flash chromatography on silica gel with AcOEt / DCM / EP = 20 / 40 / 40 afforded **4-6** (2.88g, 53% for 4 steps) as light brown oil.

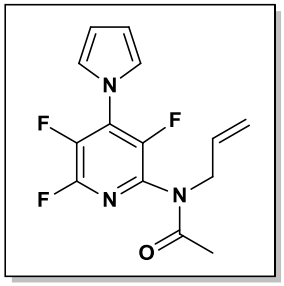
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.80 (qd, 1H, J=5.9Hz, J=11.2Hz, -C*H*=CH_2), 5.12 (t, 1H, J=12.6Hz, -CH=C*H*$_2$), 4.38 (ddd, 1H, J=2.1Hz, J=13.1Hz, J=16.1Hz, N-C*H*$_2$), 3.21 (s, 1H, N-C*H*), 2.45 (s, 3H, C*H*$_3$-CO-NCH), 2.03 (s, 3H, C*H*$_3$-CO-NCH_2), 1.01 (s, 2H, -C*H*H-C*H*H-), 0.68 (s, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.8 (*C*O-NCH), 169.6 (*C*O-NCH_2), 147.8 (d, J=255.0Hz, N-*C*F), 146.0 (dd, J=13.3Hz, J=239.9Hz, *C*F-C-NAc), 140.4 (dd, J=31.1Hz, J=268.0Hz, N-CF-*C*F), 134.6 (N-*C*-CF), 132.4 (-*C*H=CH_2), 131.4 (N-*C*-NBoc), 118.1(-CH=*C*H_2), 49.8 (*C*H_2-NAc), 31.4 (*C*H-NAc), 22.3 (*C*H_3-CO-NCH), 21.9 (d, J=2.0Hz, *C*H_3-CO-NCH_2), 9.49 (-*C*H_2-*C*H_2-)

IR (ν, cm^{-1}, $CDCl_3$) 3018, 1682, 1618, 1484, 1464, 1423, 1376, 1316, 1257, 1230, 1186, 1104, 1035, 981

HRMS (EI+) Calcd. for $C_{15}H_{16}F_3N_3O_2$: 327.1195 Found : 327.1193

_N_-allyl-_N_-(3,5,6-trifluoro-4-(1_H_-pyrrol-1-yl)pyridin-2-yl)acetamide (4-7)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 440mg pyrrole (6.45 mmol, 1.1 eq.) and 292mg NaH (7.04 mmol, 1.2 eq.) in 6ml anhydrous THF (1.1 mmol/ml), with 992mg pentafluoropyridine (5.86 mmol, 1.0 eq.) in 6ml anhydrous THF (1.0 mmol/ml) for 10 minutes. Flash chromatography on silica gel with DCM / EP = 5 / 95 afforded 2,3,5,6-tetrafluoro-4-(1*H*-pyrrol-1-yl)pyridine (783mg, 62%) as a white solid.

Then the reaction was carried out with 783mg 4-substituted tetrafluoropyridine (3.6 mmol, 1.0 eq.) and 2.2mg allylamine (29 mmol, 8.1 eq.) in 2.4ml THF (1.5 mmol/ml) refluxing for 1 hour. After work-up, the crude product as a light brown oil was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step and 1.04ml acetyl chloride (14.6mmol, 4.1 eq.) in 4.6ml dichloromethane (0.7 mmol/ml) for about 40 hours at room temperature. Flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **4-7** (1.03g, 97% for 2 steps) as a light yellow oil.

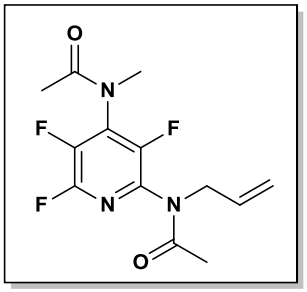
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.12 (m, 2H, C*H*-N-C*H*), 6.46 (m, 2H, CH-C*H*-C*H*-CH), 5.83 (qd, 1H, J=5.8Hz, J=11.0Hz, C*H*), 5.17 (dd, 2H, J=13.8Hz, J=19.7Hz, CHCH_2), 4.41 (d, 2H, J=5.8Hz, CH-CH_2-N), 2.10 (s, 3H, CO-CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.5 (*C*O), 146.91 (dd, J=14.5Hz, J=241.5Hz, N-*C*F), 144.41 (dd, J=5.5Hz, J=260.7Hz, N-CF-*C*F), 136.93 (dd, J=31.9Hz, J=266.3Hz, CO-N-

C-*C*F), 135.67 (d, J=6.4Hz, CF-*C*-N-CO), 132.3(*C*H), 129.5 (CF-CF-*C*), 122.1 (t, J=4.7Hz, *C*H-N-*C*H), 118.2 (CH*C*H_2), 112.0 (CH-*C*H-*C*H-CH), 50.2 (N-*C*H_2-CH), 22.0 (CO-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2927, 2855, 1677, 1619, 1519, 1468, 1377, 1265, 1201, 1177, 1102, 1026, 981

HRMS (EI+) Calcd. for $C_{14}H_{12}F_3N_3O$: 295.0932 Found : 295.0927

_N_-allyl-_N_-(3,5,6-trifluoro-4-(_N_-methylacetamido)pyridin-2-yl)acetamide (4-8)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 2.80g pentafluoropyridine (16.58 mmol, 1.0 eq.) and 3.58ml $MeNH_2$ (34.82 mmol, 2.1 eq.) in 14ml EtOH (1.2 mmol/ml) for 30 minutes. After work-up, the crude product as a white acicrilar crystal was divided into two eq.alent parts and one of them was used directly in the next step without further purification.

Then the reaction was carried out with 1.49g 4-substituted tetrafluoropyridine (8.3 mmol, 1.0 eq.) and 13ml allylamine (29 mmol, 20.9 eq.) in 5.5ml THF (1.5 mmol/ml) refluxing for 117 hours. After work-up, the crude product as a dark brown oil was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step and 0.95ml acetyl chloride (13.4mmol, 1.6 eq.) in 8.0ml dichloromethane (1.0 mmol/ml) for about 1.5 hours at room temperature. Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 afforded 2-*N*-allylamine protected pyridine (1.04g, 48% for 3 steps) alone with 4-

methylamine protected pyridine (116mg, 5.4% for 3 steps). Then 802mg of 2-N-allylamine protected pyridine (3.10mmol, 1.0 eq.) was dissolved by 2.0ml acetyl chloride (28.1mmol, 9.1 eq.) and refluxed overnight to complete the acetylation. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-8** (813mg, 87%) as yellow oil.

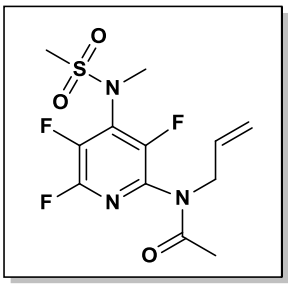
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.85-5.78 (m, 1H, C*H*), 5.15 (t, *J* = 13.45 Hz, 2H, CHCH_2), 4.48-4.37 (m, 2H, CH-CH_2-N), 3.27 (br s, 3H, N-CH_3), 2.31-1.98 (m, 6H, N-CO-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.7 (CH_3-N-*C*O + N-*C*O), 147.5 (d, *J* = 258.91 Hz, N-*C*F), 146.1 (d, *J* = 241.62 Hz, N-CF-*C*F), 140.1 (d, *J* = 252.95 Hz, CO-N-C-*C*F), 136.18-134.08 (m, CF-*C*-N-CO), 133.8-132.6 (m, CF-CF-*C*), 132.4 (*C*H), 118.1 (CH-*C*H_2), 51.6-48.3 (m, CO-N-*C*H_2), 37.9 + 35.5(m, N-*C*H_3), 22.0 + 21.3 (N-*C*O-CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2942, 1681, 1618, 1489, 1471, 1468, 1464, 1422, 1376, 1332, 1300, 1245, 1204, 1124, 1036, 1011, 980

HRMS (EI+) Calcd. for $C_{13}H_{14}F_3N_3O_2$ **:** 301.1038 Found : 301.1035

***N*-allyl-*N*-(3,5,6-trifluoro-4-(*N*-methylmethylsulfonamido)pyridin-2-yl)acetamide (4-9)**



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 2.80g pentafluoropyridine (16.58 mmol, 1.0 eq.) and 3.58ml $MeNH_2$ (34.82 mmol, 2.1 eq.) in 14ml EtOH (1.2 mmol/ml) for 30 minutes. After work-up, the crude

product as a white acicrilar crystal was divided into two eq.alent parts and one of them was used directly in the next step without further purification.

The crude product of last step was dissolved in 8.3ml anhydrous THF (1.0 mmol/ml) in an ice-bain under nitrogen, and then 346mg sodium hydride (9.12mmol, 1.1 eq.) was slowly added to this stirring solution. The mixture was kept stirring for about 15 minutes followed by adding drop by drop 0.8ml methanesulfonyl chloride (9.95mmol, 1.2 eq.). The reaction mixture was then stirring at room temperature for 45 minutes until the starting material was totally consumed. After work-up, the crude product was purified with flash chromatography on silica gel with DCM / EP = 45 / 55 afforded 4-substituted tetrafluoropyridine (891mg, 42% for 2 steps) as a light yellow oil.

Then the reaction was carried out with 880mg 4-substituted tetrafluoropyridine (3.41 mmol, 1.0 eq.) and 1.02ml allylamine (13.6 mmol, 4.0 eq.) in 7.3ml THF (0.5 mmol/ml) stirring at room temperature for 1 hour. After work-up, the crude product as an orange oil was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step, which was dissolved by 2.3ml acetyl chloride (32.3mmol, 9.5 eq.) and stirred at room temperature overnight and then refluxed for 20 minutes to complete the acetylation. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 35 / 65 afforded **4-9** (950mg, 83% for 2 steps) as light yellow oil.

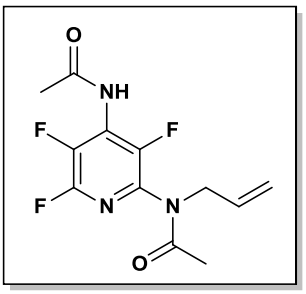
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.81 (qd, 1H, J=5.7Hz, J=10.9Hz, C*H*), 5.15 (t, 2H, J=13.2Hz, CHCH_2), 4.38 (d, 2H, J=5.7Hz, CH-CH_2-N), 3.35 (s, 3H, N-CH_3), 3.13 (s, 3H, Ms-CH_3), 2.07 (s, 3H, CO-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (*C*OMe), 148.7 (dd, J=6.8Hz, J=262.5Hz, N-*C*F), 146.1 (ddd, J=2.4Hz, J=14.5Hz, J=17.3Hz, CH_3-N-C-*C*F), 141.6 (dd, J=30.3Hz, J=269.0Hz, CO-N-C-*C*F), 135.2 (m, N-C-N), 132.2 (s, *C*H), 130.3 (m, CH_3-N-*C*-CF), 118.1 (s, N-CH_2-CH-*C*H_2), 50.1 (m, N-*C*H_2), 39.0 (s, SO_2-*C*H_3), 37.3 (s, N-*C*H_3), 21.9 (d, J=1.8Hz, CO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2940, 1710, 1681, 1618, 1484, 1467, 1430, 1359, 1329, 1244, 1222, 1162, 993, 964

HRMS (EI+) Calcd. for $C_{12}H_{14}F_3N_3O_3S$:337.0708 Found : 337.0726

***N*-(4-acetamido-3,5,6-trifluoropyridin-2-yl)-*N*-allylacetamide (4-10)**



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 2.5g pentafluoropyridine (14.8 mmol, 1.0 eq.) and 10ml ammonia (25%) (64.4mmol, 4.3eq.) in 12ml EtOH (1.2 mmol/ml) refluxing for 16 hours. After work-up, the crude product as 2.09g white solid was used directly in the next step without further purification. Then 2.09g crude product of last step was dissolved by 12ml acetyl chloride (168.8mmol, 13.4 eq.) and refluxed overnight to complete the reaction. After work-up, the crude product as 2.48g white solid was used directly in the next step without further purification.

Then the reaction was carried out with 1.07g crude product of last step (5.12 mmol, 1.0 eq.) and 1.54ml allylamine (20.5 mmol, 4.0 eq.) in 3.4ml THF (1.5 mmol/ml). The mixture was stirring at room temperature overnight and then refluxed for 1 hour to complete the reaction. After work-up, the crude product as a light pink solid was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step which was dissolved by 3.4ml acetyl chloride (47.8mmol, 9.3 eq.) and was stirring at room temperature

overnight and then refluxed for 1 hour to complete the acetylation. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **4-10** (1.20g, 66% for 4 steps) as a white solid.

m.p. 126-127 ^{o}C

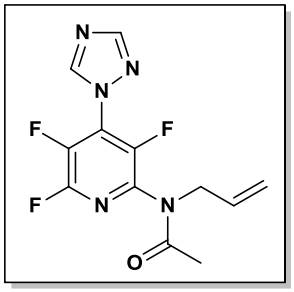
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.89 (s, 1H, N*H*), 5.79 (m, 1H, C*H*), 5.15 (m, 2H, CHCH_2), 4.33 (d, J=5.78 Hz, 2H, CH-CH_2-N), 2.23 (s, 3H, NH-CO-CH_3), 2.01 (brs, 3H, N-CO-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 170.4 (NH-*C*O), 169.9 (N-*C*O), 146.2 (ddd, *J* = 239.97, 14.43, 2.43 Hz, N-*C*F), 145.7 (dd, *J* = 260.56, 2.93 Hz, N-CF-*C*F), 138.5 (dd, *J* = 267.64, 31.28 Hz, CO-N-C-*C*F), 134.06 (m, CF-*C*-N-CO), 132.0 (*C*H), 127.0 (m, CF-CF-*C*), 118.2 (CH*C*H_2), 50.0 (N-*C*H_2-CH), 23.0 (NHCO-*C*H_3), 21.9 (NCO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3419, 2930, 1727, 1681, 1621, 1500, 1472, 1449, 1382, 1224

HRMS (EI+) Calcd. for $C_{12}H_{12}F_3N_3O_2$: 287.0882 Found : 287.0881

***N*-allyl-*N*-(3,5,6-trifluoro-4-(1*H*-1,2,4-triazol-1-yl)pyridin-2-yl)acetamide (4-11)**



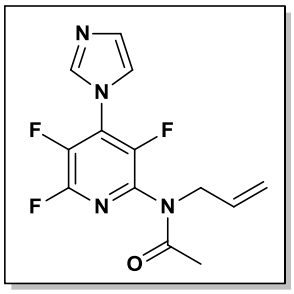
Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 500mg pentafluoropyridine (2.96 mmol, 1.0 eq.), 252mg triazole (3.64mmol, 1,2 eq.) and 0.5ml TEA (3.55mmol, 1.2 eq.) in 2.5ml EtOH (1.2 mmol/ml) stirring at room temperature for 16 hours. After work-up, the crude product was used directly in the next step without further purification.

Then the reaction was carried out with the crude product of last step (2.96 mmol, 1.0 eq.) and 0.88ml allylamine (11.8 mmol, 4.0 eq.) in 6ml THF (0.5 mmol/ml). The mixture was stirring at room temperature overnight and then refluxed for 20 minutes to complete the reaction. After work-up, the crude product was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step which was dissolved by 2.0ml acetyl chloride (28.1mmol, 9.5 eq.) and was refluxed for 1 hour to complete the acetylation. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **4-11** (869mg, 99% for 3 steps) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.59 (s, 1H, C-N-C*H*), 8.26 (s, 1H, C-N-N-C*H*), 5.83 (qd, *J* = 10.68, 5.59 Hz, 1H, C*H*), 5.18 (t, *J* = 14.72 Hz, 2H, CHCH_2), 4.43 (d, *J* = 5.55 Hz, 2H, CH-CH_2-N), 2.15 (s, 3H, CO-CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (N-*C*O), 153.5 (C-N-N-*C*), 146.3 (ddd, *J* = 242.25, 14.08, 2.75 Hz, N-*C*F), 145.4 (m, CF-*C*-N-CO), 144.1 (ddd, *J* = 265.85, 6.08, 2.80 Hz, N-CF-*C*F), 137.1 (dd, *J* = 273.21, 32.83 Hz, CO-N-C-*C*F), 132.1 (*C*H), 125.6 (m, CF-CF-*C*), 118.3 (CH*C*H_2), 50.3 (N-*C*H_2-CH), 22.0 (*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3692, 3606, 3138, 2931, 1682, 1623, 1603, 1531, 1522, 1471, 1420, 1387, 1377, 1328, 1265, 1241, 1201, 1171, 1130, 993, 981
HRMS (EI+) Calcd. for $C_{12}H_{10}F_3N_5O$: 297.0837 Found : 297.0848

***N*-allyl-*N*-(3,5,6-trifluoro-4-(1*H*-imidazol-1-yl)pyridin-2-yl)acetamide (4-12)**



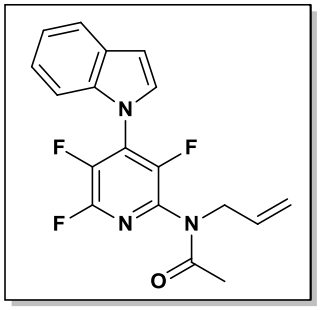
Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 500mg pentafluoropyridine (2.96 mmol, 1.0 eq.) and 239mg imidazole (3.51mmol, 1,2 eq.) in 2.5ml EtOH (1.2 mmol/ml) stirring at room temperature for 19 hours. After work-up, the crude product was used directly in the next step without further purification.

Then the reaction was carried out with the crude product of last step (2.96 mmol, 1.0 eq.) and 0.88ml allylamine (11.8 mmol, 4.0 eq.) in 6ml THF (0.5 mmol/ml). The mixture was stirring at room temperature overnight and then refluxed for 20 minutes to complete the reaction. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded the product as a white solid.

Finally, the acetylation was carried out with 306mg crude product of last step. It was dissolved by 12ml anhydrous DMF (0.1 mmol/ml) and 58mg of NaH (60%) (1.45mmol, 1.2 eq.) was added little by little. Then 0.41ml acetyl chloride (6.01mmol, 5 eq.) was added drop by drop. The mixture was refluxed for several hours until the starting material was totally consumed. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / DCM = 35 / 65 afforded **4-12** (302mg, 84% for 3 steps) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.95 (s, 1H, N-C*H*-N), 7.38 (s, 1H, C-N-C*H*), 7.30 (s, 1H, C-N-CH-C*H*), 5.84 (qd, *J* = 10.77, 5.60 Hz, 1H, C*H*), 5.19 (t, *J* = 14.77 Hz, 2H, CHCH_2), 4.43 (d, *J* = 5.65 Hz, 2H, CH-CH_2-N), 2.15 (s, 3H, CO-CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (N-*C*O), 146.5 (ddd, *J* = 241.38, 14.46, 2.66 Hz, N-*C*F), 144.0 (ddd, *J* = 7.94, 6.75, 2.07 Hz, N-CF-*C*F), 137.3 (t, *J* = 5.22 Hz, N-*C*H-N), 136.7 (dd, *J* = 268.39, 32.47 Hz, CO-N-C-*C*F), 136.4-133.5 (m, CF-*C*-N-CO), 132.2 (*C*H), 130.7 (N-*C*H-CH), 127.8-124.5 (m, CF-CF-*C*), 119.3 (t, *J* = 3.64 Hz, N-CH-*C*H_2), 118.2 (CH*C*H_2), 50.4 (N-*C*H_2-CH), 30.90 (s,1C), 22.0 (d, *J* = 1.14 Hz, *C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3692, 1681, 1621, 1518, 1471, 1380, 1243, 1207, 1175, 1077
HRMS (EI+) Calcd. for $C_{13}H_{11}F_3N_4O$: 296.0885 Found : 296.0882

N-allyl-N-(3,5,6-trifluoro-4-(1H-indol-1-yl)pyridin-2-yl)acetamide (4-13)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 350mg indole (2.99 mmol, 1.0 eq.) and 118mg NaH (60%) (2.96 mmol, 1.0 eq.) in 3ml anhydrous THF (1.0 mmol/ml), with 500mg pentafluoropyridine (2.96 mmol, 1.0 eq.) in 3ml anhydrous THF (1.0 mmol/ml) for 1 hour. After work-up, the crude product was used directly in the next step without further purification.

Then the reaction was carried out with the crude product of last step and 1.1ml allylamine (14 mmol, 4.7 eq.) in 3.5ml THF (0.9 mmol/ml) stirring overnight. After work-up, the crude product as was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of the last step and 3ml acetyl chloride (42mmol, 14 eq.) refluxing for 1 hour to complete the reaction. Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **4-13** (848mg, 83% for 3 steps) as a light yellow solid.

m.p. 82-84 ^{o}C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.70 (d, *J* = 7.74 Hz, 1H, N-C*H*), 7.36-7.27 (m, aromatic 4H), 6.85 (d, *J* = 3.4 Hz, 1H, N-CH-C*H*), 5.88 (dt, *J* = 10.8, 5.7 Hz, 1H, C*H*), 5.21 (dd, *J* = 21.8, 13.8 Hz, 2H, CHCH_2), 4.47 (d, *J* = 5.7 Hz, 2H, CH-CH_2-N), 2.17 (s, 3H, CO-CH_3)

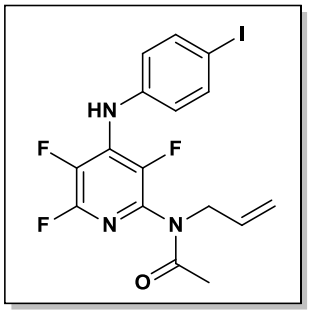
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (N-*C*O), 146.6 (ddd, *J* = 241, 14, 2.6 Hz, N-*C*F), 145.9 (dd, *J* = 263, 5.0 Hz, N-CF-*C*F), 138.5 (dd, *J* = 269, 31 Hz, CO-N-C-*C*F), 135.6

(m, CF-*C*-N-CO), 135.4 (*C*H), 132.4, 129.0, 127.4, 123.7, 122.1, 121.4 (6s, aromatic C), 128.4 (m, CF-CF-*C*), 118.1 (CH*C*H_2), 111.0 (N-CH-*C*H), 107.3 (N-*C*H), 50.3 (N-*C*H_2-CH), 22.1 (*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3692, 2930, 1678,1609, 1532,1508, 1467, 1380, 1259,1242, 1209, 1173, 1096

HRMS (EI+) Calcd. for $C_{18}H_{14}F_3N_3O$: 345.1089 Found : 345.1084

***N*-allyl-*N*-(3,5,6-trifluoro-4-((4-iodophenyl)amino)pyridin-2-yl)acetamide (4-14)**



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 946mg pentafluoropyridine (5.6 mmol, 1.9eq.) and 626mg 4-iodoaniline (2.9mmol, 1.0eq.) in 8ml EtOH (0.4 mmol/ml) stirring at room temperature for 120 hours. After work-up, the crude product was used directly in the next step without further purification.

Then the reaction was carried out with 409mg crude product of last step (1.11 mmol, 1.0 eq.) and 1.34ml allylamine (17.9 mmol, 16eq.) in 2ml THF (0.5 mmol/ml). The mixture was refluxed for 4 days to complete the reaction. After work-up, the crude product was purified with flash chromatography on silica gel with DCM / EP = 60 / 40 to give the intermediate (1.07g, 91% for 2 steps) as brown oil.

Finally, the acetylation was carried out with 1.07g crude product of last step. It was dissolved by 9ml DCM (0.3 mmol/ml) and 0.76ml acetyl chloride (10.7mmol, 4eq.) was added drop by

drop under ice-bain. The mixture was refluxed for 3 hours until the starting material was totally consumed. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 20 / 80 to afford **4-14** (1.08g, 84% for 3 steps) as white solid.

m.p. 154~157^{o}C

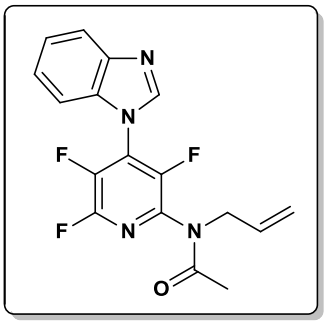
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.64 (d, 2H, *J* = 8.6 Hz, aromatic-C*H*), 6.81 (d, 2H, *J* = 8.3 Hz, aromatic-C*H*), 6.49 (br s, 1H, N*H*), 5.80 (dt, 1H, *J* = 10.7, 5.6 Hz, C*H*=CH_2), 5.36-5.02 (dd,2H, *J* = 21.6, 10.4 Hz, CH=CH_2), 4.35 (d, 2H, *J* = 5.9 Hz, CHCH_2), 2.01 (br s, 3H, CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 170.0 (*C*O), 146.9 (dd, *J* = 237.3, 13.2 Hz, N-*C*F), 142.7 (dd, *J* = 254.1, 3.9 Hz, *C*F-C-NAc), 138.5 (NH-*C*-CH), 138.0 (2 *C*H-C-I), 134.2 (dd, *J* = 259.3, 33.5 Hz, CF-*C*F-CNH), 134.1 (*C*-NH), 132.5 (*C*H=CH_2), 131.9 (d, *J* = 11.4 Hz, *C*-NAc), 123.0 (2 *C*H-C-NH), 118.1 (CH=*C*H_2), 88.3 (*C*-I), 49.8 (NAc-*C*H_2), 22.0 (d, *J* = 1.5 Hz, *C*H_3),

IR (ν, cm^{-1}, CCl_4) 3418, 2959, 1688, 1657, 1621, 1585, 1476, 1371, 1306, 1264, 1235, 1117, 1094, 1059, 1008, 979, 929

HRMS (EI+) Calcd. for $C_{16}H_{13}F_3IN_3O$: 447.0055 Found : 447.0055

N-(4-(1H-benzo[d]imidazol-1-yl)-3,5,6-trifluoropyridin-2-yl)-N-allylacetamide (4-15)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 458mg benzimidazole (3.9 mmol, 1.1eq.) and 0.6ml TEA (4.3mmol, 1.2eq.) with 597mg pentafluoropyridine (3.5 mmol, 1.0eq.) in 3ml EtOH (1.0 mmol/ml) stirring

overnight at room temperature. After work-up, the crude product was used directly in the next step without further purification.

Then the reaction was carried out with the crude product of last step and 1.1ml allylamine (14 mmol, 4.0eq.) in 2.4ml THF (1.5 mmol/ml) stirring overnight. After work-up, the crude product was used directly in the next step without further purification.

Finally, the acetylation was carried out with the crude product of last step in 3ml acetyl chloride (1.2mmol/ml) stirring overnight at room temperature, and then refluxing for 1 hour to complete the reaction. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 40 / 60 to give **4-15** (770mg, 63% for 3 steps) as light yellow sticky oil.

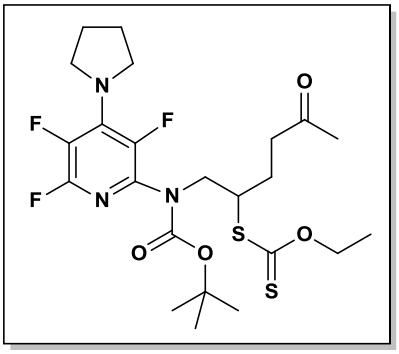
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.11 (s, 1H, NC*H*), 7.90-7.88 (m, 1H, C*H*CHCHCH), 7.42-7.40 (m, 2H, CHC*H*C*H*CH), 7.32 (brs, 1H, CHCHCHC*H*), 5.87 (tdd, *J* = 16.02, 10.57, 5.44 Hz, 1H, CH_2C*H*), 5.26-5.18 (m, 2H, CH=CH_2), 4.47 (d, *J* = 5.32 Hz, 2H, NCH_2), 2.20 (brs, 3H, N-CO-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (N-*C*O), 147.9 (ddd , *J* = 276.05, 14.43, 2.43 Hz, N-*C*F), 146.3 (dd, *J* = 242.42, 11.84 Hz, N-CF-*C*F), 143.1 (CF-C-N-*C*), 141.5 (N*C*H), 136.7 (dd, *J* = 250.40, 14.52 Hz, CO-N-C-*C*F), 134.1-133.9 (m, CF-*C*-N-CO), 132.3 (N-CH-N-*C*), 132.2 (CH_2*C*H), 127.7-127.5 (m, CF-CF-*C*), 125.0 (CH*C*HCHCH), 124.1 (CHCH*C*HCH), 121.0 (*C*HCHCHCH), 118.0 (CH*C*H_2), 111.0 (CHCHCH*C*H), 50.4 (N-*C*H_2-CH), 22.0 (NCO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3605, 3113, 3088, 3020, 2986, 2935, 1682, 1648, 1622, 1612, 1515, 1477, 1468, 1452, 1417, 1380, 1324, 1304, 1291, 1257, 1239, 1204, 1178, 1154, 1076, 1033, 1012, 980

HRMS (EI+) Calcd. for $C_{17}H_{13}F_3N_4O$: 346.1041 Found : 346.1047

tert-butyl (2-((ethoxycarbonothioyl)thio)-5-oxohexyl)(3,5,6-trifluoro-4-(pyrrolidin-1-yl) pyridin-2-yl)carbamate (4-16)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-1** (886mg, 2.48mmol, 2.0 eq.) and the corresponding xanthate **Xa-i** (223mg, 1.24mmol, 1.0 eq.) in AcOEt (1.3ml, 1.0 mmol/ml), with DLP (100mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / PE = 20 / 80 afforded **4-16** (455mg, 68%) as a light yellow oil.

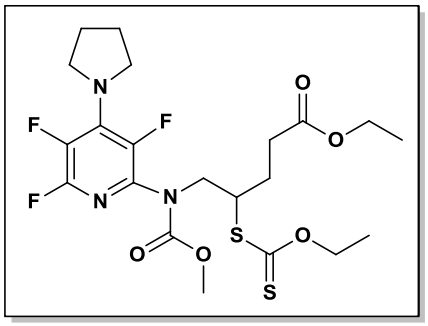
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.59 (q, 2H, J=7.1Hz, -C*H*$_2$CH$_3$), 4.04-3.97 (m, 1H, C*H*H-NBoc), 3.91-3.83 (m, 2H, CH*H*-NBoc + C*H*-Xa), 3.72 (br s, 4H, -CH$_2$C*H*$_2$NC*H*$_2$CH$_2$-), 2.70-2.53 (m, 2H, C*H*$_2$-COMe), 2.17-2.09 (m+s (2.13), 4H, CH*H*-CH-Xa + COC*H*$_3$), 1.93 (t, 4H, J=6.1Hz, -C*H*$_2$CH$_2$NCH$_2$C*H*$_2$-), 1.88-1.77 (m, 1H, C*H*H-CH-Xa), 1.44 (s, 9H, C(C*H*$_3$)$_3$), 1.38 (t, 3H, J=7.1Hz, -CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.1 (*C*=S), 207.4 (*C*OMe), 153.2 (*C*OOtBu), 147.4 (dd, J=14.4Hz, J=231.6Hz, N-*C*F), 141.6 (d, 1H, J=248.7Hz, *C*F-C-NBoc), 136.0 (ddd, 1H, J=3.1Hz, J=6.1Hz, J=7.1Hz, N-*C*-NBoc), 133.9 (t, J=16.0Hz, N-*C*-CF), 132.8 (dd, J=5.5Hz, J=31.8Hz, J=250.3Hz, N-CF-*C*F), 81.5 (*C*Me$_3$), 70.0 (O*C*H$_2$CH$_3$), 51.2 (t, J=6.1Hz, -*C*H$_2$-N-*C*H$_2$-), 49.9 (*C*H-Xa), 49.7 (*C*H$_2$-NBoc), 40.5 (*C*H$_2$-COMe), 29.9 (CO*C*H$_3$), 28.1(C(*C*H$_3$)$_3$), 25.6 (-*C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$-), 25.0 (*C*H$_2$-CHXa), 13.6 (OCH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 2979, 2888, 1721, 1616, 1514, 1471, 1368, 1224, 1156, 1114, 1054

HRMS (EI+) Calcd. for $C_{23}H_{32}F_3N_3O_4S_2$: 535.1786 Found : 535.1789

Ethyl 4-(ethoxycarbonothioylthio)-5-(methoxycarbonyl(3,5,6-trifluoro-4-(pyrrolidin-1-yl)pyridin-2-yl)amino)pentanoate (4-17)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-2** (316mg, 1.00mmol, 0.5eq.) and the corresponding xanthate **Xa-h** (416mg, 2.00mmol, 1.0eq.) in AcOEt (1.0ml, 2.0mmol/ml), with DLP (240mg, 0.30 eq.). Flash chromatography on silica gel with AcOEt / PE = 25 / 75 afforded **4-17** (328mg, 63%) as a light yellow oil.

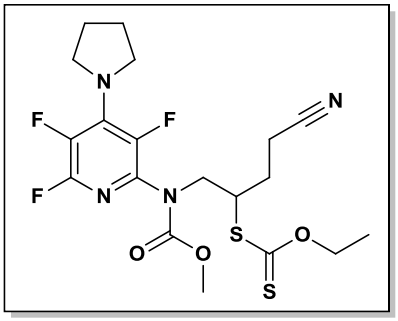
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.58 (dq, 1H, J=2.1Hz, J=7.1 Hz, -C*H*$_2$-CH_3), 4.11 (q, 1H, J=7.1 Hz, COO-C*H*$_2$-CH_3), 4.06-4.01 (m, 1H, CO-N-C*H*H), 3.95-3.85 (m, 2H, CO-N-CH*H* + Xa-C*H*), 3.73 (br s, 7H, -C*H*$_2$-N-C*H*$_2$- + COOC*H*$_3$), 2.56-2.38 (m, 2H, C*H*$_2$-COOEt), 2.24-2.15 (m, 1H, C*H*H-CH_2-COOEt), 1.94-1.83 (m, 5H, CH*H*-CH_2-COOEt + CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.66 (br s, 6H, C*H*$_2$-C*H*$_2$-C*H*$_2$), 1.38 (t, 3H, J=7.1 Hz, CSO-CH_2-C*H*$_3$), 1.24 (t, 3H, J=7.1Hz, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.9 (*C*=S), 172.6 (*C*OOEt), 155.0 (*C*OOMe), 147.64 (dd, J=15.4Hz, J=231.6Hz, N-*C*F), 141.90 (d, J=251.3Hz, *C*F-C-NCO), 136.3-136.1 (m, $(CH_2)_2$N-*C*), 133.08 (ddd, J=4.5Hz, J=32.6Hz, J=251.1Hz, $(CH_2)_2$N-C-*C*F-CF), 133.21 (dt, 1H, J=3.7Hz, J=17.0Hz, N-*C*-N-CO), 70.0 (CSO-*C*H_2-CH_3), 60.5 (COO-*C*H_2-CH_3), 53.4 (COO*C*H_3), 51.3 (t, J=6.2Hz), *C*H_2-N-*C*H_2), 50.5 (CO-N-*C*H_2), 49.4 (Xa-*C*H), 31.5 (*C*H_2-COOEt), 26.3 (Xa-CH-*C*H_2), 25.6 (*C*H_2-CH_2-N-CH_2-*C*H_2), 14.2(COO-CH_2-*C*H_3), 13.6 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2982, 2958, 2891, 2338, 1721, 1616, 1564, 1519, 1473, 1449, 1337, 1354, 1222, 1140, 1114, 1051

HRMS (EI+) Calcd. for $C_{21}H_{28}F_3N_3O_5S_2$:523.1422 Found : 523.1420

methyl 2-(ethoxycarbonothioylthio)hex-5-ynyl(3,5,6-trifluoro-4-(pyrrolidin-1-yl) pyridin-2-yl)carbamate (4-18)



Following the general procedure E for radical addition of xanthate, the reaction was carried out with the protected olefin (285 mg, 0.904 mmol, 0.5 eq.) and the corresponding xanthate (303mg, 1.88mmol, 1.0 eq.) in AcOEt (0.9ml, 1.0 mmol/ml), with DLP (108mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / PE = 25 / 75 afforded **017.1** (307 mg, 71%) as a light yellow oil.

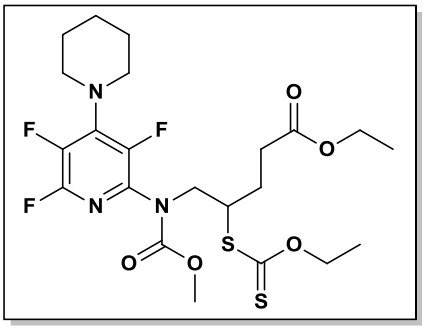
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.60 (dq, *J* = 7.08, 3.04 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.05 (dd, *J* = 14.01, 8.21 Hz, 1H, CO-N-C*H*H), 3.98-3.84 (m, 2H, CO-N-C*H*H + Xa.-C*H*), 3.73 (br s, 7H, N(C*H*$_2$)$_2$ + COOC*H*$_3$), 2.77-2.39 (m, 2H, CN-C*H*$_2$), 2.39-2.17 (m, 1H, CN-CH_2-C*H*H), 2.00-1.85 (m, 5H, CN-CH_2-C*H*H + CH_2-C*H*$_2$- C*H*$_2$-CH_2), 1.39 (t, *J* = 7.12 Hz, 3H, CSO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.6 (*C*=S), 155.1 (*C*OOCH$_3$), 147.8 (dd, *J* = 232.29, 14.88 Hz, N-*C*F), 146.9 (dd, *J* = 254.76, 8.68 Hz, *C*F-C-NCO), 141.9 (d, *J* = 251.04 Hz, $(CH_2)_2$N-C-*C*F-CF), 136.4-136.2 (m, $(CH_2)_2$N-*C*), 133.0-132.3 (m, N-*C*-N-CO), 118.8 (*C*N), 70.5 (CSO-*C*H_2-CH_3), 53.5 (COO*C*H_3), 51.3 (t, *J* = 6.18 Hz, N(*C*H_2)$_2$), 50.2 (OOC-N-*C*H_2), 48.4 (Xa.-*C*H), 26.9 (CN-CH_2-*C*H_2), 25.5 (CH_2-(*C*H_2)-CH_2), 15.0 (CN-*C*H_2), 13.6 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2981, 2958, 2890, 2253, 1716, 1616, 1520, 1473, 1449, 1377, 1354, 1309, 1279, 1229, 1140, 1114, 1050

HRMS (EI+) Calcd. for $C_{19}H_{23}F_3N_4O_3S_2$: 476.1164 Found : 476.1146

ethyl 4-((ethoxycarbonothioyl)thio)-5-((methoxycarbonyl)(3,5,6-trifluoro-4-(piperidin-1-yl)pyridin-2-yl)amino)pentanoate (4-19)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-3** (491mg, 1.49mmol, 2.0 eq.) and the corresponding xanthate **Xa-h** (153mg, 0.74mmol, 1.0 eq.) in AcOEt (0.75ml, 1.0 mmol/ml), with DLP (59mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / PE = 15 / 85 afforded **4-19** (241mg, 61%) as light yellow oil.

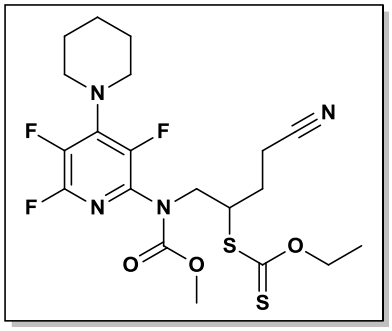
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.58 (dq, 2H, J=1.3Hz, J=7.1Hz, CSO-C*H*$_2$-CH$_3$), 4.11 (q, 2H, J=7.1Hz, COO-C*H*$_2$-CH$_3$), 4.08-4.03 (m, 1H, CO-N-C*H*H), 3.97-3.84 (m, 2H, CO-N-CH*H* + Xa-C*H*), 3.74 (s, 3H, COOC*H*$_3$), 3.36 (br s, 4H, C*H*$_2$-N-C*H*$_2$), 2.55-2.38 (m, 2H, C*H*$_2$-COOEt), 2.23-2.15 (m, 1H, C*H*H-CH$_2$-COOEt), 1.92-1.83 (m, 1H, CH*H*-CH$_2$-COOEt), 1.66 (br s, 6H, C*H*$_2$-C*H*$_2$-C*H*$_2$), 1.38 (t, 3H, J=7.1Hz, CSO-CH$_2$-C*H*$_3$), 1.23 (t, 3H, J=7.1Hz, COO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*=S), 172.5 (*C*OOEt), 154.9 (*C*OOMe), 147.0 (ddd, J=1.5Hz, J=15.1Hz, J=234.8Hz, N-*C*F), 145.0 (dd, J=3.3Hz, J=254.8Hz, *C*F-C-NCO), 139.4-139.1 (m, (CH$_2$)$_2$N-*C*), 136.5 (ddd, J=3.0Hz, J=30.8Hz, J=256.2Hz, (CH$_2$)$_2$N-C-*C*F), 133.2 (dt, J=3.8Hz, J=15.9Hz, N-*C*-N-CO), 70.0 (CSO-*C*H$_2$-CH$_3$), 60.4 (COO-*C*H$_2$-CH$_3$), 53.4 (COO*C*H$_3$), 51.5 (t, J=4.6Hz, *C*H$_2$-N-*C*H$_2$), 50.4 (CO-N-*C*H$_2$), 49.5 (Xa-*C*H), 31.4 (*C*H$_2$-COOEt), 26.4 (Xa-CH-*C*H$_2$), 26.3 (*C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$), 24.0 (-N-CH$_2$-CH$_2$-*C*H$_2$), 14.1(COO-CH$_2$-*C*H$_3$), 13.6 (CSO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2942, 2857, 1722, 1617, 1570, 1515, 1452, 1378, 1286, 1226, 1156, 1105, 1051, 995, 959

HRMS (EI+) Calcd. for $C_{19}H_{25}F_3N_3O_4$: 416.1797 Found : 416.1789

methyl (4-cyano-2-((ethoxycarbonothioyl)thio)butyl)(3,5,6-trifluoro-4-(piperidin-1-yl) pyridin-2-yl)carbamate (4-20)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-3** (884mg, 2.68mmol, 2.0 eq.) and the corresponding xanthate **Xa-a** (216mg, 1.34mmol, 1.0 eq.) in AcOEt (1.4ml, 1.0 mmol/ml), with DLP (80mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / PE = 15 / 85 afforded **4-20** (494mg, 75%) as light yellow oil.

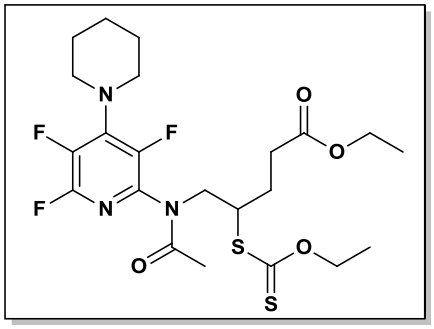
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.60 (dq, 1H, J=1.6Hz, J=7.1Hz, CSO-C*H*$_2$-CH$_3$), 4.14-4.05 (m, 1H, CO-N-C*H*H), 3.97-3.85 (m, 2H, CO-N-CH*H* + Xa-C*H*), 3.75 (s, 3H, COOC*H*$_3$), 3.38 (br s, 4H, C*H*$_2$-N-C*H*$_2$), 2.64-2.46 (m, 2H, C*H*$_2$-CN), 2.34-2.25 (m, 1H, C*H*H-CH$_2$-CN), 1.98-1.88 (m, 1H, CH*H*-CH$_2$-CN), 1.67 (br s, 6H, C*H*$_2$-C*H*$_2$-C*H*$_2$), 1.39 (t, 3H, J=7.1Hz, CSO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.6 (*C*=S), 155.0 (*C*OOMe), 147.2 (dd, J=16.1Hz, J=235.4Hz, N-*C*F), 145.1 (d, J=255.7Hz, *C*F-C-NCO), 139.4 ((CH$_2$)$_2$N-*C*), 136.7 (dd, J=30.9Hz, J=256.6Hz, (CH$_2$)$_2$N-C-*C*F), 132.9 (dt, J=3.6Hz, J=15.9Hz, N-*C*-N-CO), 118.7 (*C*N), 70.5 (CSO-*C*H$_2$-CH$_3$), 53.7 (COO*C*H$_3$), 51.5 (t, J=4.6Hz, *C*H$_2$-N-*C*H$_2$), 50.1 (CO-N-*C*H$_2$), 48.6 (Xa-*C*H), 27.0 (Xa-CH-*C*H$_2$), 26.3 *C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$), 24.0 (-N-CH$_2$-CH$_2$-*C*H$_2$), 15.0 (*C*H$_2$-CN), 13.6 (CSO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2943, 2858, 1718, 1617, 1515, 1471, 1451, 1379, 1227, 1156, 1105, 1050, 995

HRMS (EI+) Calcd. for $C_{20}H_{25}F_3N_4O_3S_2$: 490.1320 Found : 490.1315

S-4-(ethoxycarbonyl)-1-(N-(3,5,6-trifluoro-4-(piperidin-1-yl)pyridin-2-yl) acetamido) butan-2-yl O-ethyl carbonodithioate (4-21)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-4** (2.01g, 6.43mmol, 2.0 eq.) and the corresponding xanthate **Xa-h** (664mg, 3.20mmol, 1.0 eq.) in AcOEt (3.2ml, 1.0 mmol/ml), with DLP (254mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / PE = 30 / 70 afforded **4-21** (934mg, 56%) as a yellow oil.

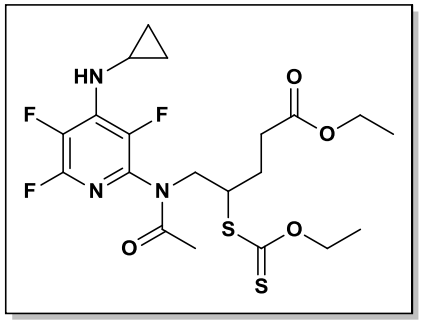
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.57 (dq, 2H, J=1.7Hz, J=7.1Hz, CSO-C*H*$_2$-CH$_3$) 4.22 (dd, 1H, J=10.1Hz, J=15.6Hz, C*H*H-NAc), 4.10 (q, 2H, J=7.1Hz, COO-C*H*$_2$-CH$_3$), 3.78 (d, 2H, J=8.6Hz, CH*H*-NAc + Xa-C*H*), 3.39 (br s, 4H, C*H*$_2$-N-C*H*$_2$), 2.56-2.36 (m, 2H, C*H*$_2$-COOEt), 2.24-2.15 (m, 1H, C*H*H-CH$_2$-COOEt), 1.95-1.84 (s + m, 4H, COC*H*$_3$ + CH*H*-CH$_2$-COOEt), 1.68 (br s, 4H, C*H*$_2$-CH$_2$-C*H*$_2$), 1.65 (br s, 2H, CH$_2$-C*H*$_2$-CH$_2$), 1.37 (t, 3H, J=7.1Hz, CSO-CH$_2$-C*H*$_3$), 1.23 (t, 3H, J=7.1Hz, COO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (*C*=S), 172.6 (*C*OOEt), 170.3 (*C*OMe), 147.5 (dd, J=15.4Hz, J=236.1Hz, N-*C*F), 145.1 (d, J=253.1Hz, *C*F-C-NCO), 139.6-139.3 (m, N(piperidine)-*C*), 136.8 (dd, J=33.5Hz, J=257.5Hz, C-*C*F-CF), 134.5-134.1 (m, N-*C*-N-CO), 70.1(CSO-*C*H$_2$-CH$_3$), 60.4 (COO-*C*H$_2$-CH$_3$), 51.6 (t, J=4.6Hz, *C*H$_2$-N-*C*H$_2$), 49.2 (Xa-*C*H), 49.0 (CO-N-*C*H$_2$), 31.6 (*C*H$_2$-COOEt), 26.3 (Xa-CH-*C*H$_2$ + *C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$), 23.9 (-N-CH$_2$-CH$_2$-*C*H$_2$), 21.8 (CO*C*H$_3$), 14.2 (COO-CH$_2$-*C*H$_3$), 13.7 (CSO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2943, 2858, 1728, 1675, 1612, 1516, 1463, 1329, 1284, 1225, 1157, 1109, 1052, 1003

HRMS (EI+) Calcd. for $C_{19}H_{25}F_3N_3O_3$: 400.1848 Found : 400.1849

_S_-4-(ethoxycarbonyl)-1-(_N_-(4-(cyclopropylamino)-3,5,6-trifluoropyridin-2-yl)acetamido) butan-2-yl _O_-ethyl carbonodithioate (4-22)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-5** (304mg, 1.07mmol, 1.0eq.) and the corresponding xanthate **Xa-h** (333mg, 1.60mmol, 1.5eq.) in AcOEt (1.6ml, 1.0mmol/ml), with DLP (95.5mg, 0.15 eq.). Flash chromatography on silica gel with Acetone / DCM = 3 / 97 afforded **4-22** (382mg, 72%) as light yellow oil.

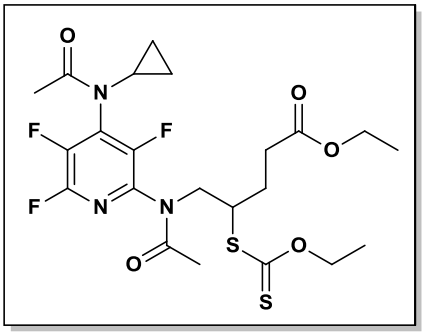
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.79 (br s, 1H, N*H*), 4.57 (dq, 2H, J=2.1Hz, J=7.1Hz, CS-OC*H*$_2$CH$_3$), 4.27-4.17 (m, 1H, C*H*H-NAc), 4.11 (q, 1H, J=7.1Hz, CO-OC*H*$_2$CH$_3$), 3.84-3.74 (m, 2H, CH*H*-NAc + C*H*-Xa), 2.99-2.98 (m, 1H, NH-C*H*), 2.56-2.49 (m, 1H, CH*H*-COOEt), 2.44-2.32 (m, 1H, C*H*H-COOEt), 2.24-2.15 (m, 1H, CH*H*-CH-Xa), 1.96 (s, 3H, COC*H*$_3$), 1.96-1.84 (m, 1H, C*H*H-CH-Xa), 1.38 (t, 3H, J=7.1Hz, CS-OCH$_2$-C*H*$_3$), 1.23 (t, 3H, J=7.1Hz, CO-OCH$_2$-C*H*$_3$), 0.87 (q, 2H, J=6.7Hz, -C*H*H-C*H*H-), 0.71 (m, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.1 (*C*=S), 172.6 (*C*OOEt), 170.3 (*C*OMe), 147.0 (dd, J=15.1Hz, J=234.2Hz, N-*C*F), 141.2 (d, J=250.0Hz, *C*F-C-NAc), 136.7 (dd, J=7.1Hz, J=14.1Hz, N-*C*-NAc), 133.2 (m, N-*C*-CF), 132.6 (dd, J=32.1Hz, J=255.5Hz, N-CF-*C*F), 70.1 (CS-O*C*H$_2$CH$_3$), 60.4 (CO-O*C*H$_2$CH$_3$), 49.1(*C*H$_2$-NAc), 49.0 (*C*H-Xa), 31.6 (*C*H$_2$-COOEt), 26.7 (NH-*C*H), 26.2 (*C*H$_2$-CHXa), 21.8 (CO*C*H$_3$), 14.1 (CO-OCH$_2$-*C*H$_3$), 13.6 (CS-OCH$_2$-*C*H$_3$), 8.7 (-*C*H$_2$-*C*H$_2$-)

IR (ν, cm^{-1}, $CDCl_3$) 3428, 2985, 2938, 1728, 1676, 1624, 1527, 1475, 1381, 1361, 1224, 1182, 1111, 1051

HRMS (EI+) Calcd. for $C_{17}H_{21}F_3N_3O_3$: 372.1535 Found : 372.1526

_S_-4-(ethoxycarbonyl)-1-(_N_-(4-(_N_-cyclopropyl-_N_-acetylamino)-3,5,6-trifluoropyridin-2-yl)acetamido)butan-2-yl _O_-ethyl carbonodithioate (4-23)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-6** (398mg, 1.22mmol, 1.0eq.) and the corresponding xanthate **Xa-h** (389mg, 1.82mmol, 1.5eq.) in AcOEt (1.8ml, 1.0mmol/ml), with DLP (109mg, 0.15 eq.). Flash chromatography on silica gel with Acetone / DCM = 5 / 95 afforded **4-23** (545mg, 84%) as light yellow oil.

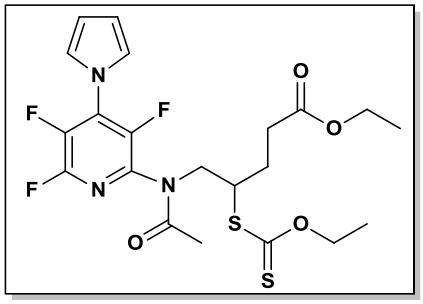
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.57 (q, 2H, J=7.1Hz, CS-OC*H*$_2$CH$_3$), 4.39-4.27 + 3.83-3.70 (br s, 1H, CH*H*-NAc), 4.28-4.17 + 4.07-3.99 (br s, 1H, C*H*H-NAc), 4.10 (q, 2H, J=7.1Hz, CO-OC*H*$_2$CH$_3$), 3.88-3.81 (m, 1H, C*H*-Xa), 3.20 (br s, 1H, NAc-C*H*), 2.55-2.44 (m, 2H, C*H*$_2$-COOEt), 2.44 (br s, 3H, CH-N-COC*H*$_3$), 2.23-2.14 (m, 1H, CH*H*-CH-Xa), 1.99 (br s, 3H, CH$_2$-N-COC*H*$_3$), 1.93-1.84 (m, 1H, C*H*H-CH-Xa), 1.37 (t, 3H, J=7.1Hz, CS-OCH$_2$-C*H*$_3$), 1.23 (t, 1H, J=7.1Hz, CO-OCH$_2$-C*H*$_3$), 1.01 (br s, 2H, -C*H*H-C*H*H-), 0.75 (br s, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*=S), 172.5 (*C*OOEt), 171.7 (CHN-*C*OMe), 170.2 (CH$_2$N-*C*OMe), 147.97 (dd, 1H, J=5.9Hz, J=260.5Hz, N-CF-*C*F), 146.06 (dd, 1H, J=14.9Hz, J=241.3Hz, N-*C*F), 140.44 (d, 1H, J=263.8Hz, *C*F-C-NAc), 134.7 (m, N-*C*-NAc), 131.7 (m, AcN-*C*-CF), 70.2 (CS-O*C*H$_2$CH$_3$), 60.5 (CO-O*C*H$_2$CH$_3$), 49.7 (*C*H-Xa), 48.8 (*C*H$_2$-NAc), 31.5 (*C*H$_2$-COOEt + NAc-*C*H), 26.5 (*C*H$_2$-CHXa), 22.3 (CHN-CO*C*H$_3$), 21.7 (CH$_2$N-CO*C*H$_3$), 14.2 (CO-OCH$_2$-*C*H$_3$), 13.6 (CS-OCH$_2$-*C*H$_3$), 10.1(-*C*H$_2$-CH$_2$-), 9.2 (-CH$_2$-*C*H$_2$-)

IR (ν, cm^{-1}, $CDCl_3$) 3692, 2985, 2940, 1729, 1686, 1618, 1466, 1377, 1309, 1228, 1187, 1112, 1051

HRMS (EI+) Calcd. for $C_{22}H_{28}F_3N_3O_5S_2$: 535.1422, -Xa. 414.1641 Found : 414.1641

4-(ethoxycarbonothioylthio)-5-(*N*-(3,5,6-trifluoro-4-(1*H*-pyrrol-1-yl)pyridin-2-yl) acetamido) pentanoate (4-24)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-7** (1.03 g, 3.49 mmol, 2.0 eq.) and the corresponding xanthate **Xa-h** (359mg, 1.72mmol, 1.0 eq.) in AcOEt (1.75ml, 1.0 mmol/ml), with DLP (140mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / PE = 25 / 75 afforded **4-24** (470mg, 53%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.13 (m, 2H, J=2.1Hz, -C*H*-CH), 6.46 (m, 2H,-CH-C*H*), 4.56 (q, 2H, J=6.9Hz, CSO-C*H*$_2$-CH_3), 4.28-4.33 (m, 1H, CO-N-C*H*H), 4.10 (q, 2H, J=7.1Hz, COO-C*H*$_2$-CH_3), 3.93-3.83 (m, 2H, CO-N-CH*H* + Xa-C*H*), 2.56-2.39 (m, 2H, C*H*$_2$-COOEt), 2.27-2.18 (m, 1H, C*H*H-CH_2-COOEt), 2.06 (br s, 3H, COC*H*$_3$), 1.93-1.83 (m, 1H, CH*H*-CH_2-COOEt), 1.36 (t, 3H, J=7.1Hz, CSO-CH_2-C*H*$_3$), 1.23 (t, 3H, J=7.1Hz, COO-CH_2-C*H*$_3$)

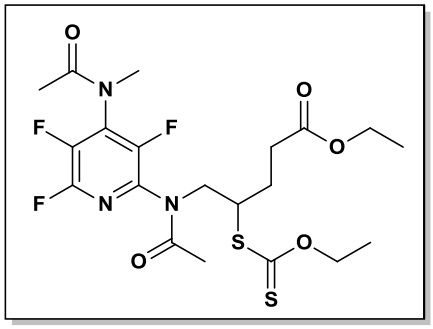
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (*C*=S), 172.5 (*C*OOEt), 169.9 (*C*OMe), 146.90 (dd, J=14.7Hz, J=240.8Hz, N-*C*F), 144.72 (dd, J=4.6Hz, J=261.0Hz, *C*F-C-NCO), 137.21 (dd, J=32.3Hz, J=267.9Hz, $(CH_2)_2$N-C-*C*F-CF), 135.6.3-135.3 (m, $(CH_2)_2$N-*C*), 129.8-129.6 (m, N-*C*-N-CO), 70.4 (COO-*C*H_2-CH_3), 60.5 (CSO-*C*H_2-CH_3), 49.5 (CO-N-*C*H_2

+ 49.4 (Xa-*C*H), 31.3 (*C*H_2-COOEt), 26.3 (Xa-CH-*C*H_2), 22.00 (d, J=2.4Hz,CO-*C*H_3), 14.2(COO-CH_2-*C*H_3), 13.6 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2927, 2855, 1728, 1682, 1619, 1519, 1468, 1379, 1222, 1194, 1103, 1052

HRMS (EI+) Calcd. for $C_{21}H_{24}F_3N_3O_5S_2$:503.1160 Found : 503.1174

4-(ethoxycarbonothioylthio)-5-(*N*-(3,5,6-trifluoro-4-(*N*-methylacetamido)pyridin-2-yl) acetamido)pentanoate (4-25)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-8** (223mg, 0.74 mmol, 0.7 eq.) and the corresponding xanthate **Xa-h** (231mg, 1.11mmol, 1.0 eq.) in AcOEt (0.8ml, 1.0 mmol/ml), with DLP (44mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded **4-25** (317mg, 84%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.57 (q, *J* = 7.09 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.32-4.27 (m, 1H, CO-N-C*H*H), 4.09 (q, *J* = 7.12 Hz, 2H, COO-C*H*$_2$-CH_3), 4.04-3.63 (m, 2H, CO-N-C*H*H + Xa-C*H*), 3.41-3.27 (m, 3H, N-C*H*$_3$), 2.53-2.40 (m, C*H*$_2$-COOEt) 2.24-2.14 (m, 1H, C*H*H-CH_2-COOEt), 2.02 (br s, 6H, COC*H*$_3$), 1.93-1.79 (m, 1H, CH*H*-CH_2-COOEt), 1.39 (t, *J* = 7.10 Hz, 3H, CSO-CH_2-C*H*$_3$), 1.23 (t, *J* = 7.12 Hz, 3H, COO-CH_2-C*H*$_3$)

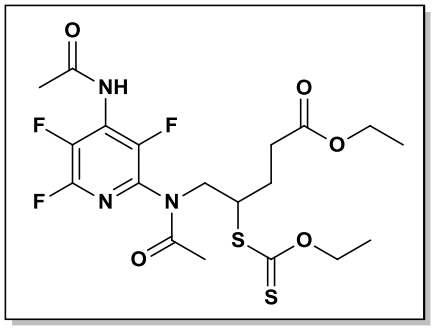
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (*C*=S), 172.5 (*C*OOEt), 170.3-168.7 (N-*C*OMe + CH_3N-*C*OMe), 147.7 (d, *J* = 260.75 Hz, N-*C*F), 146.1 (dd, *J* = 242.98, 13.78 Hz, *C*F-C-NCO), 140.4 (d, *J* = 265.23 Hz, $(CH_2)_2$N-C-*C*F-CF), 132.3 ($(CH_2)_2$N-*C*), 118.0 (N-*C*-N-CO), 70.5 (CSO-*C*H_2-CH_3), 60.4 (COO-*C*H_2-CH_3), 49.7 (CO-N-*C*H_2 + Xa-*C*H), 37.8 +

35.5 (N-*C*H_3), 31.2 (*C*H_2-COOEt), 26.3 (Xa-CH-*C*H_2), 21.9 + 21.4 (NCO-*C*H_3+ CH_3-NCO-*C*H_3), 14.1 +13.6 (CSO-CH_2-*C*H_3 + COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3607, 2985, 2940, 1728, 1682, 1618, 1489, 1464, 1422, 1375, 1330, 1301, 1227, 1151, 1113, 1051

HRMS (EI+) Calcd. for $C_{20}H_{26}F_3N_3O_5S_2$: 509.1266 Found : 509.1245

5-(*N*-(4-acetamido-3,5,6-trifluoropyridin-2-yl)acetamido)-4-(ethoxycarbonothioyl thio)pentanoate (4-26)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-10** (268 mg, 0.93 mmol, 1.0 eq.) and the corresponding xanthate **Xa-h** (195 mg, 0.94 mmol, 1.0 eq.) in AcOEt (0.93 ml, 1.0 mmol/ml), with DLP (75 mg, 0.40 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-26** (291 mg, 63%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.76 (s, 1H, N*H*), 4.56 (q, *J* = 7.10 Hz, 1H, CSO-C*H*$_2$-CH_3), 4.33-4.19 (m, 1H, CO-N-C*H*H), 4.10 (q, *J* = 7.09 Hz, 2H, COO-C*H*$_2$-CH_3), 3.88 (dd, *J* = 13.79, 5.92 Hz, 1H, CO-N-CH*H*), 3.82-3.73 (m, 1H, Xa-C*H*), 2.58-2.36 (m, 2H, C*H*$_2$-COOEt), 2.29 (s, 3H, NH-CO-C*H*$_3$), 2.24-2.11 (m, 1H, C*H*H-CH_2-COOEt), 2.02 (s, 3H, COC*H*$_3$), 1.92-1.78 (m, 1H, CH*H*-CH_2-COOEt), 1.37 (t, *J* = 7.11 Hz, 3H, CSO-CH_2-C*H*$_3$), 1.23 (t, *J* = 7.14 Hz, 3H, COO-CH_2-C*H*$_3$)

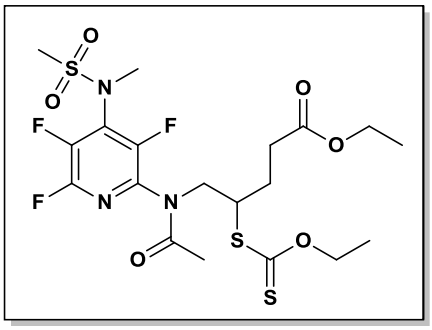
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.9 (*C*=S), 172.7 (*C*OOEt), 170.4 (*C*OMe), 167.2 (NH-*C*O), 146.2 (ddd, *J* = 240.48, 14.37, 2.23 Hz, N-*C*F), 145.7 (dd, *J* = 259.65, 5.36 Hz,

*C*F-C-NCO), 138.5 (dd, *J* = 267.98, 31.49 Hz, $(CH_2)_2$N-C-*C*F-CF), 134.5-134.0 (m, $(CH_2)_2$N-*C*), 127.3-126.4 (m, N-*C*-N-CO), 70.3 (COO-*C*H_2-CH_3), 60.6 (CSO-*C*H_2-CH_3), 49.3 (CO-N-*C*H_2 + Xa-*C*H), 31.5 (*C*H_2-COOEt), 26.2 (Xa-CH-*C*H_2), 23.2 (NH-CO-*C*H_3), 21.9 (d, *J* = 2.45 Hz, CO-*C*H_3), 14.1 (COO-CH_2-*C*H_3), 13.6 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3418, 2985, 2939, 1727, 1682, 1622, 1501, 1476, 1448, 1379, 1223, 1113, 1051

HRMS (EI+) Calcd. for $C_{16}H_{19}F_3N_3O_4$: 374.1328 Found : 374.1324

4-(ethoxycarbonothioylthio)-5-(*N*-(3,5,6-trifluoro-4-(*N*-methylmethylsulfonamido) pyridin-2-yl)acetamido)pentanoate (4-27)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-9** (278mg, 0.82mmol, 1.2 eq.) and the corresponding xanthate **Xa-h** (139mg, 0.67mmol, 1.0 eq.) in AcOEt (0.65ml, 1.0 mmol/ml), with DLP (40mg, 0.15eq.). Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 afforded **4-27** (316mg, 71%) as a light yellow oil.

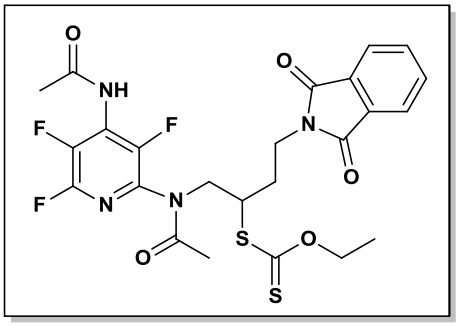
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.58 (dq, *J* = 7.08, 2.63 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.28 (dd, *J* = 14.12, 7.32 Hz, 1H, CO-N-C*H*H), 4.10 (q, *J* = 7.15 Hz, 2H, COO-C*H*$_2$-CH_3), 3.92 (dd, *J* = 13.46, 6.34 Hz, 1H, CO-N-CH*H*), 3.85-3.74 (m, 1H, Xa-C*H*), 3.37 (s, 3H, N-C*H*$_3$), 3.14 (s, 3H, SO_2-C*H*$_3$), 2.51-2.41 (m, 2H, C*H*$_2$-COOEt), 2.27-2.11 (m, 1H, C*H*H-CH_2-COOEt), 2.03 (s, 3H, COC*H*$_3$), 1.94-1.78 (m, 1H, CH*H*-CH_2-COOEt), 1.40 (t, *J* = 7.11 Hz, 3H, CSO-CH_2-C*H*$_3$), 1.24 (t, *J* = 7.12 Hz, 3H, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.0 (*C*=S), 172.5 (*C*OOEt), 170.0 (*C*OMe), 146.2 (dd, *J* = 243.01, 17.46 Hz, N-*C*F), 144.8 (dd, *J* = 263.85, 14.39 Hz, *C*F-C-NCO), 139.2 (dd, *J* = 263.88, 28.30 Hz, $(CH_2)_2$N-C-*C*F-CF), 134.7-134.10 (m, $(CH_2)_2$N-*C*), 128.1-127.1 (m, N-*C*-N-CO), 70.4 (COO-*C*H_2-CH_3), 60.5 (CSO-*C*H_2-CH_3), 49.6 (CO-N-*C*H_2 + Xa-*C*H), 39.0 (SO_2-*C*H_3), 37.3 (N-*C*H_3), 31.3 (*C*H_2-COOEt), 26.3 (Xa-CH-*C*H_2), 21.9 (d, *J* = 2.45 Hz, CO-*C*H_3), 14.2 (CSO-CH_2-*C*H_3), 13.7 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3692, 3606, 2985, 2940, 1720, 1684, 1602, 1489, 1383, 1330, 1301, 1227, 1151, 1097

HRMS (EI+) Calcd. for $C_{16}H_{21}F_3N_3O_5S$: 424.1154 Found : 424.1167

S-1-(*N*-(4-acetamido-3,5,6-trifluoropyridin-2-yl)acetamido)-4-(1,3-dioxoisoindolin-2-yl)butan-2-yl *O*-ethyl carbonodithioate (4-28)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-10** (217mg, 0.76mmol, 0.7 eq.) and the corresponding xanthate **Xa-c** (319mg, 1.13mmol, 1.0 eq.) in AcOEt (0.76ml, 1.0 mmol/ml), with DLP (137mg, 0.30eq.). Flash chromatography on silica gel with AcOEt / EP = 50 / 50 afforded **4-28** (315mg, 73%) as a colourless solid.

m.p. 59-61 °C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.87-7.81 (m, 3H, N*H* + C-C*H*-CH), 7.81-7.70 (m, 2H, C-CH-C*H*), 4.52 (q, *J* = 7.09 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.23 (dd, *J* = 14.18, 7.51 Hz, 1H, CH_3-CO-N-C*H*H), 3.99 (dd, *J* = 14.24, 6.47 Hz, 1H, CH_3-CO-N-C*H*H), 3.88-3.73 (m, 2H,

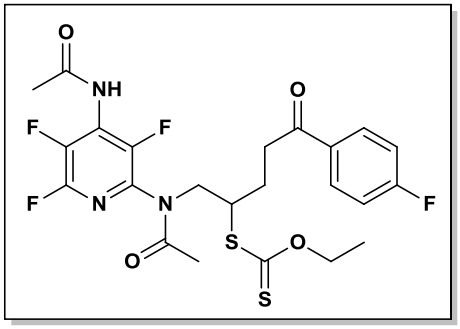
C*H*$_2$-NCO-C), 3.73-3.63 (m, 1H, Xa-C*H*), 2.31 (s, 3H, NH-CO-C*H*$_3$), 2.22-2.10 (m, 1H, C*H*H-CH$_2$- NCO-C), 2.00 (m, 4H, C*H*H-CH$_2$- NCO-C + N-COC*H*$_3$), 1.33 (t, *J* = 7.07 Hz, 3H, CSO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*=S), 170.4 (*C*OMe), 168.2 (N*C*OC), 167.2 (NH-*C*O), 146.3 (dd, *J* = 241.01, 14.72 Hz, N-*C*F), 145.8 (dd, *J* = 259.62, 5.32 Hz, *C*F-C-NCO), 138.7 (dd, *J* = 268.79, 31.68 Hz, (CH$_2$)$_2$N-C-*C*F-CF), 134.0 (C-CH-*C*H), 133.8-133.3 (m, (CH$_2$)$_2$N-*C*), 132.0 (*C*-CH-CH), 128.2-125.2 (m, N-*C*-N-CO), 123.2 (C-*C*H-CH), 70.3 (CSO-*C*H$_2$-CH$_3$), 48.8-48.5 (m, CO-N-*C*H$_2$), 47.3 (Xa-*C*H), 35.6 (*C*H$_2$-NCO-C), 29.9 (Xa.-*C*H$_2$-CH$_2$), 23.3 (NH-CO-*C*H$_3$), 21.9 (N-CO-*C*H$_3$), 13.6 (CSO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3606, 2928, 1714, 1602, 1476, 1447, 1398, 1379, 1226, 1050

HRMS (EI+) Calcd. for $C_{24}H_{23}F_3N_4O_5S_2$: 568.1062 Found : 568.1062

_S_-1-(_N_-(4-acetamido-3,5,6-trifluoropyridin-2-yl)acetamido)-5-(4-fluorophenyl)-5-oxopentan-2-yl _O_-ethyl carbonodithioate (4-29)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-10** (318mg, 1.11 mmol, 0.7 eq.) and the corresponding xanthate **Xa-g** (431 mg, 1.66 mmol, 1.0 eq.) in AcOEt (1.10 ml, 1.0 mmol/ml), with DLP (99mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / DCM = 30 / 70 afforded **4-29** (598mg, 85%) as a white solid.

m.p. 55-58 ^{o}C

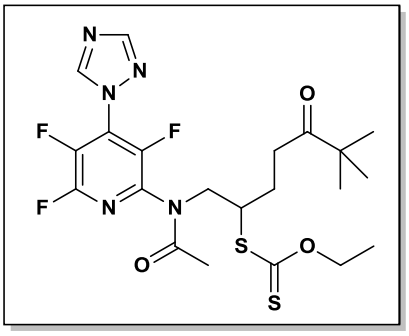
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.04 (s, 1H, N*H*), 7.95 (dd, *J* = 8.26, 5.84 Hz, 2H, CO-C-C*H*), 7.11 (t, *J* = 8.57 Hz, 2H, F-C-C*H*), 4.53 (dq, *J* = 7.39, 7.05, 2.81 Hz, 2H, CSO-CH_2-CH_3), 4.30 (dd, *J* = 12.16, 7.68 Hz, 1H, CH_3-CO-N-C*H*H), 4.03-3.88 (m, 1H, Xa.-C*H*), 3.88-3.76 (m, 1H, CH_3-CO-N-C*H*H), 3.17-3.08 (m, 2H, CH_2-CO-C), 2.30 (s, 4H, NH-CO-CH_3 + Xa.-CH*H*-CO), 2.01 (s, 4H, N-COCH_3 + Xa.-CH*H*-CO), 1.35 (t, *J* = 7.12 Hz, 3H, CSO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*=S), 197.4 (Xa.-CH_2-*C*O), 170.5 (N-*C*OMe), 167.4 (NH-*C*O), 167.0 (*C*O-C-CH), 164.5 (CO-*C*-CH), 146.2 (ddd, *J* = 240.88, 14.47, 2.34 Hz, N-*C*F), 145.8 (dd, *J* = 259.59, 5.33 Hz, *C*F-C-NCO), 138.5 (dd, *J* = 268.08, 31.68 Hz, $(CH_2)_2$N-C-*C*F-CF), 135.5-133.6 (m, $(CH_2)_2$N-*C*), 133.0 (d, *J* = 2.97 Hz, CH-*C*-F), 130.6 (d, *J* = 9.33 Hz, CO-C-*C*H), 128.1-125.7 (m, N-*C*-N-CO), 115.7 (d, *J* = 21.87 Hz, *C*H-C-F), 70.3 (CSO-*C*H_2-CH_3), 49.2 (CO-N-*C*H_2 + Xa.-*C*H), 35.5 (*C*H_2-CO-C), 25.1 (Xa.-*C*H_2-CH_2), 23.2 (NH-CO-*C*H_3), 21.9 (d, *J* = 1.95 Hz, N-CO-*C*H_3), 13.60 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3418, 2938, 1727, 1685, 1622, 1599, 1504, 1476, 1448, 1380, 1284, 1226, 1157, 1113, 1051

HRMS (EI+) Calcd. for $C_{20}H_{18}F_4N_3O_3$: 424.1284 Found : 424.1290

_S_-6,6-dimethyl-5-oxo-1-(_N_-(3,5,6-trifluoro-4-(1_H_-1,2,4-triazol-1-yl)pyridin-2-yl) acetamido)heptan-2-yl _O_-ethyl carbonodithioate (4-30)



Following the general procedure **4-30** for radical addition of xanthate, the reaction was carried out with **4-11** (168 mg, 0.45 mmol, 0.7 eq.) and the corresponding xanthate **Xa-d** (207 mg, 0.93 mmol, 1.0 eq.) in AcOEt (0.50 ml, 1.0 mmol/ml), with DLP (185 mg, 0.5 eq.).

Flash chromatography on silica gel with AcOEt / DCM = 30 / 70 afforded **4-30** (186 mg, 82%) as a yellow oil.

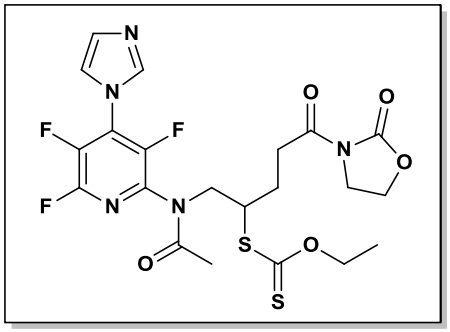
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.76 (s, 1H, C-N-C*H*), 8.28 (s, 1H, C-N-N-C*H*), 4.58 (q, *J* = 7.10 Hz, 2H, CSO-CH_2-CH_3), 4.39-4.29 (m, 1H, CO-N-CH*H*), 4.01-3.92 (m, 1H, CO-N-CH*H*), 3.73-3.71 (m, 1H, S-C*H*), 2.76-2.59 (m, 2H, CO-CH_2), 2.21-2.13 (m, 4H, CO-CH_2-CH*H* + CO-CH_3), 1.76-1.67 (m, 1H, CO-CH_2-CH*H*), 1.37 (t, *J* = 7.13 Hz, 3H, CSO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.9 (*C*=S), 213.1 (*C*O-CH_2), 169.7 (*C*OMe), 153.6 (C-N-N-*C*H), 146.4 (dd, *J* = 241.24, 17.15 Hz, N-*C*F), 146.0 (C-N-*C*H), 144.7 (dd, *J* = 252.73, 17.35 Hz, *C*F-C-NCO), 137.7 (dd, *J* = 245.15, 30.44 Hz, $(CH_2)_2$N-C-*C*F-CF), 135.7-135.5 (m, $(CH_2)_2$N-*C*), 126.3-125.9 (m, N-*C*-N-CO), 70.5 (CSO-*C*H_2-CH_3),), 49.4 (Xa-*C*H + CO-N-*C*H_2), 44.1 (CO-*C*), 33.1 (*C*H_2-CO-C), 26.4 (C(*C*H_3)$_3$), 24.6 (S-CH-*C*H_2), 22.1 (CO-*C*H_3), 13.7 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2970, 1699, 1624, 1527, 1469, 1438, 1368, 1230, 1181, 1129, 1112, 1051, 997

HRMS (EI+) Calcd. for $C_{18}H_{21}F_3N_5O_2$: 396.1647 Found : 396.1648

O-ethyl S-5-oxo-5-(2-oxooxazolidin-3-yl)-1-(N-(3,5,6-trifluoro-4-(1H-imidazol-1-yl) pyridin-2-yl)acetamido)pentan-2-yl carbonodithioate (4-31)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-12** (229 mg, 0.77 mmol, 1.1 eq.) and the corresponding xanthate **Xa-f** (179

mg, 1.72 mmol, 1.0 eq.) in AcOEt (0.80 ml, 1.0 mmol/ml), with DLP (58 mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / DCM = 45 / 55 afforded **4-31** (118 mg, 56%) as a yellow oil.

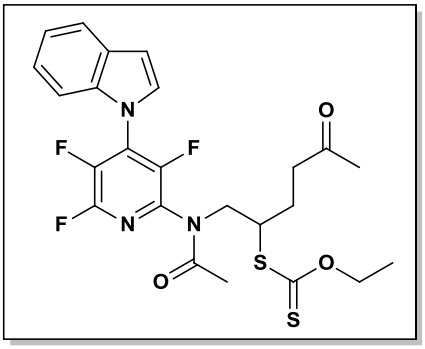
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.00 (s, 1H, N-C*H*-N), 7.41 (s, 1H, C-N-C*H*-CH), 7.30 (s, 1H, C-N-CH-C*H*), 4.57 (q, *J* = 7.07 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.39 (t, *J* = 7.89 Hz, 2H, N-CH_2-C*H*$_2$-O), 4.35-4.30 (m, 1H, CO-N-C*H*H), 4.02-3.94 (m, 3H, N-C*H*$_2$-CH_2-O + Xa-C*H*), 3.87-3.77 (m, 1H, CO-N-CH*H*), 3.16-3.01 (m, 2H, N-CO-C*H*$_2$), 2.32-2.23 (m, 1H, N-CO-CH_2-C*H*H), 2.11 (br s, 3H, COC*H*$_3$), 2.27-2.18 (m, 1H, C*H*H-CH_2-COOEt), 1.94-1.84 (m, 1H, CH*H*-CH_2-CO-N), 1.38 (t, *J* = 7.10 Hz, 3H, CSO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.4 (*C*=S), 172.2 (*C*OOEt), 169.8 (*C*OMe), 153.5 (N-*C*OO-CH_2), 146.6 (d, *J* = 230.40 Hz, N-*C*F), 144.7 (d, *J* = 262.51 Hz, *C*F-C-NCO), 137.5 (N-*C*H-N), 137.1 (d, *J* = 266.41 Hz, $(CH_2)_2$N-C-*C*F-CF), 135.6 (m, $(CH_2)_2$N-*C*), 130.8 (C-N-CH-*C*H), 126.4 (m, N-*C*-N-CO), 119.5 (C-N-*C*H-CH), 70.7 (CSO-*C*H_2-CH_3), 62.2 (COO-*C*H_2), 49.8 (CO-N-*C*H_2), 49.4 (Xa-*C*H), 42.5 (COO-CH_2-*C*H_2), 32.2 (*C*H_2-CO-N), 25.6 (Xa-CH-*C*H_2), 22.1 (d, J=2.4Hz,CO-*C*H_3), 13.7 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3693, 1783, 1693, 1602, 1519, 1470, 1386, 1225, 1051

HRMS (EI+) Calcd. for $C_{18}H_{17}F_3N_5O_4$: 424.1233 Found : 424.1221

_O_-ethyl S-5-oxo-1-(_N_-(3,5,6-trifluoro-4-(1_H_-indol-1-yl)pyridin-2-yl)acetamido) hexan-2-yl carbonodithioate (4-32)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-13** (144 mg, 0.42 mmol, 0.7 eq.) and the corresponding xanthate **Xa-i** (111 mg, 0.62 mmol, 1.0 eq.) in AcOEt (0.42 ml, 1.0 mmol/ml), with DLP (87 mg, 0.35 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-32** (166 mg, 75%) as a dark yellow oil.

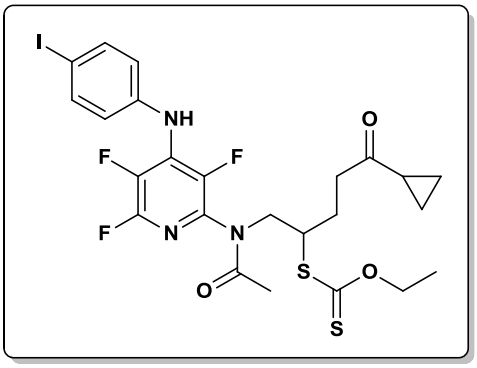
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.75 (d, *J* = 7.67 Hz, 1H, N-C*H*), 7.43-7.23 (m, 4H, aromatic H), 6.89 (d, *J* = 3.36 Hz, 1H, N-CH-C*H*), 4.60 (dq, *J* = 7.10, 3.01 Hz, 2H, CSO-C*H*$_2$-CH_3), 4.41-4.36 (m, 1H, CO-N-CH*H*), 4.04-4.00 (m, 1H, CO-N-CH*H*), 3.88 (dd, *J* = 5.87, 3.35 Hz, 1H, Xa.-C*H*), 2.79-2.58 (m, 2H, CO-C*H*$_2$), 2.18 (s, 7H, CH_2CO-C*H*$_3$ + N-CO-C*H*$_3$ + CO-CH_2-CH*H*), 1.91-1.86 (m, 1H, CO-CH_2-CH*H*), 1.38 (t, *J* = 7.11 Hz, 3H, CSO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (*C*=S), 207.2 (*C*O-CH_2), 169.9 (*C*OMe), 146.6 (dd, *J* = 241.91, 15.06 Hz, N-*C*F), 146.4 (dd, *J* = 263.08, 5.40 Hz, N-C-*C*F-CF), 138.8 (dd, *J* = 269.61, 31.69 Hz, *C*F-C-NCO), 136.6-136.4 (m, CH-N-*C*), 128.8-128.6 (m, N-*C*-N-CO), 135.5, 129.0, 127.6, 123.7, 121.4, 111.1 (6s, aromatic C), 122.1 (N-*C*H), 107.3 (N-CH-*C*H), 70.5 (CSO-*C*H_2-CH_3), 53.4 (CO-N-*C*H_2), 49.6 (Xa.-*C*H), 40.3 (CO-*C*H_2), 30.0 (CH_2-CO-*C*H_3), 24.9 (Xa.-CH-*C*H_2), 22.1 (d, *J* = 2.00 Hz, N-CO-*C*H_3), 13.6 (CSO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2928, 2855, 1716, 1683,1610, 1531, 1508, 1465, 1451, 1372, 1230, 1209, 1180, 1112, 1046

HRMS (EI+) Calcd. for $C_{21}H_{19}F_3N_3O_2$: 402.1429 Found : 402.1427

S-(5-cyclopropyl-5-oxo-1-(N-(3,5,6-trifluoro-4-((4-iodophenyl)amino)pyridin-2-yl) acetamido)pentan-2-yl) O-ethyl carbonodithioate (4-33)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with the protected olefin **4-14** (375 mg, 0.84 mmol, 0.7 eq.) and the corresponding xanthate **Xa-l** (257 mg, 1.25 mmol, 1.0 eq.) in AcOEt (0.84 ml, 1.0 mmol/ml), with DLP (75 mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **4-33** (491 mg, 90%) as a light yellow sticky oil.

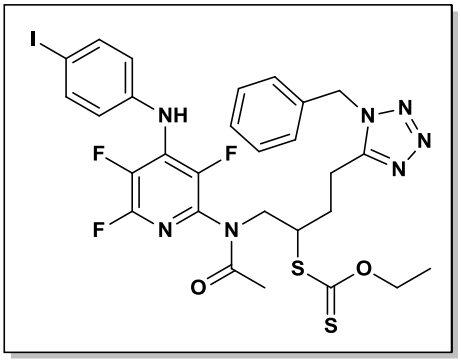
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.65 (d, *J* = 8.58 Hz, 2H, ICC*H*), 6.86 (d, *J* = 8.05 Hz, 2H, NHCC*H*), 6.47 (brs, 1H, N*H*), 4.57 (dq, *J* = 7.08, 2.20 Hz, 2H, C$H_2$$CH_3$), 4.27-4.22 (m, 1H, N-CH*H*), 3.87-3.84 (m, 1H, N-C*H*H), 3.80-3.76 (m, 1H, S-C*H*), 2.82-2.64 (m, 2H, COCH_2), 2.19-2.10 (m, 1H, $COCH_2$CH*H*), 1.99 (brs, 3H, COCH_3), 1.92-1.84 (m, 2H, $COCH_2$C*H*H + COC*H*), 1.38 (t, *J* = 7.12 Hz, 3H, CH_2CH_3), 1.00-0.96 (m, 2H, COCH-CH_2), 0.87-0.83 (m, 2H, COCH-CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (*C*=S), 209.4 (*C*OCH), 170.1 (N*C*O), 146.8 (dd, *J* = 236.81, 12.49 Hz, N-*C*F), 142.7 (d, *J* = 254.26 Hz, NCF*C*F), 138.3 (NH*C*CH), 138.1 (NHC*C*H), 134.3 (dd, *J* = 260.72, 32.92 Hz, *C*F-C-NCO), 134.3-133.9 (N*C*N), 132.2-131.9 (CFCF*C*), 123.3 (IC*C*H), 88.7 (I*C*), 70.3 ($CSOCH_2CH_3$), 49.5 ($CONCH_2$), 49.1 (S*C*H), 40.2 (NCH_2), 25.0 ($COCH_2$), 21.9 (CO*C*H), 20.5 ($COCH_2CH_2$), 13.7 (CH_2CH_3), 10.8 ($COCHCH_2CH_2$)

IR (ν, cm^{-1}, $CDCl_3$) 3692, 3607, 3411, 1681, 1621, 1602, 1527, 1475, 1386, 1233, 1113, 1051, 1007

MS (NH_3 ionisation) 530 (-Xa.)

_S_-(4-(1-benzyl-1_H_-tetrazol-5-yl)-1-(_N_-(3,5,6-trifluoro-4-((4-iodophenyl)amino)pyridin-2-yl)acetamido)butan-2-yl) _O_-ethyl carbonodithioate (4-34)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with **4-14** (333 mg, 0.75mmol, 1.0eq.) and the corresponding xanthate **Xa-i** (220mg, 0.75mmol, 1.0eq.) in AcOEt (0.75ml, 1.0 mmol/ml), with DLP (60mg, 0.2eq.). Flash chromatography on silica gel with Et_2O / DCM = 15 / 85 afforded **4-34** (426mg, 77%) as light yellow oil.

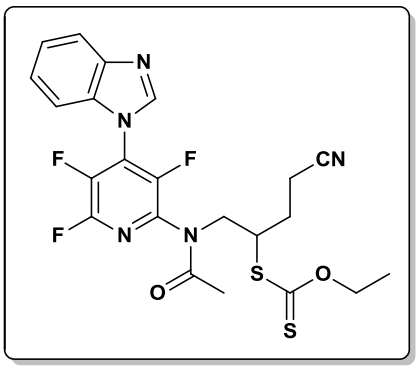
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.66 (d, 2H, *J* = 6.8 Hz, ICC*H*), 7.38-7.34 (m, 3H, C*H*-Ph), 7.24-7.16 (m, 2H, C*H*-Ph), 6.89 (d, 2H, *J* = 7.8 Hz, NHCC*H*), 6.56 (br s, 1H, N*H*), 5.90-5.20 (m, 2H, CH_2-Ph), 4.65-4.48 (m, 2H, CH_2CH_3), 4.39-4.19 (m, 1H, NAc-C*H*H), 3.95-3.68 (m, 2H, NAc-CH*H* + S-C*H*), 3.10-2.79 (m, 2H, tetrazole C-CH_2), 2.34-2.18 (m, 1H, CH-CH*H*-CH_2), 2.03-1.96 (m, 1H, CH-C*H*H-CH_2), 1.96 (br s, 3H, COCH_3), 1.36 (t, 3H, *J* = 6.9 Hz, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.4 (*C*=S), 170.2 (N*C*O), 154.1 (*C*-tetrazole), 147.0 (dd, *J* = 236.5, 14.1 Hz, N-*C*F), 142.9 (dd, *J* = 253.6, 4.1 Hz, NCF*C*F), 138.3 (NH*C*CH), 138.0 (2 NHC*C*H), 134.3 (dd, *J* = 264.0, 31.5 Hz, *C*F-C-NCO), 133.8-133.4 (N*C*N), 133.2 (*C*-benzene), 132.4-132.1 (CFCF*C*), 129.2 (2 *C*H-benzene), 128.9 (*C*H-benzene), 127.6 (2 *C*H-benzene), 123.3 (ICCH), 88.7 (I*C*), 70.5 (CSOCH_2CH_3), 50.7 (*C*H_2-Ph), 48.5 (br s, S*C*H + NAc*C*H_2), 28.0 (CH_2-*C*H_2-CH), 21.9 (*C*H_3), 20.6 (tetrazole C-*C*H_2), 13.6 (CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3409, 2986, 2937, 2247, 1678, 1622, 1585, 1527, 1477, 1381, 1343, 1278, 1234, 1113, 1051, 1007

HRMS (EI+) Calcd. for $C_{28}H_{27}F_3IN_7O_2S_2$: 741.0664 Found : 741.0688

S-(1-(N-(4-(1H-benzo[d]imidazol-1-yl)-3,5,6-trifluoropyridin-2-yl)acetamido)-4-cyanobutan-2-yl) O-ethyl carbonodithioate (4-35)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with the protected olefin **4-15** (255 mg, 0.74 mmol, 0.6 eq.) and the corresponding xanthate **Xa-a** (199 mg, 1.23 mmol, 1.0 eq.) in AcOEt (1.2 ml, 0.6 mmol/ml), with DLP (74 mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-35** (335 mg, 90%) as a yellow sticky oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.14 (s, 1H, NC*H*), 7.92-7.90 (m, 1H, C*H*CHCHCH), 7.44-7.42 (m, 2H, CHC*H*C*H*CH), 7.34-7.32 (m, 1H, CHCHCHC*H*), 4.58-4.55 (m, 2H, C$H_2$$CH_3$), 4.39 (dd, *J* = 14.06, 7.46 Hz, 1H, NCH*H*), 3.97 (dd, *J* = 14.20, 5.76 Hz, 1H, NC*H*H), 3.92-3.85 (m, 1H, SC*H*), 2.65-2.47 (m, 2H, NCCH_2), 2.32-2.23 (m, 1H, $NCCH_2$CH*H*), 2.12 (brs, 3H, NCOCH_3), 2.01-1.91 (m, 1H, $NCCH_2$C*H*H), 1.35 (t, *J* = 7.11 Hz, 3H, CH_3)

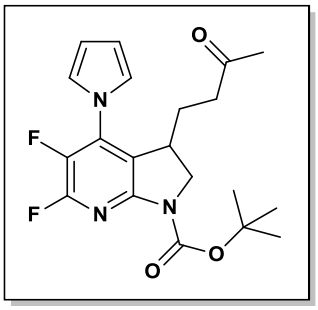
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.8 (*C*=S), 169.8 (N-*C*OCH_3),), 146.6 (ddd, *J* = 244.08, 13.88, 2.43 Hz, N-*C*F), 145.8 (dd, *J* = 265.44, 5.97 Hz, NCF*C*F), 143.2 (CN*C*CH), 141.6 (N*C*H), 138.69 (dd, *J* = 272.40, 31.41 Hz, *C*F-C-NCO), 135.6-135.3 (N*C*N), 132.3

(CHN*C*), 126.0-125.7 (CFCF*C*), 125.0 (CH*C*HCHCH), 124.2 (CHCH*C*HCH), 121.8 (*C*HCHCHCH), 118.5 (*C*N), 110.8 (CHCHCH*C*H), 71.0 (CSO*C*H_2CH$_3$), 49.0 (S*C*H), 48.9 (CON*C*H_2), 26.9 (NCH$_2$*C*H_2), 22.0 (NCO*C*H_3), 15.0 (NC*C*H_2), 13.6 (COOCH$_2$*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3607, 3109, 3062, 2989, 2963, 2938, 2872, 1687, 1622, 1612, 1515, 1477, 1468, 1451, 1424, 1380, 1330, 1302, 1275, 1236, 1197, 1152, 1112, 1051, 1012, 1002

HRMS (EI+) Calcd. for $C_{22}H_{20}F_3N_5O_2S_2$: 507.1011 –Xa. 386.1229 Found : 386.1232

tert-butyl 5,6-difluoro-2,3-dihydro-3-(3-oxobutyl)-4-(1*H*-pyrrol-1-yl)pyrrolo[2,3-b] pyridine-1-carboxylate (4-36')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-16** (108mg, 0.20mmol) and 2,6-lutidine (0.02 ml, 0.20mmol, 1eq.) in chlorobenzene (4.0 ml, 0.05 mmol/ml), with DTBP (0.19ml, 1.0mmol, 5.0eq.) for 3h. Flash chromatography on silica gel with AcOEt / PE = 30 / 70 afforded **4-36'** (14.2 mg, 18%) as a yellow oil.

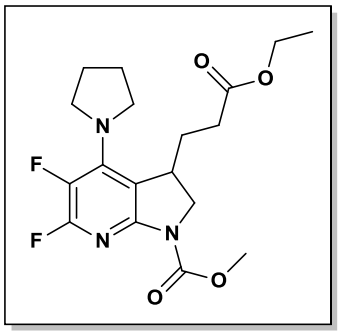
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.92 (dd, 2H, J=1.8Hz, J=3.7Hz, –CH=C*H*-N-C*H*=CH-), 6.42 (t, 2H, J=1.9Hz, –C*H*=CH-N-CH=C*H*-), 4.11 (t, 1H, J=10.4Hz, CH*H*-NBoc), 3.75 (dd, 1H, J=3.6Hz, J=11.4Hz, C*H*H-NBoc), 3.62-3.54 (m, 1H, C*H*-CH$_2$-NBoc), 2.19-2.01 (m, 2H, C*H*$_2$-COMe), 1.98 (s, 3H, COC*H*$_3$), 1.57 (s, 9H, C(C*H*$_3$)$_3$), 1.52-1.41 (m, 2H, C*H*$_2$-CH$_2$-COMe)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 207.2 (*C*OMe), 151.8 (dd, J=15.8Hz, J=236.6Hz, N-*C*F), 150.4 (*C*OOtBu), 149.2 (dd, J=4.1Hz, J=17.0Hz N-*C*-NBoc), 136.5 (d, J=15.1Hz, N-*C*-CF), 134.6 (dd, J=27.8Hz, J=251.7Hz, N-CF-*C*F), 121.2 (=*C*H-N-*C*H=), 118.8 (*C*-C-NBoc), 111.5 (-*C*H=CH-N-CH=*C*H-), 82.4 (*C*Me_3), 52.9 (*C*H_2-NBoc), 39.1 (*C*H_2-COMe), 35.2 (*C*H-CH_2-NBoc), 29.7 (CO*C*H_3), 28.2 (C(*C*H_3)$_3$), 27.4 (*C*H_2-CH_2-COOMe)

IR (ν, cm^{-1}, CCl_4) 2982, 2931, 1706, 1620, 1601, 1513, 1431, 1369, 1344, 1265, 1162, 1146, 1088

HRMS (EI+) Calcd. for $C_{20}H_{23}F_2N_3O_3$: 391.1707 Found : 391.1697

Methyl 3-(3-ethoxy-3-oxopropyl)-5,6-difluoro-4-(pyrrolidin-1-yl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (4-37)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-17** (97 mg, 0.19 mmol) and 2,6-lutidine (0.03 ml, 0.19mmol, 1.2eq.) in chlorobenzene (3.8 ml, 0.05 mmol/ml), with DTBP (0.17 ml, 0.92mmol, 5.0eq.) for 3h. Flash chromatography on silica gel with AcOEt / PE = 40 / 60 afforded **4-37** (18.4 mg, 26 %) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.10 (dq, 1H, J=1.6Hz, J=7.1Hz, COO-C*H*$_2$-CH_3), 3.92-3.84 (m, 5H, CO-N-C*H*$_2$ + COOC*H*$_3$), 3.75-3.68 (m, 2H, CH*H*-N-CH*H*), 3.50-3.54 (m, 2H, C*H*H-N-C*H*H), 3.36-3.31 (m, 1H, , C*H*H-CH_2-COOEt), 2.30 (t, 2H, J=7.6Hz, C*H*$_2$-COOEt), 2.10-2.02 (m, 2H, CH_2-C*H*H-CH*H*-CH_2), 1.89-1.81 (m, 3H, CH*H*-CH_2-COOEt +

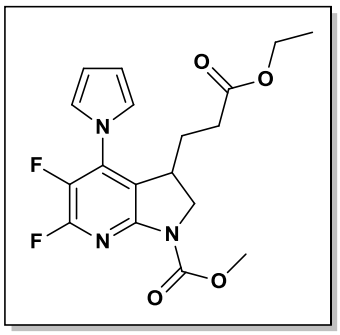
CH_2-C*H*H-CH*H*-CH_2), 1.63-1.54 (m, 1H, CH*H*-CH_2-COOEt), 1.25 (t, 3H, J=7.1Hz, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.8 (*C*OOEt), 152.9 (*C*OOMe), 152.6 (dd, J=16.0Hz, J=230.7Hz , N-*C*F), 147.6 (dd, J=2.7Hz, J=19.8Hz, N-*C*-N-CO), 143.1 (t, J=5.8Hz, $(CH_2)_2$N-*C*), 132.1 (dd, J=29.7Hz, J=244.1Hz, $(CH_2)_2$N-C-*C*F), 109.5 (d , J=3.4Hz, *C*-C-NCO), 60.6 (COO-*C*H_2-CH_3), 53.2 (COO*C*H_3), 51.0 (d, J=3.0Hz, N-(*C*H_2)$_2$), 50.9 (CO-N-*C*H_2), 36.9 (*C*H), 30.3 (*C*H_2-COOEt), 28.7 (CH-*C*H_2), 25.8 (d, J=2.0Hz, *C*H_2-CH_2-N-CH_2-*C*H_2), 14.2 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3690, 2981, 2957, 2877, 1727, 1699, 1617, 1507, 1444, 1368, 1332, 1237, 1195, 1125, 1114, 1029

HRMS (EI+) Calcd. for $C_{18}H_{23}F_2N_3O_4$:383.1657 Found : 383.1660

Methyl 3-(3-ethoxy-3-oxopropyl)-5,6-difluoro-4-(1*H*-pyrrol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate.(4-37')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-17** (97 mg, 0.19 mmol) and 2,6-lutidine (0.03 ml, 0.19mmol, 1.2eq.) in chlorobenzene (3.8 ml, 0.05 mmol/ml), with DTBP (0.17 ml, 0.92mmol, 5.0eq.) for 3h. Flash chromatography on silica gel with AcOEt / PE = 30 / 70 afforded **4-37'** (20.8 mg, 30 %) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.92 (dd, 2H, J=2.0Hz, J=4.1Hz, C*H*-N-C*H*), 6.42 (t, 2H, J=2.1Hz, CH-C*H*-C*H*-CH), 4.18 (dd, 1H, J=9.7Hz, J=11.4Hz, CO-N-CH*H*), 4.11 (q, 2H,

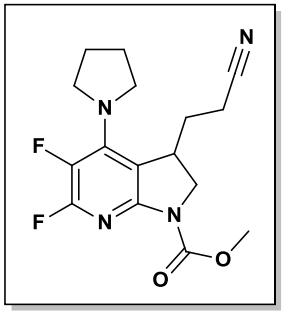
J=7.1 Hz, COO-C*H*$_2$-CH$_3$), 3.90 (s, 3H, COOC*H*$_3$), 3.87 (dd, 1H, J=3.9Hz, J=11.4Hz, CO-N-CH*H*), 3.67 (m, 1H, C*H*), 2.08 (m, 2H, CH-CH$_2$-C*H*$_2$), 1.48 (td, 2H, J=4.8Hz, J=7.8Hz, CH-C*H*$_2$-CH$_2$), 1.21 (t, 3H, J=7.2Hz, COO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.2 (*C*OOEt), 151.9 (dd, J=15.0Hz, J=237.8Hz, N-*C*F), 152.2 (*C*OOMe), 148.4 (dd, J=4.1Hz, J=17.8Hz, N-C-N), 136.8 (dd, J=4.9Hz, J=9.5Hz, N-*C*-CF), 134.9 (dd, J=28.8Hz, J=255.3Hz, N-C-*C*F), 121.1 (d, 1H, J=2.7Hz, *C*H-N-*C*H), 118.7 (dd, J=3.0Hz, J=5.6Hz, *C*-C-N), 111.6 (CH-*C*H-*C*H-CH), 60.6 (COO*C*H$_2$CH$_3$), 53.4 (COO*C*H$_3$), 52.4 (CO-N-*C*H$_2$), 35.5 (*C*H-CH$_2$-N), 30.3 (CH-CH$_2$-*C*H$_2$), 28.0 (CH-*C*H$_2$-CH$_2$), 14.1 (COO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 2984, 2958, 2930, 1731, 1622, 1603, 1515, 1445, 1348, 1312, 1265, 1237, 1189, 1032, 964

HRMS (EI+) Calcd. for $C_9H_8F_4N_2$: 379.1344 Found : 379.1354

Methyl 3-(2-cyanoethyl)-5,6-difluoro-4-(1*H*-pyrrolidine-1-yl)-2,3-dihydro-1*H*-pyrrolo [2,3-b] pyridine-1-carboxylate.(4-38)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-18** (293 mg, 0.62 mmol) and 2,6-lutidine (0.09 ml, 0.74mmol, 1.2eq.) in chlorobenzene (12ml, 0.05 mmol/ml), with DTBP (0.57 ml, 3.1mmol, 5.0eq.) for 2h. Flash chromatography on silica gel with AcOEt / PE = 40 / 60 afforded **4-38** (58.2 mg, 29%) as light yellow solid.

m.p. 160~165^{o}C

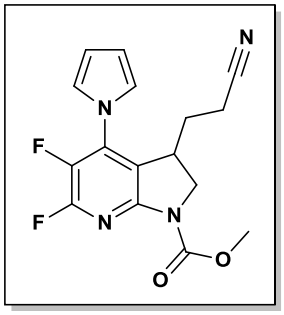
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 3.96 (dd, *J* = 11.38, 8.27 Hz, 1H, CO-N-CH*H*), 3.87 (s, 4H, CO-N-CH*H* + COOC*H*$_3$), 3.71 (dq, *J* = 9.94, 9.73, 3.87 Hz, 2H, CH_2-CH_2-CH_2-C*H*$_2$), 3.58 (t, *J* = 7.29 Hz, 2H, C*H*$_2$-CH_2-CH_2-CH_2), 3.49 (t, *J* = 9.00 Hz, 1H, C*H*), 2.38 (dd, *J* = 10.63, 4.62 Hz, 2H, CN-C*H*$_2$), 2.27-1.98 (m, 2H, CH_2-C*H*$_2$-CH_2-CH_2), 1.97-1.75 (m, 3H, CH_2-CH_2-C*H*$_2$-CH_2 + $CNCH_2$-CH*H*), 1.64 (m, 1H, $CNCH_2$-CH*H*)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 152.9 (dd, *J* = 231.83, 15.98 Hz, N-*C*F), 152.8 (*C*$OOCH_3$), 147.6 (dd, *J* = 20.23, 2.93 Hz, N-*C*-N), 143.7-142.9 (m, *C*-N$(CH_2)_2$), 132.1 (dd, *J* = 244.91, 29.58 Hz, N-C-*C*F), 118.8 (CH_2-*C*N), 108.2 (d, *J* = 3.39 Hz,CO-N-C-*C*), 51.2 (d, *J* = 6.71 Hz, COO-*C*H_3), 50.6 (N-(*C*H_2)$_2$), 36.6 (*C*H), 29.3 (d, *J* = 9.09 Hz,CN-CH_2-*C*H_2), 25.8 (d, *J* = 1.98 Hz, CH_2-*C*H_2-*C*H_2-CH_2), 13.9 (CN-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 2957, 2879, 1733, 1699, 1617, 1507, 1444, 1366, 1328, 1261, 1237, 1125, 1114, 1029

HRMS (EI+) Calcd. for $C_{16}H_{18}F_2N_4$: 336.1398 Found : 336.1413

Methyl 3-(2-cyanoethyl)-5,6-difluoro-4-(1*H*-pyrrol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b] pyridine-1-carboxylate.(4-38')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-18** (293 mg, 0.615 mmol) and 2,6-lutidine (0.09 ml, 0.74 mmol) in chlorobenzene (12 ml, 0.05 mmol/ml), with DTBP (0.56 ml, 3.08 mmol) for 1.5 h. Flash chromatography on silica gel with AcOEt / PE = 40 / 60 afforded **4-38'** (41.3 mg, 21 %) as a yellow oil.

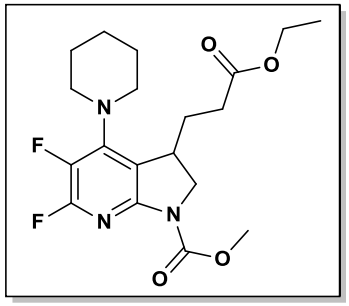
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.94 (dd, 2H, J=2.0Hz, J=4.1Hz, N-(CH_2)$_2$), 6.46 (m, 2H, CH_2-CH_2-CH_2-CH_2), 4.27 (dd, 1H, J=9.8Hz, J=11.5Hz, CO-N-CH), 3.91 (s, 3H, COO-CH_3), 3.87 (dd, 1H, J=4.0Hz, J=11.6Hz, CO-N-CH), 3.76 (m, 1H, CH), 2.16 (m, 2H, CH_2-CN), 1.46 (m, 2H, CH_2-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 152.3 (dd, J=14.8Hz, J=239.0Hz, N-CF), 152.1 (COOCH$_3$), 148.4 (dd, J=4.1Hz, J=17.5Hz, N-C-N), 136.9 (dd, J=5.1Hz, J=9.6Hz, C-N(CH_2)$_2$), 134.9 (dd, J=28.8Hz, J=256.1Hz, N-C-CF), 121.0 (d, J=2.6Hz, N-(CH_2)$_2$), 118.1 (CH_2-CN), 117.33 (dd, J=2.8Hz, J=5.5Hz, CH-C), 112.2 (CH_2-CH_2-CH_2-CH_2), 53.5 (COO-CH_3), 52.1 (CO-N-CH_2), 35.3 (CH), 28.4 (CH_2-CH_2-CN), 14.0 (CH_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3690, 2958, 2253, 1737, 1708, 1621, 1604, 1515, 1482, 1444, 1349, 1311, 1190, 1140, 1089

HRMS (EI+) Calcd. for $C_9H_8F_4N_2$: 332.1085 Found : 332.1091

methyl 3-(2-(ethoxycarbonyl)ethyl)-5,6-difluoro-2,3-dihydro-4-(piperidin-1-yl) pyrrolo[2,3-b]pyridine-1-carboxylate (4-39)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-19** (90 mg, 0.17 mmol) and 2,6-lutidine (0.12 ml, 1.0mmol, 6eq.) in chlorobenzene (3.4 ml, 0.05 mmol/ml), with DTBP (0.15 ml, 0.84mmol, 5.0eq.) for 3h. Flash chromatography on silica gel with AcOEt / PE = 30 / 70 afforded **4-39** (21.8 mg, 33%) as yellow oil.

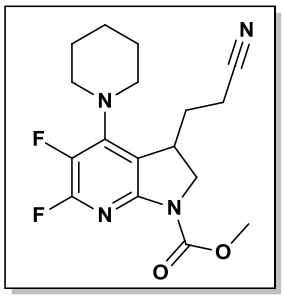
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.12 (dq, 2H, J=2.3Hz, J=7.1Hz, COO-C*H*$_2$-CH$_3$), 4.00 (dd, 1H, J=9.2Hz, J=11.4Hz, CO-N-C*H*H), 3.86 (s, 3H, COOC*H*$_3$), 3.83 (dd, 1H, J=3.0Hz, J=11.4Hz, CO-N-CH*H*), 3.39-3.33 (m, 3H, Xa-C*H* + C*H*H-N-C*H*H), 3.17-3.12 (m, 2H, CH*H*-N-CH*H*), 2.35-2.23 (m, 2H, C*H*$_2$-COOEt), 2.10-2.01 (m, 1H, C*H*H-CH$_2$-COOEt), 1.80-1.68 (m, 3H, CH*H*-CH$_2$-COOEt + C*H*H-CH$_2$-C*H*H), 1.67-1.60 (m, 4H, CH*H*-C*H*$_2$-CH*H*), 1.25 (t, 3H, J=7.1Hz, COO-CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.7 (*C*OOEt), 152.7 (*C*OOMe), 152.3 (dd, J=15.7Hz, J=234.5Hz, , N-*C*F), 147.8 (dd, J=3.2Hz, J=18.7Hz, N-*C*-N-CO), 147.3 (dd, J=4.8Hz, J=6.8Hz, $(CH_2)_2$N-*C*), 135.7 (dd, J=27.5Hz, J=248.6Hz, $(CH_2)_2$N-C-*C*F), 115.5 (d, J=4.4Hz, *C*-C-NCO), 60.6 (COO-*C*H$_2$-CH$_3$), 53.2 (COO*C*H$_3$), 51.6 (CO-N-*C*H$_2$), 51.3 (d, J=4.4Hz, *C*H$_2$-N-*C*H$_2$), 36.3 (*C*H), 30.6 (*C*H$_2$-COOEt), 28.7 (CH-*C*H$_2$), 26.2 (*C*H$_2$-CH$_2$-N-CH$_2$-*C*H$_2$), 24.0 (-N-CH$_2$-CH$_2$-*C*H$_2$), 14.2 (COO-CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 2941, 2855, 1730, 1696, 1616, 1444, 1427, 1384, 1331, 1300, 1197, 1099, 996

HRMS (EI+) Calcd. for $C_{19}H_{25}F_2N_3O_4$: 397.1813 Found : 397.1809

methyl 3-(2-cyanoethyl)-5,6-difluoro-2,3-dihydro-4-(piperidin-1-yl)pyrrolo[2,3-b] pyridine-1-carboxylate (4-40)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of **4-20** (100 mg, 0.20 mmol) and 2,6-lutidine (0.14ml, 1.2mmol, 6eq.) in chlorobenzene (4.1ml, 0.05 mmol/ml), with DTBP (0.19ml, 1.0mmol,

5.0eq.) for 2h. Flash chromatography on silica gel with AcOEt / PE = 50 / 50 afforded **4-40** (19.2 mg, 27%) as white solid.

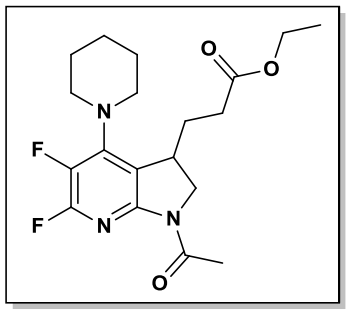
m.p. 142~146°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.06 (dd, 1H, J=9.1Hz, J=11.4Hz, CO-N-C*H*H), 3.87 (s, 3H, COOCH_3), 3.83 (dd, 1H, J=2.6Hz, J=11.5Hz, CO-N-CH*H*), 3.47 (t, 1H, J=9.3Hz, CON-CH_2-C*H*), 3.39-3.34 (m, 2H, C*H*H-N-C*H*H), 3.19-3.15 (m, 2H, CH*H*-N-CH*H*), 2.42-2.38 (m, 2H, CH_2-CN), 2.16-2.08 (m, 1H, C*H*H-CH_2-CN), 1.82-1.71 (m, 3H, CH*H*-CH_2-CN + C*H*H-CH_2-C*H*H), 1.70-1.61 (m, 4H, CH*H*-CH_2-CH*H*)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 152.5 (*C*OOMe), 152.8 (dd, J=15.5Hz, J=221.2Hz, N-*C*F), 147.7 (d, J=15.8Hz, N-*C*-N-CO), 147.3 (dd, J=4.9Hz, J=6.6Hz, $(CH_2)_2$N-*C*), 135.9 (dd, J=26.8Hz, J=249.9Hz, $(CH_2)_2$N-C-*C*F), 118.7 (*C*N), 114.5 (d, J=4.4Hz, *C*-C-NCO), 53.3 (COO*C*H_3), 51.6 (d, J=4.6Hz, *C*H_2-N-*C*H_2), 51.3 (CO-N-*C*H_2), 35.9 (*C*H), 28.7 (CH-*C*H_2), 26.3 (*C*H_2-CH_2-N-CH_2-*C*H_2), 23.9 (-N-CH_2-CH_2-*C*H_2), 14.3 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3606, 2943, 2855, 1733, 1698, 1603, 1444, 1428, 1384, 1301, 1198, 1136, 1093, 996

ethyl 3-(1-acetyl-5,6-difluoro-2,3-dihydro-4-(piperidin-1-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-41)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 147mg **4-21** (0.29mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.35mmol, 1.2 eq.) in chlorobenzene (5.8ml, 0.05 mmol/ml), with 0.16ml DTBP (0.87mmol,

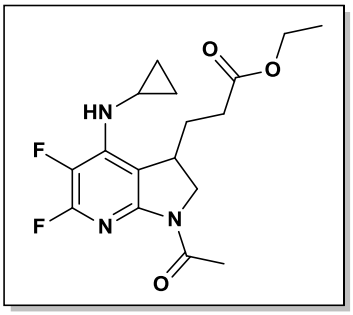
3.0 eq.) for 3 hours. Flash chromatography on silica gel with Acetone / DCM = 3 / 97 afforded **4-41** (29mg, 31%) as a colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.10 (dq, 2H, J=3.3Hz, J=7.1Hz, COO-C*H*$_2$-CH_3), 3.94 (dq, 2H, J=6.1Hz, J=12.3Hz, C*H*$_2$-NAc), 3.38-3.34 (m, 3H, C*H*-CH_2NAc + C*H*H-N-C*H*H), 3.17-3.13 (m, 2H, CH*H*-N-CH*H*), 2.56 (s, 3H, COC*H*$_3$), 2.30-2.26 (m, 2H, C*H*$_2$-COOEt), 2.10-2.02 (m, 1H, C*H*H-CH_2-COOEt), 1.75-1.63 (m, 7H, CH*H*-CH_2-COOEt + C*H*$_2$-C*H*$_2$-C*H*$_2$), 1.24 (t, 3H, J=7.1Hz, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.7 (*C*OOEt), 169.7 (*C*OMe), 151.8 (dd, J=15.9Hz, J=234.3Hz, N-*C*F), 147.7 (d, J=3.3Hz, N-*C*-N-CO), 147.5 (m, N(piperidine)-*C*), 135.6 (dd, J=27.4Hz, J=248.4Hz, C-*C*F-CF), 116.3 (d, J=4.3Hz, *C*-C-N-CO), 60.6 (COO-*C*H_2-CH_3), 51.2 (d, J=4.4Hz, *C*H_2-N-*C*H_2), 50.6 (CO-N-*C*H_2), 35.5 (AcN-CH_2-*C*H), 30.5 (*C*H_2-COOEt), 28.7 (*C*H_2-CH_2-COOEt), 26.2 (*C*H_2-CH_2-N-CH_2-*C*H_2), 24.6 (CO*C*H_3), 23.9 (-N-CH_2-CH_2-*C*H_2), 14.2 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 2941, 2856, 1727, 1651, 1615, 1505, 1477, 1424, 1388, 1322, 1250, 1216, 1158, 1104, 1031, 972

ethyl 3-(1-acetyl-4-(cyclopropylamino)-5,6-difluoro-2,3-dihydro-1H-pyrrolo[2,3-b] pyridin-3-yl)propanoate (4-42)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 149mg **4-22** (0.30mmol, 1.0 eq.) and 0.07ml 2,6-lutidine (0.6mmol, 2.0eq.) in chlorobenzene (6.0ml, 0.05mmol/ml), with 0.28ml DTBP (1.5mmol,

5.0eq.) for 4.5hours. Flash chromatography on silica gel with Acetone / DCM = 2 / 98 afforded **4-42** (13mg, 12%) as a colourless oil.

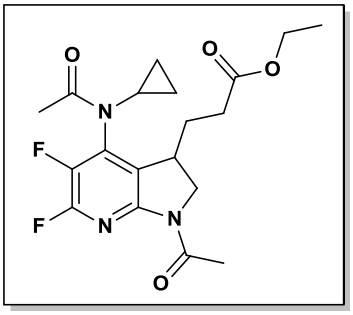
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.42 (br s, 1H, N*H*), 4.17 (q, 1H, J=7.1Hz, CO-OC*H*$_2$CH$_3$), 3.94 (dq, 2H, J=5.5Hz, J=12.2Hz, C*H*$_2$-NAc), 3.10 (t, 1H, J=9.1Hz, C*H*- CH_2-NAc), 3.00 (tq, 1H, J=3.2Hz, J=6.5Hz, NH-C*H*), 2.57 (s, 3H, COC*H*$_3$), 2.48-2.32 (m, 2H, C*H*$_2$-COOEt), 1.98-1.98 (m, 1H, C*H*H-CH_2-COOEt), 1.54-1.48 (m, 1H, CH*H*-CH_2-COOEt), 1.28 (t, 3H, J=7.2Hz, CO-OCH_2-C*H*$_3$), 0.89-0.82 (m, 1H, -C*H*H-CH_2-), 0.81-0.74 (m, 1H, -CH_2-C*H*H-), 0.72-0.63 (m, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.9 (*C*OOEt), 169.9 (*C*OMe), 151.7 (dd, J=14.6Hz, J=231.0Hz, N-*C*F), 146.7 (m, N-*C*-N-CO), 143.1 (t, J=6.3Hz, HN-*C*), 130.9 (dd, J=30.5Hz, J=244.7Hz, HN-C-*C*F), 109.8 (d, J=3.4Hz, *C*-C-NCO), 61.0 (COO-*C*H_2-CH_3), 52.2 (CO-N-*C*H_2), 33.8 (*C*H), 30.7 (*C*H_2-COOEt), 28.6 (CH-*C*H_2), 26.7 (d, J=5.2Hz, HN-*C*H), 24.3 (CO*C*H_3), 14.2 (COO-CH_2-*C*H_3), 8.85 (d, J=3.2Hz, -*C*H_2-CH_2-), 8.54 (d, J=3.2Hz, -CH_2-*C*H_2-)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3607, 2929, 1718, 1651, 1623, 1603, 1526, 1435, 1417, 1383, 1352, 1219, 1182

HRMS (EI+) Calcd. for $C_{17}H_{21}F_2N_3O_3$: 353.1551 Found : 353.1545

ethyl 3-(1-acetyl-4-(N-cyclopropylacetamido)-5,6-difluoro-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-43)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 161mg **4-23** (0.30mmol, 1.0 eq.) and 0.08ml 2,6-lutidine (0.68mmol, 2.3eq.) in chlorobenzene (7.0ml, 0.04mmol/ml), with 0.33ml DTBP (1.7mmol, 5.6 eq.) for 4 hours. Flash chromatography on silica gel with AcOEt / EP = 60 / 40 afforded **4-43** (58mg, 46%) as yellow oil.

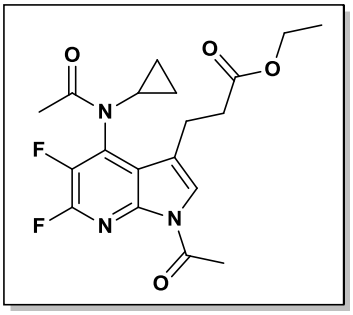
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.13 (q, J = 7.2 Hz, 3H, C*H*$_2$CH$_3$ + NC*H*H), 3.77 (dd, J = 12, 4.6 Hz, NCH*H*), 3.24-3.11 (m, 1H, NCH$_2$C*H*), 3.36-3.25 (m, 1H, NC*H*), 2.58 (s, 3H, NCOC*H*$_3$), 2.47 (s, 3H, NCOC*H*$_3$), 2.27 (t, J = 6.6Hz, 2H, COC*H*$_2$), 1.83-1.69 (m, 1H, COCH$_2$CH*H*), 1.47-1.34 (m, 1H, COCH$_2$C*H*H), 1.26 (t, J = 7.13 Hz, 3H, CH$_2$C*H*$_3$), 1.18-1.04 (m, 1H, NCHCH*H*), 0.99-0.80 (m, 2H, NCH(CH*H*)$_2$), 0.52-0.47 (m, 1H, NCHC*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.7 (*C*OOEt), 172.5 (CHN*C*OCH$_3$), 169.5 (CH$_2$N*C*OCH$_3$), 151.9 (dd, J = 17, 14 Hz, N-*C*-N-CO), 148.4 (dd, J = 238, 16 Hz, N-*C*F), 138.4 (dd, J = 5.9, 4.2 Hz, CHN-*C*), 136.7 (d, J = 253 Hz, CHN-C-*C*F), 124.4 (dd, J = 5.0, 2.96 Hz, CH*C*), 123.04 (dd, J = 4.3, 2.1 Hz, CH*C*), 60.7 (COO*C*H$_2$CH$_3$), 51.6 (CON*C*H$_2$), 35.5 (NCH$_2$*C*H), 32.3 (N*C*H), 30.7 (*C*H$_2$COOEt), 28.1 (CH*C*H$_2$CH$_2$), 24.6 (CH$_2$NCO*C*H$_3$), 22.9 (CHNCO*C*H$_3$), 14.2 (COOCH$_2$*C*H$_3$), 10.9 (NCH*C*H$_2$), 7.8 (NCH*C*H$_2$)

IR (ν, cm^{-1}, $CDCl_3$) 3322, 2984, 2963, 2931, 1727, 1671, 1618, 1484, 1424, 1380, 1328, 1254, 1227, 1183, 1101, 1084, 1035, 973

HRMS (EI+) Calcd. for $C_{19}H_{23}F_2N_3O_4$: 395.1657 Found : 395.1661

ethyl 3-(1-acetyl-4-(N-cyclopropylacetamido)-5,6-difluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-43')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 161mg **4-23** (0.30mmol, 1.0 eq.) and 0.08ml 2,6-lutidine (0.68mmol, 2.3eq.) in chlorobenzene (7.0ml, 0.04mmol/ml), with 0.33ml DTBP (1.7mmol, 5.6 eq.) for 4 hours. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-43'** (21mg, 18%, rotamers 1:3) as yellow solid.

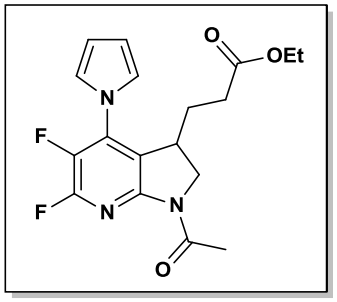
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.81 (s, 0.25H, C*H*-aromatic), 7.72 (s, 0.75H, C*H*-aromatic), 4.35-3.97 (m, 2H, CO-OCH_2CH$_3$), 3.26 (m, 1H, NAc-C*H*), 2.98-2.88 (m, 0.5H, CH_2), 2.94 (s, 0.75H, COCH_3), 2.91 (s, 2.25H, COCH_3), 2.85-2.80 (m, 1.5H, CH_2), 2.71-2.59 (m, 2H, CH_2), 2.49 (s, 2.25H, COCH_3), 1.90 (s, 0.75H, COCH_3), 1.32-1.20 (m, 3H, CO-OCH$_2$-CH_3), 1.09-0.98 (m, 1H, -C*H*H-CH$_2$-), 0.97-0.83 (m, 2H, -CH*H*-CH$_2$- + -CH$_2$-CH*H*-), 0.63 (m, 1H, -CH$_2$-C*H*H-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.8 (*C*OOEt), 172.5 (*C*OMe), 167.9 (*C*OMe),149.2 (d, *J* = 268.8 Hz, *C*F), 139.1 (d, *J* = 252.3 Hz, *C*F), 138.6 (*C*-aromatic), 133.7 (*C*-aromatic), 123.0 (d, *J* = 4.3 Hz, CO-N-*C*H), 119.8 (*C*-aromatic), 117.7 (*C*-aromatic), 60.7 (COO-*C*H$_2$-CH$_3$), 33.0 and 32.7 (*C*H$_2$), 32.4 and 32.3 (*C*H), 25.5 (CO*C*H$_3$), 23.0 and 22.5 (CO*C*H$_3$), 20.5 and 20.4 (*C*H$_2$), 14.2 (COO-CH$_2$-*C*H$_3$), 9.8 (-*C*H$_2$-CH$_2$-), 8.4 (-*C*H$_2$-CH$_2$-)

IR (ν, cm^{-1}, CCl_4) 3420, 2930, 1700, 1675, 1625, 1510, 1420, 1378, 1330, 1240, 1180, 1030

HRMS (EI+) Calcd. for $C_{19}H_{21}F_2N_3O_4$: 393.1500 Found : 393.1502

3-(1-acetyl-5,6-difluoro-4-(1*H*-pyrrol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl) propanoate (4-44)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 147mg **4-24** (0.29mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.35mmol, 1.2 eq.) in chlorobenzene (5.8ml, 0.05 mmol/ml), with 0.16ml DTBP (0.87mmol, 5.0 eq.) for 3 hours. Flash chromatography on silica gel with Acetone / DCM = 3 / 97 afforded **4-44** (29mg, 38%) as a colourless oil.

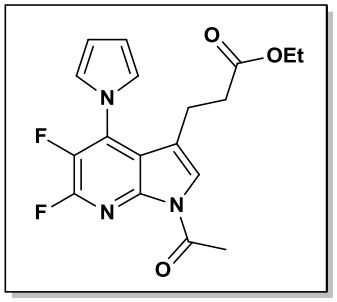
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.98 (dd, 2H, J=2.0Hz, J=4.1Hz, C*H*-N-C*H*), 6.48 (m, 2H, CH-C*H*-C*H*-CH), 4.23 (dd, 1H, J=9.7Hz, J=12.3Hz, CO-N-CH*H*), 4.10 (dq, 2H, J=3.3Hz, J=7.2Hz, COO-CH_2-CH_3), 3.98 (dd, 1H, J=4.0Hz, J=12.3Hz, CO-N-CH*H*), 3.72 (m, 1H, C*H*), 2.66 (s, 3H, CO-CH_3), 2.15 (m, 2H, CO-CH_2-CH_2), 1.53 (m, 2H, CO-CH_2-CH_2), 1.26 (t, 3H, J=7.1Hz, COO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.2 (*C*OOEt), 169.5 (*C*OMe), 151.5 (dd, J=15.3Hz, J=238.1Hz, N-*C*F), 148.3 (dd, J=4.0Hz, J=16.9Hz, N-C-N), 137.2 (dd, J=5.0Hz, J=9.1Hz, N-*C*-CF), 135.0 (dd, J=28.4Hz, J=255.3Hz, N-C-*C*F), 121.1 (d, J=2.7Hz, *C*H-N-*C*H), 119.7 (dd, J=2.8Hz, J=5.5Hz, *C*-C-N), 111.7 (CH-*C*H-*C*H-CH), 60.6 (COO*C*$H_2$$CH_3$), 51.5 (CO-N-*C*$H_2$), 34.7 (*C*H), 30.3 (CO*C*H_2-CH_2), 28.0 (COCH_2-*C*H_2), 24.8 (*C*H_3-CO-N), 14.1 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3139, 2984, 2931, 2856, 1724, 1601, 1562, 1516, 1439, 1405, 1382, 1328, 1289, 1240, 1190, 1086, 1038

HRMS (EI+) Calcd. for $C_{18}H_{19}F_2N_3O_3$:361.1238 Found : 361.1237

3-(1-acetyl-5,6-difluoro-4-(1*H*-pyrrol-1-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-44')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 147mg **4-24** (0.29mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.35mmol, 1.2 eq.) in chlorobenzene (5.8ml, 0.05 mmol/ml), with 0.16ml DTBP (0.87mmol, 5.0 eq.) for 3 hours. Flash chromatography on silica gel with Acetone / DCM = 2 / 97 afforded **4-44'** (11mg, 14%) as a yellow oil.

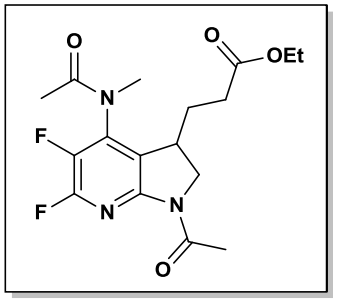
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.79 (s, 1H, CH_3-CO-N-C*H*), 6.89 (dd, 2H, J=2.0Hz, J=3.1Hz, C*H*-N-C*H*), 6.45 (t, 2H, J=2.1Hz, CH-C*H*-C*H*-CH), 4.06 (q, 2H, J=7.1Hz, COO-CH_2-CH_3), 2.96 (s, 3H, COO-CH_2-CH_3), 2.65 (t, 2H, J=7.4Hz, CO-CH_2-CH_2), 2.16 (t, 2H, J=7.4Hz, CO-CH_2-CH_2), 1.20 (t, 3H, J=7.1Hz, COO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.2 (*C*OOEt), 167.8 (*C*OMe), 148.5 (dd, J=16.5Hz, J=239.4Hz, N-*C*F), 138.9 (dd, J=3.5Hz, J=17.1Hz, N-C-N), 138.1 (dd, J=28.7Hz, J=255.4Hz, N-C-*C*F), 132.5 (dd, J=4.8Hz, J=10.5Hz, N-*C*-CF), 124.2 (d, J=4.4Hz, CO-N-*C*H), 123.0 (s, *C*H-N-*C*H), 118.2 (dd, J=2.1Hz, J=4.3Hz, *C*-C-N), 117.6 (dd, J=1.2Hz, J=3.2Hz, CH_2-*C*), 110.9 (CH-*C*H-*C*H-CH), 60.5 (COO*C*H_2CH_3), 33.2 (CO*C*H_2-CH_2), 25.6 (*C*H_3-CO-N), 21.3 ($COCH_2$-*C*H_2), 14.2 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3139, 2984, 2931, 2856, 1724, 1601, 1562, 1516, 1439, 1405, 1382, 1328, 1289, 1240, 1190, 1086, 1038

HRMS (EI+) Calcd. for $C_{18}H_{19}F_2N_3O_3$:361.1238 Found : 361.1237

3-(1-acetyl-5,6-difluoro-4-(*N*-methylacetamido)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-45)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 117mg **4-25** (0.23mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.34mmol, 1.4 eq.) in chlorobenzene (6.0ml, 0.04 mmol/ml), with 0.27ml DTBP (1.47mmol, 6.0 eq.) for 3 hours. Flash chromatography on silica gel with AcOEt / DCM = 30 / 70 afforded **4-45** (38mg, 44%) as a yellow oil.

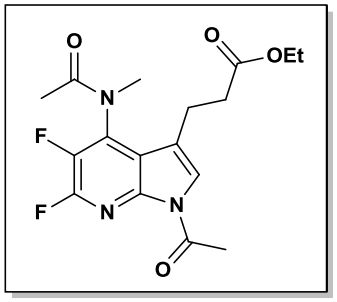
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.29-4.15 (m, 3H, CO-N-CH*H* + COO-C*H*$_2$-CH_3), 3.96, 3.86 (dd, *J* = 12.34, 5.04 Hz, dd, *J* = 12.08, 4.72 Hz, 1H, CO-N-CH*H*), 3.45, 3.42, 3.30, 3.28 (4H, C*H* + CH_3-N-CO-C*H*$_3$), 2.65-2.63 (m, 3H, N-CH_3), 2.43-2.31 (m, 3H, CO-C*H*$_2$ + N-CO-C*H*$_3$), 2.18-2.10 (m, 3H, CH-C*H*H-CH_2 + N-CO-C*H*$_3$), 1.73-1.64 (m, 1H, CH-C*H*H-CH_2), 1.30 (t, *J* = 7.08 Hz, 3H, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.5 (*C*OOEt), 169.3 (N*C*OMe), 168.9 (CH_3-N-*C*O-CH_3), 151.1 (dd, *J* = 253.45, 14.45 Hz,, N-*C*F), 147.7 (d, *J* = 16.20 Hz, N-*C*-CF), 140.9 (d, *J* = 11.16 Hz, N-C-N), 137.0 (ddd, *J* = 255.85, 28.10, 11.62 Hz, N-C-*C*F), 124.7 (d, *J* = 5.21 Hz, *C*-C-N), 60.8 (COO*C*H$_2$CH$_3$), 51.4 (CO-N-*C*H$_2$), 38.3, 37.3 (CH_3-N-CO-*C*H$_3$), 35.3 (*C*H), 30.5 (CO*C*H$_2$-CH_2), 28.1 (COCH$_2$-*C*H$_2$), , 24.6 (N-*C*H$_3$), 21.8, 21.3 (N-CO-*C*H$_3$), 14.1 (COO-CH_2-*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3693, 2930, 1730, 1673, 1691, 1476, 1429, 1380, 1343, 1325, 1255, 1191, 1034

HRMS (EI+) Calcd. for $C_{17}H_{21}F_2N_3O_4$: 369.1500 Found : 369.1503

3-(1-acetyl-5,6-difluoro-4-(N-methylacetamido)-1H-pyrrolo[2,3-b]pyridin-3-yl) propanoate (4-45')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 117mg **4-25** (0.23mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.34mmol, 1.4 eq.) in chlorobenzene (6.0ml, 0.04 mmol/ml), with 0.27ml DTBP (1.47mmol, 6.0 eq.) for 3 hours. Flash chromatography on silica gel with AcOEt / DCM = 15 / 85 afforded **4-45'** (12mg, 15%) as a yellow oil.

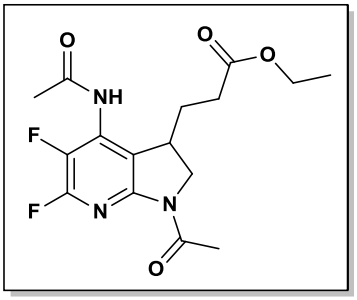
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.82, 7.75 (s, 1H, CH_3-CO-N-C*H*), 4.13 (q, 2H, J=7.15Hz, COO-CH_2-CH_3), 3.44, 3.31 (s, 3H, CH_3-N-CO-CH_3), 2.94 (s, 3H, N-CH_3), 2.92 (t, 2H, *J* = 7.21 Hz, , CO-CH_2-CH_2), 2.69 (t, 2H, *J* = 6.95 Hz, CO-CH_2-CH_2), 2.06, 2.37, 1.92 (s, 3H, C-NCO-CH_3), 1.25 (t, *J* = 6.92 Hz, 3H, COO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.9 (*C*OOEt), 169.7 (CH_3N-*C*O-CH_3), 167.6 (C-N-*C*OMe), 148.7 (dd, *J* = 241.03, 16.65 Hz, N-*C*F), 139.1 (dd, *J* = 254.60, 27.67 Hz, N-C-*C*F), 139.0 (d, *J* = 13.42 Hz, N-C-N), 135.1 (dd, *J* = 11.73, 4.28 Hz, N-*C*-CF), 123.9 (d, *J* = 4.52 Hz, CO-N-*C*H), 119.1 (dd, *J* = 4.46, 1.61 Hz, *C*-C-N), 117.5 (dd, *J* = 3.20, 1.04 Hz, CH-*C*), 60.8 ($COOCH_2CH_3$), 38.8, 36.4 (CH_3-N-CO-*C*H_3)), 33.5, 32.9 (CO-CH_2-*C*H_2), 25.5 (*C*H_3-CO-N-C), 21.9, 21.6 (C-NCO-*C*H_3), 20.7, 20.3 (CO-*C*H_2-CH_2), 14.2 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3151, 2984, 2938, 1726, 1674, 1598, 1562, 1439, 1404, 1379, 1341, 1284, 1234, 1031

HRMS (EI+) Calcd. for $C_{17}H_{19}F_2N_3O_4$:367.1344 Found : 367.1348

3-(4-acetamido-1-acetyl-5,6-difluoro-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl) propanoate (4-46)



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 160mg **4-26** (0.32 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.39 mmol, 1.2 eq.) in chlorobenzene (6.5 ml, 0.05 mmol/ml), with 0.30 ml DTBP (1.62 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 25 / 75 afforded **4-46** (58 mg, 50%) as a white solid.

m.p. 134-136 ^{o}C

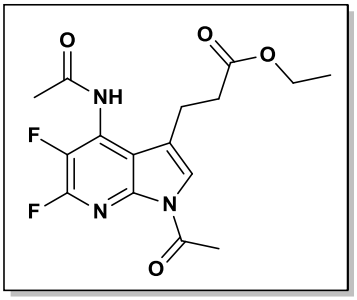
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.03 (s, 1H, N*H*), 4.21-4.04 (m, 3H, CO-N-CH*H* + COO-C*H*$_2$-CH_3), 3.89 (dd, *J* = 12.12, 3.50 Hz, 1H, CO-N-CH*H*), 3.48-3.34 (m, 1H, C*H*), 2.58 (s, 3H, NH-CO-C*H*$_3$), 2.40-2.23 (m, 5H, CO-C*H*$_2$ + N-CO-C*H*$_3$), 1.97-1.82 (m, 1H, CH-C*H*H-CH_2), 1.72-1.56 (m, 1H, CH-C*H*H-CH_2), 1.27 (t, *J* = 7.13 Hz, 3H, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.6 (*C*OOEt), 169.7 (N*C*OMe), 167.8 (NH-*C*O-CH_3), 150.5 (dd, *J* = 237.56, 15.76 Hz, N-*C*F), 147.8 -147.5 (N-*C*-CF), 134.65 (dd, *J* = 251.54, 29.15 Hz, N-C-*C*F), 133.7-133.5 (m, N-C-N), 119.78 (d, *J* = 5.13 Hz, *C*-C-N), 60.1 (COO*C*$H_2$$CH_3$), 52.2 (CO-N-*C*$H_2$), 35.2 (*C*H), 30.8 (CO*C*H_2-CH_2), 28.4 (COCH_2-*C*H_2), 24.6 (*C*H_3-CO-NH), 23.6 (N-CO-*C*H_3), 14.1 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2928, 1720, 1663, 1623, 1501, 1472, 1425, 1380, 1328, 1238

HRMS (EI+) Calcd. for $C_{16}H_{19}F_2N_3O_4$: 355.1344 Found : 355.1340

3-(1-acetyl-5,6-difluoro-4-(N-methylacetamido)-1H-pyrrolo[2,3-b]pyridin-3-yl) propanoate (4-46')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 160mg **4-26** (0.32 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.39 mmol, 1.2 eq.) in chlorobenzene (6.5 ml, 0.05 mmol/ml), with 0.30 ml DTBP (1.62 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 15 / 85 afforded **4-46'** (23 mg, 20%) as a white solid.

m.p. 169-173 °C

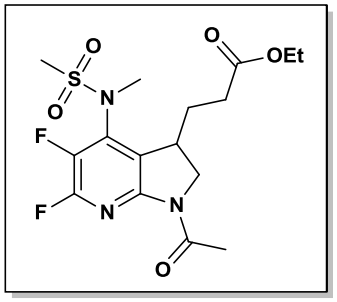
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 9.50 (s, 1H, N*H*), 7.75 (s, 1H, C*H*), 4.11 (q, *J* = 7.15 Hz, 2H, COO-C*H*$_2$-CH_3), 3.03-3.00 (m, 2H, CO-CH_2-C*H*$_2$), 2.92 (s, 3H, NH-CO-C*H*$_3$), 2.77-2.74 (m, 2H, CO-C*H*$_2$-CH_2), 2.32 (s, 3H, N-CO-C*H*$_3$), 1.21 (t, *J* = 7.13 Hz, 3H, COO-CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 175.0 (*C*OOEt), 168.4 (N*C*OMe), 168.1 (NH-*C*O-CH_3), 149.1 (dd, *J* = 237.90, 17.12 Hz, N-*C*F), 138.1 (dd, *J* = 17.51, 3.13 Hz, N-*C*-CF), 137.8 (dd, *J* = 256.05, 29.00 Hz, N-C-*C*F), 129.0-128.7(m, N-C-N), 124.1 (d, *J* = 4.50 Hz, *C*H), 118.0 (m, *C*-C-N), 116.7 (d, *J* = 4.20 Hz,CH-*C*), 61.6 (COO*C*H$_2$CH$_3$), 36.5 (CO*C*H$_2$-CH_2), 25.6 (*C*H$_3$-CO-N), 23.3 (*C*H$_3$-CO-NH), 19.5 ($COCH_2$-*C*H$_2$), 14.1 (COO-CH_2-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3420, 3280, 2986, 1713, 1600, 1505, 1437, 1396, 1283, 1250, 1213, 1094

HRMS (EI+) Calcd. for $C_{16}H_{17}F_2N_3O_4$: 353.1187 Found : 353.1194

3-(1-acetyl-5,6-difluoro-4-(*N*-methylmethylsulfonamido)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-47)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 162 mg **4-27** (0.30 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.36mmol, 1.2 eq.) in chlorobenzene (6.0ml, 0.05 mmol/ml), with 0.27ml DTBP (1.47mmol, 5.0 eq.) for 2 hours. Flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **4-47** (52 mg, 43%) as a yellow oil.

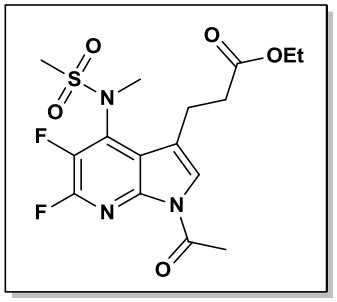
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.81 (s, 1H, CH_3-CO-N-C*H*), 4.13 (q, 2H, J=7.2Hz, COO-CH_2-CH_3), 3.44 (s, 3H, SO_2-CH_3), 3.22 (m, 2H, CO-CH_2-CH_2), 3.11 (d, 3H, J=1.7Hz, N-CH_3), 2.91 (s, 3H, CO-CH_3), 2.73 (dt, 2H, J=3.5Hz, J=7.1Hz, CO-CH_2-CH_2), 1.25 (t, 3H, J=7.1Hz, COO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.4 (*C*OOEt), 169.3 (*C*OMe), 150.8 (dd, *J* = 239.30, 15.17 Hz, N-*C*F), 148.5 (dd, *J* = 16.65, 3.70 Hz, N-C-N), 138.4 (dd, *J* = 259.72, 23.32 Hz, N-C-*C*F), 137.3 (m, N-*C*-CF), 127.7 (m, *C*-C-N), 60.7 (COO*C*H_2CH_3), 51.4 (CO-N-*C*H_2), 37.7, 37.4 (N-*C*H_3 + SO_2-*C*H_3), 34.7 (*C*H), 30.8 (CO*C*H_2-CH_2), 29.6 ($COCH_2$-*C*H_2), 24.6 (N-CO-*C*H_3), 14.1 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2984, 1729, 1664, 1621, 1594, 1480, 1430, 1379, 1354, 1326, 1252, 1195, 1160, 1034

HRMS (EI+) Calcd. for $C_{16}H_{19}F_2N_3O_5S$:405.1170 Found : 405.1156

3-(1-acetyl-5,6-difluoro-4-(N-methylmethylsulfonamido)-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (4-47')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 162 mg **4-27** (0.30 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.36mmol, 1.2 eq.) in chlorobenzene (6.0ml, 0.05 mmol/ml), with 0.27ml DTBP (1.47mmol, 5.0 eq.) for 2 hours. Flash chromatography on silica gel with AcOEt / DCM = 3 / 97 afforded **4-47'** (22 mg, 18%) as a yellow oil.

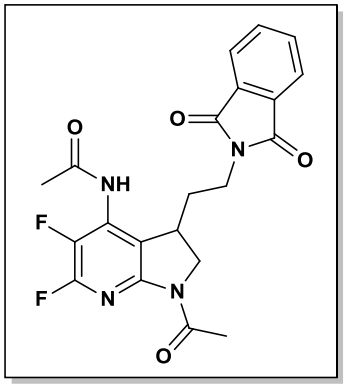
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.81 (s, 1H, CH_3-CO-N-C*H*), 4.13 (q, 2H, J=7.2Hz, COO-CH_2-CH_3), 3.44 (s, 3H, SO_2-CH_3), 3.22 (m, 2H, CO-CH_2-CH_2), 3.11 (d, 3H, J=1.7Hz, N-CH_3), 2.91 (s, 3H, CO-CH_3), 2.73 (dt, 2H, J=3.5Hz, J=7.1Hz, CO-CH_2-CH_2), 1.25 (t, 3H, J=7.1Hz, COO-CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.5 (*C*OOEt), 167.6 (*C*OMe), 148.3 (dd, J=16.6Hz, J=239.6Hz, N-*C*F), 140.5 (dd, J=28.1Hz, J=253.8Hz, N-C-*C*F), 139.2 (d, J=16.9Hz, N-C-N), 132.1 (dd, J=3.8Hz, J=10.6Hz, N-*C*-CF), 124.4 (d, J=4.5Hz, CO-N-*C*H), 121.6 (d, J=4.5Hz, *C*-C-N), 118.8 (*C*H-*C*), 60.6 (COO*C*$H_2$$CH_3$), 37.90 (dd, J=4.5Hz, J=17.4Hz, N-*C*H_3 + SO_2-*C*H_3),33.3 (CO-*C*H_2-CH_2), 25.5 (*C*H_3-CO-N), 20.7 ($COCH_2$-*C*H_2), 14.2 (COO-CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3692, 3607, 1725, 1602, 1436, 1404, 1381, 1352, 1278, 1159, 1009

HRMS (EI+) Calcd. for $C_{16}H_{19}F_2N_3O_5S$:403.1013 Found : 403.1019

N-(1-acetyl-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-5,6-difluoro-2,3-dihydro-1H-pyrrolo [2,3-b]pyridin-4-yl)acetamide (4-48)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 101mg **4-28** (0.18 mmol, 1.0 eq.) and 0.02ml 2,6-lutidine (0.21 mmol, 1.2 eq.) in chlorobenzene (3.6 ml, 0.05 mmol/ml), with 0.16 ml DTBP (0.89 mmol, 5.0 eq.) for 3.5 hours. Flash chromatography on silica gel with AcOEt / EP = 45 / 55 afforded **4-48** (41 mg, 53%) as a white solid.

m.p. 207-210 ^{o}C

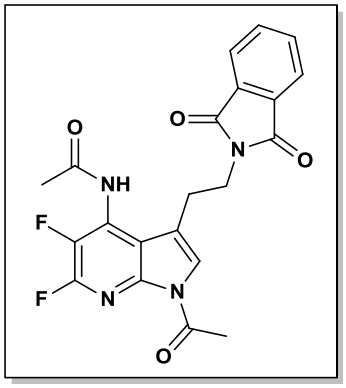
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.84 (dd, *J* = 5.46, 3.05 Hz, 2H, C-C*H*-CH), 7.73 (dd, *J* = 5.45, 3.05 Hz, 2H, C-CH-C*H*), 7.49 (s, 1H, N*H*), 4.34 (dd, *J* = 12.27, 10.26 Hz, 1H, CO-N-CH*H*), 3.97 (dd, *J* = 12.34, 5.31 Hz, 1H, CO-N-CH*H*), 3.79 (ddd, *J* = 14.16, 9.57, 6.19 Hz, 1H, CH_2-C*H*), 3.72-3.56 (m, 2H, CH-CH_2-CH_2), 2.58 (s, 3H, NH-CO-CH_3), 2.19 (s, 3H, N-CO-CH_3), 2.09 (dddd, *J* = 14.00, 9.61, 6.98, 2.65 Hz, 1H, CO-N-CH_2-CH*H*), 1.59 (dddd, *J* = 14.12, 10.20, 6.15, 4.29 Hz, 1H, CO-N-CH_2- CH*H*)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.6 (N*C*OMe), 168.5 (N-*C*O-C), 167.5 (NH-*C*O-Me), 149.7 (dd, *J* = 235.44, 14.82 Hz, N-*C*F), 148.4 (dd, *J* = 16.27, 3.53 Hz, N-*C*-CF), 134.2 (C-CH-*C*H), 133.9 (dd, *J* = 248.76, 28.76 Hz, N-C-*C*F), 133.5 (dd, *J* = 10.22, 4.72 Hz, N-C-N), 132.1 (*C*-CH-CH), 123.2 (C-*C*H-CH), 119.6 (dd, *J* = 5.33, 2.59 Hz, *C*-C-N), 51.8 (CO-N-*C*H_2), 34.8 (CH_2-*C*H), 34.2 (CO-N-*C*H_2-CH_2), 30.2 (CO-N-CH_2-*C*H_2), 24.9 (NH-CO-*C*H_3), 23.6 (N-CO-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3691, 3606, 3417, 2927, 2855, 1772, 1712, 1660, 1603, 1426, 1398, 1380, 1328, 1241

HRMS (EI+) Calcd. for $C_{21}H_{18}F_2N_4O_4$: 428.1296 Found : 428.1291

N-(1-acetyl-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-5,6-difluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)acetamide (4-48')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 101mg **4-28** (0.18 mmol, 1.0 eq.) and 0.02ml 2,6-lutidine (0.21 mmol, 1.2 eq.) in chlorobenzene (3.6 ml, 0.05 mmol/ml), with 0.16 ml DTBP (0.89 mmol, 5.0 eq.) for 3.5 hours. Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **4-48'** (11 mg, 15%) as a white solid.

m.p. 245-249 °C

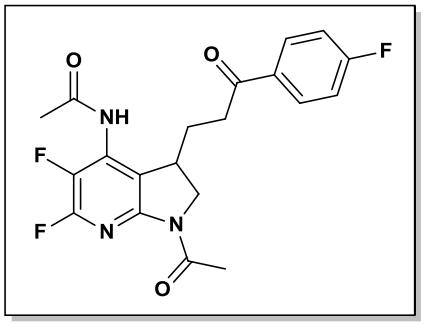
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.39 (s, 1H, N*H*), 7.90-7.86 (m, 3H, CO-C-C*H* + N-C*H*), 7.78 (dd, *J* = 5.44, 3.07 Hz, 2H, C-CH-C*H*), 3.82-3.78 (m, 2H, CO-N-CH_2), 3.07-3.02 (m, 2H, CH-C-CH_2), 2.93 (s, 3H, NH-CO-CH_3), 2.41 (s, 3H, N-CO-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.4 (N*C*OMe), 168.4 (N-*C*O-C), 168.0 (NH-*C*O-CH_3), 148.1 (dd, *J* = 233.17, 17.36 Hz, N-*C*F), 137.3 (dd, *J* = 257.91, 23.13 Hz, N-C-*C*F), 135.4-135.2(m, N-*C*-CF), 134.5 (N-CO-*C*), 131.9 (C-*C*H-CH), 128.0-127.9 (m, N-C-N), 124.5 (d, *J* = 4.23 Hz, *C*H), 123.7 (C-CH-*C*H), 120.7-120.4 (m, *C*-C-N), 119.1-119.0 (CH-*C*), 38.7 (CON-*C*H_2-CH_2), 25.6 (*C*H_3-CO-N), 25.3 (C-*C*H_2), 23.3 (*C*H_3-CO-NH)

IR (ν, cm^{-1}, $CDCl_3$) 2933, 1773, 1714, 1503, 1437, 1395, 1383, 1274, 1094

HRMS (EI+) Calcd. for $C_{19}H_{13}F_2N_4O_3$: 384.1034 Found : 384.1023

N-(1-acetyl-5,6-difluoro-3-(3-(4-fluorophenyl)-3-oxopropyl)-2,3-dihydro-1H-pyrrolo [2,3-b]pyridin-4-yl)acetamide (4-49)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 151mg **4-29** (0.28 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.33 mmol, 1.2 eq.) in chlorobenzene (5.5 ml, 0.05 mmol/ml), with 0.25 ml DTBP (1.38 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 25 / 75 afforded **4-49** (55 mg, 50%) as a white solid.

m.p. 226-230 °C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.27 (s, 1H, N*H*), 8.04-7.94 (m, 2H, CO-C(C*H*)$_2$), 7.21-7.09 (m, 2H, CF-(C*H*)$_2$), 4.11 (dd, *J* = 12.03, 9.41 Hz, 1H, CO-N-CH*H*), 3.96 (dd, *J* = 12.10, 3.46 Hz, 1H, CO-N-CH*H*), 3.43-3.31 (m, 1H, CH_2-C*H*), 3.08-3.03 (m, CO-C*H*$_2$-CH_2), 2.58 (s, 3H, NH-CO-C*H*$_3$), 2.38 (s, 3H, N-CO-C*H*$_3$), 2.15-2.03 (m, 1H, CO-CH_2-CH*H*), 1.81-1.66 (m, 1H, CO-CH_2-CH*H*)

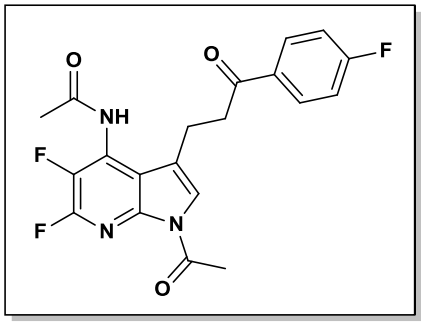
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 198.3 (CH_2-*C*O), 169.9 (N-*C*O-CH_3), 168.0 (NH-*C*O-CH_3), 166.20 (d, *J* = 256.48 Hz, *C*F(CH)$_2$), 151.8 (dd, *J* = 238.30, 23.90 Hz, N-*C*F), 145.0.1-145.8 (m, N-*C*-CF), 138.6 (dd, *J* = 252.63, 21.09 Hz, N-C-*C*F), 133.76 (d, *J* = 5.18 Hz, CO-*C*), 130.81 (d, *J* = 9.44 Hz,CO-C(*C*H)$_2$), 126.7-126.5 (m, N-C-N), 119.3-119.1 (m,

C-C-N), 116.1 (d, *J* = 21.97 Hz, CF(*C*H)$_2$), 52.5 (N-*C*H$_2$), 35.2 (CH$_2$-*C*H), 34.9 (CO-*C*H$_2$), 27.7 (CO-CH$_2$-*C*H$_2$), 24.6 (NH-CO-*C*H$_3$), 23.7 (N-CO-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3418, 1719, 1673, 1622, 1599, 1505, 1424, 1381, 1330, 1240, 1157

HRMS (EI+) Calcd. for $C_{20}H_{18}F_3N_3O_3$: 405.1300 Found : 405.1299

N-(1-acetyl-5,6-difluoro-3-(3-(4-fluorophenyl)-3-oxopropyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)acetamide (4-49')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 151mg **4-29** (0.28 mmol, 1.0 eq.) and 0.04ml 2,6-lutidine (0.33 mmol, 1.2 eq.) in chlorobenzene (5.5 ml, 0.05 mmol/ml), with 0.25 ml DTBP (1.38 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 15 / 85 afforded **4-49'** (13 mg, 12%) as a white solid.

m.p. 235-237 °C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 9.93 (s, 1H, N*H*), 8.04-7.95 (m, 2H, CO-C-C*H*), 7.76 (s, 1H, CO-N-C*H*), 7.16-7.12 (m, 2H, F-C-C*H*), 3.51-3.41 (m, 2H, CO-CH$_2$-C*H$_2$*), 3.21-3.11 (m, 2H, CO-C*H$_2$*-CH$_2$), 2.90 (s, 3H, NH-CO-C*H$_3$*), 2.38 (s, 3H, N-CO-C*H$_3$*)

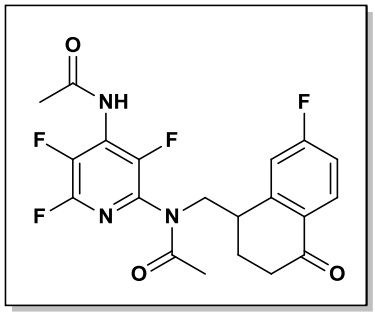
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 199.9 (CH$_2$-*C*O), 168.3 (N-*C*O-CH$_3$), 168.1 (NH-*C*O-CH$_3$), 166.3 (d, *J* = 257.06 Hz, *C*F-CH), 149.2 (dd, *J* = 238.18, 16.85 Hz, N-*C*F), 138.1-137.9 (m, N-*C*-CF), 137.7 (dd, *J* = 256.06, 29.14 Hz, N-C-*C*F), 132.41 (d, *J* = 2.97 Hz, CO-*C*), 131.1 (d, *J* = 9.53 Hz,CF-CH-*C*H), 129.2-129.0 (m, N-C-N), 123.78 (d, *J* = 4.44 Hz, N-

*C*H), 118.7-118.6 (m, *C*-C-N), 116.6 (d, *J* = 4.14 Hz,N-CH-*C*), 116.0 (d, *J* = 21.97 Hz, CF-*C*H), 41.1 (CO-*C*H_2), 25.5 (N-CO-*C*H_3), 23.4 (NH-CO-*C*H_3), 18.5 (CO-CH_2-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 3277, 1709, 1678, 1598, 1507, 1472, 1439, 1383, 1285, 1234, 1157, 1093

HRMS (EI+) Calcd. for $C_{20}H_{16}F_3N_3O_3$: 403.1144 Found : 403.1155

_N_-(4-acetamido-3,5,6-trifluoropyridin-2-yl)-_N_-((7-fluoro-4-oxo-1,2,3,4-tetrahydro naphthalen-1-yl)methyl)acetamide (4-49")



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 240mg **4-29** (0.44 mmol, 1.0 eq.) in chlorobenzene (8.8 ml, 0.05 mmol/ml), with 0.40 ml DTBP (2.2 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 15 / 85 afforded **4-49"** (18 mg, 10%)

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.26 (s, 1H, N*H*), 8.04-8.00, 7.00-6.95 (m, 3H, aromatic H), 4.18 (dd, *J* = 13.96, 10.33 Hz, 1H, CO-N-CH*H*), 3.90 (dd, *J* = 13.62, 4.34 Hz, 1H, CO-N-CH*H*), 3.21 (td, *J* = 13.58, 4.31 Hz, 1H, CH_2-C*H*), 2.88-2.79 (m, 1H, CO-CH*H*), 2.57-2.50 (m, 1H, CO-CH*H*), 2.30 (s, 3H, NH-CO-C*H*$_3$), 2.23-2.17 (m, 1H, CO-CH_2-CH*H*), 2.13-2.08 (m, 1H, CO-CH_2-CH*H*), 2.00 (s, 3H, N-CO-C*H*$_3$)

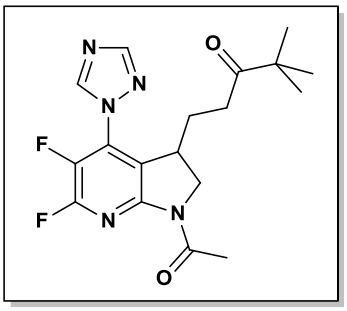
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 196.5 (CH_2-*C*O), 170.6 (N-*C*O-CH_3), 167.5 (NH-*C*O-CH_3), 165.8 (d, *J* = 256.32 Hz, *C*F-CH), 147.2 (d, *J* = 8.88 Hz,CO-*C*), 146.2 (dd, *J* = 239.63, 13.79 Hz, N-*C*F-CF), 145.5 (dd, *J* = 260.14, 5.41 Hz,1C, NH-C-*C*F-C), 138.5 (dd, *J* = 267.78, 31.46 Hz, N-C-*C*F), 134.7-134.3 (m, N-*C*-CF), 130.6 (d, *J* = 9.64 Hz, CF-CH-*C*H),

128.86 (d, *J* = 2.63 Hz, CF-CH-*C*), 127.5-127.0 (m, N-C-N), 115.7, 115.1 (dd, *J* = 21.85, 6.66 Hz, dd, *J* = 21.78, 4.67 Hz, CF-*C*H), 50.2 (CO-N-*C*H_2), 37.2 (CH_2-*C*H), 34.2 (CO-*C*H_2), 24.2 (CO-CH_2-*C*H_2), 23.1 (NH-CO-*C*H_3), 22.0 (NH-CO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3418, 2931, 1726, 1682, 1608, 1500, 1476, 1452, 1380, 1249, 1224, 1157, 1106

HRMS (EI+) Calcd. for $C_{20}H_{17}F_4N_3O_3$: 423.1206 Found : 423.1214

1-(1-acetyl-5,6-difluoro-4-(1*H*-1,2,4-triazol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-4,4-dimethylpentan-3-one (4-50)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 167mg **4-30** (0.33 mmol, 1.0 eq.) and 0.05 ml 2,6-lutidine (0.40 mmol, 1.2 eq.) in chlorobenzene (6.6 ml, 0.05 mmol/ml), with 0.30 ml DTBP (1.65 mmol, 5.0 eq.) for 1.5 hours. Flash chromatography on silica gel with AcOEt / DCM = 25 / 75 afforded **4-50** (74 mg, 61%) as a yellow solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.74 (d, *J* = 3.43 Hz, 1H, C-N-C*H*), 8.21 (s, 1H, C-N-N-C*H*), 4.12 (dd, *J* = 11.99, 9.42 Hz, 1H, CO-N-CH*H*), 4.05-3.89 (m, 2H, CO-N-CH*H* + CH_2-C*H*), 2.62 (s, 3H, CO-C*H*$_3$), 2.49-2.38 (m, 2H, CO-C*H*$_2$), 1.54 (dd, *J* = 14.24, 7.22 Hz, 2H, CH-C*H*$_2$), 1.06 (s, 9H, C(C*H*$_3$)$_3$)

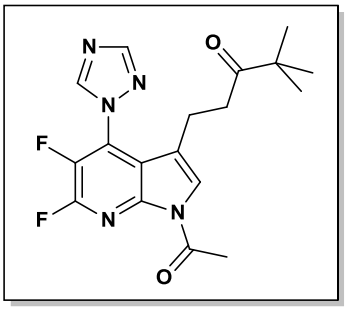
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.0 (*C*O-CH_2), 169.5 (*C*O-CH_3), 152.7 (C-N-N-*C*H), 150.9 (dd, *J* = 238.20, 15.22 Hz, N-*C*F), 148.9 (dd, *J* = 16.27, 3.93 Hz, N-C-N), 145.5 (d, *J* = 12.92 Hz, C-N-*C*H), 133.0 (dd, *J* = 255.06, 30.50 Hz, N-C-*C*F), 132.2 (dd, *J* = 8.62,

4.74 Hz, N-*C*-CF), 112.0 (dd, *J* = 5.73, 3.30 Hz, *C*-C-N), 51.5 (N-*C*H_2), 44.0 (CO-*C*), 35.3 (CH_2-*C*H), 32.7 (CO-*C*H_2), 27.8 (CH-*C*H), 26.2 (C(*C*H_3)$_3$), 24.7 (CO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3052, 2985, 2930, 1730, 1671, 1623, 1519, 1479, 1435, 1391, 1314, 1265, 1174, 1131, 992

HRMS (EI+) Calcd. for $C_{18}H_{21}F_2N_5O_2$:377.1663 Found : 377.1675

1-(1-acetyl-5,6-difluoro-4-(1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-4,4-dimethylpentan-3-one (4-50')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 167mg **4-30** (0.33 mmol, 1.0 eq.) and 0.05 ml 2,6-lutidine (0.40 mmol, 1.2 eq.) in chlorobenzene (6.6 ml, 0.05 mmol/ml), with 0.30 ml DTBP (1.65 mmol, 5.0 eq.) for 1 hours. Flash chromatography on silica gel with AcOEt / DCM = 15 / 85 afforded **4-50'** (21 mg, 18%) as a yellow solid.

m.p. 108-111 °C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.54 (d, *J* = 2.19 Hz, 1H, C-N-C*H*), 8.25 (s, 1H, C-N-N-C*H*), 7.82 (s, 1H, CO-N-C*H*), 2.97 (s, 3H, CO-C*H*$_3$), 2.69-2.46 (m, 4H, CO-C*H*$_2$-C*H*$_2$), 1.06 (s, 9H, C(C*H*$_3$)$_3$)

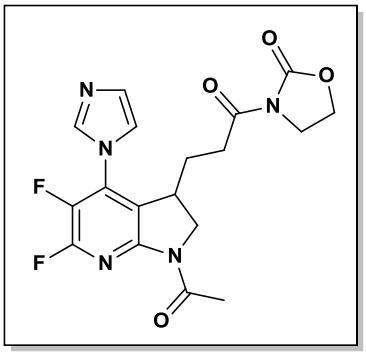
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.7 (*C*O-CH_2), 167.5 (*C*O-CH_3), 153.1 (C-N-N-*C*H), 147.9 (dd, *J* = 240.39, 16.43 Hz, N-*C*F), 145.7 (C-N-*C*H), 139.0 (dd, *J* = 16.51, 3.01 Hz, N-C-N), 137.2 (dd, *J* = 257.31, 29.65 Hz, N-C-*C*F), 129.5-126.2 (m, N-*C*-CF), 125.2 (d,

J = 4.24 Hz, CO-N-*C*H), 119.1-117.8 (m, CH_2-*C*), 117.5-117.4 (m, *C*-C-N), 43.9 (CO-*C*), 35.9 (CO-*C*H_2), 26.4 (C(*C*H_3)$_3$), 25.6 (CO-*C*H_3), 19.9 (C-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 2970, 1721, 1596, 1561, 1518, 1473, 1455, 1418, 1382, 1348, 1280, 1239, 1176, 1130, 1080, 1005

HRMS (EI+) Calcd. for $C_{18}H_{19}F_2N_5O_2$:375.1507 Found : 375.1509

3-(3-(1-acetyl-5,6-difluoro-4-(1*H*-imidazol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)propanoyl)oxazolidin-2-one (4-51)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 66mg **4-31** (0.12 mmol, 1.0 eq.) and 0.01 ml 2,6-lutidine (0.14 mmol, 1.2 eq.) in chlorobenzene (2.5 ml, 0.05 mmol/ml), with 0.11 ml DTBP (0.60 mmol, 5.0 eq.) for 3 hours. Flash chromatography on silica gel with Acetone / DCM = 10 / 90 afforded **4-51** (18 mg, 38%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.84, 7.34, 7.30 (3s, 3H, NC*H*-N + N-C*H* + N-C*H*), 4.62-4.34 (m, 2H, COO-C*H*$_2$), 4.24 (dd, *J* = 12.28, 9.38 Hz, 1H, CO-N-CH*H*), 4.09-3.93 (m, 3H, CO-N-CH*H* + COO-CH$_2$-C*H*$_2$), 3.80-3.65 (m, 1H, CH$_2$-C*H*), 2.88-2.70 (m, 2H, CO-C*H*$_2$), 2.67 (s, 3H, N-CO-C*H*$_3$), 1.73-1.52 (m, 2H, CO-CH$_2$-C*H*$_2$)

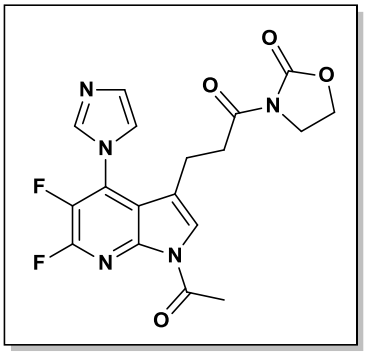
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.5 (*C*OO-CH$_2$), 169.5 (N-*C*O-CH$_3$), 153.4 (*C*O-N-CO), 151.5 (dd, *J* = 243.96, 25.20 Hz, N-*C*F), 148.8-148.6 (m, N-*C*-CF), 136.8, 130.8, 119.2 (3C, imidazole C), 134.7 (dd, *J* = 259.39, 26.12 Hz, N-C-*C*F), 133.8-133.6 (m, N-C-N),

120.3-120.1 (m, *C*-C-N), 62.2 (COO-*C*H_2), 52.0 (CH_3-CO-N-*C*H_2), 42.4 (COO-CH_2-*C*H_2), 34.3 (CH_2-*C*H), 31.3 (*C*H_2-CO-N-CO), 27.9 (CO-CH_2-*C*H_2), 24.8 (N-CO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2926, 1782, 1677, 1625, 1512, 1433, 1383, 1318, 1183, 1077, 1041

HRMS (EI+) Calcd. for $C_{18}H_{17}F_2N_5O_4$: 405.1249 Found : 405.1258

3-(3-(1-acetyl-5,6-difluoro-4-(1*H*-imidazol-1-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl) propanoyl)oxazolidin-2-one (4-51')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 66mg **4-31** (0.12 mmol, 1.0 eq.) and 0.01 ml 2,6-lutidine (0.14 mmol, 1.2 eq.) in chlorobenzene (2.5 ml, 0.05 mmol/ml), with 0.11 ml DTBP (0.60 mmol, 5.0 eq.) for 3 hours. Flash chromatography on silica gel with Acetone / DCM = 10 / 90 afforded **4-51'** (9 mg, 19%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.84, 7.80,7.34, 7.26 (4s, 4H, NC*H*-N + N-C*H* + N-C*H* + CO-N-C*H*), 4.40 (t, *J* = 8.00 Hz, 2H, COO-C*H*$_2$), 3.95 (t, *J* = 8.00 Hz, 2H, COO-CH_2-C*H*$_2$), 2.97 (s, 3H, N-CO-C*H*$_3$), 2.90 (t, *J* = 7.29 Hz, 2H, CO-C*H*$_2$), 2.62 (t, *J* = 7.37 Hz, 2H, CO-CH_2-C*H*$_2$)

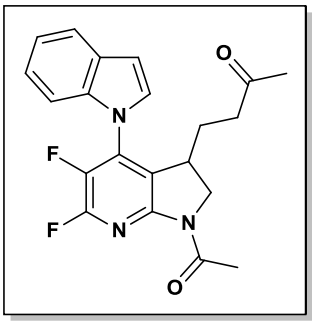
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.4 (*C*OO-CH_2), 168.1 (N-*C*O-CH_3), 153.5 (*C*O-N-CO), 148.5 (dd, *J* = 243.96, 25.20 Hz, N-*C*F), 142.8-142.6 (m, N-*C*-CF), 138.1, 130.1, 119.3 (3C, imidazole C), 133.2 (dd, *J* = 259.39, 26.12 Hz, N-C-*C*F), 132.5-132.4 (m, N-C-N),

125.0 (CO-N-*C*H), 120.3-120.1 (m, *C*-C-N), 117.2 (CH_2-*C*), 62.2 (COO-*C*H_2), 42.4 (COO-CH_2-*C*H_2), 34.5 (*C*H_2-CO-N-CO), 25.6 (N-CO-*C*H_3), 19.9 (CO-CH_2-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 3688, 3632, 3470, 2944, 2839, 1782, 1707, 1602, 1387, 1018

HRMS (EI+) Calcd. for $C_{18}H_{15}F_2N_5O_4$: 403.1092 Found : 403.1096

4-(1-acetyl-5,6-difluoro-4-(1*H*-indol-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-3-yl) butan-2-one (4-52)



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 154mg **4-32** (0.29 mmol, 1.0 eq.) and 0.04 ml 2,6-lutidine (0.35 mmol, 1.2 eq.) in chlorobenzene (6.0 ml, 0.05 mmol/ml), with 0.27 ml DTBP (1.47 mmol, 5.0 eq.) for 2 hours. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-52** (47 mg, 42%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.13-6.59 (m, 6H, aromatic H), 4.25 (dd, *J* = 21.56, 10.77 Hz, 1H, CO-N-CH*H*), 3.92 (ddd, *J* = 23.90, 12.38, 3.85 Hz, 1H CO-N-CH*H*), 3.72-3.55, 3.43-3.30 (m, 1H, CH_2-C*H*), 2.70 (s, 3H, N-CO-C*H*$_3$), 2.15-1.84 (m, 2H, CO-C*H*$_2$), 1.81, 1.67 (s, 3H, CH_2-CO-C*H*$_3$), 1.37-1.27 (m, 2H, CO-CH_2-C*H*$_2$)

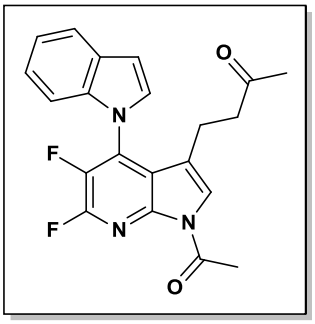
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 206.7, 206.6 (*C*O-CH_2), 169.5 (N-*C*O-CH_3), 151.3 (dd, *J* = 238.56, 13.90 Hz, N-*C*F), 148.6-148.3 (m, N-*C*-CF), 136.38 (dd, *J* = 261.49, 23.91 Hz, N-C-*C*F), 135.6-135.6 (m, N-C-N), 135.8, 134.4, 129.1, 128.7, 127.8, 125.8, 123.8, 123.4, 121.9, 121.7, 121.5, 110.7, 110.4, 106.9, 106.1 (8C, aromatic C), 122.5-122.2 (m, *C*-

C-N), 52.2, 52.0 (CO-N-*C*H_2), 39.4, 38.7 (CO-*C*H_2), 35.4, 34.2 (CH_2-*C*H), 29.2 (CH_2-CO-*C*H_3), 27.1 (CO-CH_2-*C*H_2), 24.8 (N-CO-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2934, 1716, 1666, 1621, 1523, 1504, 1472, 1429, 1382, 1346, 1334, 1317, 1259, 1211, 1176

HRMS (EI+) Calcd. for $C_{21}H_{19}F_2N_3O_2$: 383.1445 Found : 383.1442

4-(1-acetyl-5,6-difluoro-4-(1*H*-indol-1-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)butan-2-one (4-52')



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 154mg **4-32** (0.29 mmol, 1.0 eq.) and 0.04 ml 2,6-lutidine (0.35 mmol, 1.2 eq.) in chlorobenzene (6.0 ml, 0.05 mmol/ml), with 0.27 ml DTBP (1.47 mmol, 5.0 eq.) for 2 hours. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-52'** (21 mg, 18%) as a yellow oil.

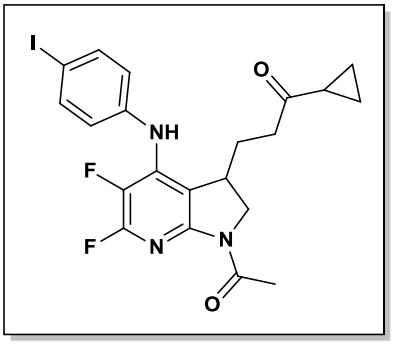
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.76 (s, 1H, CO-N-C*H*), 7.74-6.78 (m, 6H, aromatic H), 3.00 (s, 3H, N-CO-C*H*$_3$), 2.46-2.25 (m, 2H, CO-C*H*$_2$), 2.01 (dddd, *J* = 23.49, 17.61, 8.59, 6.29 Hz, 2H, CO-CH_2-C*H*$_2$), 1.69 (s, 3H, CH_2-CO-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 206.5 (*C*O-CH_2), 167.7 (N-*C*O-CH_3), 148.6 (dd, *J* = 238.99, 16.13 Hz, N-*C*F), 140.5-140.0 (m, N-*C*-CF), 139.0 (dd, *J* = 256.11, 27.69 Hz, N-C-*C*F), 137.2, 128.5, 128.4, 123.5, 121.5, 121.4, 110.1, 105.5 (8C, aromatic C), 130.3-130.1 (m, N-C-N), 124.4 (d, *J* = 4.38 Hz, N-*C*H), 119.3-119.2 (m, *C*-C-N), 118.0 (N-CH-*C*), 42.4 (CO-*C*H_2), 29.2 (CH_2-CO-*C*H_3), 25.6 (N-CO-*C*H_3), 20.0 (CO-CH_2-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 2928, 2855, 1718, 1594, 1562, 1505, 1472, 1459, 1438, 1403, 1380, 1344, 1328, 1256, 1233, 1212, 1179, 1095

HRMS (EI+) Calcd. for $C_{21}H_{17}F_2N_3O_2$: 381.1289 Found : 381.1279

3-(1-acetyl-5,6-difluoro-4-((4-iodophenyl)amino)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl)-1-cyclopropylpropan-1-one (4-53)



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 100mg xanthate **4-33** (0.15 mmol, 1.0 eq.) and 0.03 ml 2,6-lutidine (0.23 mmol, 1.2 eq.) in chlorobenzene (3.5 ml, 0.05 mmol/ml), with 0.14 ml DTBP (0.76 mmol, 5.0 eq.) for 2h. Flash chromatography on silica gel with AcOEt / PE = 30 / 70 afforded **4-53** (41.3 mg, 53 %) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.72 (brs, 1H, N*H*), 7.62 (d, J = 8.57Hz, 2H, 2 ICC*H*), 6.85 (dd, J = 8.70, 2.85 Hz, 2H, 2 NCC*H*), 3.98 (ddd, J = 14.8, 12.1, 5.9 Hz, 2H, NCH_2), 2.89 (t, J = 8.92 Hz, 1H, NCH_2CH), 2.69-2.64 (m, 2H, $COCH_2$), 2.59 (s, 3H, CH_3), 1.96-1.89 (m, 2H, COC*H* + $COCH_2CHH$), 1.51-1.43 (m, 1H, $COCH_2CHH$), 1.06-1.05 (m, 2H, $COCHCH_2$), 0.96-0.93 (m, 2H, $COCHCH_2$)

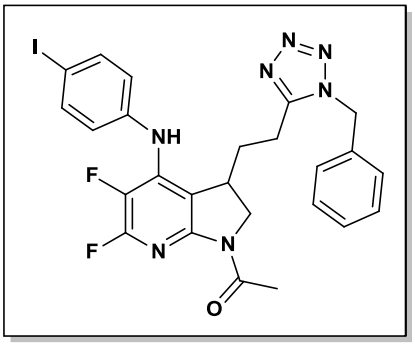
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.9 (CH*C*O), 169.8 (N*C*OCH3), 151.7 (dd, J = 233, 14 Hz, N-*C*F), 147.0 (dd, J = 18, 3 Hz, NHC*C*F), 139.9 (d, J = 1.1 Hz, NH*C*CH), 138.0 (dd, J = 7.2, 6.0 Hz, N=*C*-N-CO), 137.7 (NHC*C*H), 132.1 (dd, J = 250, 30Hz, NHC*C*F), 122.4 (d, J = 3.1 Hz, IC*C*H), 114.0 (d, J = 3.8 Hz, NHC*C*), 86.7 (I-*C*), 53.0 ($CONCH_2$), 39.9

($COCH_2$), 34.0 (CH_2CH), 27.7 (CO-CH_2-CH_2), 24.4 ($NCOCH_3$), 21.0 (COCH), 11.72, 11.69 ($COCH(CH_2)_2$)

IR (ν, cm^{-1}, CCl_4) 3690, 3607, 3512, 3410, 3296, 3217, 3098, 3013, 2929, 2856, 1716, 1685, 1655, 1623, 1586, 1527, 1485, 1421, 1394, 1380, 1349, 1280, 1265, 1234, 1194, 1182, 1143, 1121, 1077, 1040, 1007, 972

HRMS (EI+) Calcd. for $C_{21}H_{20}F_2IN_3O_2$: 511.0568 Found : 511.0575

1-(3-(2-(1-benzyl-1H-tetrazol-5-yl)ethyl)-5,6-difluoro-4-((4-iodophenyl)amino)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)ethanone (4-54)



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 325mg **4-34** (0.44mmol, 1.0eq.) and 0.06 ml 2,6-lutidine (0.53mmol, 1.2eq.) in chlorobenzene (8.8ml, 0.05 mmol/ml), with 0.40ml DTBP (2.17mmol, 4.9eq.) for 3 hours. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-54** (68mg, 26%) as yellow oil.

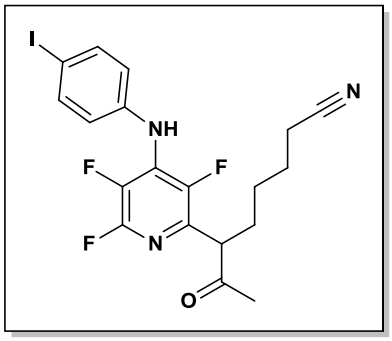
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.54 (s, 1H, N*H*), 7.67 (d, J = 8.66 Hz, 2H, 2 ICC*H*), 7.46-7.42 (m, 3H, Ph-C*H*), 7.23 (dd, J = 6.46, 2.97 Hz, 2H, Ph-C*H*), 6.98 (dd, J = 8.65, 3.42 Hz, 1H, NHCC*H*), 5.54 (s, 2H, Ph-CH_2), 3.97 (d, J = 5.67 Hz, 2H, NCH_2CH), 3.26 (td, J = 7.39, 6.07 Hz, 1H, C*H*CH_2), 2.74 (dd, J = 5.07, 3.94 Hz, 1H, $CHCH_2CH$*H*), 2.69-2.59 (m, 4H, $CHCH_2C$*H*H + CH_3), 2.32 (dt, J = 12.80, 2.34 Hz, 1H, CHC*H*HCH_2), 1.83 (ddt, J = 9.01, 5.45, 3.62 Hz, 1H, CHCH*H*CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.8 (N*C*OCH_3), 154.2 (*C*=N), 152.0 (dd, J = 234, 14 Hz, N-*C*F), 147.0 (dd, J = 19, 2.4 Hz,NH*C*CF), 139.9 (NH*C*CH), 138.2 (dd, J = 7.0, 6.1 Hz, N=*C*-N-CO), 137.7 (NHC*C*H), 132.3 (Ph-CH_2*C*), 132.1 (dd, J = 251, 30 Hz, NHC*C*F), 129.4 (2 Ph-*C*H), 129.3 (Ph-*C*H), 127.6 (2 Ph-*C*H), 122.1 (d, J = 3.2 Hz, IC*C*H), 113.4 (d, J = 3.7 Hz, NHC*C*), 86.5 (I*C*), 52.8 (NCH_2CH), 51.1 (*C*H_2Ph), 39.9 (CO*C*H_2), 33.4 (CH_2*C*H), 29.6 (CH_2*C*H_2CH), 24.3 (NCO*C*H_3), 21.1 (N=C*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 3409, 3273, 3209, 3092, 3070, 3035, 2960, 2930, 2873, 2856, 1720, 1659, 1622, 1585, 1529, 1485, 1421, 1394, 1380, 1350, 1324, 1280, 1263, 1236, 1145, 1113, 1096, 1075, 1060, 1006

MS (NH_3 ionisation) 602 (MH^+)

N-(4-cyanobutyl)-N-(5,6-difluoro-4-((4-iodophenyl)amino)pyridin-2-yl)acetamide.(4-54")



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 325mg **4-34** (0.44mmol, 1.0eq.) and 0.06 ml 2,6-lutidine (0.53mmol, 1.2eq.) in chlorobenzene (8.8ml, 0.05 mmol/ml), with 0.40ml DTBP (2.17mmol, 4.9eq.) for 3 hours. Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **4-54"** (35mg, 17%) as yellow oil.

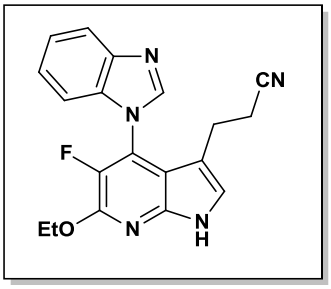
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.67 (d, J = 8.59 Hz, 2H, ICC*H*), 6.85 (d, J = 7.59 Hz, 2H, NHCC*H*), 6.40 (s, 1H, N*H*), 3.77 (t, J = 6.46 Hz, 2H, NCH_2), 2.39 (t, J = 6.55 Hz, 2H, NCCH_2), 1.97 (s, 3H, CH_3), 1.74-1.67 (m, 4H, NCH_2CH_2CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.9 (N*C*O), 147.0 (dd, J = 251, 12 Hz, N-*C*F), 142.6 (d, J = 257 Hz, NCF*C*F), 138.1 (NHC*C*H), 138.0 (NH*C*CH), 134.3 (dd, J = 261, 33 Hz, *C*F-C-NCO), 134.3-133.9 (N*C*N), 132.2-131.9 (CFCF*C*), 123.3 (IC*C*H), 119.4 (*C*N), 88.9 (I*C*), 45.8 (CON*C*H_2), 27.0 (*C*H_2), 22.4 (*C*H_2), 21.9 (*C*H_3), 16.8 (*C*H_2CN)

IR (ν, cm^{-1}, $CDCl_3$) 3694, 3606, 3412, 2940, 2246, 1674, 1621, 1600, 1586, 1528, 1478, 1469, 1462, 1453, 1423, 1305, 1266, 1237, 1123, 1059, 1007

MS (NH_3 ionisation) 488 (MH^+)

3-(4-(1H-benzo[d]imidazol-1-yl)-6-ethoxy-5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl) propanenitrile (4-55)



Following the general procedure **4-III** for the cyclization using DTBP, the reaction was carried out with the solution of 151mg xanthate **4-35** (0.30 mmol, 1.0 eq.) and 0.04 ml 2,6-lutidine (0.35 mmol, 1.2 eq.) in chlorobenzene (6.0 ml, 0.05 mmol/ml), with 0.27 ml DTBP (1.48 mmol, 5.0 eq.) for 3 hours. After evaporating the solvent, the crude cyclization products were directly used in next step.

The deprotection was carried out with the solution of the crude cyclization products and potassium carbonate (205 mg, 1.48 mmol, 5.0 eq.) refluxing for 5h in EtOH (6.0 ml, 0.05 mmol/ml). After work-up, the crude deprotection products were dissolved by DMSO (4.3 ml, 0.07 mmol/ml) and 134mg IBX (0.33 mmol, 1.1 eq.) was added, then stirring at 50^{o}C for 6 h. Flash chromatography on silica gel with AcOEt / DCM = 30 / 70 afforded **4-55** (38 mg, 23% for 3steps) as a white solid.

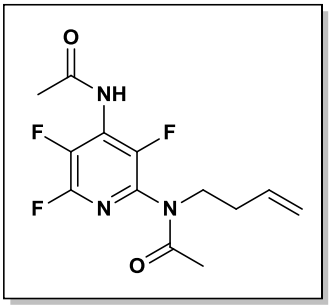
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.70 (s, 1H, N*H*), 8.11 (s, 1H, N-C*H*=N), 7.94 (d, J = 8.14 Hz, 1H, C-N-C-C*H*), 7.41-7.31 (m, 2H, CH-C*H*-C*H*), 7.21 (d, J = 8.10 Hz, 1H, CH=N-C-C*H*), 7.14 (s, 1H, NH-C*H*), 4.55 (q, J = 7.07 Hz, 2H, CH_2-CH_3), 2.35 (t, J = 6.65 Hz, 2H, NC-CH_2-CH_2), 2.02-1.86 (m, 2H, NC-CH_2-CH_2), 1.51 (t, J = 7.08 Hz, 3H, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 150.6 (d, J = 13 Hz, CH_2O-*C*), 143.0 (C-N-*C*), 142.8 (C-N-C-*C*H), 141.6 (d, J = 3.0 Hz, N-*C*-NH), 139.7 (d, J = 254 Hz, EtO-C-*C*-F), 134.7 (CH=N-*C*), 124.5 (CH-*C*H-CH-CH), 123.6 (d, J = 11 Hz,FC-*C*-N), 123.4 (CH-CH-*C*H-CH), 122.0 (NH-*C*H), 120.8 (C-N-C-*C*H), 118.8 (*C*N), 111.1 (d, J = 3.9 Hz, NH-C-*C*), 110.4 (CH=N-C-*C*H), 108.9 (NH-CH-*C*), 63.2 (CH_3*C*H_2O), 21.9 (NC-*C*H_2), 18.4 (NC-CH_2-*C*H_2), 14.5 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3692, 3465, 2932, 1685, 1623, 1580, 1548, 1519, 1493, 1469, 1445, 1423, 1385, 1355, 1306, 1211, 1184, 1092, 1026

HRMS (EI+) Calcd. for $C_{19}H_{16}FN_5O$:349.1339 Found : 349.1335

N-(4-acetamido-3,5,6-trifluoropyridin-2-yl)-N-(but-3-en-1-yl)acetamide (4-56)



Following the general procedure **4-I** for preparing the olefinic precursors, the reaction was carried out with 2.5g pentafluoropyridine (14.8 mmol, 1.0 eq.) and 10ml ammonia (25%) (64.4 mmol, 4.3 eq.) in 12 ml EtOH (1.2 mmol/ml) refluxing for 16 hours. After work-up, 2.09 g of crude product as white solid was used directly in the next step without further purification.

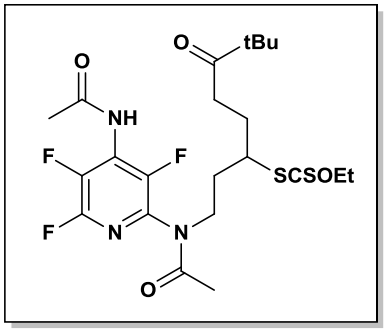
The crude product of last step was dissolved by 12 ml acetyl chloride (168.8 mmol, 13.4 eq.) and refluxed overnight to complete the reaction. After work-up, 2.48g of crude product as white solid was used directly in the next step without further purification.

Then the reaction was carried out with 203mg crude product of last step (0.99 mmol, 1.0 eq.), 310 mg but-3-en-1-amine hydrochloride(3.91 mmol, 4.0 eq.) and 0.68 ml TEA (4.89 mmol, 4.9 eq.) in 6.0 ml THF (1.5 mmol/ml). The mixture was refluxing overnight. After work-up, the crude product was used directly in the next step without further purification.

Finally the acetylation was carried out by dissolving the crude product of the last step with 5.0 ml acetyl chloride (0.02 mmol/ml) and refluxing overnight. After work-up, the crude product was purified with flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **4-56** (196 mg, 67% for 2 steps) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.24 (s, 1H, N*H*), 5.68 (tdd, *J* = 17.0, 10.2, 6.8 Hz, 1H, CH_2CH), 5.05-4.97 (m, 2H, $CH=CH_2$), 3.79 (t, *J* = 7.40 Hz, 2H, NCH_2), 2.31-2.27 (m, 5H, $NH\text{-}CO\text{-}CH_3 + CH=CH_2$), 1.99 (brs, 3H, $N\text{-}CO\text{-}CH_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 170.2 ($NHCOCH_3$), 167.6 ($NCOCH_3$), 146.2 (ddd, *J* = 2340, 14, 2.1 Hz, N-*C*F), 145.7 (dd, *J* = 260, 5.4 Hz, N-CF-*C*F), 138.5 (dd, *J* = 268, 32 Hz, CO-N-C-*C*F), 134.4-134.1 (m, CF-*C*-N-CO), 127.0-126.7 (m, CF-CF-*C*), 117.1 ($CHCH_2$), 47.1 (*C*H), 32.6 ($N\text{-}CH_2\text{-}CH$), 23.1 ($NHCO\text{-}CH_3$), 22.0 ($NCO\text{-}CH_3$)
IR (ν, cm-1, $CDCl_3$) 3690, 3606, 3521, 3418, 2970, 2932, 1733, 1645, 1629, 1510, 1486, 1468, 1456, 1433, 1419, 1379, 1321, 1280, 1222, 1170, 1089, 1037, 1007, 975
MS (NH_3 ionisation) 302 (MH^+)

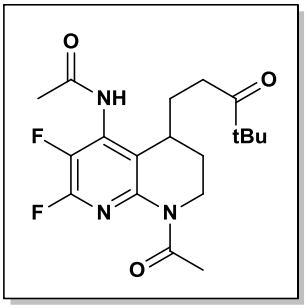
S-(1-(N-(4-acetamido-3,5,6-trifluoropyridin-2-yl)acetamido)-7,7-dimethyl-6-oxooctan-3-yl) O-ethyl carbonodithioate (4-57)



Following the general procedure **4-II** for radical addition of xanthate, the reaction was carried out with the protected olefin **4-56** (196 mg, 0.65 mmol, 0.5 eq.) and the corresponding xanthate (279 mg, 1.30 mmol, 1.0 eq.) in AcOEt (0.7 ml, 0.5 mmol/ml), with DLP (160 mg, 0.30 eq.). Flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **4-57** (145 mg, 43%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.26 (brs, 1H, N*H*), 4.58 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.82 (t, *J* = 7.3 Hz, 2H, NC*H*$_2$), 3.68-3.61 (m, 1H, SC*H*), 2.71-2.54 (m, 2H, COC*H*$_2$), 2.28 (s, 3H, NHCOC*H*$_3$), 2.03 (s, 3H, NCOC*H*$_3$), 2.01-1.96 (m, 3H, NCH$_2$C*H*$_2$ + COCH$_2$CH*H*), 1.78-1.69 (m, 1H, COCH$_2$C*H*H), 1.39 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.10 (s, 9H, C(C*H*$_3$)$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 215.5 (*C*=S), 213.8 (*C*OCH$_2$), 170.0 (NH*C*OCH$_3$), 167.3 (N*C*OCH$_3$), 146.3 (dd, *J* = 241, 14 Hz, N-*C*F), 145.6 (dd, *J* = 260, 5.9 Hz, NCF*C*F), 138.7 (dd, *J* = 268, 30 Hz, *C*F-C-NCO), 134.7-134.3 (N*C*N), 127.0-126.8 (CFCF*C*), 70.2 (CSO*C*H$_2$CH$_3$), 48.9 (CON*C*H$_2$), 45.6 (*C*(CH$_3$)$_3$), 44.2 (S*C*H), 33.4 (CO*C*H$_2$), 23.1 (NHCO*C*H$_3$), 21.9 (NCO*C*H$_3$), 13.6 (CSOCH$_2$*C*H$_3$)
IR (ν, cm-1, $CDCl_3$) 3691, 3607, 3418, 2971, 1727, 1702, 1678, 1621, 1602, 1501, 1477, 1449, 1385, 1369, 1283, 1222, 1112, 1050
HRMS (EI+) Calcd. for $C_{22}H_{30}F_3N_3O_4S_2$: 521.1630 -Xa.: 400.1848 Found : 400.1848

N-(8-acetyl-5-(4,4-dimethyl-3-oxopentyl)-2,3-difluoro-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)acetamide (4-58)



Following the general procedure **4-III** for the radical cyclization using DTBP, the reaction was carried out with the solution of 63.4mg **4-57** (0.12mmol, 1.0 eq.) and 0.028ml 2,6-lutidine (0.24mmol, 2eq.) in chlorobenzene (2.4ml, 0.05mmol/ml), with 0.11ml DTBP (0.61mmol, 5 eq.) for 3 hours. Purification with preparative TLC plate with MeOH / DCM = 3 / 97 afforded **4-58** (7.3mg, 16%) as light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 9.45 (s, 1H, N*H*), 4.17 (td, 1H, *J* = 13.7, 4.5 Hz, AcN-CH*H*), 3.60 (ddd, 1H, *J* = 13.6, 10.5, 5.4 Hz, AcN-CH*H*), 2.83 (ddd, 1H, *J* = 19.3, 11.9, 1.9 Hz, CO-C*H*H), 2.69-2.54 (m, 2H, C*H* + CO-CH_2), 2.49 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.86-1.77 (m, 2H, N-CH_2-CH_2), 1.77-1.70 (m, 1H, C*H*H-CH_2CO), 1.61-1.50 (m, 1H, CH*H*-CH_2-CO), 1.22 (s, 9H, *t*Bu)

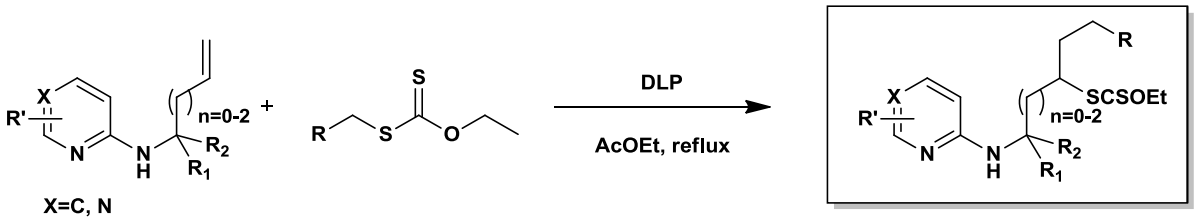
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.2 (*C*O*t*Bu), 171.4 (*C*OMe), 168.6 (*C*OMe), 148.6 (dd, *J* = 235.5, 16.7 Hz, N-*C*F), 144.6 (dd, *J* = 250.4, 20.7 Hz, N-C-*C*F), 142.3 (dd, *J* = 22.3, 13.8 Hz, N-*C*-CF), 135.3 (dd, *J* = 9.3, 5.0 Hz, N-*C*-N), 119.0 (d, *J* = 5.9 Hz, *C*-C-N), 44.4 (*C*Me_3), 38.9 (CO-N-*C*H_2), 32.8 (CO*C*H_2), 30.9 (*C*H), 27.5 (COCH_2-*C*H_2), 26.5 (C(*C*H_3)$_3$), 26.2 (*C*H_3), 24.5 (CON-CH_2-*C*H_2), 23.3 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3686, 3607, 2928, 2855, 1731, 1674, 1620, 1601, 1485, 1427, 1373, 1324, 1260, 1226, 1182, 1034

HRMS (EI+) Calcd. for $C_{19}H_{25}F_2N_3O_3$: 381.1864 Found : 381.1851

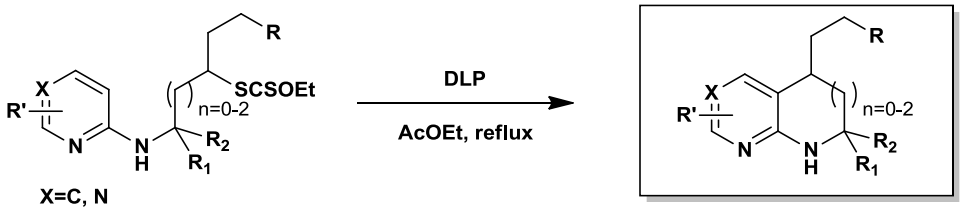
Chapter 5

General procedure 5-I for radical addition of xanthates on the olefins



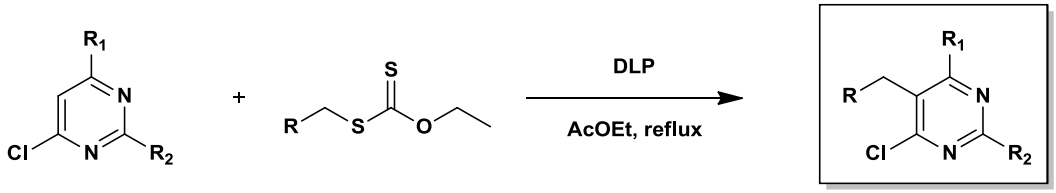
A magnetically stirred solution of the corresponding olefin (0.5-2.0 eq.) and the desired xanthates (1.0 eq.) in AcOEt (1.0M-2.0M of xanthate) was refluxed for about 20-30min under nitrogen. Lauroyl peroxide (DLP) (10%mol) was then added to the refluxing solution, followed by additional portions (5%mol) every 90min until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

General procedure 5-II for radical cyclization of the corresponding xanthates



A magnetically stirred solution of the corresponding xanthate (1.0 eq.) in AcOEt (0.05M of xanthate) was refluxed for about 15-30min under nitrogen. Lauroyl peroxide (DLP) (20%mol) was then added to the refluxing solution every 60min. The reaction was monitored by TLC every hour until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

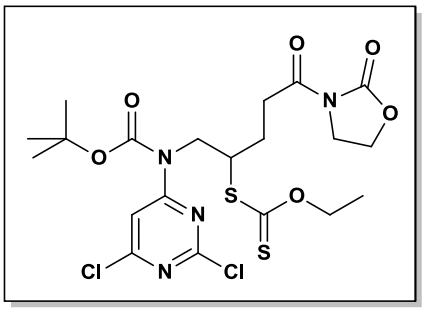
General procedure 5-III for radical addition of xanthates on the pyrimidine rings



R_1=Cl, R_2=NHMe or R_1=NHMe, R_2=Cl

A magnetically stirred solution of the corresponding aromatic ring (0.5-2.0 eq.) and the desired xanthates (1.0 eq.) in AcOEt (1.0M-2.0M of xanthate) was refluxed for about 20-30min under nitrogen. Lauroyl peroxide (DLP) (10%mol or 20%mol) was then added to the refluxing solution every 60min, until the xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

***tert*-butyl (2,6-dichloropyrimidin-4-yl)(2-((ethoxycarbonothioyl)thio)-5-oxo-5-(2-oxooxazolidin-3-yl)pentyl)carbamate (5-1)**



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *tert*-butyl allyl(2,6-dichloropyrimidin-4-yl)carbamate (1.51g, 4.96mmol, 2.0 eq.) and the xanthate **Xa-f** (618mg,

2.48mmol, 1.0 eq.) in AcOEt (2.5ml, 1.0mmol/ml), with DLP (148mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **5-1** (1.10g, 81%) as colourless oil.

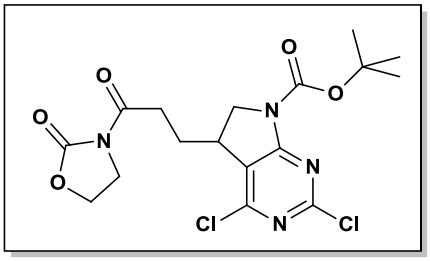
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.05 (s, 1H, *H*-aromatic), 4.58 (ttd, 2H, J=3.6Hz, J=7.1Hz, J=10.7Hz, C*H*$_2$-CH$_3$), 4.48-4.39 (m, 1H, BocN-CH*H*), 4.41 (t, 2H, J=8.1Hz, N-COO-C*H*$_2$), 4.33-4.24 (m, 2H, Xa-C*H* + BocN-C*H*H), 4.01 (t, 2H, J=8.2Hz, N-COO-CH$_2$-C*H*$_2$), 3.25-3.17 (m, 1H, CO-C*H*H), 3.12-3.04 (m, 1H, CO-CH*H*), 2.21-2.13 (m, 1H, CO-CH$_2$-C*H*H), 2.04-1.94 (m, 1H, CO-CH$_2$-CH*H*), 1.59 (s, 9H, C(C*H*$_3$)$_3$), 1.36 (t, 3H, J=7.1Hz, CH$_2$-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (C=S), 172.2 (*C*O-NCOO), 162.3 (*C*-NBoc), 162.0 (*C*-CH-C-NBoc), 158.7 (*C*-N-C-NBoc), 153.4 (*t*BuO-*C*O), 152.2 (N*C*OO-CH$_2$), 110.4 (*C*H-C-NBoc), 84.7 (*C*Me$_3$), 70.4 (*C*H$_2$-CH$_3$), 62.1 (NCOO-*C*H$_2$), 49.7 (Xa-*C*H), 48.2 (*C*H$_2$-NBoc), 42.5 (N-COO-CH$_2$-*C*H$_2$), 32.4 (N-CO-*C*H$_2$), 28.0 (C(*C*H$_3$)$_3$), 26.9 (Xa-CH-*C*H$_2$-CH$_2$), 13.7 (CH$_2$-*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 2984, 1783, 1728, 1559, 1525, 1420, 1388, 1230, 1150, 1113, 1048

HRMS (EI+) Calcd. for $C_{20}H_{26}N_4Cl_2S_2O_6$: 552.0671 Found : 552.0668

***tert*-butyl 2,4-dichloro-5-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)-5H-pyrrolo[2,3-d]pyrimidine-7(6H)-carboxylate (5-2)**



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-1** (1.03g, 1.86mmol, 1.0 eq.) in

AcOEt (28ml, 0.07mmol/ml), with DLP (1.18g, 1.6 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-2** (76mg, 10%) as yellow oil.

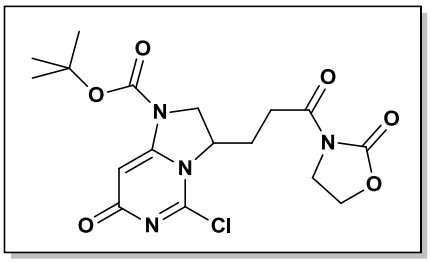
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.44 (dt, 2H, J=1.4Hz, J=8.2Hz, N-COO-C*H*$_2$), 4.09 (t, 1H, J=10.6Hz, BocN-CH*H*), 4.01 (t, 2H, J=8.3Hz, N-COO-CH$_2$-C*H*$_2$), 3.86 (ddd, 1H, J=1.4Hz, J=3.8Hz, J=11.5Hz, BocN-C*H*H), 3.41 (m, 1H, BocN-CH$_2$-C*H*), 3.01 (t, 2H, J=7.3Hz, CO-C*H*$_2$), 2.36-2.28 (m, 1H, CO-CH$_2$-C*H*H), 1.94-1.84 (m, 1H, CO-CH$_2$-CH*H*), 1.56 (d, 9H, J=1.5Hz, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.8 (*C*O-NCOO), 164.9 (*C*-NBoc), 159.9 (*C*-C-NBoc), 155.1 (*C*-N-C-NBoc), 153.5 (*t*BuO-*C*O), 149.4 (N*C*OO-CH$_2$), 121.2 (*C*-C-NBoc), 83.8 (*C*Me$_3$), 62.2 (NCOO-*C*H$_2$), 52.5 (*C*H$_2$-NBoc), 42.5 (N-COO-CH$_2$-*C*H$_2$), 34.7 (*C*H-CH$_2$-NBoc), 32.0 (N-CO-*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 27.1 (N-CO-CH$_2$-*C*H$_2$)

IR (ν, cm^{-1}, $CDCl_3$) 2984, 2930, 1783, 1741, 1699, 1588, 1547, 1482, 1445, 1389, 1309, 1252, 1151, 1041

HRMS (EI+) Calcd. for $C_{17}H_{20}N_4O_5Cl_2$: 430.0811 Found : 430.0824

***tert*-butyl 5-chloro-7-oxo-3-(3-oxo-3-(2-oxooxazolidin-3-yl)propyl)-2,3-dihydroimidazo [1,2-c]pyrimidine-1(7*H*)-carboxylate (5-3)**



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-1** (1.03g, 1.86mmol, 1.0 eq.) in AcOEt (28ml, 0.07mmol/ml), with DLP (1.18g, 1.6 eq.). Flash chromatography on silica gel with AcOEt / DCM = 40 / 60 afforded **5-3** (388mg, 51%) as white solid.

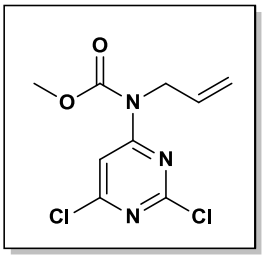
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.68 (br s, 1H, *H*-aromatic), 4.89-4.57 (m, 1H, BocN-CH_2-C*H*), 4.43 (t, 2H, *J* = 8.0 Hz, N-COO-CH_2), 4.10 (dd, 1H, *J* = 10.8, 9.6 Hz, BocN-CH*H*), 4.00 (t, 2H, *J* = 8.0 Hz, N-COO-CH_2-CH_2), 3.91 (dd, 1H, *J* = 11.1, 3.3 Hz, BocN-C*H*H), 3.02 (t, 2H, *J* = 7.4 Hz, CO-CH_2), 2.42 (dtd, 1H, *J* = 11.6, 7.3, 4.5 Hz, CO-CH_2-C*H*H), 2.21-2.07 (m, 1H, CO-CH_2-CH*H*), 1.57 (s, 9H, C(CH_3)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 171.4 (*C*O-NCOO), 167.4 (*C*-Ar), 153.6 (*t*BuO-*C*O), 152.9 (*C*-Ar), 152.3 (*C*-Ar), 149.2 (N*C*OO-CH_2), 90.3 (*C*H-Ar), 85.6 (*C*Me_3), 62.3 (N-COO-*C*H_2), 55.0 (*C*H-CH_2-NBoc), 50.4 (*C*H_2-NBoc), 42.5 (N-COO-CH_2-*C*H_2), 30.8 (N-CO-*C*H_2), 28.0 (C(*C*H_3)$_3$), 27.1 (N-CO-CH_2-*C*H_2)

IR (ν, cm^{-1}, $CDCl_3$) 3160, 2985, 2928, 2247, 1783, 1739, 1678, 1609, 1526, 1480, 1439, 1373, 1312, 1148, 1042, 1003

HRMS (EI+) Calcd. for $C_{17}H_{21}ClN_4O_6$: 412.1150 Found : 412.1146

methyl allyl(2,6-dichloropyrimidin-4-yl)carbamate (5-5)



1.22g *N*-(but-3-en-1-yl)-2,6-dichloropyrimidin-4-amine (5.99mmol, 1.0eq.) was dissolved by 13.0ml anhydrous THF (0.5mmol/ml), following by adding 294mg NaH (60% suspension in oil, 7.35mmol, 1.2eq.). Then 0.56ml methyl chloroformate (7.19 mmol, 1.2eq.) was added portionwise, and the mixture was strring for 1 hour. After work-up, flash chromatography on silica gel with DCM / EP = 60 / 40 afforded **5-5** (1.46g, 93%) as clolourless crystal.

m.p. : 30-35°C

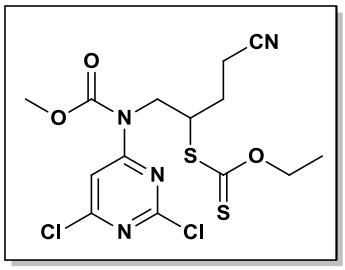
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.14 (s, 1H, *H*-aromatic), 5.87 (qd, 1H, J=5.6Hz, J=10.4Hz, CH_2-C*H*=CH_2), 5.21-5.16 (m, 2H, CH_2-CH=C*H*$_2$), 4.67 (dd, 2H, J=1.2Hz, J=5.6Hz, C*H*$_2$-CH=CH_2), 3.89 (s, 3H, C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 162.3 (CO-N-*C*-N), 161.7 (N-C-C-*C*-Cl), 159.0 (N-C-N-*C*-Cl), 154.4 (*C*O) 132.1 (CH_2-*C*H=CH_2), 117.8 (CH_2-CH=*C*H$_2$), 110.0 (Cl-C-*C*), 54.1 (COO-*C*H_3), 47.8 (*C*H_2-CH=CH_2)

IR (ν, cm^{-1}, $CDCl_3$) 1732, 1559, 1526, 1440, 1415, 1352, 1240, 1133

HRMS (EI+) Calcd. for $C_9H_9N_3O_2Cl_2$: 261.0072 Found : 261.0072

methyl (4-cyano-2-((ethoxycarbonothioyl)thio)butyl)(2,6-dichloropyrimidin-4-yl) carbamate (5-6)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of methyl allyl(2,6-dichloropyrimidin-4-yl)carbamate (874mg, 3.34mmol, 2.0 eq.) and the xanthate **Xa-a** (269mg, 1.67mmol, 1.0 eq.) in AcOEt (1.7ml, 1.0mmol/ml), with DLP (100mg, 0.15 eq.). Flash chromatography on silica gel with DCM 100% afforded **5-6** (516mg, 73%) as light yellow oil.

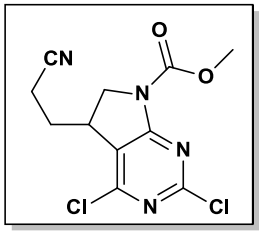
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.06 (s, 1H, *H*-aromatic), 4.61 (dq, 2H, J=3.0Hz, J=7.1Hz, C*H*$_2$-CH_3), 4.49 (dd, 1H, J=10.8Hz, J=15.8Hz, CO-N-CH*H*), 4.34-4.26 (m, 2H, CO-N-C*H*H + Xa-C*H*), 3.93 (s, 3H, C*H*$_3$), 2.67-2.52 (m, 2H, C*H*$_2$-CN), 2.18-1.99 (m, 2H, C*H*$_2$-CH_2-CN), 1.39 (t, 3H, J=7.1Hz, CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.9 (*C*=S), 162.6 (CO-N-*C*-N), 161.7 (N-C-CH-*C*-Cl), 158.8 (N-C-N-*C*-Cl), 153.9 (*C*OOMe), 118.7 (*C*≡N), 110.3 (Cl-C-*C*H), 70.8 (CH_2-CH_3), 54.4 (COO-CH_3), 49.0 (Xa-*C*H), 47.5 (CO-N-CH_2), 28.4 (Xa-CH-CH_2), 15.1 (CH_2-CN), 13.7(CH_2-CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 2960, 1737, 1558, 1528, 1439, 1419, 1353, 1226, 1147, 1050

HRMS (EI+) Calcd. for $C_{14}H_{16}N_4O_3S_2Cl_2$: 422.0041 Found : 422.0053

methyl 2,4-dichloro-5-(2-cyanoethyl)-5,6-dihydropyrrolo[2,3-d]pyrimidine-7-carboxylate (5-7)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-6** (457mg, 1.08mmol, 1.0 eq.) in AcOEt (16ml, 0.07mmol/ml), with DLP (516mg, 1.2 eq.). Flash chromatography on silica gel with Acetone / DCM = 5 / 95 afforded **5-7** (11mg, 6%) as white solid.

m.p. : 182-186°C

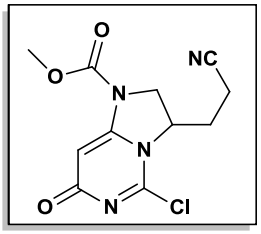
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.23 (t, 1H, J=10.7Hz, CH*H*-N-COOMe), 3.96-3.93 (m, 4H, C*H*H-N-COOMe + COOCH_3), 3.59-3.52 (m, 1H, C*H*-CH_2-N-COOMe), 2.56-2.41 (m, 2H, CH_2-CN), 2.38-2.29 (m, 1H, CH*H*-CH_2-CN), 1.99-1.90 (m, 1H, C*H*H-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 164.3 (MeOOC-N-*C*-N), 160.5 (MeOOC-N-C-C-*C*), 155.6 (MeOOC-N-C-N-*C*), 151.3 (MeO-*C*O-N), 120.1 (MeOOC-N-C-*C*), 118.0 (*C*≡N), 54.1 (N-COO*C*H_3), 52.2 (*C*H_2-N-COOMe), 34.5 (*C*H-CH_2-N-COOMe), 28.2 (*C*H_2-CH_2-CN), 14.7 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 2929, 2247, 1725, 1592, 1547, 1484, 1443, 1314, 1251, 1126

HRMS (EI+) Calcd. for $C_{11}H_{10}N_4O_2Cl_2$: 300.0181 Found : 300.0178

methyl 5-chloro-3-(2-cyanoethyl)-7-oxo-2,3-dihydroimidazo[1,2-c]pyrimidine-1(7*H*)-carboxylate (5-8)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-6** (457mg, 1.08mmol, 1.0 eq.) in AcOEt (16ml, 0.07mmol/ml), with DLP (516mg, 1.2 eq.). Flash chromatography on silica gel with Acetone / DCM = 30 / 70 afforded **5-8** (86mg, 29%) as yellow oil.

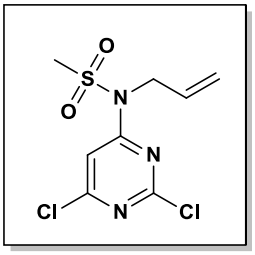
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.77 (br s, 1H, *H*-aromatic), 4.73 (ddd, 1H, *J* = 11.4, 7.5, 3.6 Hz, C*H*), 4.28 (t, 1H, *J* = 10.4 Hz, N-CH*H*), 4.09 (dd, 1H, *J* = 11.3, 3.9 Hz, N-C*H*H), 3.94 (s, 3H, CH_3), 2.82-2.33 (m, 3H, CH_2-CN + CH*H*-CH_2-CN), 2.19-2.14 (m, 1H, C*H*H-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.1 (*C*-Ar), 152.6 (*C*-Ar), 152.0 (*C*-Ar), 150.8 (MeO-*C*O-N), 118.1 (*C*≡N), 90.6 (*C*H-Ar), 55.0 (*C*H-CH_2-N), 54.6 (*C*H_3), 50.0 (*C*H_2-N), 27.9 (*C*H_2-CH_2-CN), 13.5 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3157, 2961, 2250, 1754, 1681, 1611, 1524, 1449, 1382, 1313, 1277, 1209, 1163, 1053

HRMS (EI+) Calcd. for $C_{11}H_{11}ClN_4O_3$: 282.0520 Found : 282.0508

_N_-allyl-_N_-(2,6-dichloropyrimidin-4-yl)methanesulfonamide (5-12)



1.30g *N*-(but-3-en-1-yl)-2,6-dichloropyrimidin-4-amine (6.36mmol, 1.0eq.) was dissolved by 13.0ml anhydrous THF (0.5mmol/ml), following by adding 310mg NaH (60% suspension in oil, 7.75mmol, 1.2eq.). Then 0.59ml methanesulfonyl chloride (7.63 mmol, 1.2eq.) was added portionwise, and the mixture was strring for 1 hour. After work-up, flash chromatography on silica gel with DCM / EP = 80 / 20 afforded **5-12** (1.64g, 91%) as white solid.

m.p. : 61-65°C

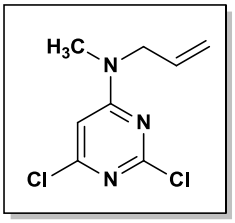
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.29 (s, 1H, *H*-aromatic), 5.92 (qd, 1H, J=5.6Hz, J=10.3Hz, CH_2-C*H*=CH_2), 5.35 (dd, 1H, J=13.8Hz, J=19.1Hz, CH_2-CH=C*H*$_2$), 4.63 (dd, 1H, J=1.2Hz, J=5.6Hz, C*H*$_2$-CH=CH_2), 3.29 (s, 3H, C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 162.6 (Ms-N-*C*-N), 161.2 (N-C-CH-*C*-Cl), 159.6 (N-C-N-*C*-Cl), 130.9 (CH_2-*C*H=CH_2), 119.8 (CH_2-CH=*C*H$_2$), 106.8 (Cl-C-*C*H), 49.4 (*C*H$_2$-CH=CH_2), 42.3 (C-SO_2)

IR (ν, cm^{-1}, $CDCl_3$) 3141, 2257, 1555, 1528, 1428, 1402, 1369, 1321, 1288, 1257, 1170, 1133

HRMS (EI+) Calcd. for $C_8H_9N_3Cl_2SO_2$: 280.9793 Found : 280.9807

_N_-allyl-2,6-dichloro-_N_-methylpyrimidin-4-amine (5-13)



1.51g *N*-(but-3-en-1-yl)-2,6-dichloropyrimidin-4-amine (7.40mmol, 1.0eq.) was dissolved by 15.0ml anhydrous THF (0.5mmol/ml), following by adding 355mg NaH (60% suspension in oil, 8.88mmol, 1.2eq.). Then 0.55ml iodomethane (8.88 mmol, 1.2eq.) was added portionwise, and the mixture was strring for 4 hours. After work-up, flash chromatography on silica gel with DCM / EP = 60 / 40 afforded **5-13** (1.34g, 83%) as colourless oil.

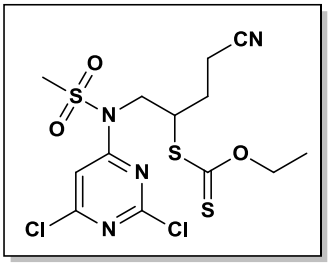
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.32 (s, 1H, *H*-aromatic), 5.77 (ddd, 1H, J=5.3Hz, J=10.4Hz, J=22.3Hz, CH_2-C*H*=CH_2), 5.20 (dd, 1H, J=13.6Hz, J=34.1Hz, CH_2-CH=C*H*$_2$), 4.12 (br d, 1H, J=115.3Hz, C*H*$_2$-CH=CH_2), 3.07 (br d, 1H, J=61.1Hz, C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 163.4 (Me-N-*C*-N), 160.0 (N-C-CH-*C*-Cl), 159.6 (N-C-N-*C*-Cl), 131.9 (CH_2-*C*H=CH_2), 117.8 (CH_2-CH=*C*H$_2$), 99.7 (Cl-C-*C*), 52.1 (*C*H$_2$-CH=CH_2), 35.5 (*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 2932, 1644, 1575, 1530, 1497, 1421, 1302, 1195, 1127, 1014, 969

HRMS (EI+) Calcd. for $C_8H_8N_3Cl_2$: 217.0174 Found : 217.0179

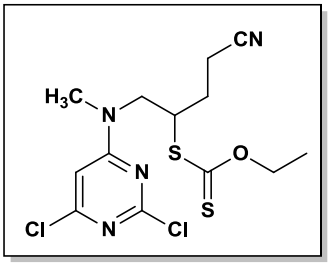
_S_-1-(_N_-(2,6-dichloropyrimidin-4-yl)-_N_-methanesulfonylamino)-4-cyanobutan-2-yl _O_-ethyl carbonodithioate (5-14)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *N*-allyl-*N*-(2,6-dichloropyrimidin-4-yl)methanesulfonamide (821mg, 2.91mmol, 2.0 eq.) and the xanthate **Xa-a** (235mg, 1.45mmol, 1.0 eq.) in AcOEt (1.5ml, 1.0mmol/ml), with DLP (87mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 35 / 65 afforded **5-14** (476mg, 74%) as light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.53 (s, 1H, *H*-aromatic), 4.64 (dq, 2H, J=1.0Hz, J=7.1Hz, C*H*$_2$-CH_3), 4.35 (ddd, 2H, J=7.4Hz, J=14.7Hz, J=21.2Hz, Ms-N-C*H*$_2$), 4.21 (m, 1H, Xa-C*H*), 3.24 (s, 3H, C*H*$_3$), 2.60 (m, 2H,), 2.25-2.17 (m, 1H, C*H*H-CH_2-CN), 2.08-1.98 (m, 1H, CH*H*-CH_2-CN), 1.41 (t, 3H, J=7.1Hz, CH_2-C*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.2 (*C*=S), 163.0 (Ms-N-*C*-N), 160.7 (N-C-CH-*C*-Cl), 159.7 (N-C-N-*C*-Cl), 118.6 (*C*≡N), 108.0 (Cl-C-*C*H), 71.1 (*C*H_2-CH_3), 48.8 (Ms-N-*C*H_2), 48.6 (Xa-*C*H) 41.0 (C-SO_2), 27.9 (Xa-CH-*C*H_2), 15.0 (*C*H_2-CN), 13.7 (CH_2-*C*H_3)
IR (ν, cm^{-1}, CCl_4) 2931, 1555, 1529, 1375, 1317, 1229, 1172, 1050
HRMS (EI+) Calcd. for $C_{13}H_{16}O_3S_3Cl_2N_4$: 441.9762 Found : 441.9778

_S_-1-(_N_-(2,6-dichloropyrimidin-4-yl)-_N_-methylamino)-4-cyanobutan-2-yl _O_-ethyl carbonodithioate (5-15)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *N*-allyl-2,6-dichloro-*N*-methylpyrimidin-4-amine (1.34g, 6.14mmol, 2.0 eq.) and the xanthate **Xa-a** (506mg, 3.14mmol, 1.0 eq.) in AcOEt (3.2ml, 1.0mmol/ml), with DLP (188mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **5-15** (1.10g, 92%) as light yellow oil.

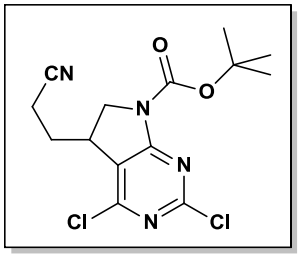
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.39 (s, 1H, *H*-aromatic), 4.66 (dq, 2H, J=3.4Hz, J=7.1Hz, C*H*$_2$-CH_3), 4.27 (s, 1H, Me-N-CH*H*), 4.13 (s, 1H, Xa-C*H*), 3.64 (s, 1H, Me-N-C*H*H), 3.13 (s, 3H, C*H*$_3$), 2.71-2.51 (m, 2H, C*H*$_2$-CN), 2.08-1.96 (m, 2H, C*H*$_2$-CH_2-CN), 1.43 (dt, 1H, J=3.4Hz, J=7.1Hz, CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.9 (*C*=S), 163.7 (Me-N-*C*-N), 160.6 (N-C-CH-*C*-Cl), 159.5 (N-C-N-*C*-Cl), 118.7 (*C*≡N), 99.8 (Cl-C-*C*H), 70.9 (*C*H_2-CH_3), 51.9 (Me-N-*C*H_2), 48.3 (Xa-*C*H), 36.8 (N-*C*H_3), 27.4 (Xa-CH-*C*H_2), 15.1 (*C*H_2-CN), 13.7 (CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2939, 2244, 1574, 1531, 1498, 1425, 1382, 1298, 1227, 1126, 1051, 1014

HRMS (EI+) Calcd. for $C_{13}H_{16}N_4OS_2Cl_2$: 378.01427 Found : 378.01370

tert-butyl 2,4-dichloro-5-(2-cyanoethyl)-5,6-dihydropyrrolo[2,3-d]pyrimidine-7-carboxylate (5-16)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-10** (935mg, 2.01mmol, 1.0 eq.) in AcOEt (30ml, 0.07mmol/ml), with DLP (1.28g, 1.6 eq.). Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **5-16** (65mg, 9%) as light yellow oil.

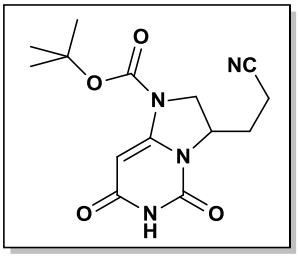
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.18 (dd, 1H, J=9.8Hz, J=11.7Hz, CH*H*-NBoc), 3.86 (dd, 1H, J=4.0Hz, J=11.7Hz, C*H*H-NBoc), 3.51 (tt, 1H, J=3.8Hz, J=9.5Hz, C*H*-CH_2-NBoc), 2.55-2.40 (m, 2H, C*H*$_2$-CN), 2.36-2.28 (m, 1H, CH*H*-CH_2-CN), 1.99-1.90 (m, 1H, C*H*H-CH_2-CN), 1.57 (s, 9H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 164.8 (BocN-*C*-N), 160.5 (BocN-C-C-*C*), 155.2 (BocN-C-N-*C*), 149.2 (*t*BuO-*C*O-N), 119.8 (BocN-C-*C*), 118.1 (*C*≡N), 84.2 (*C*Me_3), 52.1 (*C*H_2-NBoc), 34.4 (*C*H-CH_2-NBoc), 28.2 (*C*H_2-CH_2-CN), 28.0 (C(*C*H_3)$_3$), 14.6 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 2929, 2856, 1712, 1588, 1546, 1484, 1444, 1311, 1251, 1151

HRMS (EI+) Calcd. for $C_{14}H_{16}N_4O_2Cl_2$: 342.0650 Found : 342.0641

tert-butyl 3-(2-cyanoethyl)-5,7-dioxo-2,3,6,7-tetrahydroimidazo[1,2-c]pyrimidine-1(5H)-carboxylate (5-18')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-10** (935mg, 2.01mmol, 1.0 eq.) in AcOEt (30ml, 0.07mmol/ml), with DLP (1.28g, 1.6 eq.). Flash chromatography on silica gel with Acetone / EP = 30 / 70 afforded **5-17**[247] (216mg, 33%) as light yellow oil, and with Acetone / EP = 40 / 60 gave **5-18'** (115mg, 18%) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 9.44 (s, 1H, N*H*), 5.95 (s, 1H, CO-C*H*), 4.57 (tdd, 1H, *J* = 8.6, 7.4, 3.7 Hz, C*H*-CH_2-NBoc), 4.10 (dd, 1H, *J* = 11.2, 9.0 Hz, CH*H*-NBoc), 3.88 (dd, 1H, *J* = 11.3, 3.3 Hz, C*H*H-NBoc), 2.58-2.44 (m, 2H, CH_2-CN), 2.42-2.30 (m, 1H, CH*H*-CH_2-CN), 2.19-2.10 (m, 1H, C*H*H-CH_2-CN), 1.55 (s, 9H, C(CH_3)$_3$)

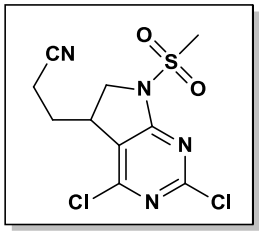
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 165.1 (*C*-NBoc), 149.6 (*C*O), 149.5 (*C*O), 148.5 (*C*O), 118.2 (*C*≡N), 85.3 (*C*Me_3), 83.3 (*C*H-Ar), 52.6 (*C*H-CH_2-NBoc), 49.9 (*C*H_2-NBoc), 28.6 (*C*H_2-CH_2-CN), 28.0 (C(*C*H_3)$_3$), 13.4 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3400, 2984, 2934, 1719, 1678, 1638, 1534, 1456, 1372, 1321, 1148, 1016

MS (NH_3 ionisation) 307 (MH^+)

[247] *N*-cyclized product **5-17** has been characterized in the reported work of: Laot, Y.; Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784-5786.

3-(2,4-dichloro-6,7-dihydro-7-methanesulfonyl-5H-pyrrolo[2,3-d]pyrimidin-5-yl) propanenitrile (5-21)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-12** (436mg, 0.98mmol, 1.0 eq.) in AcOEt (15ml, 0.07mmol/ml), with DLP (549mg, 1.4 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-21** (113mg, 36%) as white solid.

m.p. : 182-186°C

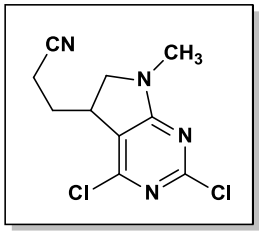
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 4.22 (dt, 1H, J=2.0Hz, J=10.1Hz, CH*H*-NMs), 3.99 (ddd, 1H, J=2.1Hz, J=3.9Hz, J=10.2Hz, C*H*H-NMs), 3.59-3.54 (m, 1H, C*H*-CH_2-NMs), 3.37 (d, 3H, J=2.2Hz, SO_2-CH_3), 2.66 (t, 2H, J=7.7Hz, CH_2-CN), 2.15-1.92 (m, 2H, CH_2-CH_2-CN)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 164.8 (MsN-*C*-N), 157.6 (MsN-C-C-*C*), 153.8 (MsN-C-N-*C*), 121.4 (MsN-C-*C*), 120.2 (*C*≡N), 53.0 (*C*H_2-NMs), 39.1 (SO_2-*C*H_3), 34.6 (*C*H-CH_2-NMs), 26.8 (*C*H_2-CH_2-CN), 13.4 (*C*H_2-CN)

IR (ν, cm^{-1}, Nujol) 2925, 1588, 1548, 1456, 1377, 1166, 1038

HRMS (EI+) Calcd. for $C_{10}H_{10}N_4O_2SCl_2$: 319.9902 Found : 319.9897

3-(2,4-dichloro-6,7-dihydro-7-methyl-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanenitrile (5-22)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-15** (594mg, 1.56mmol, 1.0 eq.) in AcOEt (24ml, 0.07mmol/ml), with DLP (624mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **5-22** (220mg, 54%) as a white solid.

m.p. : 84-87°C

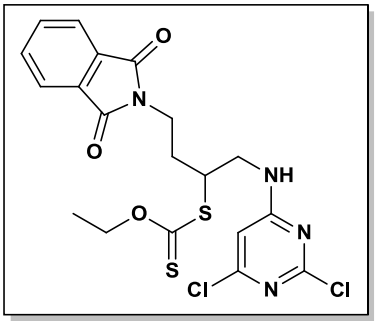
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 3.85 (t, 1H, J=9.7Hz, CH*H*-NMe), 3.56-3.46 (m, 2H, C*H*-CH_2-NMe + C*H*H-NMe), 3.01 (s, 3H, N-C*H*$_3$), 2.51-2.23 (m, 3H, C*H*$_2$-CN + CH*H*-CH_2-CN), 2.03-1.94 (m, 1H, C*H*H-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.0 (MeN-*C*-N), 160.2 (MeN-C-C-*C*), 151.4 (MeN-C-N-*C*), 118.5 (MeN-C-*C*), 116.6 (*C*≡N), 56.4 (*C*H_2-NMe), 35.6 (*C*H-CH_2-NMe), 31.2 (N-*C*H_3), 28.1 (*C*H_2-CH_2-CN), 14.5 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 2929, 2256, 1607, 1533, 1415, 1341, 1286, 1011

HRMS (EI+) Calcd. for $C_{10}H_{10}N_4Cl_2$: 256.0283 Found : 256.0274

S-1-(2,6-dichloropyrimidin-4-ylamino)-4-(1,3-dioxoisoindolin-2-yl)butan-2-yl O-ethyl carbonodithioate (5-24)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *N*-allyl-2,6-dichloropyrimidin-4-amine (274mg, 1.34mmol, 2.0 eq.) and the xanthate **Xa-c** (190mg, 0.67mmol, 1.0 eq.) in AcOEt (0.7ml, 1.0mmol/ml), with DLP (53mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-24** (210mg, 64%) as a light yellow oil.

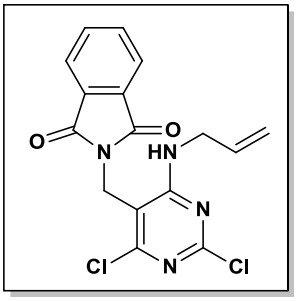
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.91-7.79 (m, 2H, 2 *H*-phthalimide), 7.76-7.70 (m, 2H, 2 *H*-phthalimide), 6.38 (br s, 1H, C*H*-Ar), 5.80 (br s, 1H, N*H*), 4.61 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.04-3.92 (m, 1H, C*H*), 3.88 (t + br s, *J* = 6.9 Hz, 4H, CH_2-phthalimide + CH_2NH), 2.24-2.11 (m, 1H, CHCH*H*), 2.11-1.99 (m, 1H, CHC*H*H), 1.38 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.9 (*C*=S), 168.3 (2 *C*O-phthalimide), 164.1 (*C*-Ar), 159.9 (*C*-Ar), 158.7 (*C*-Ar), 134.2 (2 *C*H-phthalimide), 131. 9 (2 *C*-phthalimide), 123.4 (2 *C*H-phthalimide), 102.7 (*C*H-Ar), 70.7 (OCH_2CH_3), 47.8 (*C*H), 44.4 (CH_2NH), 35.4 (CH_2-Nphthalimide), 30.5(CH_2-CH_2-Nphthalimide), 13.7 (OCH_2CH_3)

IR (ν, cm^{-1}, CCl_4) 2926, 1775, 1720, 1581, 1495, 1436, 1395, 1373, 1269, 1227, 1121, 971

HRMS (EI+) Calcd. for $C_{16}H_{13}Cl_2N_4O_2$: 363.0416 Found : 363.0413

2-((4-(allylamino)-2,6-dichloropyrimidin-5-yl)methyl)isoindoline-1,3-dione (5-24')



In the same procedure for preparing **5-24**, a second product was isolated by flash chromatography with AcOEt / EP = 30 / 70 afforded **5-24'** (8.3mg, 4%) as a white solid.

m.p. : 195-199°C

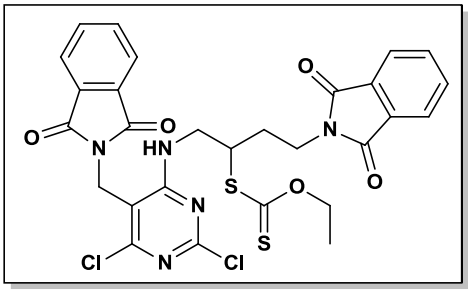
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.87 (dd, *J* = 4.9, 3.3 Hz, 2H, 2 *H*-phthalimide), 7.77 (dd, *J* = 5.1, 3.1 Hz, 2H, 2 *H*-phthalimide), 7.01 (br s, 1H, N*H*), 5.96-5.85 (m, 1H, CH_2=C*H*), 5.25 (d, 1H, J=17.1Hz, C*H*H=CH), 5.19 (d, 1H, J=10.3Hz, CH*H*=CH), 4.87 (s, 2H, CH_2-Nphthalimide), 4.10 (dd, *J* = 5.2, 5.2 Hz, 2H, CH_2-NH)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.6 (2 *C*O-phthalimide), 162.4 (*C*-Ar), 160.1 (*C*-Ar), 159.2 (*C*-Ar), 134.7 (2 *C*H-phthalimide), 133.0 (CH_2=*C*H), 131.5 (2 *C*-phthalimide), 123.8 (2 *C*H-phthalimide), 117.4 (*C*H_2=CH), 107.2 (*C*H-Ar), 44.4 (*C*H_2NH), 34.5 (*C*H_2-Nphthalimide)

IR (ν, cm^{-1}, CCl_4) 3333, 2927, 2855, 1776, 1716, 1563, 1489, 1469, 1414, 1393, 1370, 1345, 1322, 1273, 1133, 1077, 929

HRMS (EI+) Calcd. for $C_{16}H_{12}Cl_2N_4O_2$: 362.0337 Found : 362.0337

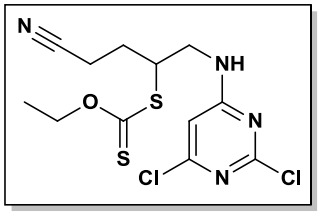
S-1-(5-(Phthalimidyl-methyl)-2,6-dichloropyrimidin-4-ylamino)-4-(1,3-dioxoisoindolin-2-yl)butan-2-yl O-ethyl carbonodithioate (5-24")



In the same procedure for preparing **5-24**, a third product was isolated by flash chromatography on silica gel with AcOEt / EP = 50 / 50 afforded **5-24"** (7.1mg, 2%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.94-7.82 (m, 4H, 4 *H*-phthalimide), 7.82-7.72 (m, 4H, 4 *H*-phthalimide), 7.27 (t, *J* = 5.4 Hz, 1H, N*H*), 4.90 (s, 2H, CH_2-Ar), 4.55 (q, *J* = 7.1 Hz, 2H, C$H_2$$CH_3$), 4.16-4.01 (m, 1H, C*H*), 3.98-3.83 (m, 4H, CH_2-Nphthalimide + CH_2-NH), 2.29-2.16 (m, 1H, CHC*H*H), 2.11-1.99 (m, 1H, CHCH*H*), 1.36 (t, *J* = 7.1 Hz, 3H, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.4 (*C*=S), 168.7 (2 *C*O-phthalimide), 168.2 (2 *C*O-phthalimide), 162.8 (*C*-Ar), 160.3 (*C*-Ar), 159.0 (*C*-Ar), 134.6 (2 *C*H-phthalimide), 134.0 (2 *C*H-phthalimide), 132.0 (2 *C*-phthalimide), 131.6 (2 *C*-phthalimide), 123.8 (2 *C*H-phthalimide), 123.3 (2 *C*H-phthalimide), 107.5 (CH_2*C*-Ar), 70.2 (*C*$H_2$$CH_3$), 47.0 (*C*H), 44.8 (C$H_2$-NH), 35.6 (C$H_2$-Nphthalimide), 34.4 (*C*H_2-Ar), 30.2 (CHCH_2), 13.6 (*C*H_3)
IR (ν, cm^{-1}, CCl_4) 3333, 2982, 2936, 1775, 1715, 1580, 1563, 1497, 1393, 1359, 1323, 1273, 1224, 1112, 1051
HRMS (EI+) Calcd. for $C_{25}H_{18}Cl_2N_5O_4$: 522.0736 Found : 522.0725

S-1-(2,6-dichloropyrimidin-4-ylamino)-4-cyanobutan-2-yl O-ethyl carbonodithioate (5-25)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *N*-allyl-2,6-dichloropyrimidin-4-amine (285mg, 1.40mmol, 2.0 eq.) and the xanthate **Xa-a** (114mg, 0.71mmol, 1.0 eq.) in AcOEt (0.7ml, 1.0mmol/ml), with DLP (42mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-25** (237mg, 91%) as a colourless oil.

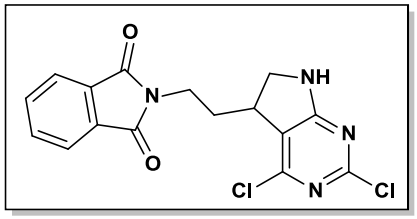
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.36 (s, 1H, *H*-Ar), 5.53 (br s, 1H, N*H*), 4.67 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3), 4.11-4.05 (m, 1H, C*H*), 3.76 (br s, 2H, NH-C*H*$_2$), 2.83-2.46 (m, 2H, C*H*$_2$-CN), 2.23-2.14 (m, 1H, CH*H*-CH_2-CN), 2.04-1.94 (m, 1H, C*H*H-CH_2-CN), 1.44 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 211.9 (*C*=S), 164.1 (*C*-Ar), 160.1 (*C*-Ar), 159.2 (*C*-Ar), 118.6 (*C*N), 102.6 (*C*H-Ar), 71.1 (*C*H_2-CH_3), 49.8 (*C*H), 44.3 (NH-*C*H_2), 27.6 (Xa-CH-*C*H_2), 15.1 (*C*H_2-CN), 13.7 (CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2926, 1578, 1495, 1266, 1233, 1196, 1124, 1052, 970

HRMS (EI+) Calcd. for $C_{12}H_{14}Cl_2N_4OS_2$: 363.9986 Found : 363.9989

2-(2-(2,4-dichloro-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)isoindoline-1,3-dione (5-26)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-24** (173mg, 0.36mmol, 1.0 eq.) in AcOEt (7.0ml, 0.05mmol/ml), with DLP (142mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 50 / 50 afforded **5-26** (14mg, 11%) as a white powder.

m.p. : 248-251°C

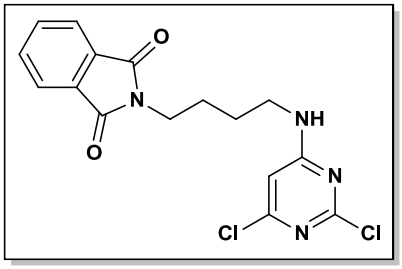
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.97-7.79 (m, 2H, *H*-phthalimide), 7.77-7.71 (m, 2H, *H*-phthalimide), 5.65 (br s, 1H, N*H*), 3.98 (dd, *J* = 9.9, 9.9 Hz, 1H, NH-C*H*H), 3.87-3.74 (m, 2H, CH_2-Nphthalimide), 3.70 (dd, *J* = 10.2, 4.6 Hz, 1H, NH-CH*H*), 3.50-3.42 (m, 1H, C*H*), 2.48-2.29 (m, 1H, CH-CH*H*), 2.01-1.91 (m, 1H, CH-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.8 (*C*-Ar), 168.3 (2*C*O-phthalimide), 159.3 (*C*-Ar), 152.3 (*C*-Ar), 134.3 (2*C*H-phthalimide), 131.9 (2*C*-phthalimide), 123.5 (2*C*H-phthalimide), 117.2 (*C*-Ar), 49.3 (NH-*C*H_2), 35.8 (*C*H), 34.9 (*C*H_2-Nphthalimide), 30.9 (*C*H_2-CH)

IR (ν, cm^{-1}, CCl_4) 3643, 2927, 2854, 1773, 1717, 1581, 1468, 1395, 1363, 1264, 1121, 1022

HRMS (EI+) Calcd. for $C_{16}H_{12}Cl_2N_4O_2$: 362.0337 Found : 362.0329

2-(4-(2,6-dichloropyrimidin-4-ylamino)butyl)isoindoline-1,3-dione (5-26')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-24** (173mg, 0.356mmol, 1.0 eq.) in AcOEt (7.0ml, 0.05mmol/ml), with DLP (142mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-26'** (36mg, 28%) as a white powder.

m.p. : 152-155°C

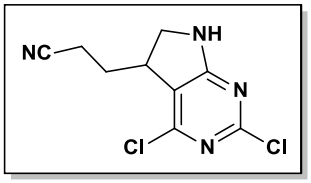
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.96-7.85 (m, 2H, 2 C*H*-phthalimide), 7.80-7.74 (m, 2H, 2 C*H*-phthalimide), 6.34 (s, 1H, C*H*-Ar), 6.09-5.37 (br d, 1H, N*H*), 3.78 (t, *J* = 6.9 Hz, 2H, CH_2-Nphthalimide), 3.65-3.25 (br d, 2H, NH-CH_2), 1.89-1.77 (m, 2H, C*H*H + C*H*H), 1.77-1.65 (m, 2H, CH*H* + CH*H*)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.5 (2 *C*O-phthalimide), 164.1 (*C*-Ar), 159.9 (*C*-Ar), 158.6 (*C*-Ar), 134.1 (2 *C*H-phthalimide), 131.9 (2 *C*-phthalimide), 123.3 (2 *C*H-phthalimide), 100.5 (*C*H-Ar), 41.3 (NH-*C*H_2), 37.2 (*C*H_2-Nphthalimide), 26.0 (2 *C*H_2)

IR (ν, cm^{-1}, CCl_4) 2928, 1770, 1712, 1581, 1498, 1434, 1394, 1353, 1267, 1215, 1121, 1048, 989, 963

HRMS (EI+) Calcd. for $C_{16}H_{14}Cl_2N_4O_2$: 364.0494 Found : 364.0502

3-(2,4-dichloro-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanenitrile (5-27)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-25** (127mg, 0.35mmol, 1.0 eq.) in AcOEt (7.0ml, 0.05mmol/ml), with DLP (139mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 70 / 30 afforded **5-27** (11mg, 13%) as a white powder.

m.p. : 175-179°C

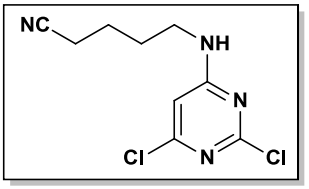
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.92 (br s, 1H, N*H*), 3.97 (dd, *J* = 9.3, 9.3 Hz, 1H, NH-C*H*H), 3.68-3.51 (m, 2H, C*H* + NH-CH*H*), 2.53-2.42 (m, 2H, CH_2-CN), 2.35-2.25 (m, 1H, CH-CH*H*), 2.08-1.97 (m, 1H, CH-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.8 (*C*-Ar), 159.7 (*C*-Ar), 152.7 (*C*-Ar), 118.5 (*C*N), 116.4 (*C*-Ar), 49.2 (NH-*C*H_2), 37.0 (*C*H), 28.1 (*C*H_2-CH), 14.6 (CN-*C*H_2)

IR (ν, cm^{-1}, CCl_4) 3645, 2926, 2854, 1602, 1464, 1264, 1021

HRMS (EI+) Calcd. for $C_9H_8Cl_2N_4$: 242.0126 Found : 242.0132

5-(2,6-dichloropyrimidin-4-ylamino)pentanenitrile (5-27')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-25** (127mg, 0.35mmol, 1.0 eq.)

in AcOEt (7.0ml, 0.05mmol/ml), with DLP (139mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-27'** (34mg, 40%) as a white powder.

m.p. : 102-105°C

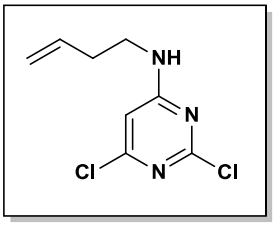
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.29 (s, 1H, C*H*-Ar), 6.04-5.13 (br s, 1H, N*H*), 3.82-2.97 (br s, 2H, NH-CH_2), 2.44 (t, *J* = 6.6 Hz, 2H, CH_2-CN), 1.82-1.71 (m, 4H, CH_2 + CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 164.2 (*C*-Ar), 160.0 (*C*-Ar), 157.1 (*C*-Ar), 119.2 (*C*N), 102.4 (*C*H-Ar), 40.4 (NH-*C*H_2), 28.2 (*C*H_2), 22.6 (*C*H_2), 16.9 (CN-*C*H_2)

IR (ν, cm^{-1}, CCl_4) 3253, 2926, 2854, 1718, 1579, 1496, 1454, 1373, 1264, 1216, 1132, 1108, 988

HRMS (EI+) Calcd. for $C_9H_{10}Cl_2N_4$: 244.0283 Found : 244.0282

***N*-(but-3-enyl)-2,6-dichloropyrimidin-4-amine (5-28)**



1.40g trichloropyrimidine (7.61mmol, 1.2 eq.) was dissolved by 6.5ml EtOH and 1.8ml TEA (12.6mmol, 2eq.) was added. Then 669mg butenylamine hydrochloride (6.22mmol, 1eq.) in 6ml EtOH was added drop by drop during 30min. After 4 hours the reaction was terminated. After work-up, flash chromatography on silica gel with AcOEt / DCM = 1/ 99 afforded **5-28** (913mg, 67%[248]) as colorless oil.

^{1}H-NMR (δ, ppm) (MeOD, 400 MHz) 6.53 (N*H*), 6.41 (s, 1H, *H*-aromatic), 5.88-5.76 (m, CH_2-C*H*=CH_2), 5.12-5.04 (m, 2H, CH_2-CH=CH_2), 3.45 (t, 2H, J=6.5Hz, NH-CH_2), 2.34-2.29 (m, CH_2-CH=CH_2)

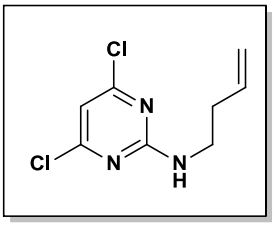
[248] The modest yield is due to the competing substitution at the 2-position (33%) of 2,4,6-trichloropyrimidine.

^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 165.9 (NH-*C*-N), 161.2 (NH-C-CH-*C*-Cl), 158.8 (NH-C-N-*C*-Cl), 136.5 (CH_2-*C*H=CH_2), 117.3 (CH_2-CH=*C*H_2), 103.6 (Cl-C-*C*H), 41.4 (NH-*C*H_2), 34.4 (*C*H_2-CH=CH_2)

IR (ν, cm^{-1}, $CDCl_3$) 3417, 2938, 1583, 1541, 1497, 1383, 1339, 1270, 1201, 1121, 995, 970

HRMS (EI+) Calcd. for $C_8H_9Cl_2N_3$: 217.0174 Found : 217.0165

***N*-(but-3-en-1-yl)-4,6-dichloropyrimidin-2-amine (5-28')**



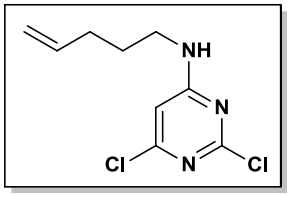
1.40g trichloropyrimidine (7.61mmol, 1.2 eq.) was dissolved by 6.5ml EtOH and 1.8ml TEA (12.6mmol, 2eq.) was added. Then 669mg butenylamine hydrochloride (6.22mmol, 1eq.) in 6ml EtOH was added drop by drop during 30min. After 4 hours the reaction was terminated. After work-up, flash chromatography on silica gel with AcOEt / DCM = 3 / 97 afforded **5-28'** (459mg, 33%) as white crystal.

m.p. : 65~68°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.59 (s, 1H, *H*-aromatic), 5.84-5.73 (m, CH_2-C*H*=CH_2), 5.40 (N*H*), 5.16-5.10 (m, 2H, CH_2-CH=C*H*$_2$), 3.52-3.48 (m, 2H, NH-C*H*$_2$), 2.38-2.29 (m, C*H*$_2$-CH=CH_2)

^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 161.6 (2 *C*-Cl), 134.8 (CH_2-*C*H=CH_2), 117.7 (CH_2-CH=*C*H_2), 109.0 (Cl-C-*C*H), 40.7 (NH-*C*H_2), 33.4 (*C*H_2-CH=CH_2)

2,6-dichloro-N-(pent-4-enyl)pyrimidin-4-amine (5-29)

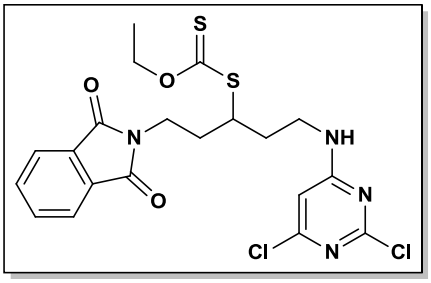


2.25g trichloropyrimidine (12.3mmol, 1.0 eq.) was dissolved by 62ml EtOH and 1.8ml TEA (13.2mmol, 1.1 eq.) was added. Then a solution of pentenylamine hydrochloride[249] (43ml, 0.30mol/ml, 12.9mmol, 1.1eq.) was added drop by drop during 30min. After 5 hours the reaction was terminated. After work-up, flash chromatography on silica gel with DCM / EP = 60 / 40 afforded **5-29** (1.73g, 61%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.26 (s, 1H, *H*-Ar), 5.84-5.72 (m, 1H, CH_2-C*H*=CH_2), 5.65 (br s, 1H, N*H*), 5.06 (d, 1H, J=16.9Hz, CH_2-CH=CH*H*), 5.03 (d, 1H, J=8.8Hz, CH_2-CH=C*H*H), 3.43 (br s, 1H, NH-CH*H*), 3.24 (br s, 1H, NH-C*H*H), 2.14 (dt, *J* = 6.9 Hz, 2H, C*H*$_2$-CH=CH_2), 1.72 (tt, *J* = 7.2 Hz, 2H, NH-CH_2-C*H*$_2$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 164.2 (*C*-Ar), 160.7 (*C*-Ar), 159.9 (*C*-Ar), 136.9 (CH_2-*C*H=CH_2), 116.0 (CH_2-CH=*C*H_2), 98.5 (*C*H-Ar), 41.2 (NH-*C*H_2), 30.8 (*C*H_2-CH=CH_2), 28.0 (NH-CH_2-*C*H_2)
IR (ν, cm^{-1}, CCl_4) 3424, 3263, 2935, 1575, 1495, 1438, 1361, 1269, 1194, 1121, 974, 919
HRMS (EI+) Calcd. for $C_9H_{11}Cl_2N_3$: 231.0330 Found : 231.0326

[249] Mark R. Crimmin, Anthony G. M. Barrett, *et al. J. Am. Chem. Soc.*, 2009, 131 (28), pp 9670–9685

S-1-(2,6-dichloropyrimidin-4-ylamino)-5-(1,3-dioxoisoindolin-2-yl)pentan-3-yl O-ethyl carbonodithioate (5-30)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-28** (95mg, 0.44mmol, 0.67 eq.) and the xanthate **Xa-c** (184mg, 0.66mmol, 1.0 eq.) in AcOEt (0.5ml, 1.3mmol/ml), with DLP (42mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-30** (128mg, 59%) as a colourless oil.

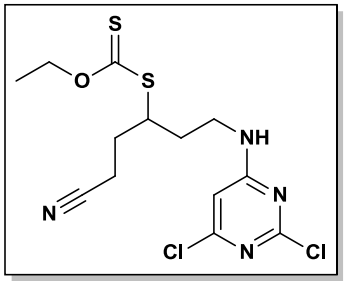
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.89-7.85 (m, 2H, *H*-phthalimide), 7.78-7.74 (m, 2H, *H*- phthalimide), 6.51-6.29 (br s, 1H, *H*-Ar), 5.84 (br s, 1H, N*H*), 4.58-4.43 (m, 2H, CH_2CH$_3$), 3.88-3.78 (m, 2H, CH_2- phthalimide), 3.67 (br s, 1H, C*H*), 3.60 (br s, H, CH*H*-NH), 3.41 (br s, H, C*H*H-NH), 2.37-2.13 (m, 2H, 2 CH-CH*H*), 2.06-1.95 (m, 1H, C*H*H-CH_2-phthalimide), 1.92-1.80 (m, 1H, C*H*H-CH_2NH), 1.33 (t, *J* = 7.1 Hz, 3H, CH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.3 (*C*S), 168.8 (2 *C*O-phth), 164.2 (*C*-Ar), 160.1 (*C*-Ar), 158.4 (*C*-Ar), 134.3 (2 *C*H-phth), 131.9 (2 *C*-phth), 123.4 (2 *C*H-phth), 103.0 (*C*H-Ar), 70.5 (CH_2CH_3), 45.5 (CH_2NH), 38.3 (*C*H), 35.3 (CH_2-phth), 35.0 (CH_2-CH_2phth), 31.6 (CH_2-CH_2NH), 13.7 (CH_2CH_3)

IR (ν, cm^{-1}, CCl_4) 3370, 2941, 1774, 1712, 1583, 1496, 1470, 1442, 1397, 1357, 1269, 1223, 1118, 1052, 1004, 970, 908

HRMS (EI+) Calcd. for $C_{17}H_{15}Cl_2N_4O_2$: 377.0572 Found : 377.0560

S-1-(2,6-dichloropyrimidin-4-ylamino)-5-cyanopentan-3-yl O-ethyl carbonodithioate (5-31)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-28** (116mg, 0.53mmol, 0.67 eq.) and the xanthate **Xa-a** (129mg, 0.80mmol, 1.0 eq.) in AcOEt (0.7ml, 1.1mmol/ml), with DLP (48mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-31** (161mg, 80%) as a light yellow oil.

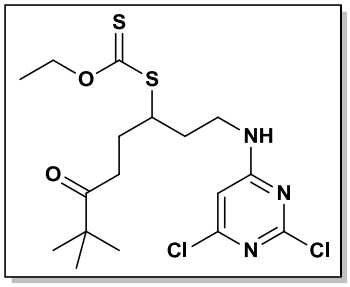
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.30 (s, 1H, *H*-Ar), 6.05-5.33 (br s, 1H, N*H*), 4.84-4.62 (m, 2H, CH_2CH$_3$), 4.06-3.90 (m, 1H, C*H*), 3.75 (br s, 1H, CH*H*NH), 3.47 (br s, 1H, C*H*HNH), 2.73-2.45 (m, 2H, CH_2CN), 2.34-1.86 (m, 4H, 2 CH_2), 1.44 (t, *J* = 7.1 Hz, 3H, CH$_2$CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.6 (*C*S), 164.0 (*C*-Ar), 160.1 (*C*-Ar), 158.2 (*C*-Ar), 118.8 (*C*N), 102.9 (*C*H-Ar), 71.1 (*C*H$_2$CH$_3$), 48.0 (*C*H), 38.6 (*C*H$_2$NH), 33.8 (*C*H$_2$), 30.7 (*C*H$_2$), 15.0 (*C*H$_2$CN), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 2928, 1581, 1544, 1497, 1441, 1365, 1271, 1225, 1122, 1054, 971

HRMS (EI+) Calcd. for $C_{13}H_{16}Cl_2N_4OS_2$: 378.0143 Found : 378.0125

S-1-(2,6-dichloropyrimidin-4-ylamino)-7,7-dimethyl-6-oxooctan-3-yl O-ethyl carbonodithioate (5-32)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-28** (111mg, 0.51mmol, 0.5 eq.) and the xanthate **Xa-d** (241mg, 1.09mmol, 1.0 eq.) in AcOEt (0.6ml, 1.8mmol/ml), with DLP (44mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-32** (197mg, 82%) as a light yellow oil.

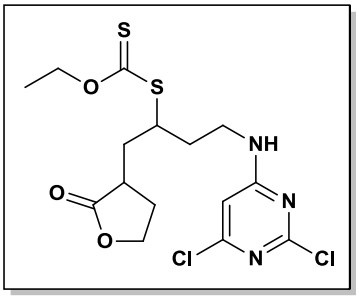
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.31 (s, 1H, *H*-Ar), 5.96 (br s, 1H, N*H*), 4.62 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.80-3.68 (m, 1H, C*H*), 3.63 (br s, 1H, NH-CH*H*), 3.42 (br s, 1H, NH-C*H*H), 2.83-2.67 (m, 1H, CO-CH*H*), 2.67-2.55 (m, 1H, CO-C*H*H), 2.22-2.05 (m, 1H, COCH$_2$-CH*H*), 2.03-1.93 (m, 1H, NHCH$_2$-C*H*$_2$), 1.84-1.66 (m, 1H, COCH$_2$-C*H*H), 1.40 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.13 (s, 9H, C(C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 215.8 (*C*O), 214.5 (*C*S), 164.1 (*C*-Ar), 160.1 (*C*-Ar), 158.7 (*C*-Ar), 102.9 (*C*H-Ar), 70.5 (*C*H$_2$CH$_3$), 48.7 (*C*H), 44.2 (*C*Me$_3$) 39.2 (NH-*C*H$_2$), 34.7 (NHCH$_2$-*C*H$_2$), 33.6 (CO-*C*H$_2$), 27.3 (COCH$_2$-*C*H$_2$), 26.5 (C(*C*H$_3$)$_3$), 13.7 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3366, 2969, 2872, 1741, 1707, 1591, 1499, 1477, 1442, 1368, 1273, 1219, 1121, 1053, 970, 908

HRMS (EI+) Calcd. for $C_{17}H_{25}Cl_2N_3O_2S_2$: 437.0765 Found : 437.0765

S-4-(2,6-dichloropyrimidin-4-ylamino)-1-(tetrahydro-2-oxofuran-3-yl)butan-2-yl O-ethyl carbonodithioate (5-33)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-28** (119mg, 0.55mmol, 0.5 eq.) and the xanthate **Xa-e** (225mg, 1.09mmol, 1.0 eq.) in AcOEt (0.6ml, 1.8mmol/ml), with DLP (44mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 35 / 65 afforded **5-33** (181mg, 74%) as a light yellow oil.

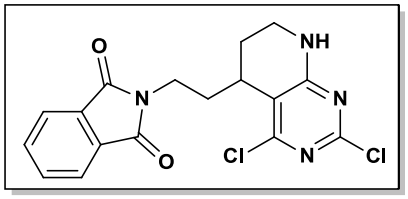
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.32 (s, 0.5H, *H*-Ar), 6.30 (s, 0.5H, *H*-Ar), 5.90 (br s, 0.5H, N*H*), 5.71 (br s, 0.5H, N*H*), 4.79-4.54 (m, 2H, C*H*$_2$CH$_3$), 4.43-4.32 (m, 1H, COO-CH*H*), 4.26-4.14 (m, 1H, COO-C*H*H), 4.12-4.01(m, 0.5H, Xa-C*H*), 3.98-3.85 (m, 0.5H, Xa-C*H*), 3.70-3.31 (m, 2H, C*H*$_2$NH), 2.92-2.65 (m, 1H, COC*H*), 2.53-2.39 (m, 1H, COOCH$_2$-CH*H*), 2.37-2.15 (m, 1H, XaCH-CH*H*), 2.14-1.90 (m, 3H, COOCH$_2$-C*H*H + NHCH$_2$-C*H*$_2$), 1.90-1.75 (m, 1H, XaCH-C*H*H), 1.44 and 1.41 (2 t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.01 (*C*S), 178.7 (*C*O), 164.1 (*C*-Ar), 160.1 (*C*-Ar), 158.9 (*C*-Ar), 102.9 (*C*H-Ar), 71.0 and 70.6 (*C*H$_2$CH$_3$), 66.6 (COO*C*H$_2$), 47.6 and 47.1 (Xa-*C*H), 38.6 (*C*H$_2$NH), 37.5 and 37.4 (CO*C*H), 35.1 and 34.8 (COCH-*C*H$_2$), 33.8 (*C*H$_2$-CH$_2$NH), 29.5 and 29.4 (COOCH$_2$-*C*H$_2$), 13.8 and 13.7 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3372, 2926, 1782, 1582, 1558, 1498, 1441, 1374, 1265, 1217, 1149, 1121, 1048, 1030

HRMS (EI+) Calcd. for $C_{12}H_{14}Cl_2N_3O_2$: 302.0463 Found : 302.0468

2-(2-(2,4-dichloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)ethyl)isoindoline-1,3-dione (5-34)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-30** (120mg, 0.24mmol, 1.0 eq.) in AcOEt (5.0ml, 0.05mmol/ml), with DLP (114mg, 1.2 eq.). Flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **5-34** (40mg, 44%) as a white powder.

m.p. : 183-187°C

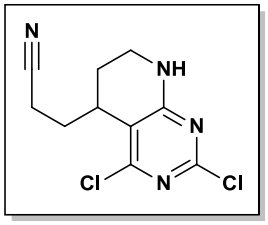
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.91-7.80 (m, 2H, *H*-phth), 7.78-7.71 (m, 2H, *H*-phthalimide), 6.30 (s, 1H, N*H*), 3.91-3.74 (m, 2H, NH-CH_2), 3.60-3.44 (m, 2H, CH_2-N phthalimide), 3.07 (dd, *J* = 5.8, 4.5 Hz, 1H, C*H*), 2.29 (br s, 0.5H, phthalimideNCH_2-CH*H*), 2.26 (br s, 0.5H, phthalimideNCH_2-CH*H*), 2.12-2.01 (m, 1H, NHCH_2-CH*H*), 1.86-1.76 (m, 1H, phthalimideNCH_2-C*H*H), 1.75-1.63 (m, 1H, NHCH_2-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.3 (*C*O), 161.3 (*C*-Ar), 157.2 (*C*-Ar), 157.1 (*C*-Ar), 134.2 (*C*H-phthalimide), 131.9 (*C*-phthalimide), 123.4 (*C*H-phthalimide), 111.6 (*C*-Ar), 36.7 (*C*H_2-Nphthalimide), 35.1 (NH-*C*H_2), 31.2 (NHCH_2-*C*H_2), 29.5 (*C*H), 22.2 (*C*H_2-CH_2N phthalimide)

IR (ν, cm^{-1}, CCl_4) 3439, 3247, 2944, 1775, 1718, 1602, 1578, 1550, 1395, 1377, 1339, 1279, 1226, 1160, 908

HRMS (EI+) Calcd. for $C_{17}H_{14}Cl_2N_4O_2$: 376.0494 Found : 376.0488

3-(2,4-dichloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)propanenitrile (5-35)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-31** (71mg, 0.19mmol, 1.0 eq.) in AcOEt (5.2ml, 0.04mmol/ml), with DLP (103mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **5-35** (34mg, 71%) as a white solid.

m.p. : 177-181°C

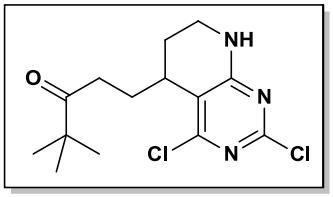
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.27 (s, 1H, N*H*), 3.60-3.53 (m, 1H, C*H*H-NH), 3.43 (dt, 1H, J=3.7Hz, J=13.1Hz, CH*H*-NH), 3.25-3.22 (m, 1H, C*H*), 2.57-2.44 (m, 2H, CH_2-CN), 2.08-1.97 (m, 2H, C*H*H-CH_2-NH + C*H*H-CH_2-CN), 1.91-1.82 (m, 1H, CH*H*-CH_2-NH), 1.82-1.72 (m, 1H, CH*H*-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.3 (*C*-Ar), 157.5 (*C*-Ar), 157.3 (*C*-Ar), 118.7 (*C*N), 110.6 (*C*-Ar), 36.6 (*C*H_2-NH), 31.2 (*C*H), 28.4 (*C*H_2-CH_2CN), 22.5 (*C*H_2-CH_2NH), 15.0 (*C*H_2-CN)

IR (ν, cm^{-1}, Nujol) 3261, 1595, 1551, 1375, 1341, 1287, 1220, 1201, 1113, 1054, 863, 781

HRMS (EI+) Calcd. for $C_{10}H_{10}Cl_2N_4$: 256.0283 Found : 256.0284

1-(2,4-dichloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)-4,4-dimethylpentan-3-one (5-36)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-32** (106mg, 0.24mmol, 1.0 eq.) in AcOEt (4.8ml, 0.05mmol/ml), with DLP (116mg, 1.2 eq.). Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded **5-36** (41mg, 54%) as a white solid.

In comparative study, the reaction was carried out with the solution of **5-32** (42mg, 0.10mmol, 1.0 eq.) in DMC (1.9ml, 0.05mmol/ml), with DLP (46mg, 1.2 eq.). Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded **5-36** (17mg, 55%) as a white solid.

m.p. : 180-184°C

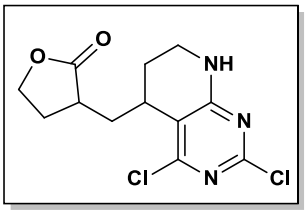
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.84 (br s, 1H, N*H*), 3.53-3.50 (m, 2H, NHCH_2), 3.11-3.06 (m, 1H, C*H*), 2.63 (t, *J* = 7.5 Hz, 2H, COCH_2), 1.94 (br s, 0.4H, $NHCH_2CHH$), 1.91 (br s, 0.6H, $NHCH_2CHH$), 1.86-1.65 (m, 3H, $NHCH_2CH$*H* + $COCH_2CH_2$), 1.15 (s, 9H, $(CH_3)_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 215.1 (*C*O), 161.4 (*C*-Ar), 157.0 (*C*-Ar), 156.8 (*C*-Ar), 112.1 (*C*-Ar), 44.2 (CMe_3), 36.8 (NH-CH_2), 33.9 (CO-CH_2), 31.5 (*C*H), 27.2 (CH_2-CH_2CO), 26.5 (3(CH_3)), 23.2 (CH_2-CH_2NH)

IR (ν, cm^{-1}, CCl_4) 3438, 3248, 3108, 2968, 2870, 1708, 1603, 1579, 1477, 1403, 1376, 1338, 1284, 1223, 1193, 1158, 1118, 1052, 997, 918

HRMS (EI+) Calcd. for $C_{14}H_{19}Cl_2N_3O$: 315.0905 Found : 315.0905

3-((2,4-dichloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)methyl)-dihydrofuran-2(3H)-one (5-37)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-33** (110mg, 0.26mmol, 1.0 eq.) in AcOEt (5.2ml, 0.05mmol/ml), with DLP (104mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded **5-37** (46mg, 59%) as a white solid.

m.p. : 195-198°C

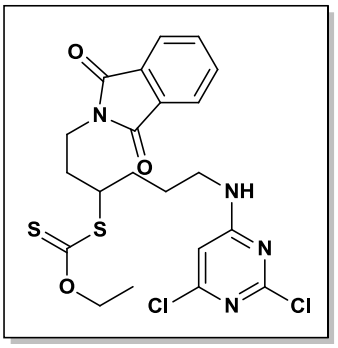
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.81 (s, 0.6H, N*H*), 6.71 (s, 0.4H, N*H*), 4.46-4.37 (m, 1H, COOCH*H*), 4.32-4.19 (m, 1H, COOC*H*H), 3.65-3.36 (m, 2.6H, NHCH_2 + C*H*-CAr), 3.22-3.07 (m, 0.4H, C*H*-CAr), 2.75-2.47 (m, 2H, COC*H* + $COOCH_2CH$*H*), 2.22-1.93 (m, 3H, $COOCH_2C$*H*H + $NHCH_2C$*H*H + COCHC*H*H), 1.92-1.73 (m, 1H, $NHCH_2CH$*H*), 1.63 (m, 1H, COCHCH*H*)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 178.7 (*C*O), 178.5 (*C*O), 161.5 (*C*-Ar), 161.4 (*C*-Ar), 157.2 (2 *C*-Ar), 157.1 (*C*-Ar), 157.0 (*C*-Ar), 111.4 (*C*-Ar), 111.2 (*C*-Ar), 66.5 ($COOCH_2$), 66.4 ($COOCH_2$), 37.0 (COCH), 36.9 (COCH), 36.7 (CH_2-NH), 36.6 (CH_2-NH), 34.1 ($COCHCH_2$), 33.5 ($COCHCH_2$), 30.5 (CH-CAr), 29.6 (CH-CAr), 29.4 ($COOCH_2CH_2$), 28.9 ($COOCH_2CH_2$), 23.8 (CH_2-CH_2NH), 21.9 (CH_2-CH_2NH)

IR (ν, cm^{-1}, CCl_4) 3427, 3249, 2947, 1769, 1583, 1546, 1382, 1338, 1277, 1225, 1192, 1160, 1027

HRMS (EI+) Calcd. for $C_{12}H_{13}Cl_2N_3O_2$: 301.0385 Found : 301.0370

S-6-(2,6-dichloropyrimidin-4-ylamino)-1-(1,3-dioxoisoindolin-2-yl)hexan-3-yl O-ethyl carbonodithioate (5-38)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-29** (254mg, 1.10mmol, 0.7 eq.) and the xanthate **Xa-c** (421mg, 1.50mmol, 1.0 eq.) in AcOEt (1.1ml, 1.4mmol/ml), with DLP (132mg, 0.30 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-38** (317mg, 56%) as a colourless oil[250].

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.93-7.80 (m, 2H, 2 *H*-phthalimide), 7.77-7.69 (m, 2H, 2 *H*-phthlimide), 6.34 (br s, 1H, *H*-Ar), 5.94 (br s, 1H, N*H*), 4.55 (q, *J* = 7.1 Hz, 1H, O*CH*$_2$CH$_3$), 3.91-3.73 (m, 2H, C*H*$_2$-phthalimide), 3.68 (br s, 1H, C*H*), 3.59-3.18 (br s, 2H, C*H*$_2$-NH), 2.34-2.10 (m, 1H, CH*H*-CH$_2$phthalimide), 2.08-1.93 (m, 2H, CH-CH*H* + C*H*H-CH$_2$phthalimide), 1.91-1.79 (m, 1H, CH*H*-CH$_2$NH), 1.77-1.61 (m, 2H, CH-C*H*H + C*H*H-CH$_2$NH), 1.34 (t, *J* = 7.1Hz, 3H, OCH$_2$C*H*$_3$)

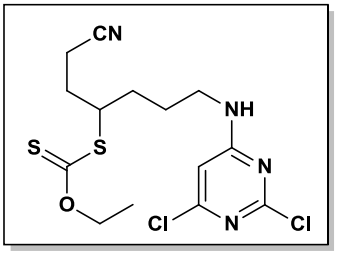
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.9 (*C*=S), 168.6 (2 *C*O-phthalimide), 164.2 (*C*-Ar), 160.0 (*C*-Ar), 158.6 (*C*-Ar), 134.1 (2 *C*H-phthalimide), 132.0 (2 *C*-phthalimide), 123.3 (2 *C*H-phthalimide), 100.7 (*C*H-Ar), 70.1 (O*C*H$_2$CH$_3$), 47.7 (*C*H), 40.4 (*C*H$_2$NH), 35.4 (*C*H$_2$-Nphthalimide), 34.5 (*C*H$_2$-CH$_2$-Nphthalimide), 29.3 (CH-*C*H$_2$), 25.7 (*C*H$_2$-CH$_2$NH), 13.7 (OCH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3386, 2941, 1773, 1709, 1581, 1499, 1437, 1397, 1358, 1274, 1222, 1113, 1052

HRMS (EI+) Calcd. for $C_{18}H_{17}Cl_2N_4O_2$: 391.0729 Found : 391.0737

[250] Similar side-product from intermolecular addition was also observed, as in the case **5-24**.

S-6-(2,6-dichloropyrimidin-4-ylamino)-1-cyanohexan-3-yl O-ethyl carbonodithioate (5-39)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-29** (105mg, 0.45mmol, 0.5 eq.) and the xanthate **Xa-a** (146mg, 0.90mmol, 1.0 eq.) in AcOEt (0.45ml, 2.0mmol/ml), with DLP (72mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-39** (153mg, 86%) as a light yellow oil.

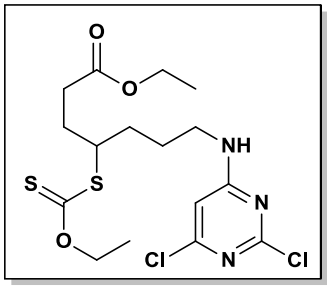
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.27 (s, 1H, *H*-Ar), 5.76 (br s, 0.5H, N*H*), 5.35 (br s, 0.5H, N*H*), 4.66 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.01-3.72 (m, 1H, C*H*), 3.40 (br s, 2H, C*H*$_2$-NH), 2.53 (t, *J* = 7.4 Hz, 2H, C*H*$_2$-CN), 2.17-2.07 (m, 1H, CH*H*-CH$_2$CN), 2.04-1.94 (m, 1H, C*H*H-CH$_2$CN), 1.89-1.68 (m, 4H, CH-C*H*$_2$ + C*H*$_2$-CH$_2$NH), 1.44 (t, *J* = 7.1Hz, 3H, OCH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.9 (*C*=S), 164.2 (*C*-Ar), 160.0 (*C*-Ar), 158.7 (*C*-Ar), 119.1 (*C*N), 102.5 (*C*H-Ar), 70.6 (O*C*H$_2$CH$_3$), 49.7 (*C*H), 41.1 (*C*H$_2$NH), 31.3 (*C*H$_2$), 30.6 (*C*H$_2$-CH$_2$CN), 26.2 (*C*H$_2$), 15.0 (*C*H$_2$-CN), 13.7 (OCH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3423, 2926, 2856, 1579, 1495, 1443, 1270, 1225, 1121, 1050, 970

HRMS (EI+) Calcd. for $C_{11}H_{13}Cl_2N_4$: 271.0517 Found : 271.0519

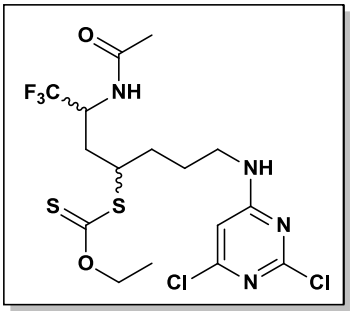
S-1-(ethoxycarbonyl)-6-(2,6-dichloropyrimidin-4-ylamino)hexan-3-yl O-ethyl carbonodithioate (5-40)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-29** (193mg, 0.66mmol, 1.0 eq.) and the xanthate **Xa-h** (160mg, 0.66mmol, 1.0 eq.) in AcOEt (0.66ml, 1.0mmol/ml), with DLP (66mg, 0.25 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-40** (235mg, 81%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.28 (s, 1H, *H*-Ar), 5.52 (br s, 1H, N*H*), 4.64 (q, *J* = 7.1 Hz, 2H, CSOC*H*$_2$CH$_3$), 4.14 (q, *J* = 7.1 Hz, 2H, COOC*H*$_2$CH$_3$), 3.85-3.77 (m, 1H, C*H*), 3.47 and 3.29 (2 br s,, 2H, C*H*$_2$NH), 2.47 (t, *J* = 7.4 Hz, 2H, C*H*$_2$COOEt), 2.14-2.04 (m, 1H, CH*H*-CH$_2$COOEt), 1.94-1.82 (m, 1H, C*H*H-CH$_2$COOEt), 1.83-1.72 (m, 4H, CHC*H*$_2$ + C*H*$_2$CH$_2$NH), 1.42 (t, *J* = 7.1 Hz, 3H, CSOCH$_2$C*H*$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, COOCH$_2$C*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.2 (*C*S), 173.0 (*C*OOEt), 164.2 (*C*-Ar), 159.8 (*C*-Ar), 159.2 (*C*-Ar), 100.7 (*C*H-Ar), 70.3 (CSO*C*H$_2$CH$_3$), 60.7 (COO*C*H$_2$CH$_3$), 50.2 (*C*H), 41.2 (*C*H$_2$NH), 31.8 (CH*C*H$_2$), 31.5 (*C*H$_2$COOEt), 29.3 (*C*H$_2$-CH$_2$COOEt), 26.0 (*C*H$_2$CH$_2$NH), 14.2 (COOCH$_2$*C*H$_3$), 13.8 (CSOCH$_2$*C*H$_3$)
IR (ν, cm^{-1}, CCl_4) 3372, 2981, 2938, 1736, 1580, 1497, 1444, 1374, 1343, 1268, 1222, 1120, 1051, 969
HRMS (EI+) Calcd. for $C_{13}H_{18}Cl_2N_3O_2$: 318.0776 Found : 318.0800

S-7-(2,6-dichloropyrimidin-4-ylamino)-2-acetamido-1,1,1-trifluoroheptan-4-yl O-ethyl carbonodithioate (5-41)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-29** (135mg, 0.58mmol, 0.67 eq.) and the xanthate **Xa-j** (240mg, 0.87mmol, 1.0 eq.) in AcOEt (0.60ml, 1.5mmol/ml), with DLP (87mg, 0.25 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-41a** (117mg, 40%) as a colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.65-6.18 (s + br s, 2H, *H*-Ar + N*H*), 5.84 (br s, 1H, N*H*Ac), 4.81-4.72 (m, 1H, C*H*-CF_3), 4.65 (q, *J* = 7.1 Hz, 2H, CSOC*H*$_2$CH$_3$), 3.73 (br s, 1H, CH*H*NH), 3.64-3.54 (m, 1H, C*H*S), 3.06 (br s, 1H, C*H*HNH), 2.20 (s, 3H, C*H*$_3$), 2.15-1.97 (m, 3H, C*H*$_2$-CH_2NH + C*H*H-CH), 1.97-1.82 (m, 1H, C*H*H-CH), 1.74-1.51 (m, 2H, 2 CH*H*-CH), 1.44 (t, *J* = 7.1 Hz, 3H, $CSOCH_2CH_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.2 (*C*S), 171.8 (*C*O), 164.2 (*C*-Ar), 159.8 (*C*-Ar), 158.0 (*C*-Ar), 124.5 (q, *J* = 281 Hz, *C*F_3), 103.0 (Ar-*C*-H), 70.4 (*C*H_2CH_3), 48.4 (q, *J* = 31 Hz, *C*H-CF_3), 45.6 (*C*HS), 39.0 (*C*H_2NH), 35.0 (*C*H_2-$CHCF_3$), 27.4 (C*H*$_2$-CHS), 25.2 (*C*H_2-CH_2NH), 23.0 (*C*H_3), 13.6 (CH_2*C*H_3)

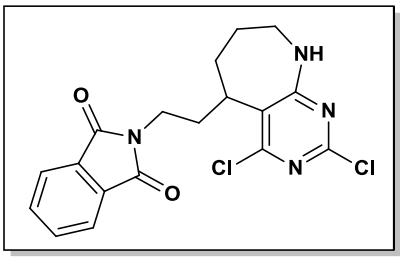
IR (ν, cm^{-1}, CCl_4) 3350, 2928, 1709, 1683, 1583, 1518, 1439, 1371, 1344, 1276, 1223, 1192, 1140, 1119, 1052, 987

HRMS (EI+) Calcd. for $C_{13}H_{16}Cl_2F_3N_4O$: 371.0653 Found : 371.0648

Flash chromatography on silica gel with AcOEt / EP = 40 / 60 **5-41b** (132mg, 48%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.31 (s, 1H, *H*-Ar), 5.93 (br s, 1H, N*H*Ac), 5.76 (br s, 1H, N*H*), 4.91-4.79 (m, 1H, C*H*-CF_3), 4.63 (q, *J* = 7.1 Hz, 2H, CSOC*H*$_2$CH$_3$), 4.05-3.85 (m, 1H, C*H*), 3.59 and 3.35 (2 br s, 2H, C*H*$_2$NH), 2.26-1.87 (m + s, 5H, C*H*$_2$-$CHCF_3$ + C*H*$_3$), 1.85-1.68 (m, 4H, C*H*$_2$-CH_2NH + C*H*$_2$-CHS), 1.41 (t, *J* = 7.1 Hz, 3H, $CSOCH_2CH_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.5 (*C*S), 169.9 (*C*O), 164.1 (*C*-Ar), 159.9 (*C*-Ar), 156.0 (*C*-Ar), 124.9 (q, *J* = 282 Hz, *C*F_3), 100.6 (Ar-*C*H), 70.7 (*C*H_2CH_3), 48.5 (q, *J* = 31 Hz, *C*H-CF_3), 46.9 (*C*H), 40.9 (*C*H_2NH), 32.5 (*C*H_2-$CHCF_3$), 31.7 (*C*H_2-CH_2NH), 25.9 (C*H*$_2$-CHS), 23.3 (*C*H_3), 13.8 (CH_2CH_3)
IR (ν, cm^{-1}, CCl_4) 2926, 1705, 1587, 1511, 1370, 1263, 1232, 1191, 1133, 1050, 980
HRMS (EI+) Calcd. for $C_{13}H_{16}Cl_2F_3N_4O$: 371.0653 Found : 371.0646

2-(2-(2,4-dichloro-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)ethyl)isoindoline-1,3-dione (5-42)

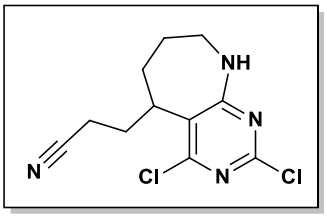


Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-38** (288mg, 0.56mmol, 1.0 eq.) in AcOEt (11ml, 0.05mmol/ml), with DLP (447mg, 2.0 eq.). Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 afforded **5-42** (95mg, 44%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.90-7.79 (m, 2H, 2 *H*-phthalimide), 7.76-7.70 (m, 2H, 2 *H*-phthalimide), 5.59 (br s, 1H, N*H*), 3.88-3.65 (m, 2H, C*H*$_2$-Nphthalimide), 3.54-3.45 (m, 1H, NHC*H*H), 3.44-3.36 (m, 1H, C*H*), 3.26-3.15 (m, 1H, NHCH*H*), 2.26-2.06 (m, 2H, 2 CH-CH*H*), 2.00-1.79 (m, 4H, $NHCH_2CH_2$ + 2 CH-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.2 (2 *C*O-phthalimide), 167.6 (*C*-Ar), 161.1 (*C*-Ar), 156.0 (*C*-Ar), 134.1 (2 *C*H-phthalimide), 132.0 (2 *C*-phthalimide), 123.3 (2 *C*H-phthalimide), 117.5 (Ar-*C*-CH), 44.6 (NH-*C*H_2), 35.8 (*C*H_2-Nphthalimide), 34.6 (*C*H), 31.3 (*C*H_2-CH_2-Nphthalimide), 26.0 (CH-*C*H_2), 22.8 (NHCH_2-*C*H_2)
IR (ν, cm^{-1}, CCl_4) 3642, 3352, 2940, 2832, 1774, 1717, 1563, 1446, 1395, 1342, 1216, 1024
HRMS (EI+) Calcd. for $C_{18}H_{16}Cl_2N_4O_2$: 390.0650 Found : 390.0649

3-(2,4-dichloro-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)propanenitrile (5-43)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-39** (57mg, 0.14mmol, 1.0 eq.) in AcOEt (2.9ml, 0.05mmol/ml), with DLP (58mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-43** (18mg, 45%) as a white crystal.

In comparative study, the reaction was carried out with the solution of **5-39** (56mg, 0.14mmol, 1.0 eq.) in PhCl (2.9ml, 0.05mmol/ml), with DTBP (0.26ml, 10.0eq.) which was added in two times and the reaction took 7 hours. Seperation using preparative TLC plate with AcOEt / EP = 20 / 80 afforded **5-43** (7.3mg, 19%) as a white crystal.

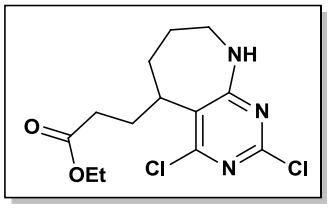
m.p. : 125-128°C
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.62 (br s, 1H, N*H*), 3.61-3.53 (m, 1H, C*H*), 3.53-3.46 (m, 1H, NHCH*H*), 3.24-3.04 (m, 1H, NHC*H*H), 2.47-2.24 (m, 2H, CH_2CN), 2.19-1.98 (m, 2H, 2 CH-C*H*H), 1.96-1.77 (m, 4H, 2 CH-CH*H* + $NHCH_2CH_2$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 167.6 (Ar-*C*), 161.4 (Ar-*C*), 156.3 (Ar-*C*), 118.8 (*C*N), 116.5 (Ar-*C*-CH), 45.0 (NH-*C*H_2), 36.3 (*C*H), 28.2 (CH-*C*H_2), 27.0 (CH-*C*H_2), 22.8 (NHCH_2-*C*H_2), 15.5 (*C*H_2CN)

IR (ν, cm^{-1}, CCl_4) 3418, 3384, 3267, 2929, 2856, 1821, 1546, 1456, 1386, 1345, 1302, 1219, 1142, 997

HRMS (EI+) Calcd. for $C_{11}H_{12}Cl_2N_4$: 270.0439 Found : 270.0446

ethyl 3-(2,4-dichloro-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)propanoate (5-44)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-40** (235mg, 0.54mmol, 1.0 eq.) in AcOEt (11ml, 0.05mmol/ml), with DLP (264mg, 1.2 eq.). Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 afforded **5-44** (92mg, 54%) as a light yellow oil.

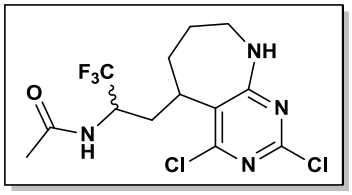
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.55 (br s, 1H, N*H*), 4.12 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.69-3.26 (m, 2H, NHC*H*H + C*H*), 3.26-3.01 (m, 1H, NHCH*H*), 2.46-2.17 (m, 2H, C*H*$_2$COOEt), 2.14-1.97 (m, 2H, 2 CH*H*-CH), 1.94-1.71 (m, 4H, 2 C*H*H-CH + NHCH$_2$C*H*$_2$), 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.9 (*C*O), 167.6 (Ar-*C*), 161.3 (Ar-*C*), 156.0 (Ar-*C*), 117.8 (Ar-*C*-CH), 60.6 (O*C*H$_2$CH$_3$), 45.3 (NH-*C*H_2), 36.6 (*C*H), 32.3 (*C*H$_2$COOEt), 27.6 (2 CH-*C*H_2), 22.9 (NHCH_2-*C*H_2), 14.2 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3419, 3386, 2936, 2857, 1736, 1576, 1456, 1385, 1376, 1344, 1308, 1264, 1217, 1159, 1136, 1023, 996

HRMS (EI+) Calcd. for $C_{13}H_{17}Cl_2N_3O_2$: 317.0698 Found : 317.0695

N-(3-(2,4-dichloro-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)-1,1,1-trifluoro-propan-2-yl)acetamide (5-45)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-41b** (128mg, 0.25mmol, 1.0 eq.) in AcOEt (5ml, 0.05mmol/ml), with DLP (100mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-45a** (26mg, 27%) as a white crystal.

m.p. : 222~226°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.71 (br s, N*H*, 1H), 5.59 (d, *J* = 10.1 Hz, 1H, N*H*-Ac), 4.95-4.72 (m, 1H, C*H*-CF_3), 3.54-3.44 (m, 1H, CH*H*NH), 3.48-3.39 (m, 1H, C*H*-C-Ar), 3.28-3.19 (m, 1H, C*H*HNH), 2.28-2.08 (m + s, 5H, 2 CH-CH*H* + C*H*$_3$), 2.06-1.93 (m, 1H, CH*H*-CH_2NH), 1.82-1.66 (m, 3H, C*H*H-CH_2NH + 2 CH-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 170.3 (*C*=O), 167.8 (Ar-*C*), 160.7 (Ar-*C*), 156.3 (Ar-*C*), 124.9 (q, *J* = 281 Hz, *C*F_3), 116.9 (Ar-*C*-CH), 48.0 (q, *J* = 31Hz, *C*H-CF_3), 44.5 (NH-*C*H_2), 32.6 (*C*H), 30.8 (CH-*C*H_2), 24.8 (CH-*C*H_2), 23.1 (*C*H_3), 22.4 (*C*H_2-CH_2NH)

IR (ν, cm^{-1}, CCl_4) 3259, 2928, 2855, 1708, 1662, 1570, 1458, 1343, 1306, 1273, 1222, 1129, 995

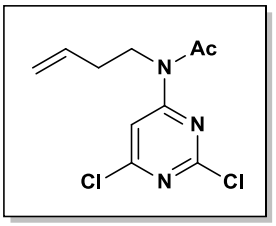
HRMS (EI+) Calcd. for $C_{13}H_{15}Cl_2F_3N_4O$: 370.0575 Found : 370.0589

Flash chromatography on silica gel with AcOEt / EP = 70 / 30 afforded **5-45b** (15mg, 16%) as a white solid.

m.p. : 204-208°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.58 (d, *J* = 9.6 Hz, 1H, N*H*-Ac), 5.51 (br s, N*H*, 1H), 4.59-4.47 (m, 1H, C*H*-CF_3), 3.74-3.57 (m, 1H, C*H*-C-Ar), 3.55-3.41 (m, 1H, CH*H*NH), 3.19-3.10 (m, 1H, C*H*HNH), 2.32-2.23 (m, 1H, CF_3CH-CH*H*), 2.13-1.99 (m + s, 4H, CH-C*H*H + CH_3), 1.97-1.80 (m, 3H, CH_2-CH_2NH + CH-CH*H*), 1.80-1.70 (m, 1H, CF_3CH-C*H*H)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.5 (*C*=O), 167.6 (Ar-*C*), 161.3 (Ar-*C*), 156.4 (Ar-*C*), 125.1 (q, *J* = 282 Hz, *C*F_3), 116.74 (Ar-*C*-CH), 48.8 (q, *J* = 30Hz, *C*H-CF_3), 45.2 (NH-*C*H_2), 33.9 (*C*H), 31.4 (CF_3CH-*C*H_2), 27.3 (CH-*C*H_2), 23.2 (*C*H_3), 23.0 (*C*H_2-CH_2NH)
IR (ν, cm^{-1}, CCl_4) 2926, 2854, 1704, 1575, 1506, 1458, 1373, 1264, 1217, 1191, 1134
HRMS (EI+) Calcd. for $C_{13}H_{15}Cl_2F_3N_4O$: 370.0575 Found : 370.0584

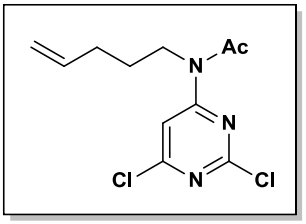
***N*-(but-3-en-1-yl)-*N*-(2,6-dichloropyrimidin-4-yl)acetamide (5-46)**



344mg *N*-(but-3-en-1-yl)-2,6-dichloropyrimidin-4-amine (1.58mmol, 1.0eq.) was dissolved by 5.0ml acetyl chloride (0.3mmol/ml), and the mixture was refluxing for 110 hours. After work-up, flash chromatography on silica gel with DCM / EP = 80 / 20 afforded **5-46** (384mg, 94%) as colorless oil.

^{1}H-NMR (δ, ppm) (MeOD, 400 MHz) 7.97 (s, 1H, *H*-aromatic), 5.80 (tdd, 1H, *J* = 17.2, 10.2, 7.0Hz, CH_2-C*H*=CH_2), 5.19-5.04 (m, 2H, CH_2-CH=C*H*$_2$), 4.13-3.98 (m, 2H, NAc-C*H*$_2$), 2.51-2.36 (m + s, 5H, C*H*$_2$-CH=CH_2 + C*H*$_3$)
^{13}C-NMR (δ, ppm) (MeOD, 100.6 MHz) 172.0 (*C*O), 162.5 (NAc-*C*-N), 161.9 (NH-C-CH-*C*-Cl), 159.1 (NH-C-N-*C*-Cl), 133.7 (CH_2-*C*H=CH_2), 118.0 (CH_2-CH=*C*H_2), 111.7 (Cl-C-*C*H), 46.4 (NAc-*C*H_2), 32.9 (*C*H_2-CH=CH_2), 25.3 (*C*H_3)

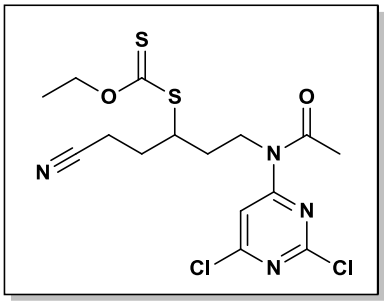
N-(2,6-dichloropyrimidin-4-yl)-N-(pent-4-en-1-yl)acetamide (5-47)



400mg **5-29** (1.58mmol, 1.0eq.) was dissolved by 5.7ml acetyl chloride (0.3mmol/ml), and the mixture was refluxing for 120 hours. After work-up, flash chromatography on silica gel with DCM afforded **5-47** (340mg, 72%) as colorless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.98 (s, 1H, *H*-aromatic), 5.82 (tdd, 1H, *J* = 16.9, 10.2, 6.6 Hz, CH_2-C*H*=CH_2), 5.07 (qdd, 2H, *J* = 13.0, 10.2, 1.4 Hz, CH_2-CH=C*H*$_2$), 3.98-3.94 (m, 2H, NAc-C*H*$_2$), 2.41 (s, 3H, C*H*$_3$), 2.14 (q, 2H, *J* = 7.1 Hz, C*H*$_2$-CH=CH_2), 1.77 (td, 2H, *J* = 15.2, 7.4 Hz, NAc-CH_2-C*H*$_2$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.1 (*C*O), 162.5 (NAc-*C*-N), 161.9 (NH-C-CH-*C*-Cl), 159.1 (NH-C-N-*C*-Cl), 136.8 (CH_2-*C*H=CH_2), 115.9 (CH_2-CH=*C*H_2), 111.5 (Cl-C-*C*H), 46.6 (NAc-*C*H_2), 30.8 (*C*H_2-CH=CH_2), 27.5 (NAc-CH_2-*C*H_2), 25.2 (*C*H_3)

***S*-(1-cyano-5-(*N*-(2,6-dichloropyrimidin-4-yl)acetamido)pentan-3-yl) *O*-ethyl carbonodithioate (5-48)**



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-46** (161mg, 0.62mmol, 1.0 eq.) and the xanthate of acetonitrile **Xa-a** (152mg, 0.93mmol, 1.5 eq.) in AcOEt (0.62ml, 1.0mmol/ml), with DLP (56mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-48** (219mg, 84%) as a light yellow oil, along with the bicycle compound **5-50** (12mg, 6%) as white solid.

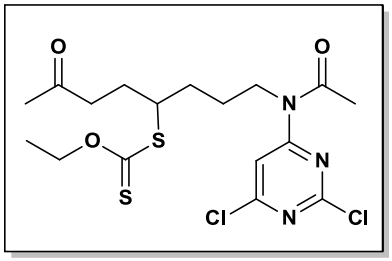
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.97 (s, 1H, *H*-aromatic), 4.67 (q, 2H, J=7.1Hz, C*H*$_2$CH$_3$), 4.11 (t, 2H, *J* = 7.8 Hz, C*H*$_2$-NAc), 3.85 (ddd, 1H, *J* = 13.5, 8.1, 5.6Hz, Xa-C*H*), 2.68-2.51 (m, 2H, C*H*$_2$-CN), 2.43 (s, 3H, COC*H*$_3$), 2.25-2.06 (m, 4H, C*H*$_2$-CH$_2$-CN + C*H*$_2$-CH$_2$-NAc), 1.45 (t, 3H, *J* = 7.1 Hz, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.3 (*C*=S) , 171.8 (*C*O), 162.8 (NAc-*C*-N), 161.7 (NAc-C-CH-*C*-Cl), 159.2 (NAc-C-N-*C*-Cl) 118.7 (*C*N), 111.6 (Cl-C-*C*H), 70.8 (*C*H$_2$CH$_3$), 47.6 (*C*H-Xa), 44.8 (NAc-*C*H$_2$), 32.8 (*C*H$_2$-CH$_2$-NAc), 29.9 (C*H*$_2$-CH$_2$-CN), 25.1 (*C*H$_3$), 15.1 (C*H*$_2$-CN), 13.8 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, CCl_4) 3691, 3155, 2986, 2254, 1817, 1794, 1699, 1602, 1556, 1525, 1470, 1409, 1383, 1331, 1248, 1219, 1140, 1097, 1051

HRMS (EI+) Calcd. for $C_{15}H_{18}Cl_2N_4O_2S_2$: 420.0248 Found : 420.0254

S-(1-(N-(2,6-dichloropyrimidin-4-yl)acetamido)-7-oxooctan-4-yl) O-ethyl carbonodithioate (5-49)



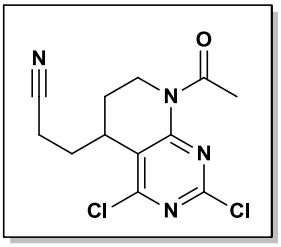
Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-47** (92mg,

0.33mmol, 1.0eq.) and the xanthate **Xa-i** (119mg, 0.67mmol, 2.0eq.) in AcOEt (0.33ml, 2.0mmol/ml), with DLP (28mg, 0.1eq.). Flash chromatography on silica gel with AcOEt / DCM = 10 / 90 afforded **5-49** (133mg, 82%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.97 (s, 1H, *H*-aromatic), 4.64 (dq, 2H, J=7.1, 1.1 Hz, C*H*$_2$CH$_3$), 4.19-3.85 (m, 2H, C*H*$_2$-NAc), 3.83-3.70 (m, 1H, Xa-C*H*), 2.78-2.53 (m, 2H, C*H*$_2$-COMe), 2.42 (s, 3H, NCOC*H*$_3$), 2.14 (s, 3H, COC*H*$_3$), 2.13-2.05 (m, 1H, C*H*H-CH$_2$-COMe), 1.87-1.72 (m, 5H, CH*H*-CH$_2$-COMe + C*H*$_2$-CH$_2$-NAc + C*H*$_2$-CH$_2$-CH$_2$-NAc), 1.42 (t, 3H, *J* = 7.1 Hz, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.3 (*C*=S), 207.5 (CH$_2$*C*O), 172.0 (N*C*O), 162.6 (NAc-*C*-N), 161.9 (NAc-C-CH-*C*-Cl), 159.1 (NAc-C-N-*C*-Cl), 111.6 (Cl-C-*C*H), 70.2 (*C*H$_2$CH$_3$), 50.5 (*C*H-Xa), 46.7 (NAc-*C*H$_2$), 40.5 (C*H*$_2$-COMe), 32.0 (*C*H$_2$), 30.1 (CO*C*H$_3$), 27.8 (*C*H$_2$-CH$_2$-COMe), 25.9 (*C*H$_2$), 25.2 (NCO*C*H$_3$), 13.8 (CH$_2$*C*H$_3$)

3-(8-acetyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)propane-nitrile (5-50)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-48** (93mg, 0.22mmol, 1.0 eq.) in AcOEt (4.4ml, 0.05mmol/ml), with DLP (106mg, 1.2eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-50** (44mg, 67%) as a white crystal.

m.p. : 129-132°C

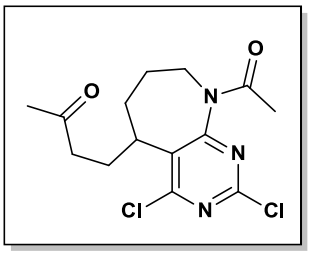
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.35 (bd, 1H, J=14.1Hz, C*H*H-NAc), 3.45 (dt, 1H, J=4.0Hz, J=13.7Hz, CH*H*-NAc), 3.35-3.30 (m, 1H, C*H*), 2.68 (s, 3H, CH_3), 2.52 (m, 2H, CH_2-CN), 2.13 (dd, 1H, J=2.9Hz, J=14.4Hz, C*H*H-CH_2-NAc), 2.04 (m, 1H, C*H*H-CH_2-CN), 1.93-1.84 (m, 1H, CH*H*-CH_2-NAc), 1.82-1.73 (m, 1H, CH*H*-CH_2-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.1 (*C*OCH_3), 160.4 (*C*-NAc), 159.4 (C-*C*-Cl), 156.8 (N-*C*-Cl), 118.3 (*C*N), 117.4 (*C*-CCl), 39.5 (*C*H_2-NAc), 32.4 (*C*H), 28.2 (*C*H_3), 27.5 (*C*H_2-CH_2CN), 23.7 (*C*H_2-CH_2NAc), 15.2 (*C*H_2-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3155, 2984, 2254, 1817, 1794, 1694, 1602, 1561, 1522, 1472, 1432, 1379, 1341, 1299, 1263, 1217, 1165, 1132, 1096, 1041

HRMS (EI+) Calcd. for $C_{12}H_{12}Cl_2N_4O$: 298.0388 Found : 298.0390

4-(9-acetyl-2,4-dichloro-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)butan-2-one (5-51)

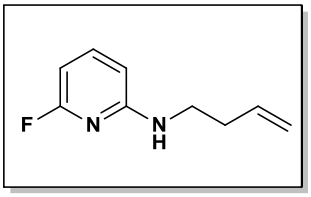


Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-49** (127mg, 0.26mmol, 1.0eq.) in AcOEt (7ml, 0.04mmol/ml), with DLP (137mg, 1.3eq.). Flash chromatography on silica gel with Acetone / DCM = 10 / 90 afforded **5-51** (33mg, 38%) as colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.73 (br s, 1H, C*H*H-NAc), 3.76-3.38 (m, 1H, C*H*), 2.88-2.51 (m, 1H, CH*H*-NAc), 2.44 (td, 1H, *J* = 14.6, 7.0 Hz, C*H*H-COMe), 2.28 (td, 1H, *J* = 17.8, 7.0 Hz, CH*H*-COMe), 2.13 (s, 3H, NCO-CH_3), 2.10 (s, 3H, CH_2CO-CH_3), 2.03-1.58 (m, 6H, 3 CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 206.8 (CH_2CO), 169.2 (N*C*O), 164.9 (NAc-*C*-N), 163.6 (NAc-C-CH-*C*-Cl), 156.8 (NAc-C-N-*C*-Cl), 129.8 (Cl-C-*C*-CH), 45.7 (CH_2-NAc), 41.0 (CH_2-COMe), 37.1 (*C*H), 30.0 ($COCH_3$), 28.3 (CH_2), 24.4 (CH_2), 23.3 ($NCOCH_3$), 22.9 (CH_2)

***N*-(but-3-enyl)-6-fluoropyridin-2-amine (5-52)**

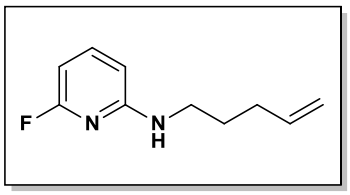


2.0ml prepared butenylamine hydrochloride solution in EtOH (2mmol estimated, 2eq.) and 119mg 2,6-difluoropyridine (1.03mmol, 1.0eq.) was dissolved by 1.9ml DMF, and then 0.35ml TEA (2.51mmol, 2.4eq.) was added. The mixture was heated to 95°C for 18 hours. After work-up, flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-52** (26mg, 15%[251]) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.46 (dd, *J* = 16.4, 7.9 Hz, 1H, *H*-aromatic), 6.18 (dd, *J* = 8.0, 2.4 Hz, 1H, *H*-aromatic), 6.13 (dd, *J* = 7.7, 2.2 Hz, 1H, *H*-aromatic), 5.81 (tdd, *J* = 17.1, 10.2, 6.8 Hz, 1H, CH_2-C*H*=CH_2), 5.21-5.04 (m, 2H, CH_2-CH=CH_2), 4.57 (br s, 1H, N*H*), 3.33 (dd, *J* = 10.0, 6.3 Hz, 2H, NH-CH_2), 2.45-2.30 (m, 2H, CH_2-CH=CH_2)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 163.2 (d, *J* = 236 Hz, *C*-F), 157.9 (d, *J* = 17 Hz, NH-*C*), 141.7 (d, *J* = 9 Hz, *C*-Ar), 135.3 (CH_2-*C*H=CH_2), 117.4 (CH_2-CH=*C*H_2), 102.5 (d, *J* = 4 Hz, *C*-Ar), 95.6 (d, *J* = 37 Hz, *C*-Ar), 41.1 (NH-*C*H_2), 33.5 (*C*H_2-CH=CH_2)
IR (ν, cm^{-1}, $CDCl_3$) 3692, 3431, 3082, 2928, 2253, 1622, 1576, 1504, 1456, 1421, 1369, 1335, 1235, 1152, 996
HRMS (EI+) Calcd. for $C_9H_{11}FN_2$: 166.0906 Found : 166.0905

[251] Similar procedure in refluxing THF only affords 7% of **5-52**. Improvement could be achieved by operating the reaction with 2,6-difluoropyridine, amine and DIPEA in a sealed tube at 110°C. See the synthesis of **5-53**.

6-fluoro-N-(pent-4-enyl)pyridin-2-amine (5-53)



236mg 2,6-difluoropyridine (2.05mmol, 1.0eq.) was mixed with 257mg 5-pentenylamine hydrochloride (2.11mmol, 1.0eq.), and 0.65ml diisopropylethylamine (3.93mmol, 1.9eq.) was added. The mixture was heated to 110°C in a sealed tube for 40 hours to complete the reaction. After work-up, flash chromatography on silica gel with Et_2O / hexane = 10 / 90 afforded **5-53** (338mg, 92%) as a light yellow oil.

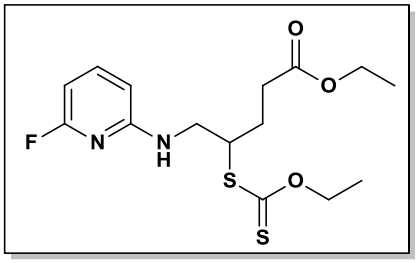
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.46 (ddd, *J* = 8.1, 8.1, 8.1 Hz, 1H, CH-C*H*-CH), 6.17 (dd, *J* = 8.0, 2.4 Hz, 1H, CH-C*H*-CNH), 6.12 (dd, *J* = 7.7, 2.3 Hz, 1H, CF-C*H*-CH), 5.82 (tdd, *J* = 16.9, 10.2, 6.7 Hz, 1H, CH_2-C*H*=CH_2), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H, CH_2-CH=C*H*H), 5.00 (dd, *J* = 10.1, 1.0 Hz, 1H, CH_2-CH=CH*H*), 4.55 (br s, 1H, N*H*), 3.27 (td, *J* = 6.6, 6.6 Hz, 2H, NH-CH_2), 2.16 (td, *J* = 14.2, 7.1 Hz, 2H, CH_2-CH=CH_2), 1.71 (tt, *J* =7.3, 7.3 Hz, 2H, CH_2-CH_2-CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 163.3 (d, *J* = 236 Hz, *C*-F), 158.0 (d, *J* = 17 Hz, NH-*C*), 141.7 (d, *J* = 9 Hz, CH-*C*H-CH), 137.7 (CH_2-*C*H=CH_2), 115.3 (CH_2-CH=*C*H_2), 102.2 (d, *J* = 4 Hz, CH-*C*H-CNH), 95.5 (d, *J* = 37 Hz, CF-C*H*-CH), 41.6 (NH-*C*H_2), 31.1 (*C*H_2-CH=CH_2), 28.5 (CH_2-*C*H_2-CH_2)

IR (ν, cm^{-1}, CCl_4) 3448, 3288, 3081, 2930, 2860, 1622, 1578, 1503, 1456, 1422, 1372, 1335, 1268, 1240, 1150, 990, 915

HRMS (EI+) Calcd. for $C_{10}H_{13}FN_2$: 180.1063 Found : 180.1062

S-4-(ethoxycarbonyl)-1-(6-fluoropyridin-2-ylamino)butan-2-yl O-ethyl carbonodithioate (5-54)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of *N*-allyl-6-fluoropyridin-2-amine [252] (67mg, 0.44mmol, 0.63 eq.) and the xanthate **Xa-h** (146mg, 0.70mmol, 1.0 eq.) in AcOEt (0.7ml, 1.0 mmol/ml), with DLP (42mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-54** (75mg, 47%) as a colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.45 (dd, *J* = 16.2, 8.1 Hz, 1H, CH-C*H*-CH), 6.25 (dd, *J* = 8.0, 2.2 Hz, 1H, C*H*-CNH), 6.14 (dd, *J* = 7.7, 2.3 Hz, 1H, C*H*-CF), 4.90 (br s, 1H, N*H*), 4.73-4.53 (m, 2H, CH_2), 4.13 (q, *J* = 7.1 Hz, 2H, CH_2), 4.07-3.97 (m, 1H, C*H*), 3.68 (m, 1H, NH-C*H*H), 3.62-3.49 (m, 1H, NH-CH*H*), 2.70-2.41 (m, 2H, CH_2-COOEt), 2.28-2.10 (m, 1H, C*H*H-CH_2-COOEt), 2.00-1.84 (m, 1H, CH*H*-CH_2-COOEt), 1.39 (t, *J* = 7.1 Hz, 3H, CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3)

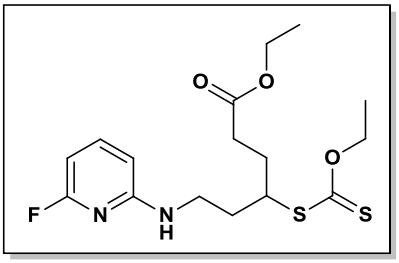
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.4 (*C*=S), 172.7 (*C*O), 163.2 (d, *J* = 237 Hz, *C*-F), 157.5 (d, *J* = 17 Hz, NH-*C*), 141.6 (d, *J* = 9. Hz, CH-*C*H-CH), 103.5 (d, *J* = 4 Hz, *C*H-CNH), 96.0 (d, *J* = 37 Hz, *C*H-CF), 70.3 (*C*H_2), 60.6 (*C*H_2), 50.5 (*C*H), 45.2 (NH-*C*H_2), 31.6 (*C*H_2-COOEt), 26.7 (*C*H_2-CH_2-COOEt), 14.2 (*C*H_3), 13.7 (*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3441, 2985, 2939, 2255, 1728, 1619, 1578, 1505, 1463, 1422, 1377, 1334, 1227, 1152, 1112, 1051

HRMS (EI+) Calcd. for $C_{15}H_{21}FN_2O_3S_2$: 360.0978 Found : 360.0977

[252] El Qacemi, M., L. Ricard, *et al. Chem. Comm*., 2006, (42): pp 4422-4424.

S-1-(ethoxycarbonyl)-5-(6-fluoropyridin-2-ylamino)pentan-3-yl O-ethyl carbonodithioate (5-55)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-52** (26mg, 0.16mmol, 0.5 eq.) and the xanthate **Xa-h** (75mg, 0.36mmol, 1.0 eq.) in AcOEt (0.2ml, 1.8 mmol/ml), with DLP (22mg, 0.30 eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-55** (38mg, 67%) as a yellow oil.

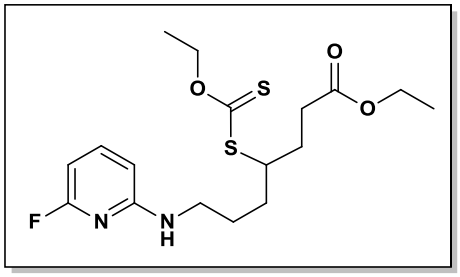
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.45 (dd, *J* = 16.2, 8.0 Hz, 1H, CH-C*H*-CH), 6.20 (dd, *J* = 8.0, 2.3 Hz, 1H, C*H*-CNH), 6.12 (dd, *J* = 7.7, 2.3 Hz, 1H, C*H*-CF), 4.81 (br s, 1H, N*H*), 4.63 (q, *J* = 7.1 Hz, 2H, CH_2), 4.13 (q, *J* = 7.1 Hz, 2H, CH_2), 3.89 (ddd, *J* = 14.1, 9.2, 5.2 Hz, 1H, C*H*), 3.52 (qd, *J* = 12.9, 6.4 Hz, 1H, NH-C*H*H), 3.40 (dt, *J* = 13.5, 13.2, 6.8 Hz, 1H, NH-CH*H*), 2.58-2.36 (m, 2H, COOEt-CH_2), 2.13 (dddd, *J* = 14.0, 12.7, 8.6, 5.1 Hz, 1H, C*H*H-CH_2COOEt), 2.03 (td, *J* = 19.8, 6.4 Hz, 1H, $NHCH_2$-C*H*H), 1.98-1.87 (m, 2H, CH*H*-CH_2COOEt + $NHCH_2$-CH*H*), 1.41 (t, *J* = 7.1 Hz, 3H, CH_3), 1.24 (t, *J* = 7.2 Hz, 3H, CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.3 (*C*=S), 172.9 (*C*O), 163.3 (d, *J* = 236 Hz, *C*-F), 157.8 (d, *J* = 17 Hz, NH-*C*), 141.5 (d, *J* = 9 Hz, CH-*C*H-CH), 103.1 (d, *J* = 4 Hz, *C*H-CNH), 95.5 (d, *J* = 37 Hz, *C*H-CF), 70.3 (*C*H_2), 60.6 (*C*H_2), 48.7 (*C*H), 39.3 (NH-*C*H_2), 34.3 ($NHCH_2$-*C*H_2), 31.6 (*C*H_2-COOEt), 29.5 (*C*H_2-CH_2COOEt), 14.2 (*C*H_3), 13.7 (*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3429, 2985, 2939, 2258, 1727, 1622, 1577, 1508, 1456, 1421, 1375, 1338, 1291, 1223, 1152, 1112, 1048

HRMS (EI+) Calcd. for $C_{16}H_{23}FN_2O_3S_2$: 374.1134 Found : 374.1131

S-1-(ethoxycarbonyl)-6-(6-fluoropyridin-2-ylamino)hexan-3-yl O-ethyl carbonodithioate (5-56)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-53** (15mg, 0.082mmol, 0.3 eq.) and the xanthate **Xa-h** (52mg, 0.24mmol, 1.0 eq.) in AcOEt (0.24ml, 1.0 mmol/ml), with DLP (20mg, 0.20 eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-56** (23mg, 71%) as a light yellow oil.

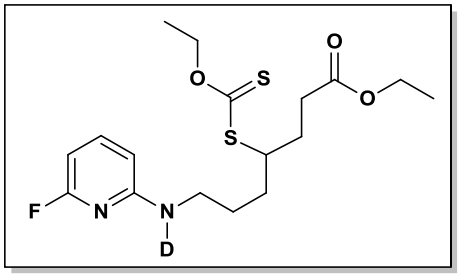
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.45 (ddd, *J* = 8.1, 8.1, 8.1 Hz, 1H, CH-C*H*-CH), 6.17 (dd, *J* = 8.0, 2.3 Hz, 1H, CH-C*H*-CNH), 6.12 (dd, *J* = 7.7, 2.2 Hz, 1H, CF-C*H*-CH), 4.64 (q, *J* = 7.1 Hz, 2H, CH_2), 4.60-4.50 (br s, 1H, N*H*), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 3.88-3.73 (m, 1H, C*H*), 3.30 (m, 2H, NH-CH_2), 2.60-2.32 (m, 2H, COOEt-CH_2), 2.09 (m, 1H, CH*H*-CH_2COOEt), 1.90 (m, 1H, C*H*H-CH_2COOEt), 1.82-1.68 (m, 4H, $NHCH_2$-CH_2-CH_2-CH), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.2 (*C*S), 172.9 (*C*O), 163.3 (d, *J* = 236Hz, *C*F), 157.9 (d, *J* = 17Hz, NH-*C*), 141.6 (d, *J* = 9Hz, CH-*C*H-CH), 102.5 (d, *J* = 4Hz, *C*HCNH), 95.5 (d, *J* = 37Hz, *C*H-CF), 70.1 (*C*H_2), 60.6 (*C*H_2), 50.5 (*C*H), 41.6 ($NHCH_2$), 31.9 ($NHCH_2CH_2$), 31.6 (*C*H_2-COOEt), 29.4 (*C*H_2-CH_2COOEt), 26.6 (*C*H_2CH), 14.2 (*C*H_3), 13.8 (*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3607, 2985, 2939, 1727, 1602, 1577, 1508, 1456, 1420, 1375, 1337, 1223, 1153, 1112, 1049

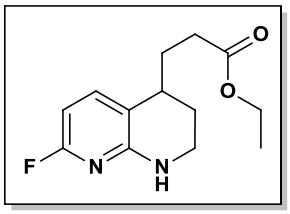
HRMS (EI+) Calcd. for $C_{17}H_{25}FN_2O_3S_2$: 388.1291 Found : 388.1289

Deuterated S-1-(ethoxycarbonyl)-6-(6-fluoropyridin-2-ylamino) hexan-3-yl O-ethyl carbonodithioate (5-56')



63mg of **5-56** (0.13mmol, 1.0eq.) was dissolved by 0.64ml DCM following by adding 0.08ml deuterated trifluoroacetic acid (1.03mmol, 8.0eq.). Under the protection of nitrogen, the mixture was kept stirring at room temperature for 30min to complete the Boc deprotection. Solvent and the rest TFA-d were removed to maximum by evaporation at 60°C under reduced pressure. Then 0.7ml D_2O, 0.7ml Et_2O with 2 drops of TEA were used to wash the crude product. After evaporating the solvent, the residue was kept *in vacuo* for 1 hour to maximum remove the rest solvent and base. Since the ^{1}H-NMR indicated no significant impurity existed, the crude product was used directly into the next step without further purification in order to avoid the active proton exchange.

ethyl 3-(7-fluoro-1,2,3,4-tetrahydro-1,8-naphthyridin-4-yl)propanoate (5-58)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-55** (36mg, 0.10mmol, 1.0 eq.) in AcOEt (1.9ml, 0.05mmol/ml), with DLP (39mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-58** (10mg, 41%) as a light yellow oil.

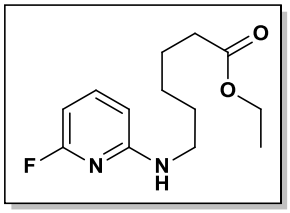
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.25 (t, *J* = 8.0 Hz, 1H, CH-C*H*-C), 6.06 (dd, *J* = 7.8, 2.3 Hz, 1H, C*H*-CF), 4.99 (br s, 1H, N*H*), 4.14 (q, *J* = 7.1 Hz, 2H, CH_2-CH_3), 3.54-3.33 (m, 2H, NH-CH_2), 2.93-2.63 (m, 1H, C*H*), 2.49-2.25 (m, 2H, COOEt-CH_2), 2.03-1.84 (m, 2H, 2 CH-C*H*H), 1.85-1.72 (m, 2H, 2 CH-CH*H*), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.3 (*C*O), 161.9 (d, *J* = 235 Hz, *C*-F), 154.0 (d, *J* = 17 Hz, NH-*C*), 140.3 (d, *J* = 9 Hz, CH-*C*H-C), 114.6 (d, *J* = 4 Hz, *C*-CNH), 95.0 (d, *J* = 37 Hz, *C*H-CF), 60.5 (*C*H_2-CH_3), 37.7 (NH-*C*H_2), 34.2 (*C*H), 31.5 (*C*H_2-COOEt), 30.3 (CH-*C*H_2), 25.3 (CH-*C*H_2), 14.2 (CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3443, 2938, 2863, 2255, 1727, 1618, 1523, 1464, 1376, 1356, 1287, 1230, 1193, 1159, 1115, 1033

HRMS (EI+) Calcd. for $C_{13}H_{17}FN_2O_2$: 252.1274 Found : 252.1278

ethyl 6-(6-fluoropyridin-2-ylamino)hexanoate (5-58')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-55** (36mg, 0.10mmol, 1.0 eq.) in AcOEt (1.9ml, 0.05mmol/ml), with DLP (39mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-58'** (12mg, 48%) as a light yellow oil.

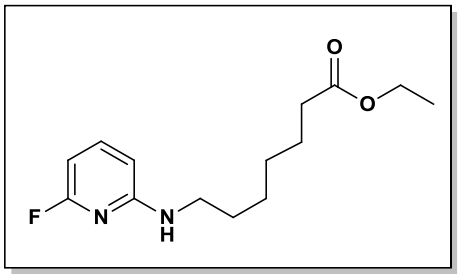
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.46 (dd, *J* = 8.0, 8.0 Hz, 1H, CH-C*H*-CH), 6.17 (dd, *J* = 8.0, 2.3 Hz, 1H, C*H*-CNH), 6.11 (dd, *J* = 7.8, 2.3 Hz, 1H, C*H*-CF), 4.57 (br s, 1H, N*H*), 4.13 (q, *J* = 7.1 Hz, 2H, CH_2-CH_3), 3.25 (t, *J* = 7.1 Hz, 2H, NH-CH_2), 2.31 (t, *J* = 7.4 Hz, 2H, CH_2-COOEt), 1.65 (m, 4H, 2 CH_2), 1.52-1.33 (m, 2H, C_2H_4-CH_2- C_2H_4), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.6 (*C*O), 163.2 (d, *J* = 236 Hz, *C*-F), 158.0 (d, *J* = 17 Hz, NH-*C*), 141.7 (d, *J* = 9 Hz, CH-*C*H-CH), 102.2 (d, *J* = 4 Hz, *C*H-CNH), 95.4 (d, *J* = 37 Hz, *C*H-CF), 60.3 (*C*H_2-CH_3), 41.9 (NH-*C*H_2), 34.2 (*C*H_2-COOEt), 29.0 (*C*H_2), 26.4 (*C*H_2), 24.6 (*C*H_2), 14.2 (CH_2-*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3691, 3432, 2937, 2863, 2254, 1726, 1623, 1576, 1508, 1457, 1420, 1375, 1338, 1226, 1189, 1153, 1032

HRMS (EI+) Calcd. for $C_{13}H_{19}FN_2O_2$: 254.1431 Found : 254.1436

ethyl 7-(6-fluoropyridin-2-ylamino)heptanoate (5-59')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-56** (22mg, 0.055mmol, 1.0 eq.) in AcOEt (1.1ml, 0.05mmol/ml), with DLP (22mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-59'** (7.8mg, 53%) as a colourless oil.

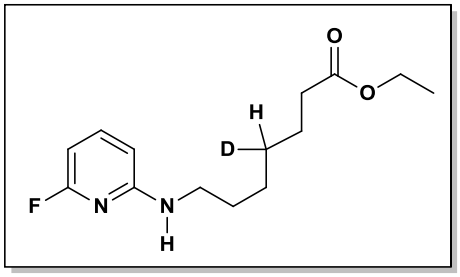
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.46 (dd, *J* = 8.1, 8.1 Hz, 1H, CH-C*H*-CH), 6.17 (dd, *J* = 8.0, 2.4 Hz, 1H, C*H*-CNH), 6.11 (dd, *J* = 7.7, 2.2 Hz, 1H, C*H*-CF), 4.52 (br s, 1H, N*H*), 4.12 (q, *J* = 7.1 Hz, 2H, C*H*$_2$-CH_3), 3.23 (dt, *J* = 13.1, 6.6 Hz, 2H, NH-C*H*$_2$), 2.29 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-COOEt), 1.77-1.60 (m, 4H, $NHCH_2$-C*H*$_2$ + C*H*$_2$- CH_2COOEt), 1.52-1.37 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$- CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2-C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.7 (*C*O), 163.3 (d, *J* = 236 Hz, *C*-F), 158.1 (d, *J* = 17 Hz, NH-*C*), 141.7 (d, *J* = 9 Hz, CH-*C*H-CH), 102.2 (d, *J* = 4 Hz, *C*H-CNH), 95.4 (d, *J* = 37 Hz, *C*H-CF), 60.2 (*C*H_2-CH_3), 42.1 (NH-*C*H_2), 34.2 (*C*H_2-COOEt), 29.2 (*C*H_2), 28.8 (*C*H_2), 26.6 (*C*H_2), 24.8 (*C*H_2), 14.3 (CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3448, 2933, 2858, 1736, 1621, 1578, 1505, 1456, 1421, 1373, 1336, 1240, 1227, 1181, 1151, 1097, 1034

HRMS (EI+) Calcd. for $C_{14}H_{21}FN_2O_2$: 268.1587 Found : 268.1588

Deuterated ethyl 7-(6-fluoropyridin-2-ylamino)heptanoate (5-59")



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-56'** (46mg, 0.12mmol, 1.0 eq.) in AcOEt (2.3ml, 0.05mmol/ml), with DLP (47mg, 1.0 eq.). Flash chromatography on silica gel with Et_2O/n-pentane = 20/80 afforded a mixture of **5-59'** and **5-59"**[253] (12mg, 44%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.45 (dd, *J* = 8.0, 8.0 Hz, 1H, CH-C*H*-CH), 6.16 (dd, *J* = 8.0, 1.8 Hz, 1H, C*H*-CNH), 6.11 (dd, *J* = 7.7, 1.6 Hz, 1H, C*H*-CF), 4.56 (br s, 1H, N*H*), 4.12 (q, *J* = 7.1 Hz, 2H, CH_2-CH_3), 3.23 (t, *J* = 7.1 Hz, 2H, NH-CH_2), 2.29 (t, *J* = 7.5 Hz, 2H, CH_2-COOEt), 1.67-1.57 (m, 4H, $NHCH_2$-CH_2 + CH_2- CH_2COOEt), 1.44-1.38 (m, 4H, CH_2-CH_2-CH_2- CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 173.7 (*C*O), 163.2 (d, *J* = 236 Hz, *C*-F), 158.1 (d, *J* = 17 Hz, NH-*C*), 141.7 (d, *J* = 9 Hz, CH-*C*H-CH), 102.2 (d, *J* = 3 Hz, *C*H-CNH), 95.4 (d, *J* = 37 Hz, *C*H-CF), 60.2 (*C*H_2-CH_3), 42.1 (NH-*C*H_2), 34.2 (*C*H_2-COOEt), 29.2 (*C*H_2), 28.8 (*C*H_2), 26.6 (*C*H_2), 24.8 (*C*H_2), 14.2 (CH_2-*C*H_3)

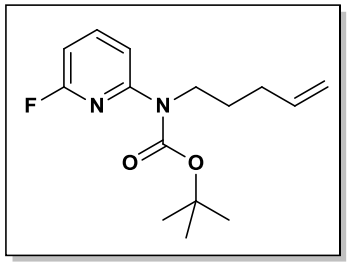
[253] Both of **5-59'** and **5-59"** are detected by Mass Spectra, with an estimation of 20-25% **5-59"** in the mixture. NMR and IR tests are made for this mixture since they are not separable.

IR (ν, cm^{-1}, CCl_4) 3449, 2933, 2859, 1736, 1621, 1578, 1503, 1456, 1421, 1373, 1336, 1227, 1181, 1151, 1096, 1034

HRMS (EI+) Calcd. for $C_{14}H_{21}FN_2O_2$: 268.1587 Found : 268.1590 **(5-59')**

HRMS (EI+) Calcd. for $C_{14}H_{20}FN_2O_2D$: 269.1650 Found : 269.1653 **(5-59")**

tert-butyl 6-fluoropyridin-2-ylpent-4-enylcarbamate (5-60)



208mg 6-fluoro-N-(pent-4-enyl)pyridin-2-amine **5-53** (1.16mmol, 1.0eq.) was dissolved by 3.0ml anhydrous DMF (0.4 mmol / ml), following by adding 65mg NaH (60% suspension in oil). The mixture was heated to 50°C for 2 hours until no bubble formed. Then 340mg di-tert-butyl dicarbonate (1.56mmol, 1.3eq.) was added portionwise. One hour later the reaction was finished. After work-up, flash chromatography on silica gel with Et_2O / hexane = 5 / 95 afforded **5-60** (265mg, 82%) as light yellow oil.

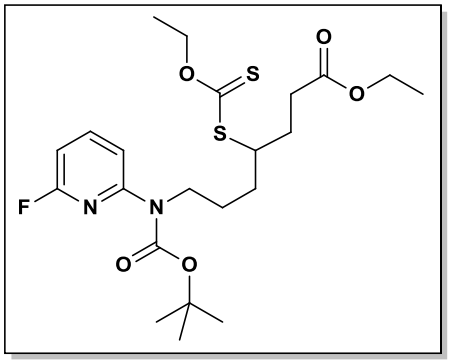
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.69 (dd, *J* = 8.1, 8.1 Hz, 1H CH-C*H*-CH), 7.60 (dd, *J* = 8.0, 1.9 Hz, 1H, CH-C*H*-CNH), 6.59 (dd, *J* = 7.8, 2.6 Hz, 1H, CF-C*H*-CH), 5.82 (tdd, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH_2-C*H*=CH_2), 5.01 (dd, *J* = 17.1, 1.7 Hz, 1H, CH_2-CH=C*H*H), 4.96 (d, *J* = 10.2 Hz, 1H, CH_2-CH=CH*H*), 3.92 (d, *J* = 7.5 Hz, 1H, NBoc-C*H*H), 3.90 (d, *J* = 7.5 Hz, 1H, NBoc-CH*H*), 2.08 (td, *J* = 14.2, 7.3 Hz, 2H, C*H*$_2$-CH=CH_2), 1.73 (tt, *J* =7.5, 7.5 Hz, 2H, CH_2-C*H*$_2$-CH_2), 1.52 (s, 9H, (C*H*$_3$)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.7 (d, *J* = 238 Hz, *C*-F), 153.8 (*C*O), 153.0 (d, *J* = 14 Hz, NH-*C*), 141.4 (d, *J* = 8. Hz, CH-*C*H-CH), 138.0 (CH_2-*C*H=CH_2), 115.5 (d, *J* = 5 Hz, CH-*C*H-CNH), 114.8 (CH_2-CH=*C*H_2), 103.3 (d, *J* = 36 Hz, CF-C*H*-CH), 81.5 (*C*(CH_3)$_3$), 46.2 (NBoc-*C*H_2), 31.1 (*C*H_2-CH=CH_2), 28.3 ((*C*H_3)$_3$), 27.9 (CH_2-*C*H_2-CH_2)

IR (ν, cm^{-1}, CCl_4) 2979, 2931, 1715, 1607, 1582, 1555, 1439, 1388, 1368, 1325, 1298, 1276, 1242, 1207, 1154, 992, 913

HRMS (EI+) Calcd. for $C_{15}H_{21}FN_2O_2$: 280.1587 Found : 280.1587

ethyl 7-((tert-butoxycarbonyl)(6-fluoropyridin-2-yl)amino)-4-((ethoxycarbonothioyl) thio)heptanoate (5-62)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-60** (145mg, 0.52mmol, 0.5 eq.) and the xanthate **Xa-h** (216mg, 1.03mmol, 1.0 eq.) in AcOEt (1.0ml, 1.0 mmol/ml), with DLP (42mg, 0.10eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-62** (113mg, 45%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.69 (dd, *J* = 8.1, 8.1 Hz, 1H, CH-C*H*-CH), 7.60 (dd, *J* = 8.0, 2.0 Hz, 1H, CH-C*H*-CNH), 6.59 (dd, *J* = 7.8, 3.0 Hz, 1H, CF-C*H*-CH), 4.62 (q, *J* = 7.1 Hz, 2H, CH_2), 4.12 (q, *J* = 7.1 Hz, 2H, CH_2), 3.91 (t, *J* = 7.0 Hz, 2H, NBoc-CH_2), 3.83-3.71 (m, 1H, C*H*), 2.53-2.35 (m, 2H, COOEt-CH_2), 2.15-2.01 (m, 1H, CH*H*-CH_2COOEt), 1.96-1.83 (m, 1H, C*H*H-CH_2COOEt), 1.84-1.65 (m, 4H, $NHCH_2$-CH_2-CH_2-CH), 1.52 (s, 9H, (CH_3)$_3$), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3)

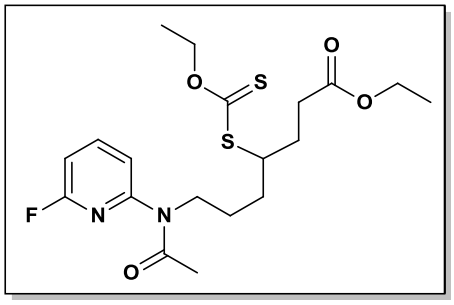
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.1 (*C*=S), 172.9 (*C*OOEt), 161.6 (d, *J* = 238 Hz, *C*-F), 153.7 (*C*OOtBu), 152.8 (d, *J* = 14 Hz, NH-*C*), 141.5 (d, *J* = 7 Hz, CH-*C*H-CH), 115.4 (d, *J* = 5 Hz, *C*H-CNH), 103.4 (d, *J* = 36 Hz, *C*H-CF), 81.7 (*C*Me_3), 69.9 (*C*H_2), 60.5 (*C*H_2),

50.5 (*C*H), 46.1 (NBoc-*C*H_2), 31.6 (NBocCH_2*C*H_2), 31.6 (*C*H_2-COOEt), 29.3 (*C*H_2-CH_2COOEt), 28.3 (3(*C*H_3)), 26.0 (*C*H_2CH), 14.2 (*C*H_3), 13.8 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2981, 2933, 1737, 1716, 1606, 1582, 1439, 1390, 1369, 1296, 1276, 1215, 1151, 1112, 1053, 992, 928, 910

HRMS (EI+) Calcd. for $C_{22}H_{33}FN_2O_5S_2$: 488.1815 Found : 488.1816

ethyl 4-((ethoxycarbonothioyl)thio)-7-(N-(6-fluoropyridin-2-yl)acetamido)heptanoate (5-63)

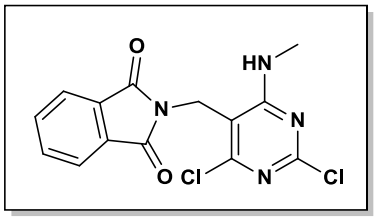


Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-61** (83mg, 0.37mmol, 0.5eq.) and the xanthate **Xa-h** (156mg, 0.75mmol, 1.0eq.) in AcOEt (0.8ml, 1.0 mmol/ml), with DLP (60mg, 0.20eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-63** (76mg, 48%) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.84 (dd, 1H, *J* = 16.0, 8.1 Hz, CH-C*H*-CH), 7.16 (d, 1H, *J* = 6.4 Hz, CH-C*H*-CNAc), 6.85 (dd, 1H, *J* = 8.0, 2.8 Hz, CF-C*H*-CH), 4.62 (q, 2H, *J* = 7.1 Hz, C*H*$_2$), 4.12 (q, 2H, *J* = 7.1 Hz, C*H*$_2$), 3.95-3.79 (m, 2H, NAc-C*H*$_2$), 3.78-3.70 (m, 1H, C*H*), 2.43 (ddd, 2H, *J* = 8.3, 6.8, 2.6 Hz, COOEt-C*H*$_2$), 2.08 (s, 3H, COC*H*$_3$), 2.08-2.00 (m, 1H, CH*H*-CH_2COOEt), 1.95-1.80 (m, 1H, C*H*H-CH_2COOEt), 1.77-1.63 (m, 4H, $NHCH_2$-C*H*$_2$-C*H*$_2$-CH), 1.41 (t, 3H, *J* = 7.1 Hz, C*H*$_3$), 1.24 (t, 3H, *J* = 7.1 Hz, C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.1 (*C*=S), 173.0 (*C*OOEt), 171.6 (d, *J* = 238.7 Hz, *C*-F), 170.3 (*C*OCH_3), 153.5 (d, *J* = 15.0 Hz, NH-*C*), 142.7 (d, *J* = 7.9 Hz, CH-*C*H-CH), 118.1 (d, *J* = 4.6 Hz, *C*H-CNH), 103.2 (d, *J* = 39 Hz, *C*H-CF), 70.0 (*C*H_2), 60.6 (*C*H_2), 50.5 (*C*H), 47.3 (*C*H_2), 31.6 (2 *C*H_2), 29.5 (*C*H_2), 25.7 (*C*H_2), 23.4 (CO*C*H_3), 14.3 (CH_2*C*H_3), 13.8 (CH_2*C*H_3)

2-((2,4-dichloro-6-(methylamino)pyrimidin-5-yl)methyl)isoindoline-1,3-dione (5-66)



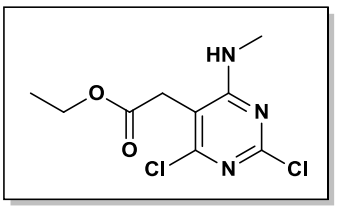
Following the general procedure **5-III** for the radical addition of xanthates on the pyrimidine rings, the reaction was carried out with the solution of 2,6-dichloro-N-methylpyrimidin-4-amine (51mg, 0.28mmol, 0.9eq.) and the xanthate **Xa-c** (90mg, 0.32mmol, 1.0eq.) in AcOEt (0.6ml, 0.5mmol/ml), with DLP (140mg, 1.1eq.). Flash chromatography on silica gel with AcOEt / DCM = 5 / 95 recovered 24mg 2,6-dichloro-N-methylpyrimidin-4-amine and afforded **5-66** (37mg, 39% and 74% as modified yield) as white needle crystal.

m.p. : 221-225°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.95-7.82 (m, 2H, 2 *H*-phthalimide), 7.80-7.73 (m, 2H, 2 *H*-phthalimide), 6.99 (d, 1H, *J* = 3.2 Hz, N*H*), 4.85 (s, 2H, CH_2), 3.02 (d, 3H, *J* = 4.7 Hz, CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 168.7 (2 *C*O-phthalimide), 163.2 (*C*-Ar), 159.8 (*C*-Ar), 159.2 (*C*-Ar), 134.7 (2 *C*H-phthalimide), 131.5 (2 *C*-phthalimide), 123.8 (2 *C*H-phthalimide), 107.2 (Ar-*C*-CH_2), 34.5 (*C*H_2), 28.9 (*C*H_3)

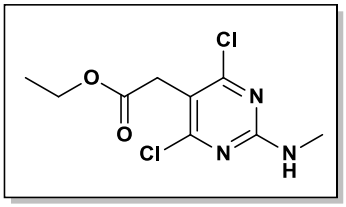
ethyl 2-(2,4-dichloro-6-(methylamino)pyrimidin-5-yl)acetate (5-67)



Following the general procedure **5-III** for the radical addition of xanthates on the pyrimidine rings, the reaction was carried out with the solution of 2,6-dichloro-N-methylpyrimidin-4-amine (10mg, 0.056mmol, 0.4eq.) and the xanthate **Xa-h** (32mg, 0.154mmol, 1.0eq.) in AcOEt (0.4ml, 0.4mmol/ml), with DLP (47.4mg, 0.8eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 recovered 2.9mg 2,6-dichloro-N-methylpyrimidin-4-amine and afforded **5-67** (8.4mg, 57% and 80% as modified yield) as colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.99 (br s, 1H, N*H*), 4.18 (q, 2H, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.61 (s, 2H, C*H*$_2$), 3.06 (d, 3H, *J* = 4.8 Hz, NHC*H*$_3$), 1.28 (t, 3H, *J* = 7.1 Hz, CH$_2$C*H*$_3$)

ethyl 2-(4,6-dichloro-2-(methylamino)pyrimidin-5-yl)acetate (5-68)



Following the general procedure **5-III** for the radical addition of xanthates on the pyrimidine rings, the reaction was carried out with the solution of 4,6-dichloro-N-methylpyrimidin-2-amine (12mg, 0.068mmol, 0.3eq.) and the xanthate **Xa-h** (56mg, 0.27mmol, 1.0eq.) in AcOEt (0.54ml, 0.5mmol/ml), with DLP (76mg, 0.7eq.). Flash chromatography on silica gel with AcOEt / EP = 15 / 85 afforded **5-68** (7.4mg, 41%) as white solid.

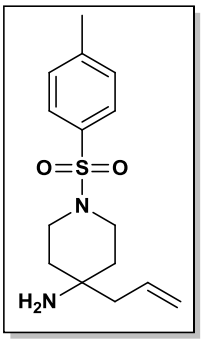
In comparative study, the reaction was carried out with the solution of 4,6-dichloro-N-methylpyrimidin-2-amine (194mg, 1.09mmol, 2.0eq.) and the xanthate **Xa-h** (114mg, 0.54mmol, 1.0eq.) in DCE (2.1ml, 0.3mmol/ml), with DLP (260mg, 1.2eq.). Flash chromatography on silica gel with AcOEt / EP = 15 / 85 afforded **5-68** (36mg, 13%) as white solid.

m.p. : 124-128°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.48 (br s, 1H, N*H*), 4.20 (dq, 2H, *J* = 7.1, 2.8 Hz, C*H*$_2$CH$_3$), 3.77 (s, 2H, C*H*$_2$), 3.00 (d, 3H, *J* = 5.1 Hz, NHC*H*$_3$), 1.27 (t, 3H, *J* = 7.1 Hz, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 169.3 (*C*O), 162.2 (NH-*C*-Ar),160.5 (2 Cl-*C*-Ar), 112.7 (CH$_2$-*C*-Ar), 61.4 (*C*H$_2$CH$_3$), 35.0 (CO-*C*H$_2$), 28.5 (NH-*C*H$_3$), 14.2 (CH$_2$*C*H$_3$)

4-allyl-1-tosylpiperidin-4-amine (5-69-0)



To 239mg 1-tosylpiperidin-4-one (0.94mmol 1.0 eq.) was added 5.2 mL a solution of ammonia in methanol (2M in MeOH, 10.4mmol, 11 eq.). The resulting solution was stirred for 15 min at rt. 0.2 ml allylboronic acid pinacolester (1.07mmol, 1.1 eq.) was then added dropwise. The reaction mixture was subseq.uently stirred for 17 hours at rt. All volatiles were removed *in vacuo* and the residue re-dissolved in Et_2O. The desired amine was then extracted with 1N HCl. The acidic aqueous extract was washed with Et_2O. The aqueous extract was next made alkaline by addition of solid NaOH. The alkaline aqueous layer was then extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and

concentrated *in vacuo* to afford a crude product of the desired amine. Flash chromatography on silica gel with AcOEt / DCM = 20 / 80 afforded the olefinic precursor for **5-69-0** (212mg, 77%) as a white powder.

m.p. : 113-117°C

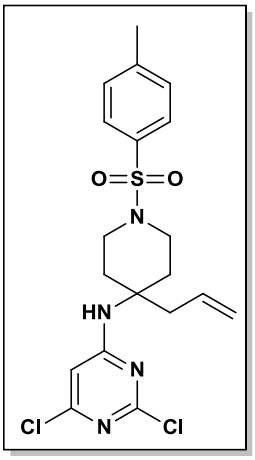
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.65 (d, *J* = 8.2 Hz, 2H, *H*-aromatic), 7.31 (d, *J* = 8.3 Hz, 2H, *H*-aromatic), 5.76 (tdd, *J* = 17.4, 10.1, 7.5 Hz, 1H, CH_2-C*H*=CH_2), 5.10 (ddd, *J* = 18.3, 13.6, 1.4 Hz, 2H, CH_2-CH=CH_2), 3.41 (td, *J* = 8.0, 3.8 Hz, 2H, 2 CH*H*-NTs), 2.78 (dt, *J* = 11.5, 2.8 Hz, 2H, 2 C*H*H-NTs), 2.43 (s, 3H, CH_3), 2.06 (d, *J* = 7.5 Hz, 2H, CH_2-CH=CH_2), 1.78-1.61 (m, 2H, 2 NHC-CH*H*), 1.41 (d, *J* = 13.4 Hz, 2H, 2 NHC-C*H*H), 0.98 (br s, 2H, NH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 143.3 (*C*-Ar), 133.5 (*C*-Ar), 132.7 (CH_2-*C*H=CH_2), 129.6 (2 *C*H-Ar), 127.6 (2 *C*H-Ar), 119.4 (CH_2-CH=*C*H_2), 48.9 (*C*H_2-CH=CH_2), 48.6 (NH_2-*C*), 42.2 (2 *C*H_2-NTs), 36.8 (2 NHC-*C*H_2), 21.5 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2927, 2855, 1639, 1599, 1464, 1443, 1361, 1347, 1305, 1248, 1166, 1094, 1051, 921

HRMS (EI+) Calcd. for $C_{15}H_{22}N_2O_2S$: 294.1402 Found : 294.1407

N-(4-allyl-1-tosylpiperidin-4-yl)-2,6-dichloropyrimidin-4-amine (5-69)



158mg trichloropyrimidine (0.86mmol, 1.2eq.) was dissolved by 1.8ml THF and then 212mg of the above precursor (0.72mmol, 1.0eq.) was added. The mixture was refluxed for 18 hours to finish the reaction. After work-up, flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **5-69** (93mg, 29%) as colorless oil.

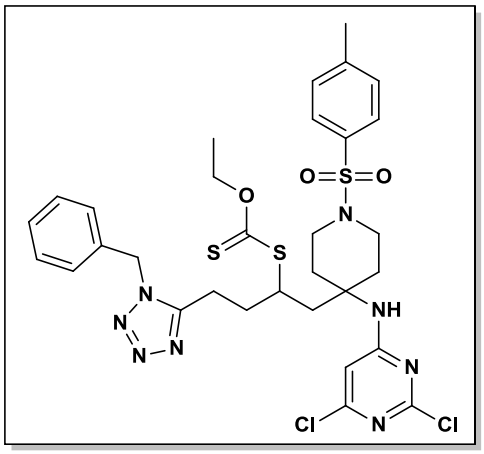
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.63 (d, *J* = 8.2 Hz, 2H, *H*-aromatic), 7.33 (d, *J* = 7.9 Hz, 2H, *H*-aromatic), 6.23 (s, 1H, , *H*-aromatic), 5.60 (qd, *J* = 10.1, 7.4 Hz, 1H, CH_2-C*H*=CH_2), 5.02 (dd, *J* = 39.6, 13.6 Hz, 2H, CH_2-CH=C*H*$_2$), 4.62 (br s, 1H, N*H*), 3.46 (d, *J* = 11.5 Hz, 2H, 2 CH*H*-NTs), 2.63 (m, 4H, 2 C*H*H-NTs + C*H*$_2$-CH=CH_2), 2.44 (s, 3H, C*H*$_3$), 2.26 (d, *J* = 12.8 Hz, 2H, 2 NHC-CH*H*), 1.85 (m, 2H, 2 NHC-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 163.5 (*C*-pyrimidine), 159.6 (*C*-pyrimidine), 159.3 (*C*-pyrimidine), 143.8 (*C*-Ar), 133.1 (*C*-Ar), 131.5 (CH_2-*C*H=CH_2), 129.8 (2 *C*H-Ar), 127.6 (2 *C*H-Ar), 119.9 (CH_2-CH=*C*H_2), 103.1 (*C*H-pyrimidine), 55.0 (NH-*C*), 41.8 (2 *C*H_2-NTs), 40.5 (*C*H_2-CH=CH_2), 34.0 (2 NHC-*C*H_2), 21.6 (*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3433, 3366, 2928, 2855, 1574, 1488, 1448, 1362, 1327, 1269, 1171, 1121, 1092, 1053, 1034, 995, 923

HRMS (EI+) Calcd. for $C_{19}H_{22}Cl_2N_4O_2S$: 440.0841 Found : 440.0812

S-1-(4-(2,6-dichloropyrimidin-4-ylamino)-1-tosylpiperidin-4-yl)-4-(1-benzyl-1H-tetrazol-5-yl)butan-2-yl O-ethyl carbonodithioate (5-70)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-69** (62mg, 0.14mmol, 0.8 eq.) and the xanthate **Xa-m** (53mg, 0.18mmol, 1.0 eq.) in AcOEt (0.14ml, 1.3 mmol/ml), with DLP (11mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 30 / 70 afforded **5-70** (63mg, 62%) as a colourless oil.

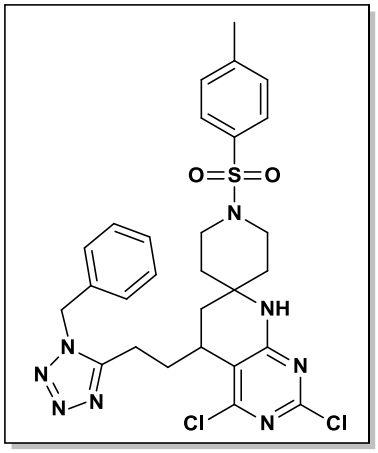
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.63 (d, *J* = 8.2 Hz, 2H, *H*-aromatic), 7.34 (m, 5H, *H*-aromatic), 7.15 (dd, *J* = 6.6, 2.9 Hz, 2H, *H*-aromatic), 6.24 (d, *J* = 1.8 Hz, 1H, *H*-pirimidine), 5.48 (d, *J* = 15.4 Hz, 1H, CH*H*-Ph), 5.40 (br s, 1H, N*H*), 5.32 (d, *J* = 15.4 Hz, 1H, C*H*H-Ph), 4.52 (dq, *J* = 7.1, 1.3 Hz, 2H, CH_2-CH_3), 3.82 (dt, *J* = 9.5, 9.3, 5.8 Hz, 1H, C*H*), 3.63-3.48 (m, 2H, 2 CH*H*-NTs), 2.78 (m, 2H, tetrazole C-CH*H* + NHC-CH*H*), 2.67-2.15 (m +s, 10H, tetrazole C-C*H*H + 2 C*H*H-NTs + CH_3 + NHC-CH*H* + CH-CH_2-C + CH-C*H*H-CH_2), 1.86 (tt, *J* = 15.0, 5.1 Hz, 1H, CH-CH*H*-CH_2), 1.80-1.68 (m, 2H, 2 NHC-C*H*H), 1.36 (t, *J* = 7.1 Hz, 3H, CH_2-CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 214.3 (*C*=S), 164.0 (*C*-pyrimidine), 159.4 (*C*-pyrimidine), 158.9 (*C*-pyrimidine), 154.3 (*C*-tetrazole), 143.7 (*C*-toluene), 133.1 (*C*-toluene), 132.7 (*C*-benzene), 129.9 (2 *C*H-toluene), 129.3 (2 *C*H-benzene), 129.1 (*C*H-benzene), 127.6 (2 *C*H-toluene + 2 *C*H-benzene), 104.0 (*C*H-pyrimidine), 70.8 (*C*H_2-CH_3), 55.3 (*C*-NH), 50.9 (*C*H_2-Ph), 45.9 (*C*H), 42.0 (NHC-*C*H_2-CH), 41.8 (2 *C*H_2-NTs), 34.8 (NHC-*C*H_2), 34.5 (NHC-*C*H_2), 32.0 (CH_2-*C*H_2-CH), 21.6 (*C*H_3), 20.9 (tetrazole C-*C*H_2), 13.8 (CH_2-*C*H_3)

IR (ν, cm^{-1}, CCl_4) 2927, 2855, 1573, 1489, 1453, 1360, 1270, 1221, 1173, 1120, 1054, 909

HRMS (EI+) Calcd. for $C_{28}H_{31}Cl_2N_8O_2S$: 613.1668 Found : 613.1658

5'-(2-(1-benzyl-1H-tetrazol-5-yl)ethyl)-2',4'-dichloro-1-tosyl-6',8'-dihydro-5'H-spiro[piperidine-4,7'-pyrido[2,3-d]pyrimidine] (5-71)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-70** (35mg, 0.048mmol, 1.0 eq.) in AcOEt (1.6ml, 0.03mmol/ml), with DLP (19mg, 1.0 eq.). Flash chromatography on silica gel with AcOEt / EP = 40 / 60 afforded **5-71** (22mg, 77%) as a white powder.

m.p. : 222-224°C

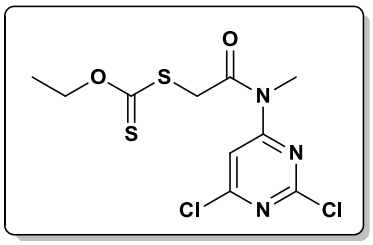
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.63 (d, *J* = 8.1 Hz, 2H, *H*-aromatic), 7.44-7.33 (m, 5H, *H*-aromatic), 7.16 (m, 2H, *H*-aromatic), 5.59-5.45 (m, 3H, CH_2-Ph + N*H*), 3.48 (m, 2H, 2 CH*H*-NTs), 3.14-2.97 (m, 1H, C*H*), 2.85-2.67 (m, 2H, tetrazole C-CH_2), 2.60-2.45 (m + s, 5H, 2 C*H*H-NTs + CH_3), 2.16 (m, 1H, CH-CH*H*-CH_2), 1.95 (dt, *J* = 14.4, 8.6 Hz, 1H, CH-C*H*H-CH_2), 1.88-1.66 (m, 5H, 2 NHC-CH_2 + CH-C*H*H-C), 1.58 (d, *J* = 13.6 Hz, 1H, CH-CH*H*-C)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 160.7 (*C*-pyrimidine), 158.2 (*C*-pyrimidine), 157.4 (*C*-pyrimidine), 153.8 (*C*-tetrazole), 144.4 (*C*-toluene), 133.1 (*C*-toluene), 132.3 (*C*-benzene), 130.1 (2 *C*H-toluene), 129.5 (2 *C*H-benzene), 129.3 (*C*H-benzene), 127.6 (2 *C*H-aromatic), 127.3 (2 *C*H-aromatic), 111.3 (*C*-pyrimidine), 51.0 (*C*H_2-Ph), 50.3 (*C*-NH), 41.8 (*C*H_2-NTs), 41.7 (*C*H_2-NTs), 37.3 (CH-*C*H_2-C), 37.1 (NHC-*C*H_2), 37.0 (NHC-*C*H_2), 30.7 (*C*H), 30.6 (CH_2-*C*H_2-CH), 21.6 (*C*H_3), 21.3 (tetrazole C-*C*H_2)

IR (ν, cm^{-1}, Nujol) 3281, 1573, 1556, 1519, 1420, 1400, 1343, 1328, 1274, 1162, 1119, 1094, 1054, 1040, 936, 924

HRMS (EI+) Calcd. for $C_{28}H_{30}Cl_2N_8O_2S$: 612.1589 Found : 612.1595

S-(2-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (5-72)



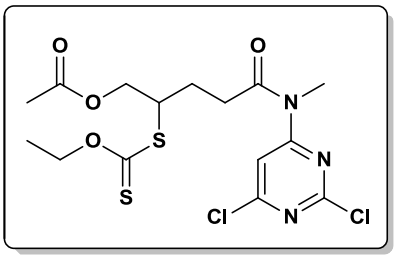
5.0g trichloropyrimidine (27.3mmol, 1.0eq.) was dissolved by 70ml THF (0.4mmol/ml) and then 4.38ml methylamine 40% aqueous solution (42.6mmol, 1.6eq.) was added drop by drop with ice-bain. The mixture was then warmed to room temperature and stirring for 2 hours to finish the reaction. After work-up, flash chromatography on silica gel with DCM / EP = 70 / 30 afforded 2,6-dichloro-*N*-methylpyrimidin-4-amine (2.95g, 61%) as white solid.

722mg 2,6-dichloro-*N*-methylpyrimidin-4-amine (4.1mmol, 1.0eq.) was dissolved by 10ml toluene (0.4mmol/ml) and then1.6ml chloroacetyl chloride (20.1mmol, 4.9eq.) was added drop by drop, followed by refluxing the mixture under the protection of nitrogen for 8 hours. After work-up, the crude product was used directly in next step, without further purification.

The crude product of last step was dissolved by 40ml acetone (0.1mmol/ml) and then 2.1g xanthate salt (13.1mmol, 3.2eq.) was added portionwise. About 30min later, the reaction finished and purification after work-up on silica gel with DCM / EP = 90 / 10 afforded **5-72** (1.71g, 42% for two steps) as yellow solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.82 (s, 1H, C*H*), 4.65 (q, *J* = 7.12 Hz, 2H, C$H_2$$CH_3$), 4.14 (s, 2H, SC$H_2$), 3.60 (s, 3H, NC$H_3$), 1.43 (t, *J* = 7.11 Hz, 3H, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.2 (*C*=S), 168.9 (*C*=O), 162.8 (*C*-Ar), 162.2 (*C*-Ar), 159.0 (*C*-Ar), 110.7 (*C*H-Ar), 71.1 (O*C*H_2), 42.2 (S*C*H_2), 34.0 (N*C*H_3), 13.8 (CH_2*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3693, 3606, 3157, 2987, 2961, 1702, 1601, 1556, 1528, 1469, 1444, 1400, 1371, 1357, 1333, 1240, 1207, 1178, 1151, 1114, 1088, 1048, 1002, 982
HRMS (EI+) Calcd. for $C_{10}H_{11}Cl_2N_3O_2S_2$: 338.9670 Found : 338.9662

5-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-((ethoxycarbonothioyl)thio)-5-oxopentyl acetate (5-73)



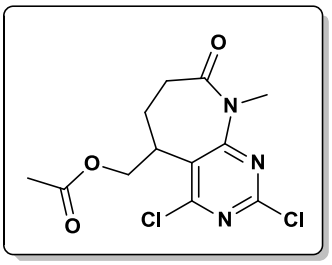
Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-72** (248mg, 0.73mmol, 1.0eq.) and allyl acetate (0.16ml, 1.46mmol, 2.0eq.) in AcOEt (0.73ml, 1.0 mmol/ml), with DLP (87mg, 0.3eq.). Flash chromatography on silica gel with AcOEt / EP = 15 / 85 afforded **5-73** (129mg, 40%) as a light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.06 (s, 1H, C*H*), 4.65 (q, *J* = 7.12 Hz, 2H, C$H_2$$CH_3$), 4.32 (ddd, *J* = 17.56, 11.42, 5.50 Hz, 2H, COOCH_2), 4.09 (dt, *J* = 10.47, 4.71 Hz, 1H, SC*H*), 3.49 (s, 3H, NCH_3), 2.97-2.83 (m, 2H, COCH_2), 2.35-2.26 (m, 1H, $COCH_2CH$*H*), 2.09 (s, 3H, COCH_3), 2.04-1.94 (m, 1H, $COCH_2$C*H*H), 1.42 (t, *J* = 7.12 Hz, 3H, CH_2CH_3)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.9 (*C*=S), 173.8 (*C*OO), 170.6 (*C*ON), 162.5 (*C*-Ar), 162.2 (*C*-Ar), 158.9 (*C*-Ar), 111.4 (*C*H-Ar), 70.6 (*C*$H_2$$CH_3$), 65.8 (COO*C*$H_2$), 49.0 (S*C*H), 34.0 (CO*C*H_2), 33.7 (N*C*H_3), 25.9 ($COCH_2$*C*H_2), 20.8 (*C*H_3COO), 13.7 (CH_2*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3515, 3457, 3435, 3153, 2985, 2940, 1741, 1708, 1591, 1556, 1525, 1443, 1400, 1374, 1334, 1230, 1150, 1112, 1050, 982

HRMS (EI+) Calcd. for $C_{12}H_{14}Cl_2N_3O_3$**:** 318.0412 Found: 318.0419

(2,4-dichloro-9-methyl-8-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]azepin-5-yl)methyl acetate (5-74)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-73** (123mg, 0.28mmol, 1.0eq.) in AcOEt (6ml, 0.05mmol/ml), with DLP (134mg, 1.2eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-74** (44mg, 49%) as white solid.

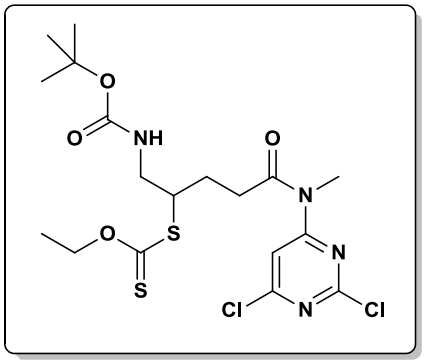
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.30-4.25 (m, 1H, COOCH*H*), 4.16-4.11 (m, 1H, COOC*H*H), 4.04-3.98 (m, 1H, C*H*), 3.43 (s, 3H, NCH_3), 2.57-2.51 (m, 1H, COCH*H*), 2.49-2.39 (m, 2H, $COCH_2CH_2$), 2.24-2.15 m, 1H, COC*H*H), 1.94 (s, 3H, $COCH_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.2 (*C*OO), 170.3 (*C*ON), 165.0 (2 *C*-Ar), 158.1 (*C*-Ar), 122.6 (*C*-Ar), 70.6 (CH_2CH_3), 64.0 ($COOCH_2$), 36.4 (*C*H), 33.5 ($COCH_2$), 33.4 (NCH_3), 29.0 ($COCH_2CH_2$), 20.5 (CH_3COO)

IR (ν, cm^{-1}, $CDCl_3$) 3693, 3519, 2928, 2856, 1803, 1744, 1695, 1601, 1541, 1526, 1457, 1394, 1373, 1353, 1320, 1299, 1254, 1230, 1136, 1042, 1020, 970

HRMS (EI+) Calcd. for $C_{12}H_{13}Cl_2N_3O_3$ **:** 317.0334 Found : 317.0338

tert-butyl (5-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-2-((ethoxycarbonothioyl) thio)-5-oxopentyl)carbamate (5-75)



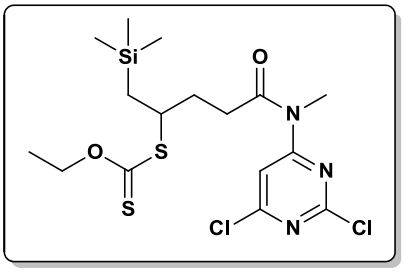
Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-72** (300mg, 0.88mmol, 1.0eq.) and Boc protected allylamine (276mg, 1.76mmol, 2.0eq.) in AcOEt (0.88ml, 1.0mmol/ml), with DLP (18mg, 0.05eq.). Flash chromatography on silica gel with AcOEt / EP = 15 / 85 afforded **5-75** (235mg, 54%) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.08 (s, 1H, C*H*), 4.88 (brs, 1H, N*H*), 4.64 (q, *J* = 7.11 Hz, 2H, C$H_2$$CH_3$), 3.93 (dt, *J* = 11.33, 5.78 Hz, 1H, SC*H*), 3.54-3.49 (m, 1H, NHCH*H*), 3.49 (s, 3H, NCH_3), 3.45-3.38 (m, 1H, NHC*H*H), 2.85 (t, *J* = 7.11 Hz, 2H, COCH_2), 2.27-2.18 (m, 1H, $COCH_2CH$*H*), 2.01-1.93 (m, 1H, $COCH_2C$*H*H), 1.43 (s, 9H, C(CH_3)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.3 (*C*=S), 173.8 (*C*ON), 162.4 (*C*-Ar), 162.2 (*C*-Ar), 158.9 (*C*-Ar), 155.9 (*C*OOtBu), 111.5 (*C*H-Ar), 79.7 (*C*(CH_3)$_3$), 70.4 (*C*$H_2$$CH_3$), 51.2 (S*C*H), 43.7 (NH*C*H_2), 34.0 (CO*C*H_2), 33.7 (N*C*H_3), 28.3 (C(*C*H_3)$_3$), 26.4 ($COCH_2$*C*H_2), 13.7 (CH_2*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 3078, 2927, 2855, 1639, 1599, 1495, 1464, 1443, 1361, 1305, 1248, 1166, 1119, 1094, 1051, 999, 921

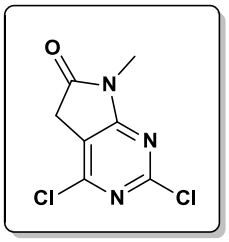
S-(5-((2,6-dichloropyrimidin-4-yl)(methyl)amino)-5-oxo-1-(trimethylsilyl)pentan-2-yl) O-ethyl carbonodithioate (5-76)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-72** (147mg, 0.43mmol, 1.0eq.) and allyl trimethylsilane (98mg, 0.86mmol, 2.0eq.) in AcOEt (0.43ml, 1.0mmol/ml), with DLP (110mg, 0.6eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-76** (53mg, 26%) as yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.09 (s, 1H, C*H*), 4.88 (brs, 1H, N*H*), 4.63 (dq, *J* = 7.10, 2.77 Hz, 2H, CH_2CH$_3$), 3.97 (ddd, *J* = 12.10, 8.58, 4.02 Hz, 1H, SC*H*), 3.48 (s, 3H, NCH_3), 2.87-2.71 (m, 2H, COCH_2), 2.32-2.24 (m, 1H, COCH$_2$CH*H*), 1.99-1.89 (m, 1H, COCH$_2$C*H*H), 1.41 (t, *J* = 7.12 Hz, 3H, CH$_2$CH_3), 1.12 (ddd, *J* = 23.05, 14.86, 7.64 Hz, 2H, SiCH_2)

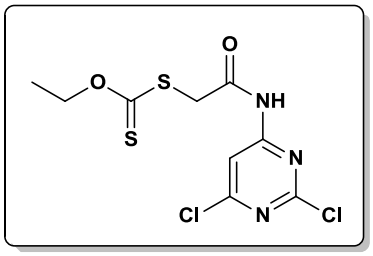
2,4-dichloro-7-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one (5-77)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-72** (81mg, 0.24mmol, 1.0eq.) in AcOEt (6ml, 0.04mmol/ml), with DLP (160mg, 1.4eq.). Flash chromatography on silica gel with AcOEt / EP = 25 / 75 afforded **5-77** (33mg, 64%) as light yellow oil.

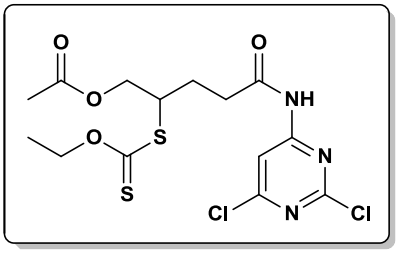
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 3.58 (s, 2H, C*H*$_2$), 3.28 (s, 3H, NC*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.4 (*C*O), 167.5 (*C*-Ar), 159.5 (*C*-Ar), 153.0 (*C*-Ar), 113.2 (*C*-Ar), 32.8 (*C*H_2), 26.2 (*C*H_3)
IR (ν, cm^{-1}, $CDCl_3$) 3690, 3606, 3502, 2928, 2856, 1754, 1606, 1562, 1498, 1466, 1406, 1390, 1372, 1342, 1294, 1231, 1222, 1119, 1078
HRMS (EI+) Calcd. for $C_{12}H_{12}F_3N_3O_2$: 216.9810 Found **:** 216.9804

S-(2-((2,6-dichloropyrimidin-4-yl)amino)-2-oxoethyl) O-ethyl carbonodithioate (5-78)



^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.49 (brs, 1H, N*H*), 7.11 (s, 1H, C*H*), 4.67 (q, *J* = 7.12 Hz, 2H, C*H*$_2$CH$_3$), 4.35 (s, 2H, SC*H*$_2$), 1.44 (t, *J* = 7.10 Hz, 3H, CH$_2$C*H*$_3$)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.7 (*C*=S), 166.2 (NH*C*O), 162.5 (2 *C*-Ar), 156.3 (*C*-Ar), 116.1 (*C*H-Ar), 71.2 (*C*H$_2$CH$_3$), 40.9 (S*C*H$_2$), 13.7 (CH$_2$*C*H$_3$)
IR (ν, cm^{-1}, $CDCl_3$) 3696, 3381, 3121, 2988, 1726, 1601, 1549, 1491, 1442, 1405, 1382, 1367, 1321, 1293, 1235, 1178, 1150, 1108, 1049, 1019, 1003
HRMS (EI+) Calcd. for $C_9H_9Cl_2N_3O_2S_2$: 324.9513 Found : 324.9506

5-((2,6-dichloropyrimidin-4-yl)amino)-2-((ethoxycarbonothioyl)thio)-5-oxopentyl acetate (5-79)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-78** (129mg, 0.40mmol, 1.0eq.) and allyl trimethylsilane (79mg, 0.79mmol, 2.0eq.) in AcOEt (0.8ml, 0.5mmol/ml), with DLP (110mg, 0.6eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded **5-79** (117mg, 69%) as yellow oil.

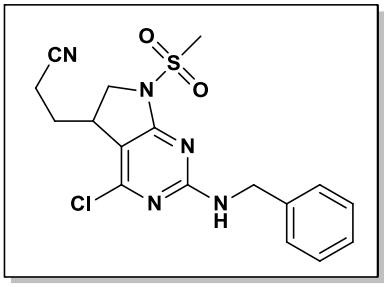
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.36 (N*H*), 8.16 (s, 1H, C*H*), 4.63 (q, *J* = 7.11 Hz, 2H, C*H*$_2$CH$_3$), 4.30 (ddd, *J* = 17.62, 11.47, 5.49 Hz, 2H, COOC*H*$_2$), 4.05 (dt, *J* = 10.64, 10.32, 4.84 Hz, 1H, SC*H*), 2.71-2.53 (m, 2H, COC*H*$_2$), 2.32-2.23 (m, 1H, COCH$_2$CH*H*), 2.09 (s, 3H, COC*H*$_3$), 2.03-1.95 (m, 1H, COCH$_2$C*H*H), 1.41 (t, *J* = 7.12 Hz, 3H, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.6 (*C*=S), 171.1 (*C*OO), 170.8 (*C*ON), 163.5 (*C*-Ar), 159.3 (*C*-Ar), 159.1 (*C*-Ar), 107.8 (*C*H-Ar), 70.7 (*C*H$_2$CH$_3$), 65.5 (COO*C*H$_2$), 48.9 (S*C*H), 34.4 (CO*C*H$_2$), 25.7 (COCH$_2$*C*H$_2$), 20.8 (*C*H$_3$COO), 13.7 (CH$_2$*C*H$_3$)

IR (ν, cm^{-1}, $CDCl_3$) 3398, 2986, 1737, 1571, 1548, 1491, 1383, 1365, 1340, 1230, 1215, 1144, 1113, 1050

HRMS (EI+) Calcd. for $C_{14}H_{17}Cl_2N_3O_4S_2$: 425.0038 Found : 425.0030

3-(2-(benzylamino)-4-chloro-7-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanenitrile (5-81)



26mg of **5-21** (0.08mmol, 1eq.) was dissolved with 0.8ml EtOH, followed by adding 0.04ml benzylamine (0.4mmol, 5eq.) and 0.03ml DIPEA (0.16mmol, 2eq.). The mixture was stirring at room temperature for 3 hours. The desired product **5-81** as white precipitation (30mg, 95%) was isolated by centrifuge.

m.p. : 209~212°C

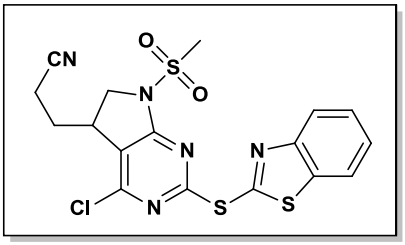
^{1}H-NMR (δ, ppm) (Acetone-d^6, 400 MHz) 7.49-7.15 (m, 5H, Ph), 4.60 (d, 2H, *J* = 5.9 Hz, NH-CH_2), 4.15 (t, 1H, J=10.1Hz, CH*H*-NMs), 3.91 (dd, 1H, *J* = 10.3, 3.6 Hz, C*H*H-NMs), 3.53-3.41 (m, 1H, C*H*-CH_2-NMs), 3.32 and 3.11 (br s, 1H, SO_2-CH_3), 2.75 (br s, 1H, N*H*), 2.64 (t, 1H, *J* = 7.5Hz, CH_2-CN), 2.27-2.19 (m, 1H, C*H*H-CH_2-CN), 2.02-1.95 (m, 1H, CH*H*-CH_2-CN)

^{13}C-NMR (δ, ppm) (Acetone-d^6, 100.6 MHz) 166.1 (Ar-*C*), 164.1 (Ar-*C*), 156.8 (Ar-*C*), 141.7 (Ar-*C*), 130.2 (3 Ph-*C*), 129.5 (2 Ph-*C*), 128.7 (Ph-*C*), 121.2 (*C*≡N), 54.4 (*C*H_2-NMs), 46.8 (NH-*C*H_2), 40.7 (SO_2-*C*H_3), 37.1 (*C*H-CH_2-NMs), 30.5 (*C*H_2-CH_2-CN), 15.6 (*C*H_2-CN)

IR (ν, cm^{-1}, CCl_4) 3284, 2925, 2854, 1619, 1592, 1463, 1377, 1341, 1160, 1152, 1036

HRMS (EI+) Calcd. for $C_{17}H_{18}ClN_5O_2S$: 391.0870 Found : 391.0867

3-(2-(benzo[d]thiazol-2-ylthio)-4-chloro-7-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanenitrile (5-82)



24mg of **5-21** (0.074mmol, 1eq.) was dissolved with 0.8ml EtOH, followed by adding 15mg 2-mercaptobenzothiazole (0.089mmol, 1.2eq.) and 0.06ml DIPEA (0.36mmol, 5eq.). The mixture was stirring at 80°C for 5 hours. The desired product **5-82** as white precipitation (32mg, 96%) was isolated by centrifuge.

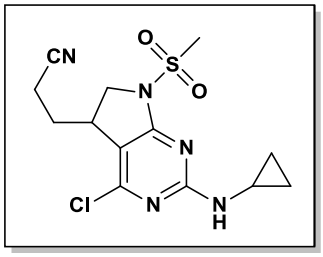
m.p. : 193~197°C

^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 8.19 (d, 1H, *J* = 7.9 Hz, *H*-aromatic), 8.03 (d, 1H, *J* = 8.0 Hz, *H*-aromatic), 7.54 (td, 2H, *J* = 23.7, 7.5 Hz, 2 *H*-aromatic), 4.24 (t, 1H, *J* = 9.8 Hz, CH*H*-NMs), 4.02 (dd, 1H, *J* = 10.3, 3.8 Hz, C*H*H-NMs), 3.68-3.52 (m, 1H, C*H*-CH_2-NMs), 3.39 (s, 3H, SO_2-C*H*$_3$), 2.69 (t, 2H, *J* = 7.4 Hz, C*H*$_2$-CN), 2.24-2.06 (m, 1H, CH*H*-CH_2-CN), 2.00 (m, 1H, C*H*H-CH_2-CN)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 163.3 (MsN-*C*-N), 157.8 (*C*-aromatic), 157.7 (*C*-aromatic), 157.2 (*C*-aromatic), 151.3 (*C*-aromatic), 136.0 (*C*-aromatic), 126.7 (*C*H-aromatic), 125.8 (*C*H-aromatic), 122.4 (*C*H-aromatic), 121.9 (*C*H-aromatic), 121.1 (MsN-C-*C*), 120.1 (*C*≡N), 53.2 (*C*H_2-NMs), 39.0 (SO_2-*C*H_3),34.5 (*C*H-CH_2-NMs), 27.1 (*C*H_2-CH_2-CN), 13.5 (*C*H_2-CN)

IR (ν, cm^{-1}, CCl_4) 2926, 2854, 1555, 1460, 1412, 1377, 1349, 1282, 1161, 1038, 960

3-(4-chloro-2-(cyclopropylamino)-7-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)propanenitrile (5-83)



22mg of **5-21** (0.068mmol, 1eq.) was dissolved with 0.7ml EtOH, followed by adding 0.01ml cyclopropylamine (0.14mmol, 2eq.) and 0.06ml DIPEA (0.34mmol, 5eq.). The mixture was stirring at 80°C for 2 hours and the suspension changed to clear solution. The desired product **5-83** as white solid (21mg, 91%) was isolated by centrifuge.

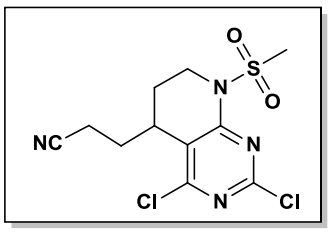
m.p. : 146~149°C

^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.84 (s, 1H, N*H*), 4.06 (t, 1H, *J* = 9.6 Hz, CH*H*-NMs), 3.81 (dd, 1H, *J* = 9.9, 3.6 Hz, C*H*H-NMs), 3.36 (br s, 4H, SO_2-CH_3 + C*H*-CH_2-NMs), 2.78-2.64 (m, 1H, NH-C*H*), 2.64-2.56 (m, 2H, CH_2-CN), 2.14-1.94 (m, 1H, C*H*H-CH_2-CN), 1.91-1.76 (m, 1H, CH*H*-CH_2-CN), 0.75-0.55 (m, 2H, -C*H*H-C*H*H-), 0.47 (br s, 2H, CH*H*-CH*H*-)

IR (ν, cm^{-1}, CCl_4) 3260, 2926, 2854, 1610, 1586, 1526, 1461, 1407, 1342, 1165, 1056

HRMS (EI+) Calcd. for $C_{13}H_{16}ClN_5O_2S$: 341.0713 Found : 341.0724

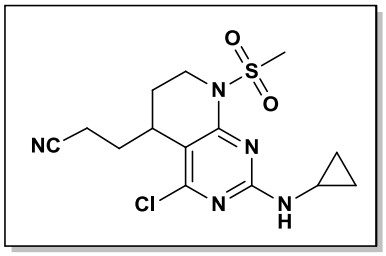
3-(2,4-dichloro-8-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)propanenitrile (5-84)



11mg of **5-35** (0.041mmol, 1.0eq.) was dissolved with 0.4ml anhydrous THF (0.1mmol/ml), followed by adding 6mg NaH (0.15mmol, 3.5eq.) and then 0.004ml methanesulfonyl chloride (0.049mmol, 1.2eq.). The mixture was stirring at room temperature for 1 hour. After work-up, the crude product was purified by flash chromatography on silica gel with Acetone / DCM = 1 / 99 to give **5-84** (12mg, 89%) as colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.31 (dt, 1H, *J* = 13.2 Hz, CH*H*-NMs), 3.60 (dd, 1H, *J* = 13.3, 3.3 Hz, C*H*H-NMs), 3.56 (s, 3H, SO_2-CH_3), 3.35-3.25 (m, 1H, C*H*-CH_2-NMs), 2.65-2.43 (m, 2H, CH_2-CN), 2.20 (ddd, 1H, *J* = 14.5, 5.2, 2.7 Hz, C*H*H-CH_2-NMs), 2.09 (dtd, 1H, *J* = 12.0, 7.6, 4.5 Hz, C*H*H-CH_2-CN), 1.95 (tt, 1H, *J* = 14.0, 4.7 Hz, CH*H*-CH_2-NMs), 1.82-1.70 (m, 1H, CH*H*-CH_2-CN)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 160.3 (*C*-Ar), 158.6 (*C*-Ar), 157.0 (*C*-Ar), 118.2 (*C*≡N), 116.0 (*C*-Ar), 43.6 (SO_2-*C*H_3), 40.3 (*C*H_2-NMs), 31.7 (*C*H-CH_2-NMs), 27.7 (*C*H_2-CH_2-CN), 23.6 (*C*H_2-CH_2-NMs), 15.1 (*C*H_2-CN)
IR (ν, cm^{-1}, CCl_4) 3691, 3607, 1711, 1602, 1559, 1529, 1426, 1360, 1224, 1166, 1122, 1023, 967

3-(4-chloro-2-(cyclopropylamino)-8-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)propanenitrile (5-85)

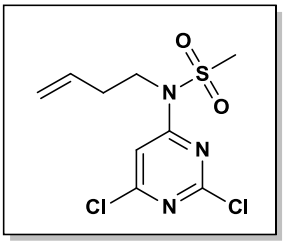


10mg of **5-84** (0.029mmol, 1.0eq.) was dissolved with 0.3ml EtOH, followed by adding 0.004ml cyclopropylamine (0.057mmol, 2.0eq.) and 0.024ml DIPEA (0.14mmol, 5.0eq.). The mixture was stirring at 80°C for 2 hours and 10mg of the desired product **5-85** (98%) was isolated.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.33 (s, 1H, N*H*), 4.24 (dt, 1H, *J* = 13.1 Hz, CH*H*-NMs), 3.59 (s, 3H, SO_2-CH_3), 3.53 (dd, 1H, *J* = 13.0, 3.3 Hz, C*H*H-NMs), 3.30-3.02 (m, 1H, C*H*-CH_2-NMs), 2.74 (dtt, 1H, *J* = 6.7, 3.6 Hz, NH-C*H*), 2.56-2.39 (m, 2H, CH_2-CN), 2.15-2.00 (m, 2H, C*H*H-CH_2-CN + C*H*H-CH_2-NMs), 1.93 (tt, 1H, *J* = 13.9, 4.7 Hz, CH*H*-CH_2-NMs), 1.73 (tdd, 1H, *J* = 14.0, 9.2, 6.9 Hz, CH*H*-CH_2-CN), 0.85-0.73 (m, 2H, -C*H*H-C*H*H-), 0.62-0.52 (m, 2H, -CH*H*-CH*H*-)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 160.1 (*C*-Ar), 159.9 (*C*-Ar), 157.7 (*C*-Ar), 118.8 (*C*≡N), 106.3 (*C*-Ar), 43.5 (SO_2-*C*H_3), 40.3 (*C*H_2-NMs), 31.5 (*C*H-CH_2-NMs), 28.6 (*C*H_2-CH_2-CN), 24.7 (*C*H_2-CH_2-NMs), 24.0 (NH-*C*H), 15.2 (*C*H_2-CN), 7.5 (-*C*H_2-CH_2-), 7.4 (-CH_2-*C*H_2-)

N-(but-3-en-1-yl)-N-(2,6-dichloropyrimidin-4-yl)methanesulfonamide (5-86)

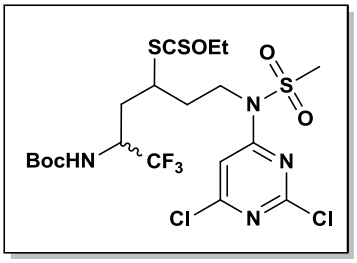


A solution of 158mg **5-28** (0.73mmol, 1eq.) was dissolved with 1.5ml anhydrous THF (0.5mmol/ml) and cooled by an ice-bain. To the colourless solution was added 36mg NaH (0.9mmol, 1.2eq.) portionwise and the mixture turned to light yellow. Then 0.06ml methanesulfonyl chloride (0.80mmol, 1.1eq.) was added to the mixture drop by drop, and the yellow solution changed to colourless immediately. The mixture was stirring at room temperature for 1 hour. After work-up, the crude product was purified by flash chromatography on silica gel with AcOEt / EP = 10 / 90 to give **5-86** (198mg, 92%) as a white crystal.

m.p. : 79~82°C

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.35 (s, 1H, *H*-aromatic), 5.81 (ddd, 1H, *J* = 10.1, 9.0, 2.7 Hz, CH_2-C*H*=CH_2), 5.13 (dd, 2H, *J* = 14.5, 4.8 Hz, CH_2-CH=C*H*$_2$), 4.09 (t, 2H, *J* = 7.3 Hz, NMs-C*H*$_2$), 3.25 (s, 1H, C*H*$_3$), 2.48 (dt, 2H, *J* = 7.1 Hz, C*H*$_2$-CH=CH_2)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 162.7 (NMs-*C*-N), 161.2 (NH-C-CH-*C*-Cl), 159.8 (NH-C-N-*C*-Cl), 133.7 (CH_2-*C*H=CH_2), 118.3 (CH_2-CH=*C*H$_2$), 107.1 (Cl-C-*C*H), 46.7 (NMs-*C*H$_2$), 41.5 (*C*H$_3$), 33.1 (*C*H$_2$-CH=CH_2)
IR (ν, cm^{-1}, CCl_4) 3692, 3155, 2985, 1817, 1794, 1557, 1525, 1471, 1381, 1170, 1096
HRMS (EI+) Calcd. for $C_9H_{11}Cl_2N_3O_2S$: 294.9949 Found : 294.9934

***tert*-butyl (6-(N-(2,6-dichloropyrimidin-4-yl)methylsulfonamido)-4-((ethoxycarbono thioyl)thio)-1,1,1-trifluorohexan-2-yl)carbamate8-(methylsulfonyl)-5,6,7,8-tetrahydro pyrido[2,3-d]pyrimidin-5-yl)propanenitrile (5-87)**



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-86** (91mg, 0.31mmol, 1.0eq.) and the xanthate **Xa-b** (197mg, 0.62mmol, 2.0eq.) in AcOEt (0.7ml, 1.0mmol/ml), with DLP (111mg, 0.45 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-87** (52mg and 77mg, 68%, dr = 1:1.5) as colourless oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.47 (s, 1H, *H*-Ar), 4.81 (d, 1H, *J* = 10.0 Hz, N*H*), 4.66 (q, 2H, *J* = 7.1 Hz, CSOC*H*$_2$CH$_3$), 4.48-4.32 (m, 1H, C*H*-CF_3), 4.24 (ddd, 1H, *J* = 14.9, 10.2, 4.6 Hz, CH*H*NMs), 3.97 (ddd, 1H, *J* = 15.5, 10.1, 5.7 Hz, C*H*HNMs), 3.75 (dd, 1H, *J* = 11.6, 7.7 Hz, C*H*S), 3.31 (s, 3H, SO_2-C*H*$_3$), 2.29 (ddd, 1H, *J* = 14.1, 9.6, 5.2 Hz, CH*H*-

CH_2-NMs), 2.18-1.96 (m, 3H, C*H*H-CH_2-NMs + CH_2-$CHCF_3$), 1.47 (s, 9H, C(CH_3)$_3$), 1.44 (t, 3H, *J* = 7.1 Hz, CSOCH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.1 (*C*S), 162.9 (*C*-Ar), 161.2 (*C*-Ar), 159.7 (*C*-Ar), 155.3 (*C*O), 124.8 (q, *J* = 281 Hz, *C*F_3), 106.8 (Ar-*C*H), 81.1 (*C*(CH_3)$_3$), 70.5 (*C*H_2CH_3), 50.3 (q, *J* = 30 Hz, *C*H-CF_3), 45.1 (*C*H_2NMs), 44.4 (*C*HS), 41.9 (SO_2-*C*H_3), 34.4 (*C*H_2-$CHCF_3$), 30.8 (*C*H_2-CH_2NMs), 28.3 (C(*C*H_3)$_3$), 13.8 (CH_2*C*H_3)

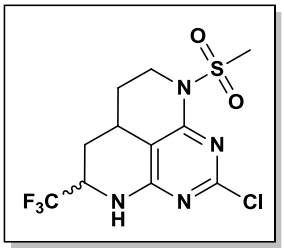
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.45 (s, 1H, *H*-Ar), 4.85 (d, 1H, *J* = 9.9 Hz, N*H*), 4.60 (qd, 1H, *J* = 7.1, 4.0 Hz, CSOC$H_2$$CH_3$), 4.56-4.47 (m, 1H, C*H*-CF_3), 4.15 (t, 2H, *J* = 7.0 Hz, CH_2NMs), 4.02-3.85 (m, 1H, C*H*S), 3.27 (s, 3H, SO_2-CH_3), 2.35-2.19 (m, 1H, CH*H*-CH_2-NMs), 2.14-1.99 (m, 3H, C*H*H-CH_2-NMs + CH_2-$CHCF_3$), 1.43 (s, 9H, C(CH_3)$_3$), 1.40 (t, 3H, *J* = 7.1 Hz, CSOCH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*S), 162.8 (*C*-Ar), 160.9 (*C*-Ar), 159.8 (*C*-Ar), 154.6 (*C*O), 125.1 (q, *J* = 281 Hz, *C*F_3), 107.6 (Ar-*C*H), 80.7 (*C*(CH_3)$_3$), 70.5 (*C*H_2CH_3), 50.2 (q, *J* = 30 Hz, *C*H-CF_3), 44.7 (*C*H_2NMs), 44.6 (*C*HS), 41.3 (SO_2-*C*H_3), 34.2 (*C*H_2-$CHCF_3$), 31.3 (*C*H_2-CH_2NMs), 28.3 (C(*C*H_3)$_3$), 13.7 (CH_2*C*H_3)

IR (ν, cm^{-1}, CCl_4) 3691, 3155, 2984, 2254, 1817, 1794, 1724, 1643, 1602, 1557, 1526, 1471, 1381, 1293, 1217, 1169, 1096

HRMS (EI+) Calcd. for $C_{19}H_{27}Cl_2F_3N_4O_5S_3$: 614.0473 Found : 614.0455

2-chloro-4-(methylsulfonyl)-8-(trifluoromethyl)-5,6,6a,7,8,9-hexahydro-4H-pyrimido[4,5,6-ij][2,7]naphthyridine (5-89)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was firstly carried out with the solution of the first fraction of **5-87** (61mg, 0.10mmol, 1.0eq.) in AcOEt (2ml, 0.05mmol/ml), with DLP (47mg, 1.2eq.). Flash chromatography on silica gel with Acetone / DCM = 1 / 99 afforded the cyclization product as a white powder (32mg, 67%, dr = 1:1.04). Then the cyclization was carried out with the solution of the second fraction of **5-87** (91mg, 0.15mmol, 1.0eq.) in AcOEt (3ml, 0.05mmol/ml), with DLP (83mg, 1.4eq.). Flash chromatography on silica gel with Acetone / DCM = 1 / 99 afforded the cyclization product as a white powder (49mg, 67%, dr = 1:1.17). Since both of the two cyclization products were mixture of two stereoisomers and their purities were not completely being satisfied for full characterization, we combined them to one fraction **5-88** and used it directly in the preliminary test to prepare the tricyclic compound.

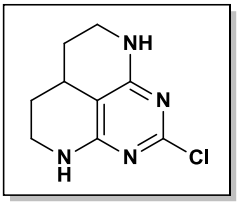
19mg **5-88** (0.038mmol, 1.0eq.) was dissolved by 0.34ml (0.1mmol/ml) of a prepared solution which contained 0.30ml of DCM and 0.035ml of TFA (0.46mmol, 12eq.). The mixture was stirring at room temperature for 80min and all starting compound was completely deprotected indicated by TLC. Then the solvent was removed under reduced pressure and the residue was dissolved by 0.76ml EtOH (0.05mmol/ml) followed by adding 0.034ml DBU (0.23mmol, 6.0eq.) and stirring at 60°C for 40min. Finally the crude product was purified by preparative TLC plate with Acetone / DCM = 1 / 99 to give **5-89** (6.8mg, 50%, dr = 1:1.5) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.14 (d, 0.4H, *J* = 4.0 Hz, N*H*), 5.56 (s, 0.6H, N*H*), 4.59-4.34 (m, 1H, CH*H*NMs), 4.21-4.01 (m, 1H, C*H*-CF_3), 3.53 (s, 3H, SO_2-C*H*$_3$), 3.52-3.43 (m, 1H, C*H*HNMs), 2.83 (tt, 1H, *J* = 12.0, 4.6 Hz, C*H*), 2.45-2.25 (m, 2H, C*H*H-CH_2-NMs + C*H*H-$CHCF_3$), 1.56 (m, 2H, CH*H*-CH_2-NMs + CH*H*-$CHCF_3$)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 159.4 (*C*-Ar, 158.9 (*C*-Ar), 157.4 (*C*-Ar), 157.0 (*C*-Ar), 155.6 (*C*-Ar), 155.5 (*C*-Ar), 94.8 (*C*-Ar), 94.5 (*C*-Ar), 53.1 (q, *J* = 30 Hz, *C*H-CF_3), 44.2 (*C*H_2), 44.1 (*C*H_3), 43.8 (*C*H_3), 43.7 (*C*H_2), 28.5 (*C*H), 27.5 (*C*H_2), 26.3 (*C*H_2), 26.0 (*C*H_2), 24.7 (*C*H_2)

MS (NH_3 ionisation) 357 (MH^+)

2-chloro-5,6,6a,7,8,9-hexahydro-4H-pyrimido[6,5,4-ij][2,7]naphthyridine (5-91)



11mg **5-34** (0.028mmol, 1.0 eq.) was dissolved by 0.15ml (0.2mmol/ml) of a prepared solution which contained 0.0027ml hydrazine (0.056mmol, 2.0 eq.) in EtOH, and then the mixture was stirring at room temperature for 3 hours and all the starting compound was completely deprotected indicated by TLC. Then the solvent was removed under reduced pressure and the residue was dissolved by 0.6ml EtOH (0.05mmol/ml) followed by adding 0.025ml DBU (0.168mmol, 6.0 eq.) and stirring at 70℃ for 1 hour, during when white precipitation formed. Finally the precipitation was seperated by centrifuge and washed by cold EtOH to afford **5-91** (5.4mg, 91%) as a white crystal.

m.p. : 320-325°C decomposed

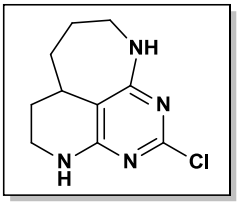
^{1}H-NMR (δ, ppm) (DMSO, 400 MHz) 7.00 (br s, *J* = 3.61 Hz, 2H, 2N*H*), 3.32-3.28 (m, 2H, 2NHC*H*H), 3.18 (dt, *J* = 12.3, 2.7 Hz, 2H, 2NHCH*H*), 2.60-2.50 (m, 1H, C*H*), 1.99 (d, *J* = 12.0 Hz, 2H, 2CHCH*H*), 1.20 (dt, *J* = 12.1, 4.4 Hz, 2H, 2CHC*H*H)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 158.4 (*C*-Ar), 156.6 (*C*-Ar), 87.1 (*C*-Ar), 39.6 (2NH*C*H_2), 29.2 (*C*H), 26.8 (2CH*C*H_2)

IR (ν, cm^{-1}, Nujol) 3222, 3088, 1584, 1334, 1287, 1170, 1109, 1091, 1016, 944, 905

HRMS (EI+) Calcd. for $C_9H_{11}ClN_4$: 210.0672 Found : 210.0675

5-chloro-1,2,3,7,8,9,10,10a-octahydro-3,4,6,7-tetraazacyclohepta[de]naphthalene (5-92)



30mg **5-42** (0.077mmol, 1.0 eq.) was dissolved by 0.39ml (0.2mmol/ml) of a prepared solution which contained 0.0077ml hydrazine (0.153mmol, 2.0 eq.) in EtOH, and then the mixture was stirring at room temperature for 2.5 hours and all the starting compound was completely deprotected indicated by TLC. Then the solvent was removed under reduced pressure and the residue was dissolved by 1.6ml EtOH (0.05mmol/ml) followed by adding 0.07ml DBU (0.46mmol, 6.0 eq.) and stirring at 75°C for 1 hour. When cooling down the flask, white precipitation formed. Finally the precipitation was seperated by centrifuge and washed by cold EtOH to afford **5-92** (13mg, 75%) as a white crystal.

m.p. : 266-270°C

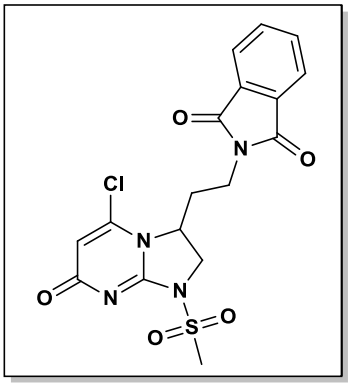
^{1}H-NMR (δ, ppm) (DMSO + TFA, 400 MHz) 7.06 (s, 1H, N*H*), 6.54 (d, *J* = 4.1 Hz, 1H, N*H*), 3.67 (dd, *J* = 11.8 Hz 1H, C*H*), 3.21-3.18 (m, 2H, CH_2NH), 3.12-3.08 (m, 2H, CH_2NH), 1.97-1.62 (m, 5H, 2 CH_2 + C*H*H), 1.39 (m, 1H, CH*H*)

^{13}C-NMR (δ, ppm) (DMSO, 100.6 MHz) 164.6 (*C*-Ar), 161.2 (*C*-Ar), 155.9 (*C*-Ar), 93.1 (*C*-Ar), 41.5 (NH*C*H_2), 38.4 (NH*C*H_2), 32.6 (*C*H_2), 30.3 (*C*H), 29.8 (*C*H_2), 27.4 (*C*H_2)

IR (ν, cm^{-1}, Nujol) 3238, 3090, 1578, 1532, 1404, 1342, 1293, 1279, 1169, 1123, 1080, 984, 928, 781

HRMS (EI+) Calcd. for $C_{10}H_{13}ClN_4$: 224.0829 Found : 224.0839

2-(2-(5-chloro-1-(methylsulfonyl)-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-a]pyrimidin-3-yl)ethyl)isoindoline-1,3-dione (5-99)

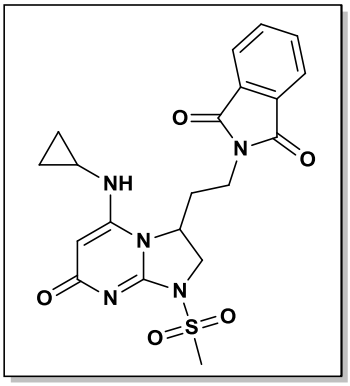


149mg of deacetylated **5-96** (0.43mmol, 1.0eq.) was dissolved with 4.3ml anhydrous THF (0.1mmol/ml), followed by adding 19mg NaH (0.48mmol, 1.1eq.) and then 0.04ml methanesulfonyl chloride (0.52mmol, 1.2eq.). The mixture was stirring at room temperature for 1 hour. After work-up, the crude product was purified by flash chromatography on silica gel with MeOH / DCM = 1 / 99 to give **5-99** (143mg, 79%) as white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.95-7.79 (m, 2H, 2 *H*-phthalimide), 7.78-7.69 (m, 2H, 2 *H*-phthalimide), 5.97 (s, 1H, *H*-aromatic), 4.66 (ddd, 1H, *J* = 12.7, 8.9, 3.7 Hz, C*H*-CH_2-NMs), 4.28 (t, 1H, *J* = 9.8 Hz, CH*H*-NMs), 4.15 (dd, 1H, *J* = 10.4, 4.2 Hz, C*H*H-NMs), 3.91 (td, 1H, *J* = 14.3, 5.7 Hz, C*H*H-phth), 3.83-3.73 (m, 1H, CH*H*-phth), 3.50 (s, 3H, SO_2-C*H*$_3$), 2.57-2.36 (m, 1H, C*H*H-CH_2-phth), 2.22 (tdd, 1H, *J* = 14.4, 9.1, 5.5 Hz, CH*H*-CH_2-phth)

MS (NH_3 ionisation) 423 (M^+)

2-(2-(5-(cyclopropylamino)-1-(methylsulfonyl)-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-a]pyrimidin-3-yl)ethyl)isoindoline-1,3-dione (5-100)

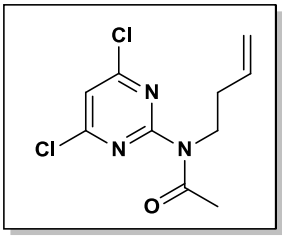


Preliminary test for the nucleophilic substitution was carried out with 11mg **5-99** (0.026mmol, 1.0 eq.), which was dissolved by 0.5ml DMF (0.05mmol/ml). Then 0.05ml cyclopropylamine (0.72mmol, 27 eq.) was added to the solution and the mixture was stirring at 90°C for 3 hours, although not all the starting material was completely consumed according to TLC. The solvent was removed under reduced pressure and the residue was purified by preparative TLC plate with MeOH / DCM = 4 / 96 to afford **5-100** (5.2mg, 60%) as a white solid, together with recovering 2.7mg reactant **5-99**.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.97-7.77 (m, 2H, 2 *H*-phthalimide), 7.77-7.68 (m, 2H, 2 *H*-phthalimide), 5.19 (s, 1H, *H*-aromatic), 5.04 (br s, 1H, N*H*), 4.72-4.44 (m, 1H, C*H*-CH_2-NMs), 4.16 (t, 1H, *J* = 9.6 Hz, CH*H*-NMs), 4.06 (dd, 1H, *J* = 10.2, 3.7 Hz, C*H*H-NMs), 3.89 (td, 1H, *J* = 14.3, 5.9 Hz, C*H*H-phth), 3.78 (ddd, 1H, *J* = 14.3, 8.6, 5.6 Hz, CH*H*-phth), 3.38 (s, 3H, SO_2-CH_3), 2.57-2.41 (m, 1H, C*H*H-CH_2-phth), 2.41-2.32 (m, 1H, NH-C*H*), 2.24-2.09 (m, 1H, CH*H*-CH_2-phth), 0.80-0.71 (m, 2H, -C*H*H-C*H*H-), 0.58-0.52 (m, 2H, -CH*H*-CH*H*-)

MS (NH_3 ionisation) 444 (MH^+)

***N*-(but-3-enyl)-*N*-(4,6-dichloropyrimidin-2-yl)acetamide (5-101)**



25ml flask was charged of 141mg **5-28'** (0.65mmol, 1.0eq.) and 1.5ml acetyl chloride (0.43mmol/ml), and the mixture was kept stirring under the protection of nitrogen for 49 hours. After work-up, the crude product was purified by flash chromatography on silica gel with DCM / EP = 80 / 20 to give **5-101** (165mg, 98%) as colourless oil.

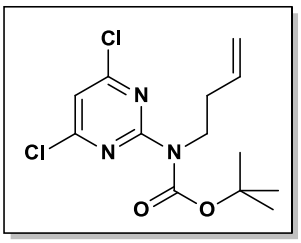
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.10 (s, 1H, *H*-aromatic), 5.83 (dt, 1H, J=6.5Hz, J=17.1Hz, CH_2-C*H*=CH_2), 5.08 (d, 1H, J=17.1Hz, CH_2-CH=C*H*H), 5.03 (d, 1H, J=10.2Hz, CH_2-CH=CH*H*), 4.19 (t, 2H, J=7.3Hz, CH_2-NAc), 2.59 (s, 1H, CH_3), 2.43 (q, 2H, J=7.1Hz, CH_2-CH=CH_2)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.3 (*C*OCH_3), 161.6 (2 *C*-Cl), 160.1 (N-*C*-NAc), 135.1 (CH_2-*C*H=CH_2), 116.8 (CH_2-CH=*C*H_2), 115.1 (Cl-C-*C*H), 45.2 (NAc-*C*H_2), 32.6 (*C*H_2-CH=CH_2), 26.9 (*C*H_3)

IR (ν, cm^{-1}, $CDCl_3$) 2980, 2338, 1687, 1558, 1529, 1451, 1423, 1391, 1370, 1245, 1223, 1124, 1092, 980

HRMS (EI+) Calcd. for $C_{10}H_{11}Cl_2N_3O$: 259.0279 Found : 259.0280

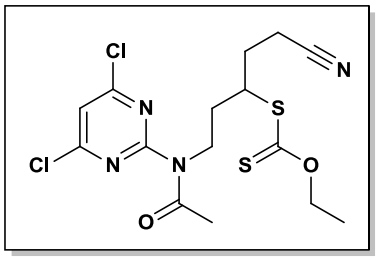
***tert*-butyl but-3-en-1-yl(4,6-dichloropyrimidin-2-yl)carbamate (5-102)**



^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.99 (s, 1H, *H*-aromatic), 5.80 (tdd, 1H, J=7.0Hz, J=10.2Hz, J=17.1Hz, CH_2-C*H*=CH_2), 5.04 (ddd, 2H, J=1.3Hz, J=13.7Hz, J=11.1Hz, CH_2-CH=CH_2), 3.98 (t, 2H, J=7.4Hz, NH-CH_2), 2.43 (dd, 2H, J=7.2Hz, J=14.4Hz, CH_2-CH=CH_2), 1.53 (s, 9H, C(CH_3)$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.4 (2 *C*-Cl), 160.2 (NBoc-*C*-N), 152.8 (*C*=O), 134.9 (CH_2-*C*H=CH_2), 116.9 (CH_2-CH=*C*H_2), 114.8 (Cl-C-*C*H), 82.6 (*C*(CH_3)$_3$), 47.0 (NH-*C*H_2), 33.1 (*C*H_2-CH=CH_2), 28.0 (C(*C*H_3)$_3$)

_S_-1-(_N_-(4,6-dichloropyrimidin-2-yl)-_N_-acethylamino)-5-cyanopentan-3-yl _O_-ethyl carbonodithioate (5-103)



Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-101** (159mg, 0.61mmol, 1.0 eq.) and the xanthate **Xa-a** (102mg, 0.63mmol, 1.0 eq.) in AcOEt (0.6ml, 1.0mmol/ml), with DLP (37mg, 0.15 eq.). Flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-103** (189mg, 80%) as light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.17 (s, 1H, *H*-aromatic), 4.64 (q, 2H, J=7.1Hz, C$H_2$$CH_3$), 4.26-4.11 (m, 2H, C$H_2$-NAc), 3.79 (dt, 1H, J=6.9Hz, J=12.0Hz, Xa-C*H*), 2.58 (s, 1H, CH_3), 2.57-2.52 (m, 2H, CH_2-CN), 2.33-2.24 (m, 1H, CH*H*-CH_2-CN), 2.13-1.98 (m, 3H, C*H*H-CH_2-CN + CH_2-CH_2-NAc), 1.43 (t, 3H, J=7.1Hz, CH_2CH_3)

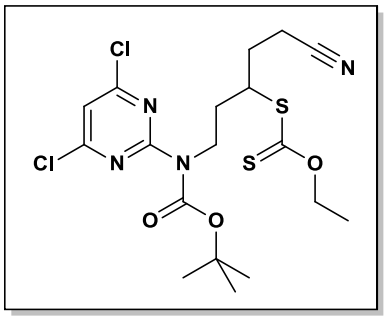
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.8 (*C*=S), 172.3 (*C*OCH_3), 161.9 (2 *C*-Cl), 159.8 (N-*C*-NAc), 118.9 (*C*N), 115.3 (Cl-C-*C*H), 70.3 (*C*$H_2$$CH_3$), 47.6 (*C*H-Xa), 43.5 (NAc-

CH_2), 32.2 (CH_2-CH_2-NAc), 29.9 (CH_2-CH_2-CN), 27.0 (CH_3), 14.9 (CH_2-CN), 13.7 (CH_2CH_3)

IR (ν, cm^{-1}, $CDCl_3$) 2962, 1688, 1558, 1530, 1450, 1423, 1392, 1369, 1241, 1112, 1049, 995

HRMS (EI+) Calcd. for $C_{15}H_{18}Cl_2N_4O_2S_2$: 420.0248 Found : 420.0244

***tert*-butyl (5-cyano-3-((ethoxycarbonothioyl)thio)pentyl)(4,6-dichloropyrimidin-2-yl)carbamate (5-104)**

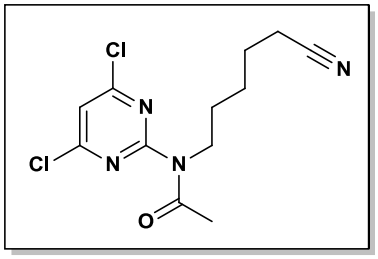


Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-102** (218mg, 0.69mmol, 1.0 eq.) and the xanthate **Xa-a** (165mg, 1.03mmol, 1.5 eq.) in AcOEt (0.7ml, 1.0mmol/ml), with DLP (41mg, 0.1 eq.). Flash chromatography on silica gel with DCM / EP = 80 / 20 afforded **5-104** (318mg, 97%) as light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.02 (s, 1H, *H*-aromatic), 4.64 (q, 2H, J=7.1Hz, C$H_2$$CH_3$), 4.04 (dd, 2H, *J* = 8.5, 6.1 Hz, CH_2-NBoc), 3.82 (dt, 1H, *J* = 12.2, 6.8 Hz, Xa-C*H*), 2.71-2.41 (m, 2H, CH_2-CN), 2.33-2.18 (m, 1H, CH*H*-CH_2-CN), 2.06 (m, 3H, C*H*H-CH_2-CN + CH_2-CH_2-NBoc), 1.54 (s, 9H, C(CH_3)$_3$), 1.43 (t, 3H, J=7.1Hz, CH_2CH_3)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 212.6 (*C*=S), 161.6 (2 *C*-Cl), 159.9 (N-*C*-NAc), 152.6 (*C*O), 119.0 (*C*N), 115.1 (Cl-C-*C*H), 83.2 (*C*Me_3), 70.3 (CH_2CH_3), 47.5 (*C*H-Xa), 45.0 (N-CH_2), 32.4 (CH_2-CH_2-NBoc), 30.0 (CH_2-CH_2-CN), 28.1 ((CH_3)$_3$), 14.9 (CH_2-CN), 13.8 (CH_2CH_3)

_N_-(5-cyanopentyl)-N-(4,6-dichloropyrimidin-2-yl)acetamide (5-105')



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-103** (98mg, 0.233mmol, 1.0eq.) in AcOEt (4.7ml, 0.05mmol/ml), with DLP (186mg, 2.0eq.). Flash chromatography on silica gel with AcOEt / EP = 10 / 90 afforded the prematurely reduced material **5-105'** (10mg, 14%) as light yellow oil.

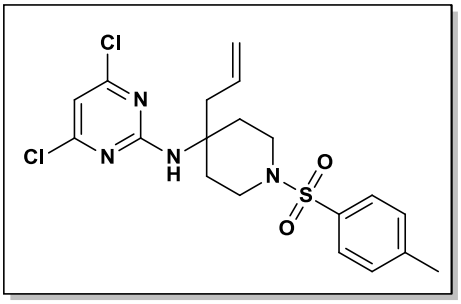
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.07 (s, 1H, *H*-aromatic), 4.06 (dd, 2H, J=7.0Hz, J=14.3Hz, C*H*$_2$-NAc), 2.55 (s, 3H, C*H*$_3$), 2.36 (t, 2H, J=7.2Hz, C*H*$_2$-CN), 1.77-1.60 (m, 4H, C*H*$_2$-CH$_2$-NAc + C*H*$_2$-CH$_2$-CN), 1.54-1.45 (C*H*$_2$-CH$_2$-CH$_2$-CN)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 172.3 (*C*OCH$_3$), 161.7 (2 *C*-Cl), 160.0 (N-*C*-NAc), 119.6 (*C*N), 115.2 (Cl-C-*C*H), 45.3 (NAc-*C*H$_2$), 26.9 (*C*H$_2$-CH$_2$-Nac + *C*H$_3$), 25.7 (*C*H$_2$-CH$_2$-CH$_2$-CN), 24.8 (*C*H$_2$-CH$_2$-CN), 17.0 (*C*H$_2$-CN)

IR (ν, cm^{-1}, $CDCl_3$) 3119, 2943, 2868, 1687, 1558, 1530, 1450, 1423, 1392, 1370, 1242, 1125, 1090, 1015, 975

HRMS (EI+) Calcd. for $C_{12}H_{14}Cl_2N_4O$: 300.0545 Found : 300.0544

N-(4-allyl-1-tosylpiperidin-4-yl)-4,6-dichloropyrimidin-2-amine (5-107)

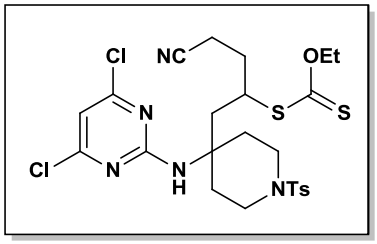


158mg trichloropyrimidine (0.86mmol, 1.2eq.) was dissolved by 1.8ml THF and then 212mg of the above precursor (0.72mmol, 1.0eq.) was added. The mixture was refluxed for 18 hours to finish the reaction. After work-up, flash chromatography on silica gel with AcOEt / EP = 20 / 80 afforded **5-107** (74mg, 23%) as white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.62 (d, *J* = 8.3 Hz, 2H, 2 *H*-Ts), 7.32 (d, *J* = 8.0 Hz, 2H, 2 *H*-Ts), 6.61 (s, 1H, *H*-aromatic), 5.63 (tdd, *J* = 17.5, 10.2, 7.4 Hz, 1H, CH_2-C*H*=CH_2), 5.00 (ddd, *J* = 18.9, 13.6, 2.0 Hz, 2H, CH_2-CH=C*H*$_2$), 4.85 (br s, 1H, N*H*), 3.54 (td, *J* = 11.8, 3.1 Hz, 2H, 2 CH*H*-NTs), 2.62 (d, *J* = 7.4 Hz, 2H, C*H*$_2$-CH=CH_2), 2.54 (dt, *J* = 12.1, 2.4 Hz, 2H, 2 C*H*H-NTs), 2.44 (s, 3H, C*H*$_3$), 2.30 (d, *J* = 13.7 Hz, 2H, 2 NHC-CH*H*), 1.77 (m, 2H, 2 NHC-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.4 (N-*C*-pyrimidine), 160.6 (2 *C*-Cl), 143.7 (*C*-Ts), 133.0 (*C*-Ts), 132.1 (CH_2-*C*H=CH_2), 129.8 (2 *C*H-Ts), 127.6 (2 *C*H-Ts), 119.3 (CH_2-CH=*C*H_2), 109.6 (*C*H-pyrimidine), 53.9 (NH-*C*), 41.8 (2 *C*H_2-NTs), 40.9 (*C*H_2-CH=CH_2), 33.8 (2 NHC-*C*H_2), 21.6 (*C*H_3)

S-(4-cyano-1-(4-((4,6-dichloropyrimidin-2-yl)amino)-1-tosylpiperidin-4-yl)butan-2-yl) O-ethyl carbonodithioate (5-108)

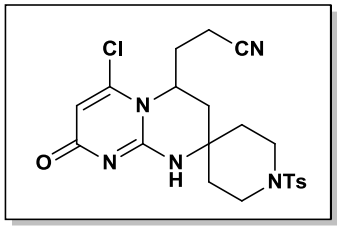


Following the general procedure **5-I** for the radical addition of xanthates on the corresponding olefins, the reaction was carried out with the solution of **5-107** (39mg, 0.089mmol, 0.5eq.) and the xanthate **Xa-a** (29mg, 0.178mmol, 1.0eq.) in AcOEt (0.4ml, 0.5mmol/ml), with DLP (11mg, 0.15eq.). Flash chromatography on silica gel with Acetone / DCM = 2 / 98 afforded **5-108** (49mg, 91%) as light yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.61 (d, 2H, *J* = 8.2 Hz, 2 *H*-Ts), 7.32 (d, 2H, *J* = 7.9 Hz, 2 *H*-Ts), 6.65 (s, 1H, , *H*-aromatic), 4.95 (s, 1H, N*H*), 4.67-4.54 (m, 2H, C*H*$_2$CH$_3$), 3.87 (dt, 1H, *J* = 9.2, 8.9, 2.1 Hz, Xa-C*H*), 3.65-3.53 (m, 2H, 2 CH*H*-NTs), 2.57-2.36 (m, 4H, 2 C*H*H-NTs + 2 NHC-CH*H*), 2.43 (s, 3H, C*H*$_3$), 2.40 (t, 2H, *J* =7.6 Hz C*H*$_2$-CN), 2.33 (dd, 1H, *J* = 15.4, 9.6 Hz, C*H*H-CHXa), 2.18 (dd, 1H, *J* = 15.4, 2.3 Hz, CH*H*-CHXa), 2.04-1.92 (m, 2H, C*H*$_2$-CH$_2$-CN), 1.77 (dt, 2H, *J* = 13.8, 13.6, 4.2 Hz, 2 NHC-C*H*H), 1.40 (t, 3H, J=7.1Hz, CH$_2$C*H*$_3$)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 213.0 (*C*=S), 161.5 (N-*C*-pyrimidine), 160.5 (2 *C*-Cl), 143.8 (*C*-Ts), 132.9 (*C*-Ts), 129.9 (2 *C*H-Ts), 127.6 (2 *C*H-Ts), 118.7 (*C*N), 110.1 (*C*H-pyrimidine), 70.9 (*C*H$_2$CH$_3$), 53.7 (NH-*C*-CH$_2$), 45.2 (*C*H-Xa), 41.7 (*C*H$_2$-NTs), 41.5 (*C*H$_2$-NTs), 40.1 (*C*H$_2$-CH-Xa), 34.6 (2 NHC-*C*H$_2$), 34.3 (2 NHC-*C*H$_2$), 33.2 (*C*H$_2$-CH$_2$-CN), 21.5 (*C*H$_3$), 14.7 (*C*H$_2$-CN), 13.8 (CH$_2$*C*H$_3$)

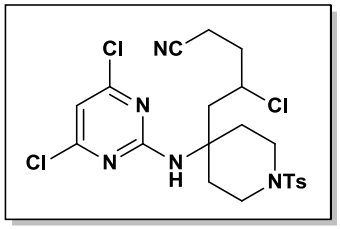
3-(6'-chloro-8'-oxo-1-tosyl-1',3',4',8'-tetrahydrospiro[piperidine-4,2'-pyrimido[1,2-a]pyrimidin]-4'-yl)propanenitrile (5-109)



Following the general procedure **5-II** for the radical cyclization of the corresponding xanthates, the reaction was carried out with the solution of **5-108** (49mg, 0.08mmol, 1.0 eq.) in AcOEt (1.4ml, 0.06mmol/ml), with DLP (32mg, 1.0eq.). Purification with preparative TLC plate with AcOEt / DCM = 20 / 80 afforded **5-109** (9.5mg, 26%) as light yellow oil, together with reduced product **5-109'** (2.8mg, 7%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.64 (d, 2H, *J* = 8.3 Hz, 2 *H*-Ts), 7.38 (d, 2H, *J* = 8.1 Hz, 2 *H*-Ts), 5.88 (s, 1H, , *H*-aromatic), 5.63 (br s, 1H, N*H*), 4.85 (tt, 1H, *J* = 6.4, 3.1 Hz, C*H*), 3.51-3.31 (m, 2H, 2 CH*H*-NTs), 2.76 (m, 2H, 2 C*H*H-NTs), 2.61-2.34 (m, 2H, CH_2-CN), 2.49 (s, 3H, CH_3), 2.23-2.12 (m, 2H, C*H*H-CH_2-CN + CH*H*-CH-C), 2.05-1.83 (m, 4H, CH*H*-CH_2-CN + 2 NHC-CH*H* + C*H*H-CH-C), 1.70-1.67 (m, 2H, 2 NHC-C*H*H)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.1 (*C*O), 158.5 (NH-*C*-pyrimidine), 151.3 (*C*-Cl), 144.4 (*C*-Ts), 132.2 (*C*-Ts), 130.1 (2 *C*H-Ts), 127.6 (2 *C*H-Ts), 118.6 (*C*N), 101.3 (*C*H-pyrimidine), 50.3 (NH-*C*-CH_2), 47.5 (*C*H), 41.9 (*C*H_2-NTs), 41.7 (*C*H_2-NTs), 38.8 (2 NHC-*C*H_2), 37.8 (2 NHC-*C*H_2), 36.2 (*C*H_2), 29.8 (*C*H_2), 21.6 (*C*H_3), 15.3 *C*H_2-CN ()
HRMS (EI+) Calcd. for $C_{21}H_{24}ClN_5O_3S$: 461.1288 Found : 461.1283

4-chloro-5-(4-((4,6-dichloropyrimidin-2-yl)amino)-1-tosylpiperidin-4-yl)pentanenitrile (5-110)



In the procedure for obtaining **5-109** and **5-109'**, a third product **5-110** was also seperated with AcOEt / EP = 30 / 70 as light yellow oil (12.6mg, 30%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.62 (d, 2H, *J* = 8.3 Hz, 2 *H*-Ts), 7.33 (d, 2H, *J* = 8.0 Hz, 2 *H*-Ts), 6.66 (s, 1H, ,*H*-aromatic), 5.01 (s, 1H, N*H*), 3.94 (td, 1H, *J* = 9.5, 7.0 Hz, Cl-C*H*), 3.58 (ddd, 2H, *J* = 12.4, 8.5, 4.4 Hz, 2 CH*H*-NTs), 2.58 (dd, 1H, *J* = 15.5, 2.0 Hz, CH*H*-CHCl), 2.57-2.40 (m, 4H, 2 C*H*H-NTs + 2 NHC-CH*H*), 2.51 (t, 2H, *J* = 7.3 Hz, CH_2-CN), 2.46 (s, 3H, CH_3), 2.22 (dd, 1H, *J* = 15.6, 9.6 Hz, C*H*H-CHCl), 1.98 (dd, 2H, *J* = 13.9, 7.0 Hz, CH_2-CH_2-CN), 1.93-1.75 (m, 2H, 2 NHC-C*H*H)

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.6 MHz) 161.6 (N-*C*-pyrimidine), 160.2 (2 *C*-Cl), 143.8 (*C*-Ar), 133.0 (*C*-Ar), 129.9 (2 *C*H-Ar), 127.6 (2 *C*H-Ar), 118.4 (*C*N), 110.1 (*C*H-pyrimidine), 55.6 (*C*H-Cl), 53.6 (NH-*C*-CH_2), 44.5(*C*H_2-CH-Cl), 41.8 (*C*H_2-NTs), 41.4 (*C*H_2-NTs), 33.8 (2 NHC-*C*H_2), 33.5 (2 NHC-*C*H_2), 35.3 (*C*H_2-CH_2-CN), 21.6 (*C*H_3), 14.6 (*C*H_2-CN)

MS (NH_3 ionisation) 517, 519, 521 (M^+), 518, 520, 522 (MH^+)