Application of Xanthates to the Synthesis of Azaindanes and to the C-H Functionalization of Heteroaromatics

Qi Huang

NNT: 2017SACLX114

Thèse de doctorat

APPLICATION OF XANTHATES TO THE SYNTHESIS OF AZAINDANES AND TO THE C-H FUNCTIONALIZATION OF HETEROAROMATICS

Thèse de doctorat de l'Université Paris-Saclay
préparée à l'École Polytechnique

École doctorale n°573 Interfaces: approches interdisciplinaires, fondements, applications et innovation
Spécialité de doctorat: Chimie

Thèse présentée et soutenue à Palaiseau, le 19 décembre 2017, par

M. Qi HUANG

Composition du Jury :

Isabelle GILLAIZEAU Professeur, Université d'Orléans (UMR 7311)	Présidente
Philippe BELMONT Professeur, Université Paris Descartes (UMR 8638)	Rapporteur
Alejandro PEREZ-LUNA Docteur, Université Pierre et Marie Curie Paris 6	Rapporteur
David BERNIER Docteur, Bayer Cropscience	Examinateur
Laurent EL KAIM Professeur, ENSTA	Examinateur
Samir Z. ZARD Professeur, Ecole Polytechnique (UMR 7652)	Directeur de thèse

THESE DE DOCTORAT

DE

L'UNIVERSITÉ PARIS-SACLAY

PRÉPARÉE À

ECOLE POLYTECHNIQUE

Ecole Doctorale n°573 Interfaces:
approches interdisciplinaires, fondements, applications et innovation

Spécialité de doctorat : CHIMIE

APPLICATION OF XANTHATES TO THE SYNTHESIS OF AZAINDANES AND TO THE C-H FUNCTIONALIZATION OF HETEROAROMATICS

Par

Monsieur

Qi HUANG

Thèse présentée et soutenue à Palaiseau, le 19 décembre 2017:

Composition du Jury :

Prof. Isabelle GILLAIZEAU	Université d'Orléans	Présidente
Prof. Philippe BELMONT	Université Paris Descartes	Rapporteur
Dr. Alejandro PEREZ-LUNA	Université Pierre et Marie Curie Paris 6	Rapporteur
Dr. David BERNIER	Bayer Cropscience	Examinateur
Prof. Laurent EL KAIM	ENSTA	Examinateur
Prof. Samir Z. ZARD	Ecole Polytechnique	Directeur de thèse

In memory of my grandparents

Acknowledgements

First of all, I would like to express my deepest gratitude to my supervisor Prof. Samir Z. Zard. It is in fact from your master classes that I began to learn how to push electrons. It is also from that time that I got to know about radical chemistry. Before that, I never thought that radical chemistry would be not as radical as we learned in bachelor courses. During the three years' Ph.D life, you have taught me how to be a real researcher with amazing thoughts, rather than a technician. You are always available for discussion. Thank you for your advices and encouragements during tough times. Your passion for chemistry has motivated me to finish these projects and light my future.

I would like to thank all the members of the jury committee, Prof. Isabelle Gillaizeau, Dr. Alejandro Luna-Perez, Prof. Philippe Belmont, Dr. David Bernier and Prof. Laurent El Kaïm for sparing your time to evaluate this manuscript and come to my defense. Thank you for your suggestions.

I want to express my special thanks to Béatrice. Every time I need something, she is always ready to help. At the beginning of the alkylation of pyrazines, since no one has studied systematically the intermolecular addition of xanthates to heteroarenes in our group, I got stuck for some time. Her suggestions in respect of xanthates have forwarded this project and allowed me to get a deeper insight into the xanthate-based Minisci reaction. I am deeply fascinated by your techniques, your thoughts and I really learn a lot of things from you.

I want to thank Dr. Yvan Six for the Monday problem sessions and your kindness. I learned a lot from the exercises.

I would also like to thank Dr. Ling Qin for the discussions we had about alkylation of pyrazines at the end of your Ph.D and also personal things. My thanks go equally to Dr. Songzhe Han and Dr. Wenbin Wu for the unforgettable time we had together.

I also want to thank Vincent R. for providing me many ideas and also many heteroarenes. Thank you also for taking time to read and correct this manuscript. I also want to express my thanks to Dr. Andrey Mikhaylov for your kind advice. I would like to thank all of the LSO members: Eloi, Oscar, Bastien, Alexis, Gabriela,

Wei, Qing, Arnaud, Geoffroy, David, Dung, Lucile, Shiguang, Xuan, Shiwei, Ricardo, Julien and finally Vincent J. for HRMS analysis.

Lastly, I want to express my love and gratitude to my family and relatives, my parents for their support, my brothers and sisters, and especially my lovely niece. It is with your encouragement and support that I can go through all the difficultites.

Thank you all!

Contents

Abbreviations

Ac	**acetyl**
AIBN	**2,2'-azo-*bis*-isobutyronitrile**
Ar	**aryl**
Boc	***tert*-butoxycarbonyl**
BOM	**benzyloxymethyl acetal**
***t*-Bu**	***tert*-butyl**
Bz	**benzoyl**
cat.	**catalytic quantity**
***m*-CPBA**	***meta*-chloroperoxybenzoic acid**
CSA	**camphorsulfonic acid**
DBP	**dibenzoyl peroxide**
DBU	**1,8-diazabicyclo[5.4.0]undec-7-ene**
DCE	**1,2-dichloroethane**
DCM	**dichloromethane**
DLP	**dilauroyl peroxide**
DMA	***N,N*-dimethylacetamide**
DMAP	**4-dimethylaminopyridine**
DMF	***N,N*-dimethylformamide**
dppm	**1,1-bis(diphenylphosphino)methane**
DTBP	**di-*tert*-butyl peroxide**
EP	**petroleum ether**
Et	**ethyl**
HMDS	**bis(trimethylsilyl)amine**
Me	**methyl**
Ms	**mesyl**
Ph	**phenyl**
PhCl	**chlorobenzene**
NBS	***N*-bromosuccinimide**
NMP	***N*-methyl-2-pyrrolidone**
NPhth	**phtalimide**
Piv	**pivalate**

***i*-Pr**	**isopropyl**
TEA	**triethylamine**
TFA	**trifluoroacetic acid**
THF	**tetrahydrofuran**
TMS	**trimethylsilyl**
Xa	***O*-ethyl xanthate**
Stoich.	**stoichiometric**
TBS	***tert*-butyldimethylsilyl**
TIPS	**triisopropylsilyl**

℃	**degree Celsius**
equiv	**equivalent**
Hz	**hertz**
h	**hour**
M	**mole per litre**
NMR	**nuclear magnetic resonance**
Nu	**nucleophile**
ppm	**parts per million**
hν	**photochemical irradiation**
TLC	**thin layer chromatography**

Avant-Propos

Dans cette thèse, nous nous concentrons sur la préparation d'hétéroaromatiques, notamment les azaindanes et les pyrazines substituées en adoptant le processus de transfert radicalaire du groupement xanthate. Ces dérivés hétérocycliques sont difficilement accessibles par d'autres méthodes. Ces travaux sont réalisés sous la direction du Prof. Samir Z. Zard au Laboratoire de Synthèse Organique de l'Ecole Polytechnique. Ce manuscrit comprend quatre chapitres et une partie expérimentale.

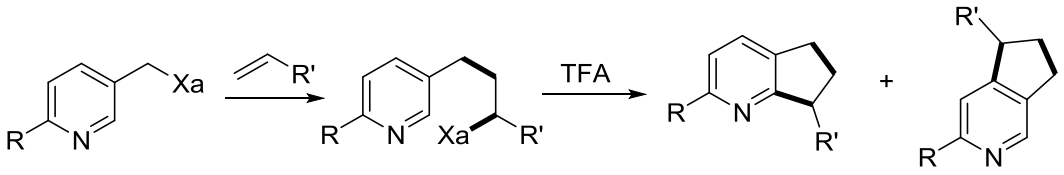
Dans le **chapitre 1**, le concept et le mécanisme général de la chimie radicalaire du xanthate sont brièvement présentés. L'application de la chimie des radicalaire de xanthate dans la fonctionnalisation C-H de différents hétéroaromatiques développés au cours des dernières trente années est ensuite résumée. La modification des hétéroaromatiques peut être réalisée généralement dans deux approches, soit par des cyclisations intramoléculaires sur des cycles hétéroaromatiques, soit par des alkylations intermoléculaires. Ce processus passe par une séquence d'addition radicalaire / oxydation / réaromatisation. Puisque le peroxyde sert à la fois d'initiateur et d'oxydant, il doit donc être utilisé en quantité stoechiométrique.

Dans le **chapitre 2**, le développement d'une nouvelle méthode pour la préparation d'azaindanes fonctionnalisés basée sur une séquence de l'addition intermoléculaire de xanthates de pyridylméthyle aux alcènes suivie de la cyclisation intramoléculaire sur des noyaux de pyridine est décrite. L'azaindane est composé d'un cycle pyridine fusionné avec un cycle à cinq atomes de carbone. En raison de la forte contrainte du cycle, cette famille de composés n'est pas facilement accessible. Les méthodes pour la préparation des azaindanes peuvent être divisée en deux catégories, par la construction du cycle pyridine ou la construction de la partie cyclopentène.

Notre méthode appartient à la cyclisation radicalaire sur le cycle pyridine pour construire le cycle cyclopentène. De multiples tentatives préliminaires dans la cyclisation pour la préparation d'azaindanes n'ont pas pu donner les azaindanes correspondants. La protonation du cycle pyridine avec le TFA est alors proposée dans l'espoir d'augmenter l'électrophilicité des pyridines vers les radicaux nucléophiles. En présence de 1,2 équivalents de TFA, la cyclisation des intermédiaires de xanthates dérivés de l'addition de 2-chloro-5-xanthylméthylpyridine à plusieurs partenaires oléfiniques s'est bien déroulée pour donner une série d'azaindanes fonctionnalisés,

avec les produits réduits non-cyclisés en rendements variables. L'atome de chlore peut également être remplacé par d'autres groupes fonctionnels, notamment les groupes fluor, trifluorométhyle, cyano, méthyle et méthoxy. Les xanthates correspondants peuvent être facilement préparés en moins de trois étapes à partir des produits de départ bon marché et facilement accessibles. Des additions intermoléculaires de ces xanthates à deux partenaires oléfiniques typiques, le *N*-vinylphtalimide et le *N*-allylphtalimide, ont été étudiées, suivies de cyclisations intramoléculaires pour donner les azaindanes désirés. Les azaindanes correspondants ont été obtenus généralement avec de bons rendements combinés et des régiosélectivités aussi élevées que 10: 1 ont été obtenues. Considérant que les pyridines réagissent intrinsèquement avec les radicaux nucléophiles aux positions C2, C4 et C6, les additions intermoléculaires et les cyclisations intramoléculaires des xanthates dérivés des 3-xanthylméthylpyridines ont également été étudiées et les azaindanes correspondants ont été obtenus avec de bons rendements.

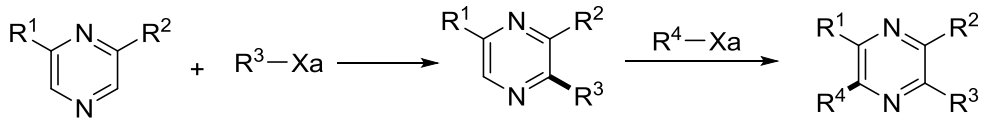
Cette stratégie est en outre étendue à la préparation de cyclohepta [*b*] pyridines basée sur une séquence de deux additions intermoléculaires, suivie d'une cyclisation intramoléculaire sur le cycle pyridine en présence de TFA. En outre, des études préliminaires sur la cyclisation des pyridines contenant le groupement xanthate sur les positions C4 et C6 ont également été effectuées et des travaux supplémentaires sont nécessaires pour divulguer l'étendue de cette méthode.



Une Route Modulaire aux Azaindanes

Dans le **chapitre 3**, nous présentons une approche expédiente pour la fonctionnalisation C-H intermoléculaire des pyrazines par la chimie radicalaire des xanthates. Sans addition de TFA, l'addition intermoléculaire de xanthate phtalimidométhyl à diverses pyrazines substituées s'est déroulée avec de bons rendements et de bonnes à excellentes régiosélectivités, en particulier pour les substrats de pyrazine hétérosubstitués. Cette méthode est également applicable à

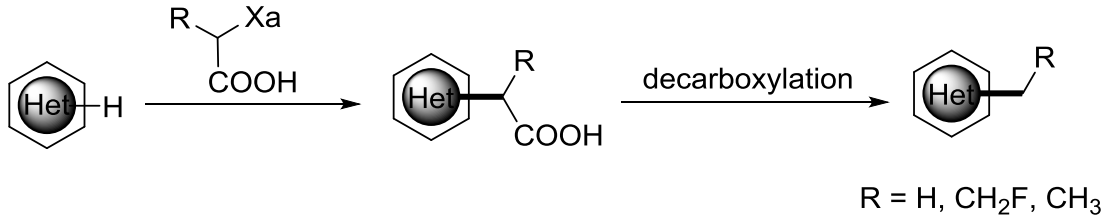
divers xanthates conduisant à des radicaux riches en électrons, donnant des pyrazines trisubstituées avec de bons rendements. Quant aux réactions impliquant des xanthates conduisant à des radicaux pauvres en électrons, le procédé est moins efficace et trois produits peuvent être obtenus. De plus, les pyrazines préparées par le présent procédé peuvent ensuite être impliquées dans une seconde alkylation pour donner des pyrazines tétrasubstituées hautement fonctionnalisées. La déprotection du groupement amine a été effectuée et plusieurs tentatives de cyclisation ont échoué à délivrer les produits bicycliques désirés jusqu'au moment. En présence de TFA, des pyrazines qui se sont avérées non réactives peuvent être alkylées pour donner les produits désirés avec de bons rendements. Cette méthode est également étendue avec succès à l'alkylation de plusieurs autres hétéroarènes, notamment la pyridine, la phtalazine, la caféine, l'isoquinoline et l'indole.



Alkylations Intermoléculaires de Pyrazines

Dans le dernier chapitre, **chapitre 4**, une méthode peu coûteuse pour la méthylation et l'éthylation des hétéroaromatiques est décrite. Le xanthate utilisé pour la méthylation, le carboxyméthylxanthate, peut être facilement préparé à l'échelle de la centaine de grammes à partir de la réaction de l'acide bromoacétique de bon marché et du sel de *O*-éthylxanthate de potassium. On a tenté d'alkyler divers hétéroaromatiques, y compris la pyrazine, la caféine, l'imidazopyridine, l'indolizidine, l'imidazopyridazine, le phénylimidazothiazole, l'imidazole, le benzothiazole, le flavone, etc. Dans plusieurs cas, la décarboxylation a eu lieu spontanément pour donner les produits méthylés. Pour ceux dont la décarboxylation ne s'est pas déroulée spontanément, les acides carboxyliques correspondants peuvent être généralement obtenus par simple trituration suivie de recristallisation. Pour ces produits d'acide carboxylique, la décarboxylation peut être induite dans des conditions assistées par micro-ondes avec du diméthylacétamide comme solvant. Des produits secondaires provenant de la transamidation de l'acide carboxylique avec du diméthylacétamide ont été isolés dans les cas où la décarboxylation a eu lieu à 220 °C. Les produits secondaires peuvent être facilement évités en remplaçant le solvant par un solvant plus robuste, la

N-méthyl-2-pyrrolidone. Cette méthode peut être étendue à la fluorométhylation ou à l'éthylation des hétéroaromatiques. Dans ce dernier cas, les acides 2-hétéroarylpropioniques correspondants appartiennent aux anti-inflammatoires non stéroïdiens les plus adoptés et le groupe éthyle peut également être révélé sous induction thermique.



Méthylation, Fluorométhylation et Ethylation des Hétéroarènes

Le manuscrit se termine par la partie expérimentale, qui compile les méthodes de préparation d'environ 220 produits décrits dans les trois chapitres précédents et leurs caractérisations par RMN ^{1}H, RMN ^{13}C, IR, HRMS et points de fusion pour les produits solides.

En résumé, basé sur la capacité des xanthates à médier à la fois l'addition intermoléculaire aux oléfines et la cyclisation intramoléculaire, nous avons développé une méthode pratique pour la préparation des azaindanes et la fonctionnalisation C-H des hétéroaromatiques. Cette méthode présente des conditions réactionnelles douces, une bonne tolérance au groupe fonctionnel et une bonne étendue du substrat et offre donc une nouvelle alternative à la fonctionnalisation des hétéroaromatiques dans le processus de développement du médicament. Les produits préparés ici seraient fastidieux à synthétiser par d'autres méthodes conventionnelles.

General Introduction

In this thesis, we focus on the preparation of heteroaromatics, notably azaindanes and substituted pyrazines by adopting the process of radical transfer of xanthate group. These heterocyclic derivatives are difficult to access by other methods.These works are accomplished under the supervison of Prof. Samir Z. Zard in the Laboratoire de Synthèse Organique in Ecole Polytechnique. This manuscript consists of four chapters and an experimental part.

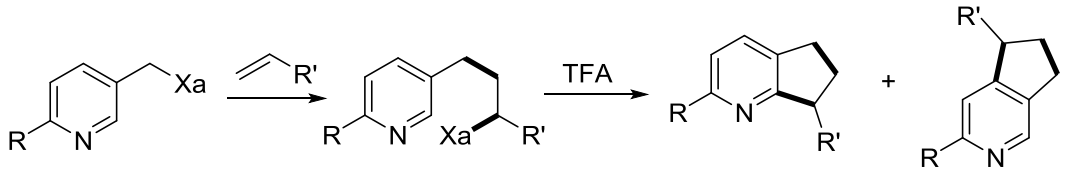
In **Chapter 1**, the concept and general mechanism of the radical chemistry of xanthate is firstly briefly introduced. Application of the xanthate radical chemistry in the C-H functionalization of different heteroaromatics developed over the last thirty years is then summarized. The modification of heteroaromatics can be achieved generally in two approaches, either by intramolecular cyclizations onto heteroaromatic rings or by intermolecular alkylations. This process proceeds *via* a sequence of radical addition/oxidation/rearomatization. Since the peroxide serves as both the initiator and oxidant, it should therefore be used in stoichiometric amount.

In **Chapter 2**, the development of a novel method for the preparation of functionalized azaindanes based on sequential intermolecular addition of pyridylmethyl xanthates to alkenes and subsequent intramolecular cyclization onto pyridine rings is described. Azaindane is composed of a pyridine ring fused with an all-carbon five-membered ring. Due to the large ring strain, this family of compounds is not easily accessible. The preparation of azaindanes can be divided into two categories, by the construction of the pyridine ring or the construction of the cyclopentene portion.

Our method belongs to the radical cyclization on pyridine ring to build the cyclopenetene ring. Multiple preliminary attempts in the cyclization for the preparation of azaindanes failed to give the corresponding azaindanes. Protonation of the pyridine ring with TFA is then proposed in the hope of increasing the electrophilicity of the pyridines towards nucleophilic radicals. In the presence of 1.2 equivalents of TFA, the cyclization of xanthate intermediates derived from addition of 2-chloro-5-xanthylmethylpyridine to several olefinic parteners proceeded well to give a series of functionalized azaindanes, together with the reduced noncyclized products in variable yields. The chlorine atom can be also replaced by other functional groups,

including fluorine, trifluoromethyl, cyano, methyl and methoxy groups. The corresponding xanthates can be easily prepared in less than three steps from the cheap and commercially available substrates. Intermolecular additions of these xanthates to two typical olefinic partners, *N*-vinylphthalimide and *N*-allylphthalimide, were studied, followed by intramolecular cyclizations to give the desired azaindanes. The corresponding azaindanes were obtained generally in good combined yields and regioselectivities as high as 10:1 were obtained. Considering that pyridines react inherently with nucleophilic radicals at C2, C4 and C6 positions, intermolecular additions and intramolecular cyclizations of xanthates derived from 3-xanthylmethylpyridines were also investigated and the corresponding azaindanes were obtained in good yields.

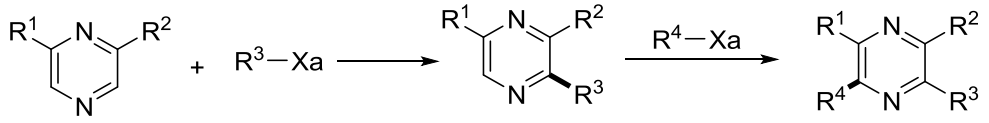
This strategy is further extended to the preparation of cyclohepta[*b*]pyridines based on two sequential intermolecular additions, followed by intramolecular cyclization on the pyridine ring in the presence of TFA. Besides, preliminary studies into the cyclization of pyridines containing the xanthate group on the C4 and C6 positions were also carried out and further work is required to disclose the scope of this method.



Modular Route to Azaindanes

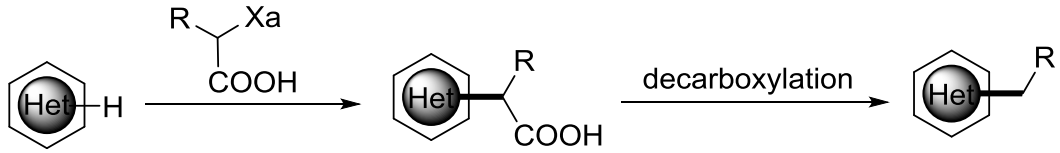
In **Chapter 3**, we present an expedient approach for the intermolecular C-H functionalization of pyrazines by the radical chemistry of xanthates. Without the addition of TFA, intermolecular addition of phthalimidomethyl xanthate to various substituted pyrazines proceeded in good yields and good to excellent regioselectivities, especially for heterosubstituted pyrazine substrates. This method is also applicable for various xanthates leading to electron rich radicals, affording trisubstituted pyrazines in good yields. As for the reactions involving xanthates leading to electron poor radicals, the process is less efficient and three products can be obtained. Moreover, pyrazines prepared by the present method can be then involved in a second alkylation to give highly functionalized tetrasubstituted pyrazines. Deprotection of the amine group was

carried out and several attempted cyclization failed to deliver the desired bicyclic products up to the moment. In the presence of TFA, pyrazines that were proved to be unreactive can be alkylated to give the desired products in good yields. This method is also successfully extended to the alkylation of several other heteroarenes, including pyridine, phthalazine, caffeine, isoquinoline and indole.



Intermolecular Alkylations of Pyrazines

In the last chapter, **Chapter 4**, an inexpensive method for the methylation and ethylation of heteroaromatics is described. The xanthate used for methylation, carboxymethyl xanthate, can be easily prepared in more than one hundred gram scale from the reaction of the cheap starting material bromoacetic acid and potassium *O*-ethyl xanthate salt. Alkylation of various heteroaromatics was attempted, including pyrazine, caffeine, imidazopyridine, indolizidine, imidazopyridazine, phenylimidazo-thiazole, imidazole, benzothiazole, flavone, etc. In several cases, the decarboxylation took place spontaneously to give the methylated products. For those of which the decarboxylation didn't proceed spontaneously, the corresponding carboxylic acids can be generally obtained by simple trituration followed by recrystallization. For these carboxylic acid products, the decarboxylation can be induced under microwave-assisted conditions with dimethylacetamide as the solvent. Side-products arising from transamidation of the carboxylic acid with dimethylacetamide were isolated in cases that the decarboxylation took place at 220 ℃. The side-products can be easily avoided by changing the solvent to a more robust solvent *N*-methyl-2-pyrrolidone. This method can be extended to the fluoromethylation or ethylation of heteroaromatics. In the latter case, the corresponding 2-heteroarylpropionic acids belong to the most adopted nonsteroidal anti-inflammatory drugs and the ethyl group can also be revealed under thermal induction.



R = H, CH_2F, CH_3

Methylation, Fluoromethylation and Ethylation of Heteroaromatics

The manuscript finishes with the experimental part, which compiles the methods for the preparation of about 220 products described in the previous three chapters and their characterization by ^{1}H NMR, ^{13}C NMR, IR, HRMS, and melting points for solid products.

In summary, based on the ability of xanthates to mediate both intermolecular addition to olefins and intramolecular cyclization, we have developed a convenient method for the preparation of azaindanes and the C-H functionalization of heteroaromatics. This method features mild reaction conditions, good functional group tolerance and good substrate scope and therefore offers a new alternative to the late-stage functionalization of heteroaromatics in the drug development process. Products prepared herein would be tedious to synthesize by other conventional methods.

Chapter 1

Introduction to the Radical Chemistry of Xanthates

1.1 Introduction

Compared to ionic chemistry, radical reactions are far less developed due to the prevailing notion that radicals are uncontrollable, unselective, difficult to scale up, etc.[1] Despite this misconception, spectacular discoveries have been made,[2] among which is the Barton-McCombie deoxygenation.

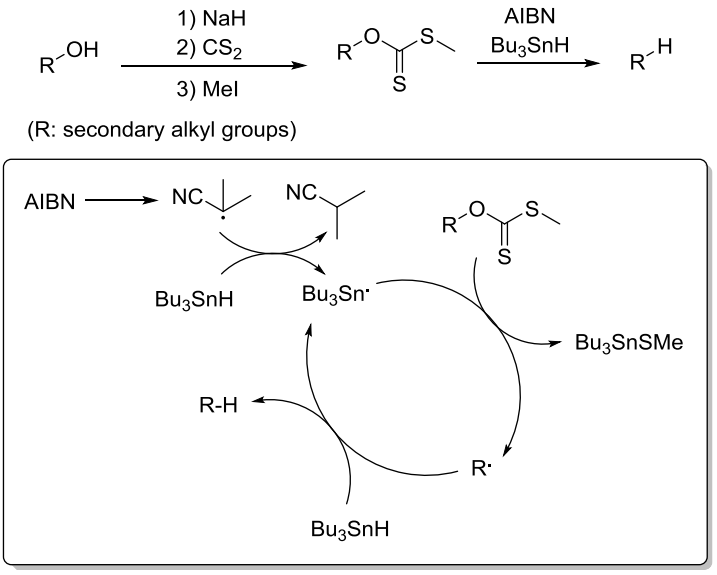
Discovered in 1975, the Barton-McCombie deoxygenation offers an efficient method to replace the hydroxyl group of secondary alcohols by a hydrogen atom (Scheme 1-1).[3] The alcohol is at first converted into the corresponding dithiocarbonate (more commonly named as xanthate) by nucleophilic addition of the alkoxide to CS_2, followed by methylation. The mechanism is as follows: Bu_3Sn•, produced from Bu_3SnH under the initiation with AIBN, adds to the radicophilic thiocarbonyl of the xanthate. This step is reversible even if the S-Sn bond is fairly strong (464 $kJ.mol^{-1}$). Cleavage of the O-R bond affords the more stable radical R• (usually secondary), which abstracts a hydrogen atom from Bu_3SnH to give the desired deoxygenated product, together with another molecule of Bu_3Sn• radical that propagates the chain. From the mechanism, the Barton-McCombie deoxygenation applies generally to secondary alcohols. For primary alcohols, fragmentation of the O-R bond is no longer favored due to the formation of a primary radical, also high in energy. As for tertiary alcohols, the thermal Chugaev elimination becomes a serious competing reaction.

---

1 (a) Walling, C. *Tetrahedron* **1985**, *41*, 3887. (b) Ingold, K. U. *Pure Appl. Chem.* **1997**, *69*, 241.

2 For selected general reviews of radical chemistry, see: (a) Kochi, J. K., Ed. *Free Radicals*, *Vol. 1: Dynamics of Elementary Processes*; Wiley- Interscience: New York, 1973. (b) Curran, D. P. *Synthesis* **1988**, *7*, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001. (e) Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*; Elsevier: Amsterdam, 2003. (f) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003.

3 Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.



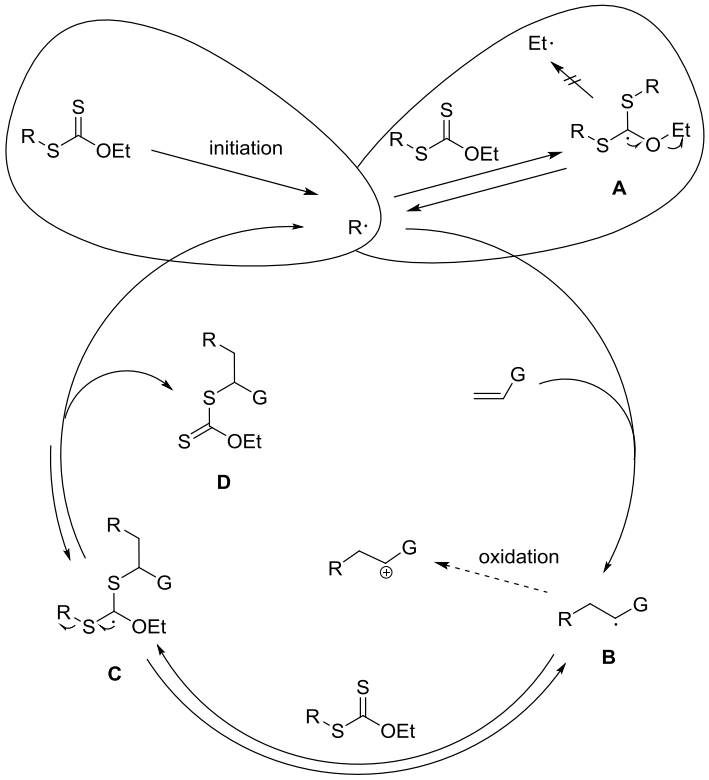
Scheme 1-1: The Barton-McCombie deoxygenation

During the clarification of the reaction mechanism, Barton *et al.* observed in one example a preferable cleavage of the weaker C-S bond.[4] This later led Zard *et al.* to the development of *S*-alkyl xanthates in the degenerative transfer of xanthates. This process provides a powerful solution to the pertaining problem, namely intermolecular C-C bond formation even with non-activated olefins. The mechanism is outlined in Scheme 1-2.[5] Radical R•, generated in a low concentration upon chemical or photochemical initiation, is captured by the radicophilic C=S bond of the starting xanthate to give tertiary intermediate **A**. Intermediate **A** is bulky and stabilized by three heteroatoms, thus avoiding disproportionation and slowing down dimerization. *β*-Scission of the C-S bond to give the active R• is more favorable compared to the cleavage of the C-O bond, which would lead to the formation of high energy ethyl radical. The reaction of R• and initial xanthate is therefore degenerate and the effective lifetime of R• is greatly increased. Since the concentration of the active radical R• is kept low, addition to even non-activated olefins can be easily achieved. Moreover, this kind of reaction can be conducted in a concentrated medium (1 M, for example, or even neat with no solvent), avoiding syringe pump techniques and high

[4] (a) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *J. Chem. Soc. Chem. Commun.* **1985**, 646. (b) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42,* 2329.
[5] Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

dilution.

Upon addition, the newly formed radical **B** can be scavenged by the starting xanthate to give another "dormant" radical **C**, which serves as a "reservoir" for radical **B**. Further reversible collapse of intermediate **C** will afford the final product **D**. It is worth mentioning that the final product is also a xanthate, which can be involved in another radical addition sequence, or modified through the rich ionic chemistry of sulfur. If **B** gets oxidized by SET to the peroxide, as is the case for the addition to arenes and heteroarenes, rearomatization delivers functionalized arenes and heteroarenes. The peroxide used therefore serves as not only the initiator, but also the oxidant, necessitating a stoichiometric amount (Scheme 1-2).

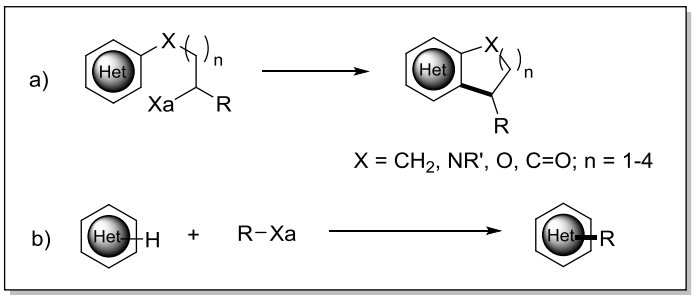


Scheme 1-2: General mechanism of the radical xanthate transfer

1.2 C-H Functionalization of heteroaromatics by xanthate radical chemistry

The degenerative radical reaction of xanthates offers a nontoxic, efficient method in organic synthesis. In the past three decades, this technology has been applied in both

addition to simple alkene and C-H functionalization of heteroaromatics. The latter can be divided into: (a) intramolecular cyclization onto heteroaromatics for the construction of polycyclic systems; and (b) intermolecular addition of xanthates directly to heteroaromatics (Scheme 1-3).



Scheme 1-3: Xanthate-mediated C-H functionalization of heteroaromatics

1.2.1 Intramolecular cyclizations onto heteroaromatics

Intramolecular addition to heteroaromatic ring constitutes an efficient approach to the formation of polycyclic systems. Xanthates applicable in this method can be prepared either from their corresponding alkyl halides or through intermolecular additions.[6]

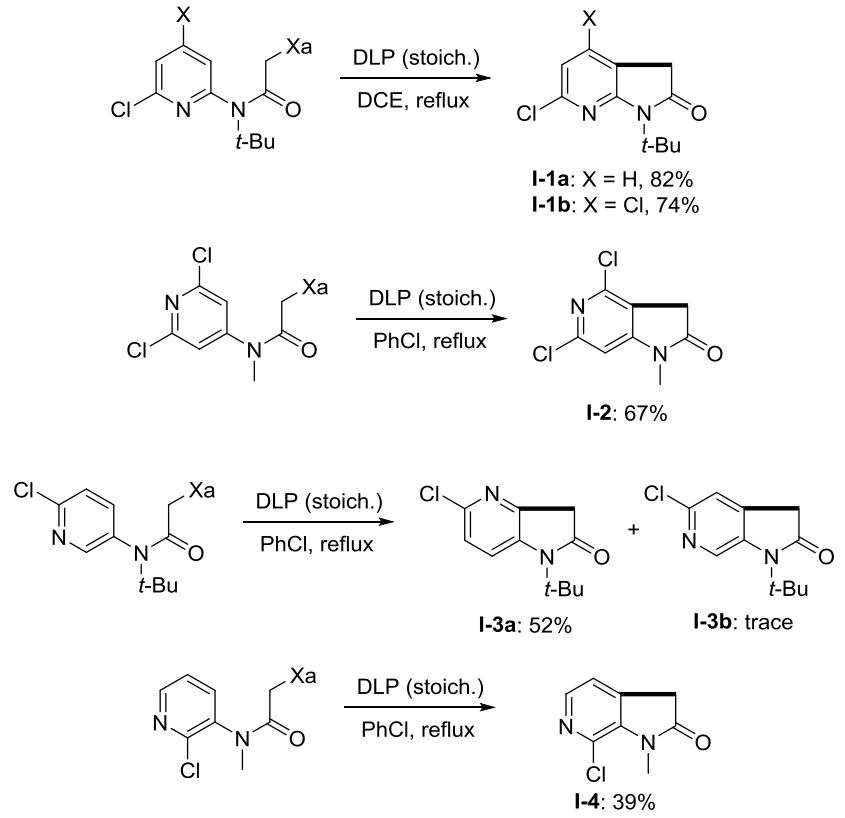
1.2.1.1. Cyclizations with xanthates prepared from alkyl halides

Cyclizations with xanthates prepared by substitution of alkyl halides can be nicely illustrated by the preparation of azaoxindoles (Scheme 1-4).[7] The four examples show the potential to prepare all isomeric azaoxindoles, starting from the appropriate aminopyridine. It should be mentioned that for the formation of 5-membered ring, the extranuclear nitrogen should bear a substituent (*e. g.*: Me, *tert*-butyl), for otherwise the reduction of xanthates will take place, instead of the desired cyclization. The *tert*-butyl group is particularly interesting since it facilitates the cyclization step through steric compression and can be removed later by treatment with trifluoroacetic acid.

---

[6] For a review of applications to the synthesis of heteroaromatics, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

[7] (a) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Heterocycles* **2012**, *84*, 291.



Scheme 1-4: Synthesis of azaoxindoles

1.2.1.2. Cyclizations with xanthates from intermolecular addition

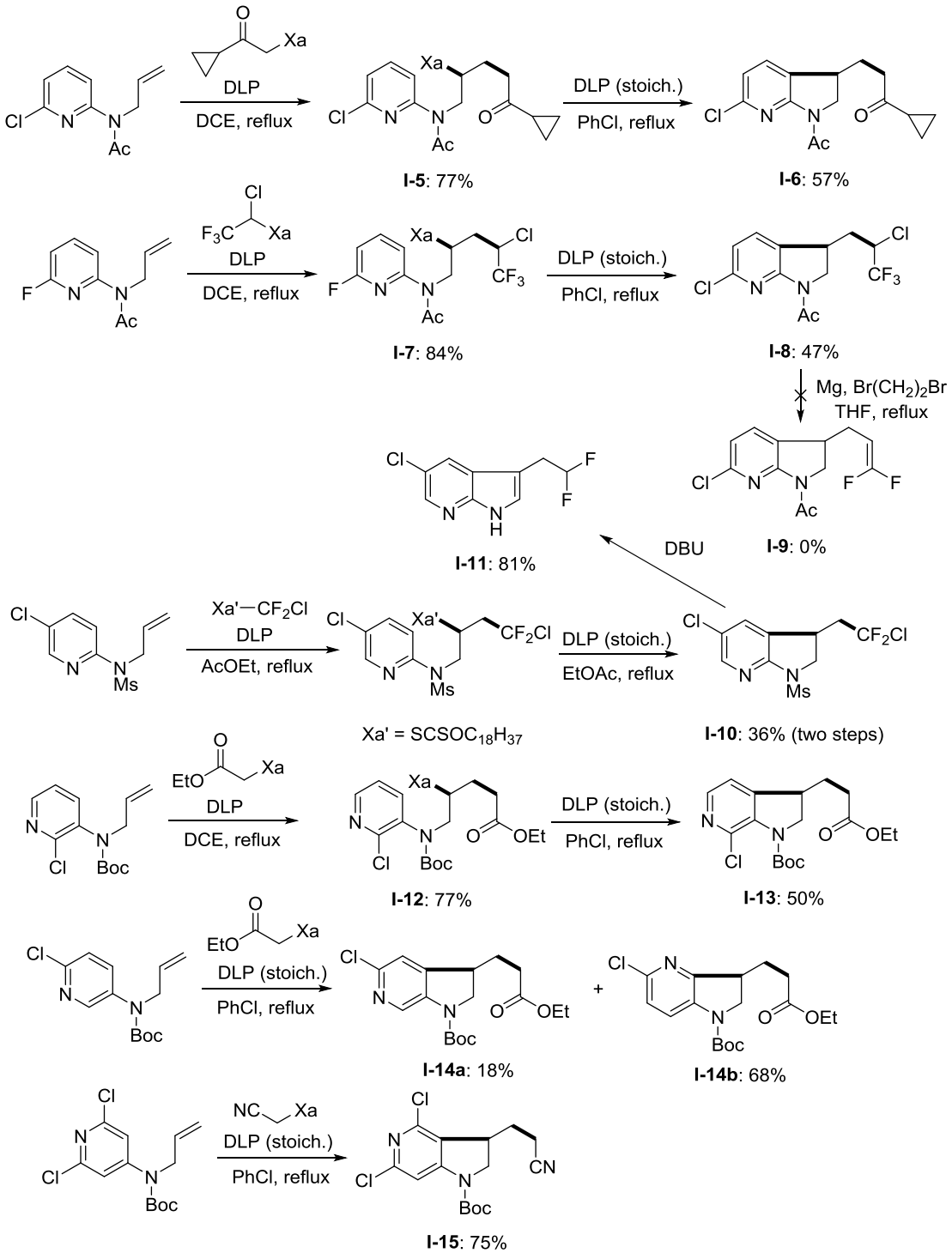
The method of intermolecular addition to olefins, followed by intramolecular cyclization, permits the construction of fused heterocycles, which would be tedious to prepare by other methods. To achieve this process, two approaches may be adopted: either the olefin or the xanthate group can be attached to the heteroaromatic ring.

Several isomeric azaindolines were readily prepared by this method from their corresponding *N*-allylaminopyridine (Scheme 1-5).[7] Generally, the bicyclic products could be obtained in useful yields. The α-chlorotrifluoromethyl derivative **I-8** could be transformed in principle into 1,1-difluoroalkene **I-9**, even though this conversion failed in this case under reaction conditions (Mg, $Br(CH_2)_2Br$ in THF under reflux) that were successful with other examples.[8] The azaindolines can also be readily converted into azaindoles. The azaindoline **I-10** containing the chlorodifluormethyl

[8] Salomon, P.; Kosnik, W.; Zard, S. Z. *Tetrahedron* **2015**, *71*, 7144.

group was obtained in a one-pot procedure in a yield of 36%. The reason the two-step process can be carried out in one pot without purification of the intermediate intermolecular adducts lies in that both steps are mediated by the same peroxide. Reaction of **I-10** with excess DBU at 90 ℃ for 14 h gave the corresponding azaindole **I-11** in 81% yield.[9] In contrast to the highly regioselective formation of **I-3a** and **I-3b**, bicyclic products **I-14a** and **I-14b** were obtained in a ratio of 1:4, with a good combined yield of 86%. Another feature of this chemistry is that the reaction is compatible with various functional groups, including halogen atoms and protected amino groups, allowing for further modifications, such as cross-coupling reactions.

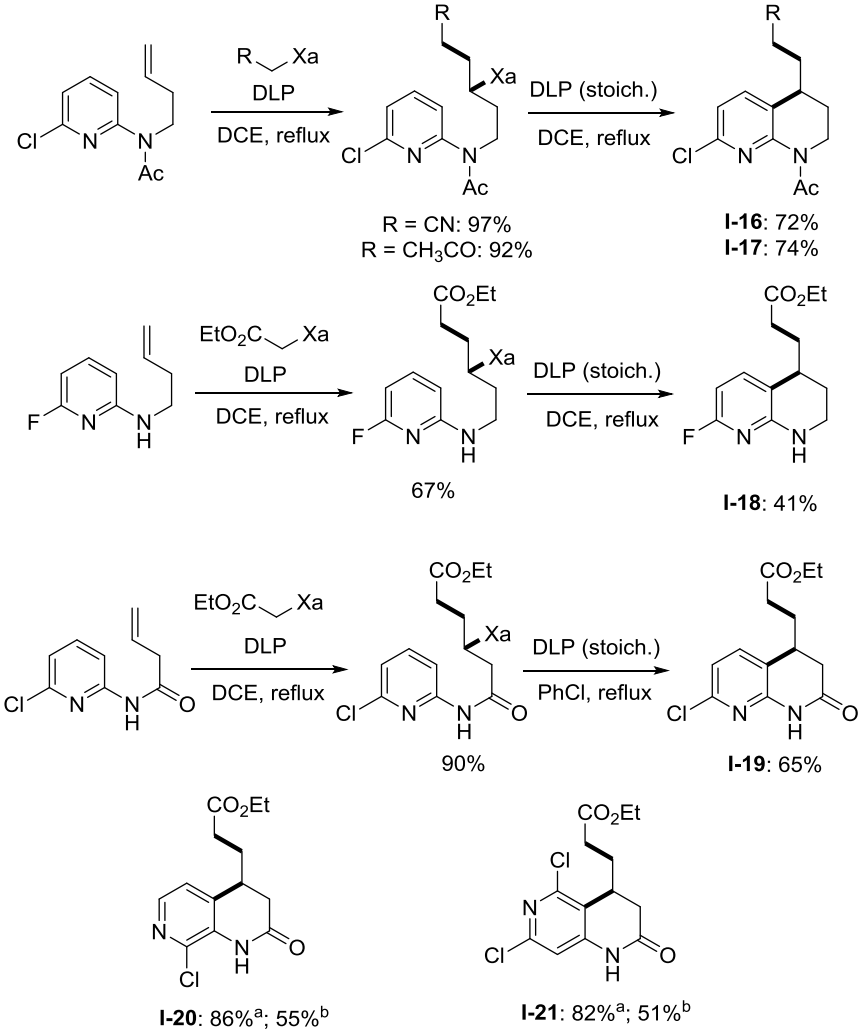
[9] Salomon, P.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 2926.



Scheme 1-5: Synthesis of azaindolines

This method also allows access to fused 6- and 7-membered rings with heteroaromatics, simply by altering the olefin counterpart. As depicted in Scheme 1-6,

the addition/cyclization sequence afforded tetrahydronaphthyridines **I-16**, **I-17**, fluorinated product **I-18**,[10] and three isomeric tetrahydronaphthyridinones **I-19**, **I-20** and **I-21** in good yields. It is worth noting that cyclization for the formation of 6-membered ring doesn't necessitate a substituent on the extranuclear nitrogen, in contrast to the cyclization for the formation of azaoxaindole in Scheme 1-4.



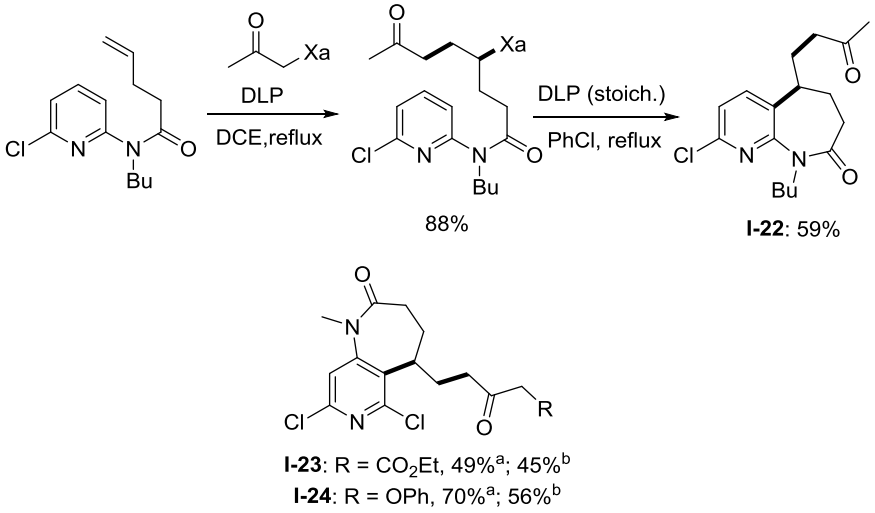
a) yields of radical addition to olefins; b) yields of cyclization

Scheme 1-6: Addition/cyclization for the formation of 6-membered rings

The formation of 7-membered rings can be illustrated by the preparation of pyridoazepinones **I-22** to **I-24** (Scheme 1-7). For the formation of **I-23** and **I-24**, in order to limit the dimerization of the cyclized radical intermediate and favor the

[10] Liu, Z.; Qin, L.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5976.

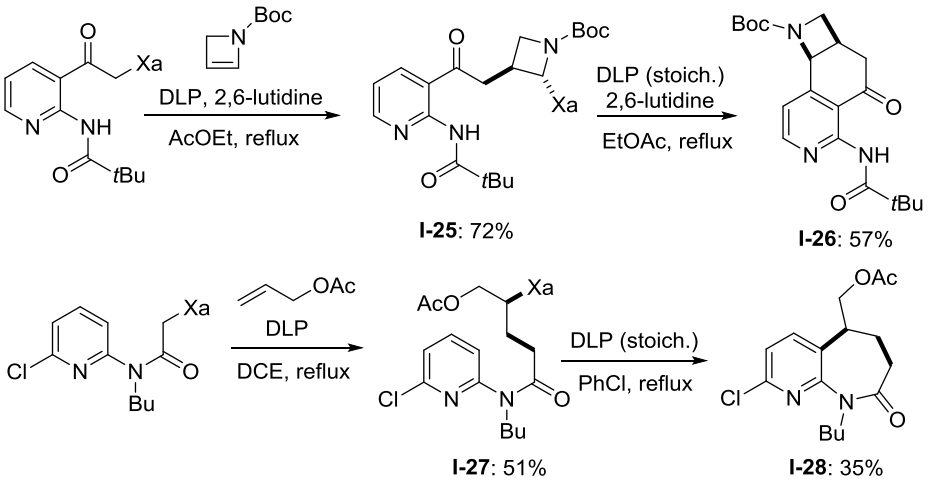
oxidation, the reaction was carried out with 1.1 equivalent of DBP at 73-75 ℃, with 20 mol % of DLP added every hour.[11]



Scheme 1-7: Addition/cyclization for the formation of 7-membered rings

The examples displayed above represent cases with the olefin attached to pyridine. The other complementary pathway, pictured in Scheme 1-8, begins with pyridines containing the xanthate group. Addition of the pyridine-bearing xanthate to Boc-protected azetine furnished the desired adduct **I-25** in 72% yield. Further treatment of this compound with stoichiometric DLP afforded the fused azatetralone **I-26** in a useful yield of 57%. The cyclization process might be favored by the hydrogen bonding between the hydrogen of the amide group and the ketone.[12] Pyridoazepinones **I-28** can be also prepared by this method. Instead of undergoing intramolecular ring closure as described in Scheme 1-4, the starting xanthate reacts preferentially with allyl acetate to give intermediate **I-27**, indicating that the cyclization process is relatively slow compared to the intermolecular addition. This complementary method greatly increases the flexibility and diversity for the construction of polyheterocycles.

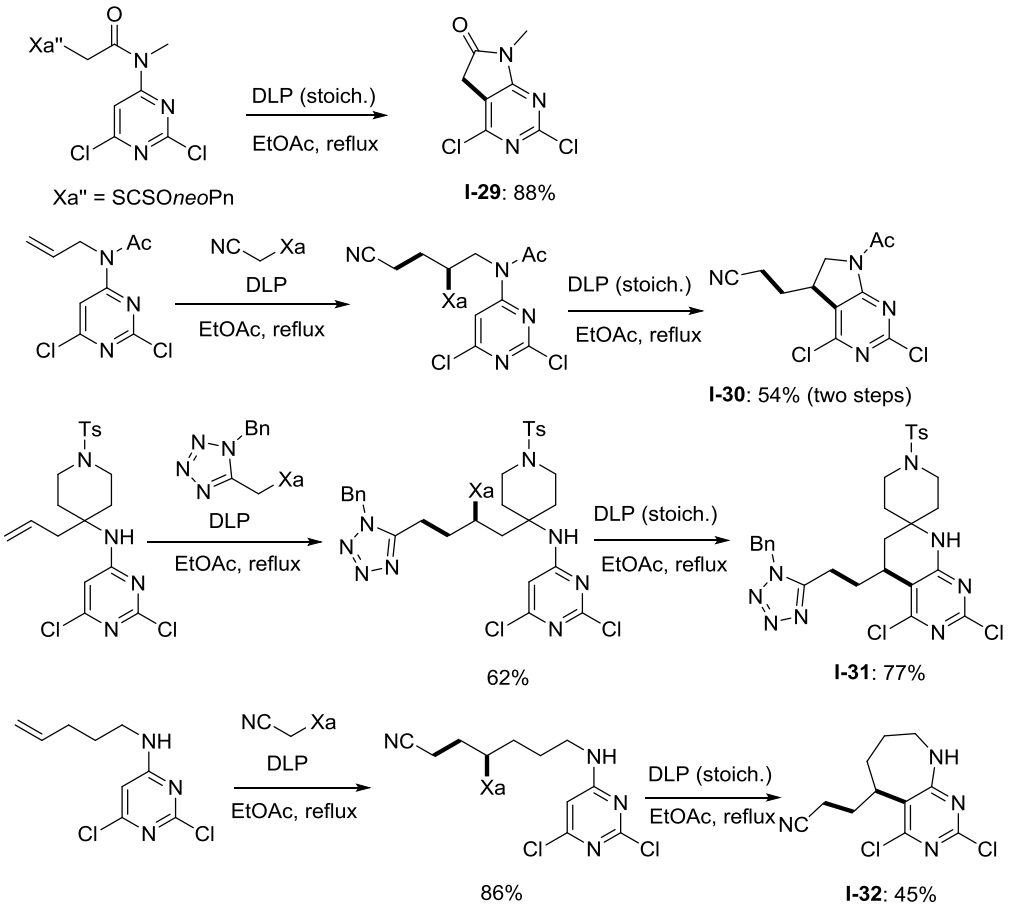
11 Petit, L.; Botez, I.; Tizot, A.; Zard, S. Z. *Tetrahedron Lett.* **2012**, *53*, 3220.
12 Han, S.; Zard, S. Z. *Tetrahedron* **2015**, *71*, 3680.



Scheme 1-8: Addition/cyclization with pyridines containing xanthates

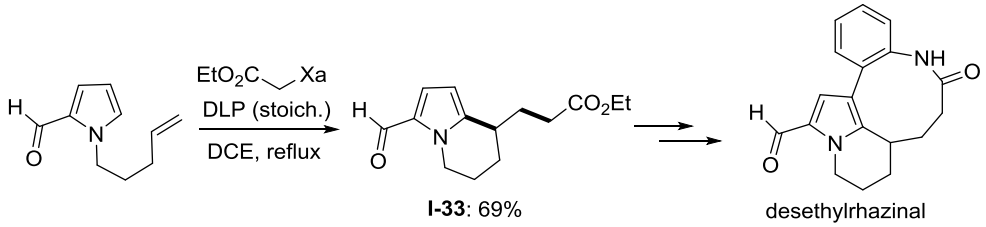
This technology was also extended to the fusion with other heteroaromatics. As shown in Scheme 1-9, annelations on pyrimidine ring afford diazaoxindole **I-29**,[13] diazaindoline **I-30**,[14] spirocyclic tetrahydroazanaphthyridine **I-31**[10] and pyrimidoazepine **I-32** in good yield. In the case of the formation of **I-30**, the acetyl group is crucial for the cyclization, since protection with Boc or other carbamates will otherwise give pyrimidinone through radical ring closure on the pyrimidine nitrogen.[14] Reasons underlying these divergent behaviors are still not clear at the moment.

[13] Laot, Y. PhD thesis, Ecole Polytechnique, 2011.
[14] Laot, Y.; Petit, L; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784.



Scheme 1-9: Ring closure on pyrimidine

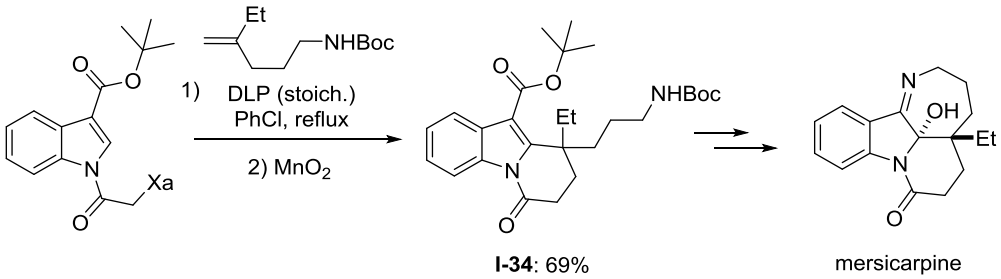
Cyclization on pyrroles, indoles and thiophenes should be in principle easier due to their lower aromaticity and easiness of oxidation. In 2011, Miranda *et al.* reported a tandem addition-cyclization sequence on a substituted pyrrole, affording the indolizidine product **I-33** in good yield.[15] This intermediate was then involved in regioselective iodination, Suzuki-Miyaura cross coupling, saponification and cyclisation to deliver the natural product (±)-desethylrhazinal .



Scheme 1-10: Annelation on pyrrole for the total synthesis of desethylrhazinal

[15] Paleo, E.; Osornio, Y. M.; Miranda, L. D. *Org. Biomol. Chem.* **2011**, *9*, 361.

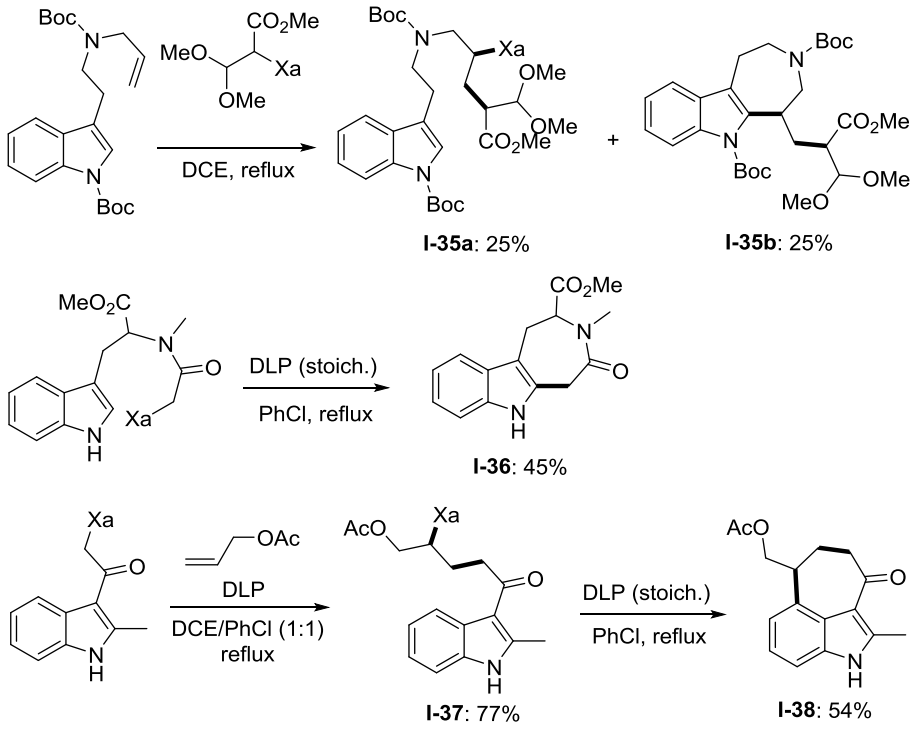
An analogous process was adopted in the formal synthesis of (±)-mersicarpine (Scheme 1-11).[16] Once the starting xanthate was totally consumed, an excess manganese dioxide was added into the crude reaction mixture to complete the oxidation. The desired intermediate **I-34** was obtained in 69% yield.



Scheme 1-11: Formal synthesis of mersicarpine

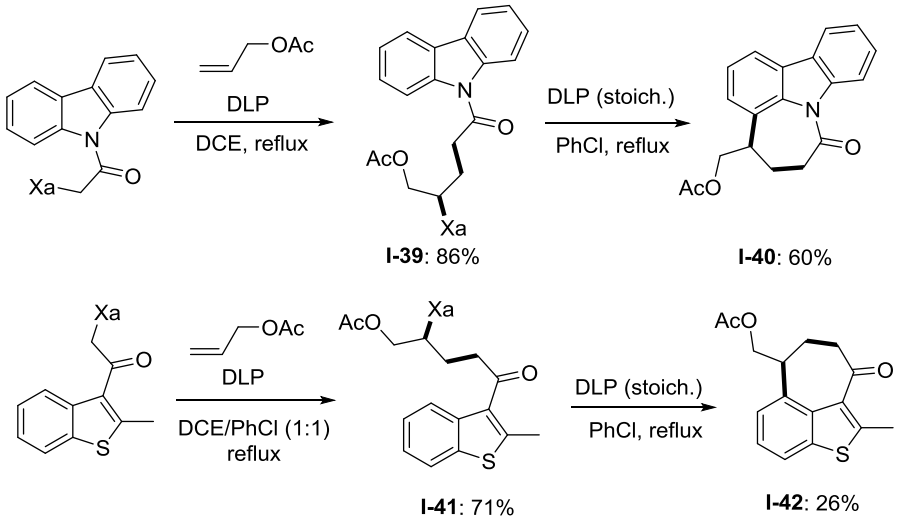
Access to indoles fused with a 7-membered ring is also possible, as illustrated in Scheme 1-12. During the synthesis of polycyclic alkaloid precursors, our colleagues prepared the key intermediate: a tryptophan-derived xanthate **I-35a**, together with a major side-product **I-35b**.[17] Bicyclic product **I-36** was obtained in 45% yield *via* cyclization of the starting xanthate at position-2. If position-2 of the indole ring is not accessible, as in the case of **I-37**, cyclization will take place preferentially at position-4 to deliver the tricyclic product **I-38** in moderate yield.[18]

16 Biéchy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800.
17 Tate, E.; Zard, S. Z. *Tetrahedron Lett.* **2002**, *43*, 4683.
18 Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731.



Scheme 1-12: Indoles fused with 7-membered rings

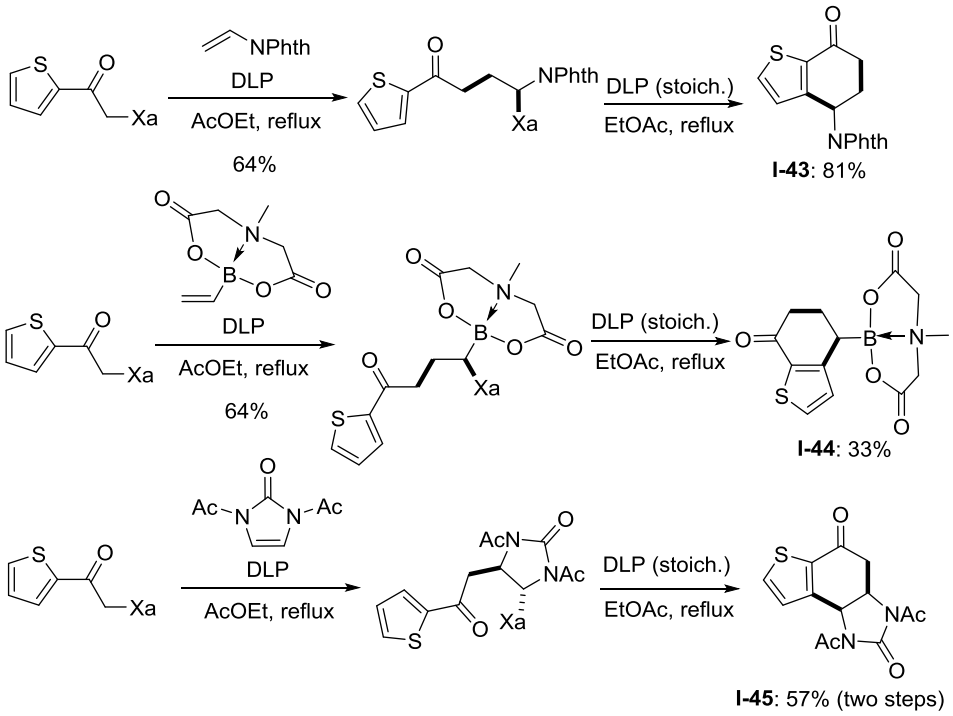
Cyclizations leading to the formation of 7-membered rings can be also applied to carbazole and benzothiophene derivatives, as shown in Scheme 1-13. The annelated tricyclic products **I-40** and **I-42** were obtained in 60% and 26% yield, respectively.[18]



Scheme 1-13: Annelation of 7-membered rings with carbazole and benzothiphene derivatives

As for thiophene, several recent examples have been reported (Scheme 1-14).

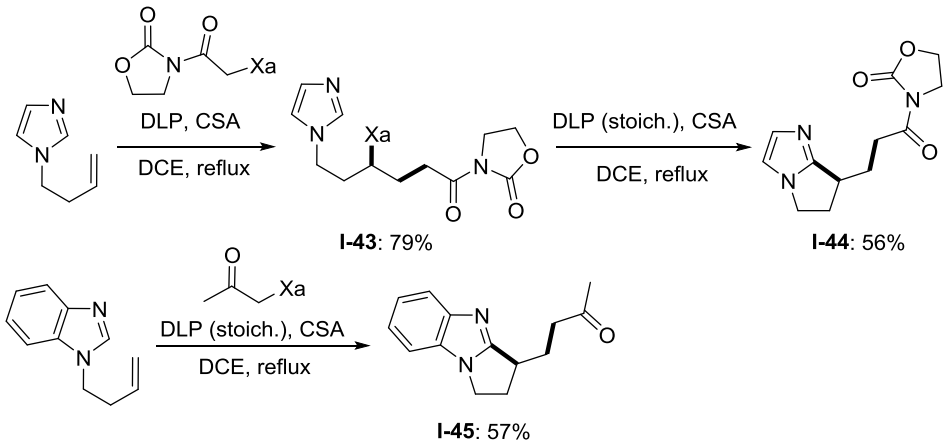
Cyclization to deliver ketone **I-43** proceeded in 81% yield, in spite of the large steric hindrance of the phthalimido group.[19] Exposure of the radical adduct containing a MIDA boronate group to stoichiometric amount of DLP afforded ketone **I-44** in only 33% yield, which might be caused by the steric hindrance of the large MIDA boronate.[20] Bicyclic product **I-45**, which contains protected 1,2-diamine motif, was obtained in a one-pot process in 57% yield.[21]



Scheme 1-14: Annelation around thiophene

Azole-derived substrates, however, requires a strong acid additive, such as CSA, which promotes the radical addition to the heteroaromatic ring. The acid also protects the sensitive xanthate group from the nucleophilic attack by the basic nitrogen of the azole. Cyclization of imidazole **I-43** afforded **I-44** in good yield in the presence of 2 equivalents of CSA. In the case of benzimidazole, the intermediate was not isolated and the desired tricyclic product **I-45** was obtained in 57% yield (Scheme 1-15).[22]

[19] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656.
[20] Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2015**, *137*, 6762.
[21] Han, S.; Zard, S. Z. *Tetrahedron* **2015**, *71*, 3680.
[22] Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345.



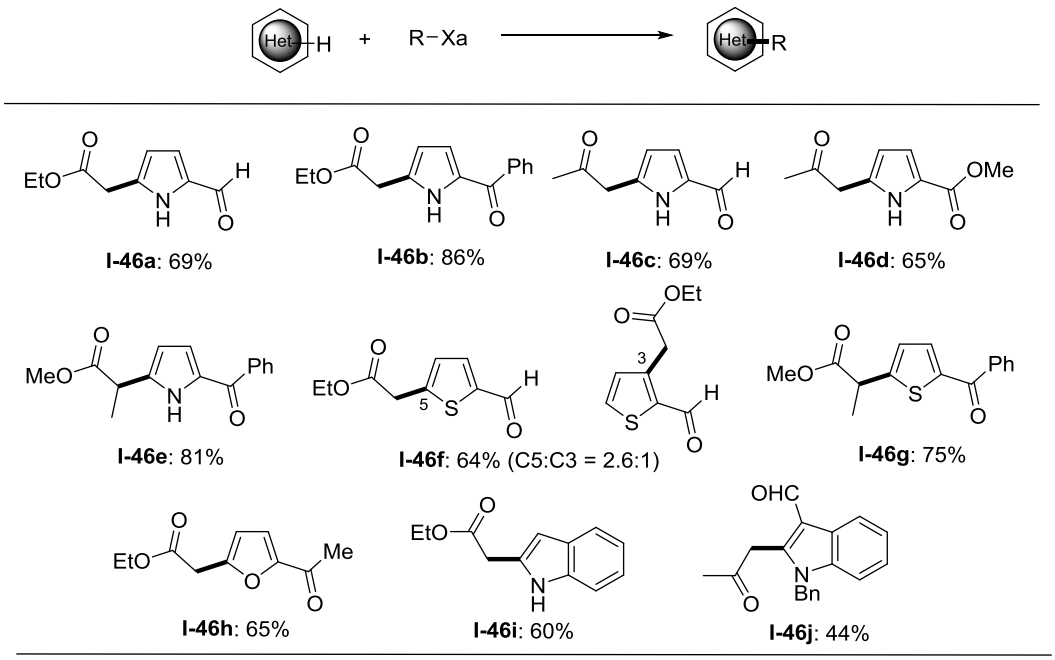
Scheme 1-15: Cyclizations on imidazole and benzimidazole derivatives

1.2.2 Intermolecular addition of xanthates to heteroaromatics

While the intramolecular addition to heteroaromatics has been well developed in our group, intermolecular alkylation remained much less explored. Recently, several examples have been disclosed by the group of Miranda. This method offers a metal-free approach to the direct functionalization of heteroarenes.

In 2003, Miranda *et al.* developed an efficient method of direct intermolecular alkylation of heteroaromatics involving xanthate radical chemistry. The reactions have been successfully applied to the functionalization of pyrroles (**I-46a-e**), thiophenes (**I-46f-g**), furans (**I-46h**), and indoles (**I-46i-j**), by treating heteroarenes and xanthates in degassed DCE with DLP, added slowly over 12 h. This type of reaction normally proceeds with good to excellent yields (Scheme 1-16).[23] The reaction can also be carried out at room temperature using triethylborane in air as the initiator, $FeSO_4$ as the co-oxidant in a mixed solvent ($DCM/H_2O/EtOH = 6:3:1$).[24]

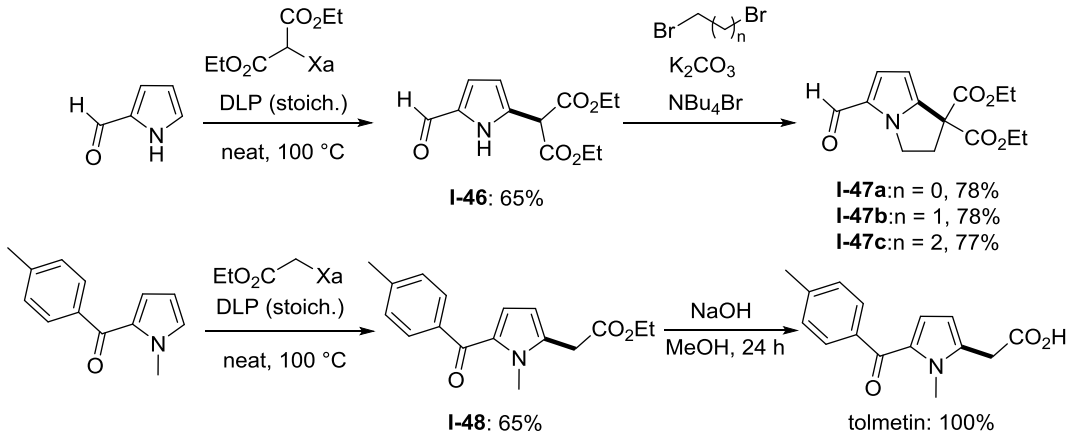
[23] Osornio, Y. M.; Cruz-Almanza, R.; Jiménez-Montaño, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316.
[24] Guerrero, M.A.; Miranda, L. D. *Tetrahedron* **2006**, *47*, 2517.



Scheme 1-16: Radical alkylation of heteroarenes

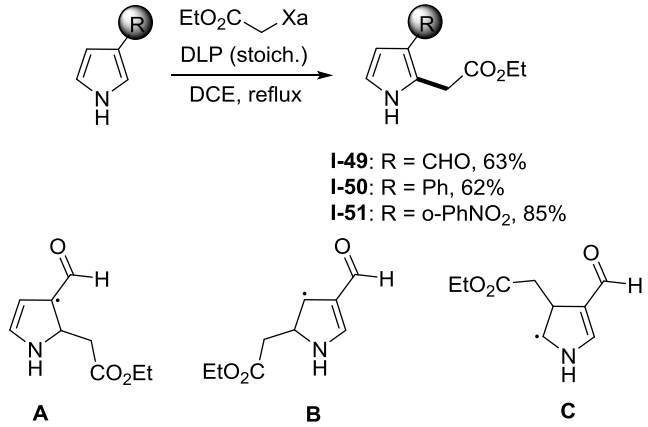
Counterintuitive is that the alkylation process is even possible under solvent-free conditions, as depicted in Scheme 1-17.[25] The liquid xanthate was chosen to solubilize the solid pyrrole. DLP was added at the end of every minute and the reaction was complete in 10 minutes. **I-46** was isolated in 65% yield and it was then utilized in the construction of bicyclic products **I-47** with different chain lengths. The alkylated product **I-48** was obtained in 65% yield, followed by hydrolysis to afford the nonsteroidal anti-inflammatory agent tolmetin in quantitative yield. The high efficiency of this method hinges on the relatively low radical concentration in the radical chemistry of xanthates.

[25] Flórez-López, E.; Gomez-Pérez, L. B.; Miranda, L. D. *Tetrahedron Lett.* **2010**, *51*, 6000.



Scheme 1-17: Intermolecular alkylations of pyrrole

The radical addition process often proceeds with high regioselectivity, as illustrated by the alkylation of 3-substituted pyrroles in Scheme 1-18.[26] Addition of the electrophilic xanthate to pyrrole takes place on the sterically more hindered position-2, delivering 2,3-disubstituted products **I-49**-**51** in good yields. Possible rationale for this high regioselectivity is the higher stability of the intermediate **A** (tertiary, allylic and α to a carbonyl group) over **B** (secondary and allylic) and **C** (secondary and α to nitrogen atom). Considering that the addition process is reversible and the oxidation step by peroxide is relatively slow, intermediate **A** is therefore dominant in the reaction medium and oxidation gives the corresponding regioisomer.



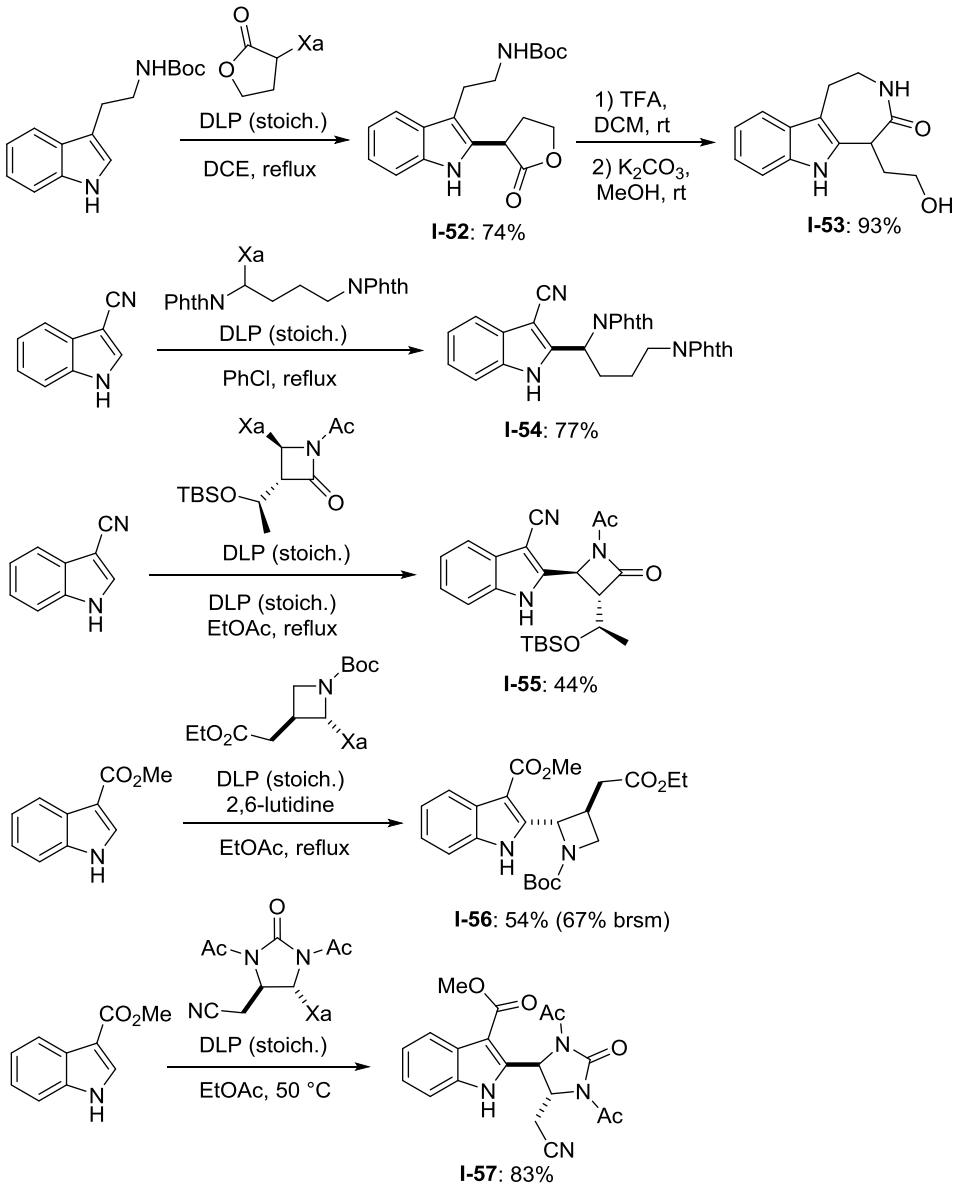
Scheme 1-18: Regioselective alkylation of 3-substituted pyrroles

Substitution of indoles has also been developed to construct complex structures

[26] Guadarrama-Morales, O.; Méndez, F.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515.

(Scheme 1-19). For the synthesis of azepino[4,5-*b*]indolone derivatives, Miranda *et al.* first implemented intermolecular oxidative additions to Boc-protected tryptamine, followed by a deprotection/cyclization sequence. The free primary amine of tryptamine needs to be protected to avoid decomposition of the xanthate group.[27] The adduct **I-52** was obtained in 74% yield, and the desired azepinoindolone **I-53** was delivered in 93% yield upon treatment with TFA and neutralization. Other moieties can also be introduced to afford heteroarenes with complex structures. The phthalimidomethyl-containing xanthate reacted readily with 3-cyanoindole to give **I-54** in good yield.[28] A complex *β*-lactam xanthate added to 3-cyanoindole to give indole **I-55** in moderate yield.[29] As for the formation of **I-56**, even though 2 equivalent of azetidine xanthate was used, part of the starting indole was recovered, implying the difficulty of this process.[12] The secondary xanthate, resulting from intermolecular addition of cyanomethyl xanthate to protected 1,2-diamine, underwent intermolecular addition to indole at 50 ℃ and afforded the desired product **I-57** in high yield of 83%.[30]

[27] Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martínez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388.
[28] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 3554.
[29] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Heterocycles* **2010**, *82*, 263.
[30] Han, S.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 5386.

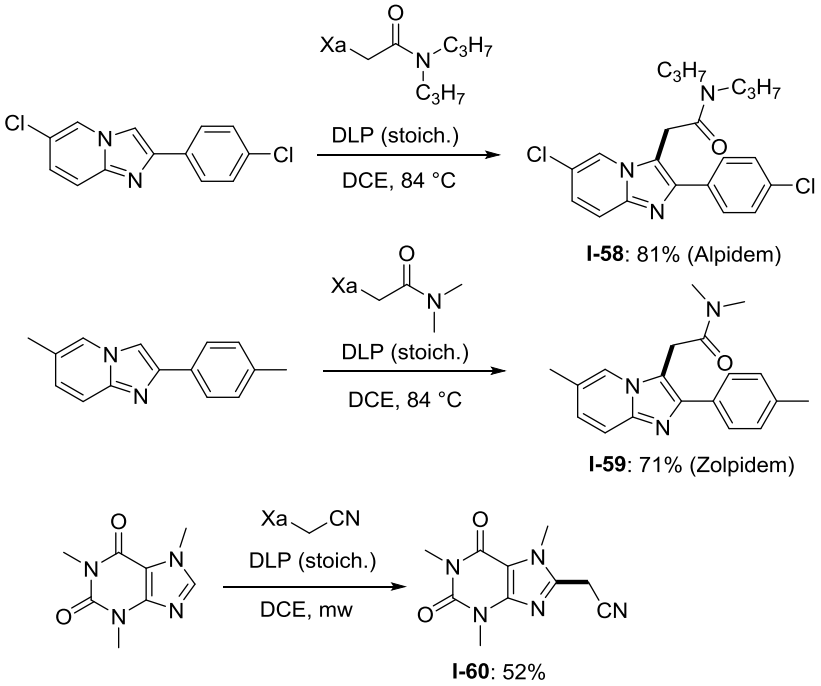


Scheme 1-19: Intermolecular addition to indoles

Recently, Li *et al.* developed the oxidative alkylation of imidazopyridine *via* xanthate radical chemistry.[31] Various electrophilic alkyl groups were introduced, including ester, cyano, ketone and amide. Formal synthesis of alpidem (**I-58**) and zolpidem (**I-59**) were also achieved in high yields. Miranda *et al.* disclosed almost simultaneously the same type of reaction under microwave irradiation.[32] The latter method was also applied to the functionalization of caffeine and substituted product

[31] Wang, S.; Huang, X.; Ge, Z.; Wang, X.; Li, R. *RSC Adv.* **2016**, *6*, 63532.
[32] Pérez, V. M.; Fregoso-López, D.; Miranda, L. D. *Tetrahedron Lett.* **2017**, *58*, 1326.

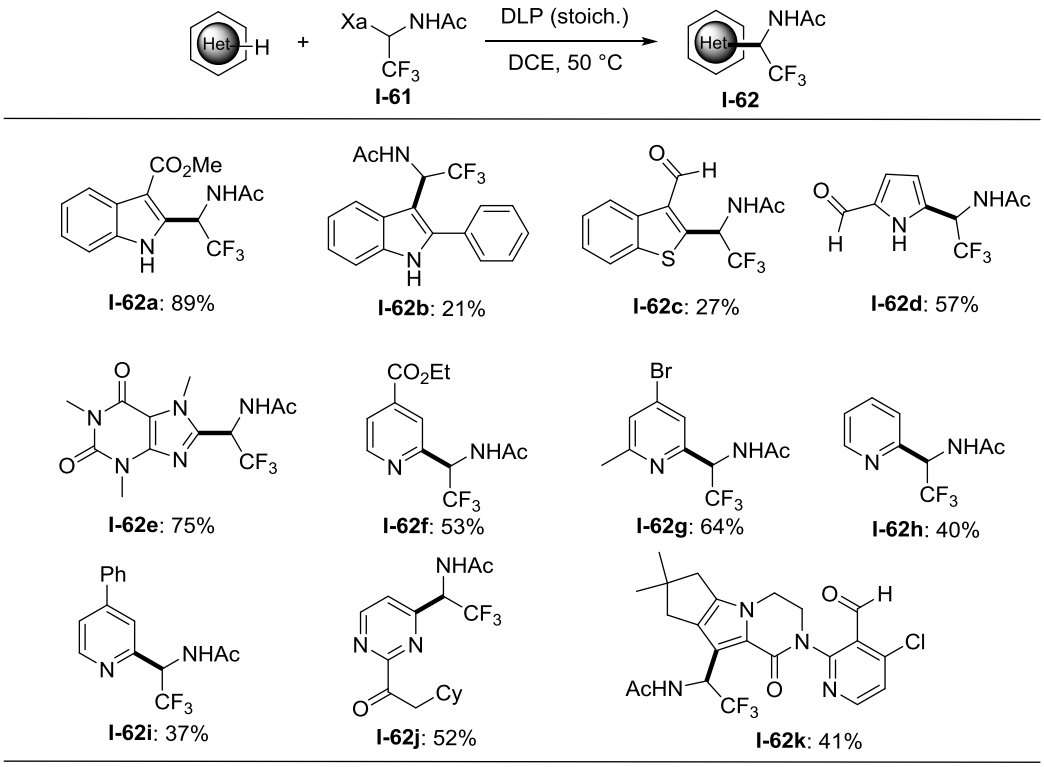
I-60 was isolated in 52% yield (Scheme 1-20).



Scheme 1-20: Alkylations of imidazopyridine and caffeine

Very recently, our colleagues developed en efficient method for the introduction of trifluoroethylamine group by adopting xanthate **I-61** (Scheme 1-21).[33] This method can be applied to the functionalization of electron-rich heteroarenes, including indoles, benzothiphenes, pyrroles, caffeine in variable but useful yields (**I-62a-e**). As for the reaction with electron-deficient heteroarenes, an equivalent of CSA was added to prevent the xanthate from decomposition by the basic nitrogen atom and activate the heterocycles toward radical addition. Functionalized pyridine (**I-62f-i**) and pyrimidine (**I-62j**) were produced in moderate to good yields. Finally, the power of this method was nicely demonstrated by the functionalization of the core of a BTK inhibitor. Addition proceeded regioselectively to pyrrole due to its lower aromaticity and the expected product **I-62k** was obtained in 41% yield.

[33] Braun, M-G.; Castanedo, G.; Qin, L.; Salvo, P.; Zard, S. Z. *Org. Lett.* **2017**, *19*, 4090.



Scheme 1-21: Selected examples for trifluoroethylamination

1.3 Conclusion

As an efficient method for C-C bond formation, xanthate radical chemistry has shown its great potential in the sequence of addition to olefins and cyclization onto heteroaromatics to deliver complex polycyclic heteroarenes. Intermolecular oxidative alkylation of heteroarenes has also emerged as a powerful tool for the direct functionalization of heteroaromatics. The outcome of this chemistry resembles to some extent the nowadays popular C-H activation, although they are not equivalent from a mechanistic point of view. Besides, xanthate radical chemistry possesses various advantages, including: experimental simplicity, mild reaction conditions, metal-free conditions, cheap and easily accessible reagents and compatibility with numerous functional groups.

In this thesis, we have undertaken an adventure to discover wider applications of xanthate chemistry in the construction of fused cycles and the direct alkylation of heteroarenes. In **Chapter II**, we tackle the problem of preparation of azaindanes by taking advantage of the ability of xanthates to mediate both intermolecular addition

and intramolecular cyclization. In **Chapter III**, an unprecedented investigation into the direct functionalization of pyrazines is described, leading to highly functionalized pyrazines in good yields and good regioselectivity. Finally, in **Chapter IV**, we describe and discuss an inexpensive method for the methylation and ethylation of heteroarenes.

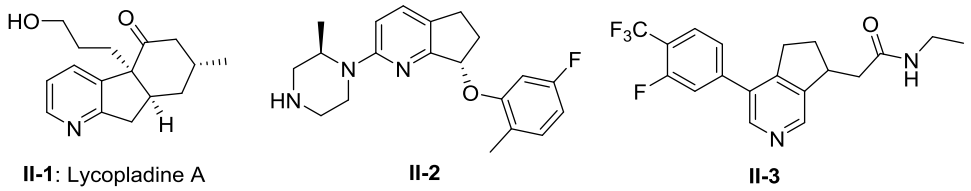
Chapter 2

Modular Route to Azaindanes

2.1 Introduction

Pyridine-containing molecules are among the most prevalent structures in natural products, agrochemicals and pharmaceuticals.[34] Devising efficient method for the preparation of diversely functionalized pyridines is therefore highly desirable. Despite much effort, some pyridine derivatives remain relatively less accessible, among which are azaindanes (cyclopentenopyridines).

Azaindane is a motif present in various natural products and bioactive molecules. All-carbon 5-membered ring fused to the pyridine nucleus can largely restrict its conformational flexibility. For example, Lycopladine A (**II-1**) is a new $C_{16}N$-type alkaloid isolated from the club moss *Lycopodium complanatum* in 2006. It shows weak but selective cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 7 μg/mL) in vitro.[35] Compound **II-2** is a conformationally restricted potent 5HT2c receptor agonist and is selected for further development by medicinal chemists at Pfizer for the treatment of obesity.[36] Azaindane **II-3** is a potent aldosterone synthase inhibitor recently disclosed by the Roche Laboratories in collaboration with R. Britton of Simon Fraser University.[37] Aldosterone is an extremely powerful mineralocorticoid and the inhibition of its biosynthesis could prove useful for combatting hypertension (Figure 2-1).



II-1: Lycopladine A **II-2** **II-3**

Figure 2-1: Examples of biologically active azaindanes

---

[34] a) Kiuru, P.; Yli-Kauhaluoma J. in *Heterocycles in Natural Product Synthesis* (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**, p. 267; b) Qiao, J.-X. in *Heterocyclic Chemistry in Drug Discovery* (Ed.: J.-J. Li), Wiley, Hoboken, **2013**, p. 398; c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

[35] Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, *47*, 3287.

[36] Liu, K. K.-C.; Cornelius, P.; Patterson, T. A.; Zeng, Y.; Santucci, S.; Tomlinson, E.; Gibbons, C.; Maurer, T. S.; Marala, R.; Brown, J.; Kong, J. X.; Lee, E.; Werner, W.; Wenzel, Z.; Vage, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 266.

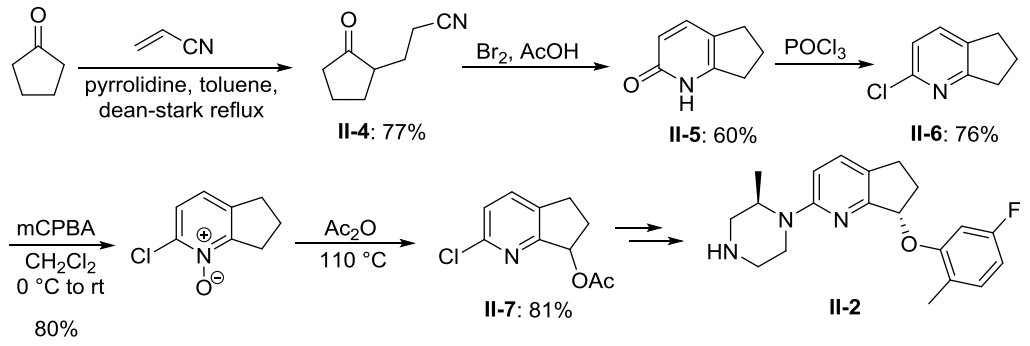
[37] Martin, R. E.; Lehmann, J.; Alzieu, T.; Lenz, M.; Carnero Corrales, M. A.; Aebi, J. D.; Märki, H. P.; Kuhn, B.; Amrein, K.; Mayweg, A. V.; Britton, R. *Org. Biomol. Chem.* **2016**, *14*, 5922.

2.2 Synthetic routes to azaindanes

Essentially, the methods for the preparation of this class of compounds can be divided into two categories: a) construction of the pyridine ring; b) construction of the cyclopentene portion.

2.2.1 Construction of the pyridine ring

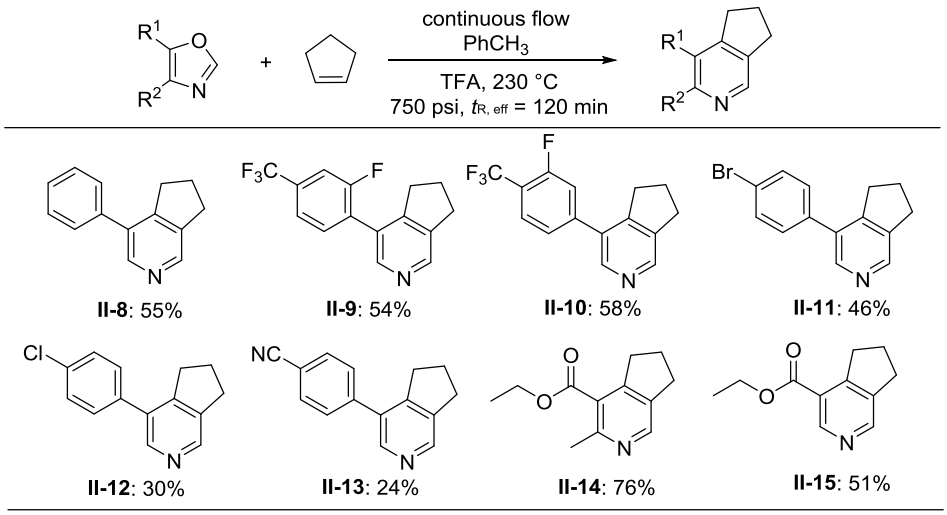
Most of the examples fall into this category. For example, azaindane **II-2** was prepared *via* a key intermediate chloropyridine **II-6**, which was prepared through a three-step process. Enamine alkylation of cyclopentanone with acrylonitrile afforded ketone **II-4** in 77% yield. Cyclization of **II-4** took place in the presence of bromine to give pyridinone **II-5** in 60% yield. Upon treatment of **II-5** with $POCl_3$, the desired azaindane **II-6** was obtained in 76% yield. Modification of the cyclopentane ring followed. Oxidation of **II-6** with mCPBA gave the *N*-oxide, which was then converted into **II-7** by reacting with acetic anhydride at elevated temperature. Chiral HPLC separation, Mitsunobu reaction, Pd-catalyzed cross-coupling and deprotection gave the target molecule **II-2** (Scheme 2-1).[36]



Scheme 2-1: Syntheis of azaindane **II-2**

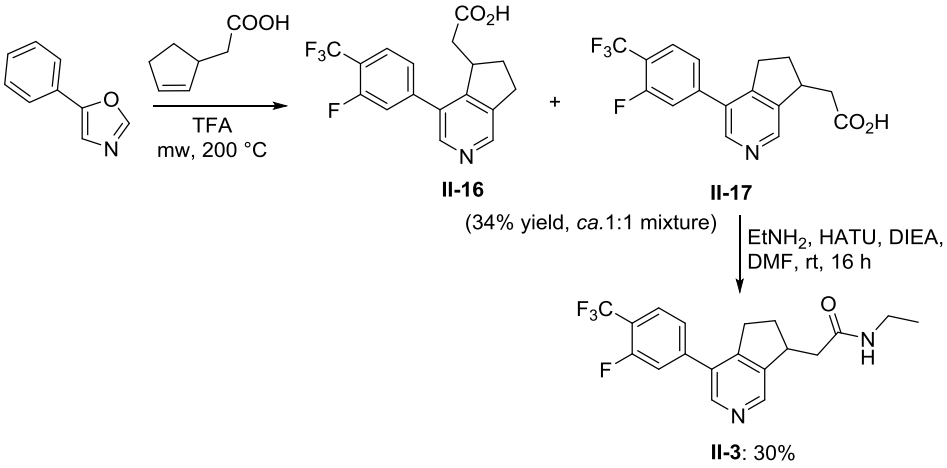
By adopting Kondrat'eva's reaction, Britton *et al.* prepared a series of azaindanes in a one-step process from oxazole and cyclopentene in continuous flow (Scheme 2-2).[37,38] Products **II-8**-**15** were obtained in variable yields of 24-76% at high temperature and pressure.

[38] Lehmann, J.; Alzieu, T.; Martin, R. E.; Britton, R. *Org. Lett.* **2013**, *15*, 3550.



Scheme 2-2: Continuous flow synthesis of azaindanes

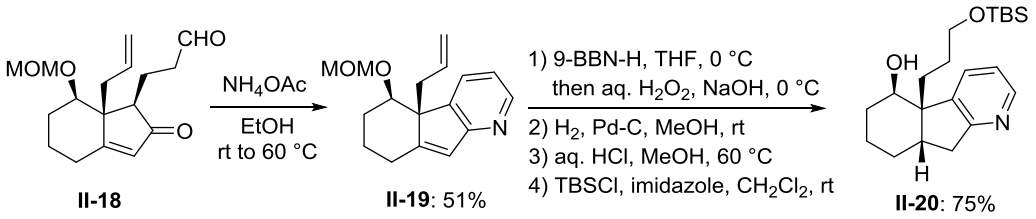
In 2016, exploiting the involatile nature of 2-cyclopentene-1-acetic acid, the same group reported the preparation of azaindanes **II-16** and **II-17** in microwave reactor (Scheme 2-3).[37] In this case, the regioisomers **II-16** and **II-17** were obtained in an approximately 1:1 ratio. **II-17** was then transformed into **II-3** by standard amide formation reaction. The formation of two regioisomers with almost no selectivity underscores one of the major limitations of this method.



Scheme 2-3: Synthesis of azaindane **II-3**

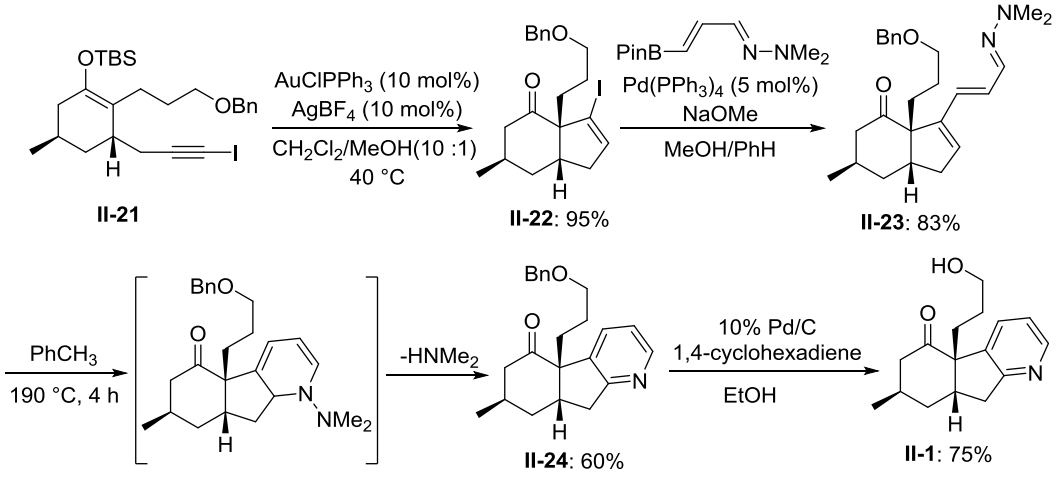
The preparation of azaindanes can be nicely presented by the total synthesis of Lycopladine A (**II-1**). In order to form the pyridine portion of **II-1**, Doi *et al.* treated intermediate **II-18** with NH_4OAc to give the corresponding dihydropyridine, which underwent auto-oxidation to afford product **II-19** in 51% yield. Hydroboration-oxidation of the terminal alkene, hydrogenation of the internal double

bond, followed by deprotection of the MOM group and selective protection of the primary alcohol group, gave the key intermediate **II-20** in 75% yield over 4 steps (Scheme 2-4).[39] A similar strategy was adopted by Yang *et al.* in 2013 for the total synthesis of the same natural product.[40]



Scheme 2-4: Total synthesis of (+)-Lycopladine A by Doi

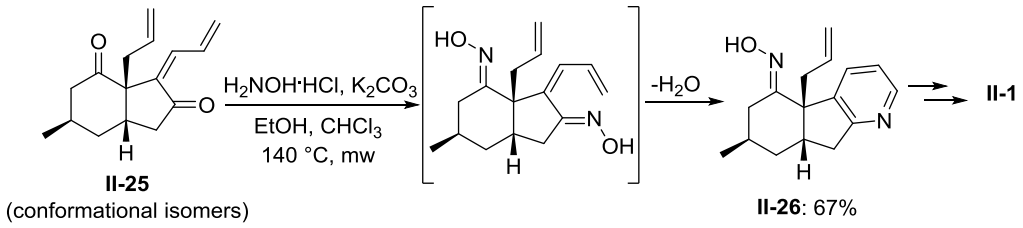
The total synthesis of (+)-Lycopladine A by Toste *et al.* features the gold(I)-catalyzed cyclization of silyl enol ether **II-21** for the construction of bicyclic product hydrindanone vinyl iodide **II-22**. Suzuki cross-coupling of the latter with boronic ester afforded **II-23** in 83% yield. Upon heating in toluene, **II-23** underwent a cascade sequence of isomerization, 6π electrocyclization, and elimination of dimethylamine to deliver pyridine **II-24** in 60% yield. Removal of the protecting group by transfer hydrogenation completed the total synthesis of **II-1 (**Scheme 2-5**)**.[41]



Scheme 2-5: Total synthesis of (+)-Lycopladine A by Toste

[39] Hiroya, K.; Suwa, Y.; Ichihashi, Y.; Inamoto, K.; Doi, T. *J. Org. Chem.* **2011**, *76*, 4522.
[40] Xu, T.; Luo, X.-L.; Yang, Y.-R. *Tetrahedron Lett.* **2013**, *54*, 2858.
[41] Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991.

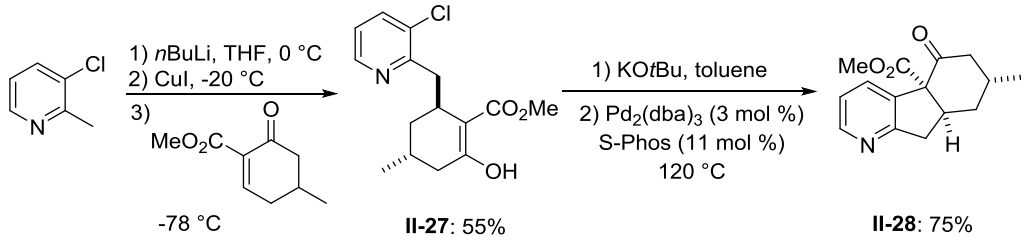
A 6π electrocyclization was also utilized by Meng for the construction of the pyridine ring. Treatment of the mixture of isomers **II-25** with H_2NOH•HCl and K_2CO_3 in EtOH/$CHCl_3$ under microwave irradiation gave the desired product **II-26** in 67% yield through a sequence of oximation, isomerization of the s-*trans*-diene, cyclization, and dehydration (Scheme 2-6). Hydroboration-oxidation of terminal olefin, reduction and removal of the oxime delivers the natural product **II-1**.[42]



Scheme 2-6: Total synthesis of (+)-Lycopladine A by Meng

2.2.2 Construction of the cyclopentene portion

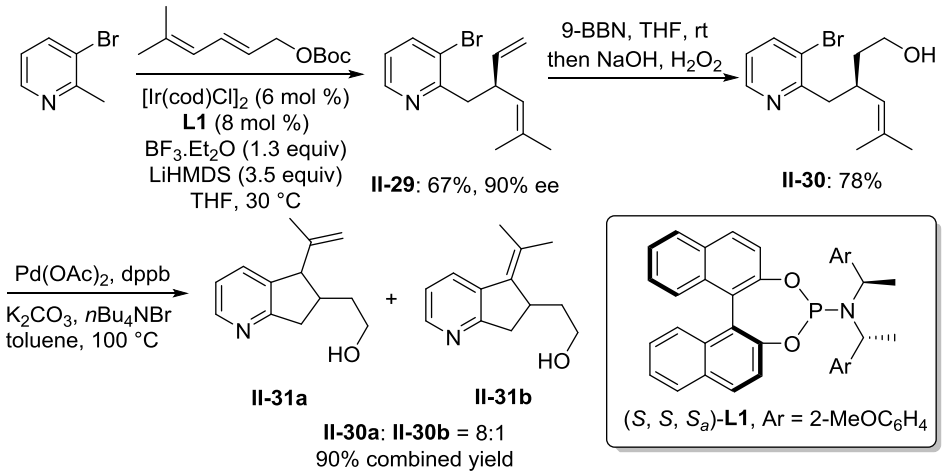
Fewer methods have been developed for the construction of the cyclopentene cycle. In 2010, Martin *et al.* developed an efficient approach to **II-1** involving sequential conjugate addition and enolate arylation reactions.[43] Deprotonation of the commercially available 3-chloro-2-methylpyridine, transmetalation with CuI, followed by conjugate addition to the unsaturated *β*-ketoester afforded **II-27** in 55% yield as a mixture of enol and keto tautomers. Cyclization of the potassium enolate of **II-27** proceeded readily in the presence of $Pd_2(dba)_3$ and *S*-Phos to afford the tricyclic compound **II-28** in 75% yield (Scheme 2-7). **II-28** was transformed into natural product **II-1** in three more steps in a total yield of 21%.



Scheme 2-7: Total synthesis of Lycopladine A by Martin

[42] Meng, L. *J. Org. Chem.* **2016**, *81*, 7784.
[43] DeLorbe, J. E.; Lotz, M. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 1576.

You *et al.* developed recently an enantioselective iridium-catalyzed allylic substitution of 2-methylpyridine.[44] Compound **II-29** was obtained in 67% yield and 90% *ee* under catalysis by an Ir catalyst. Hydroboration-oxidation of the terminal alkene gave **II-30** in 78% yield. The formation of the cyclopentane ring was accomplished *via* a palladium-catalyzed Heck reaction, generating two products **II-31** in 90% combined yield (Scheme 2-8). The major product **II-31a** was then subjected to ozonolysis, palladium-catalyzed allylic alkylation, oxidation, aldol reaction, Michael addition and hydroboration to accomplish the total synthesis of (+)-**II-1**.



Scheme 2-8: Enantioselective total synthesis of (+)-**II-1** by You

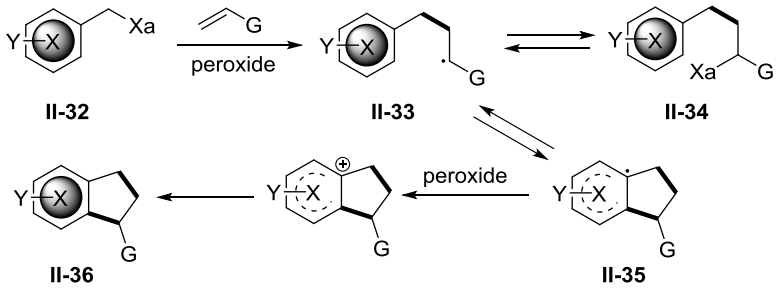
2.3 Radical-based route to azaindanes

Methods presented above, however, suffer from limitations of scope, compatibility of functional groups, harsh reaction conditions, utilization of transition metals, etc. An expedient route providing access to richly substituted azaindanes is therefore highly desirable.

Over the past two decades, using this novel radical chemistry of xanthates, we have successfully prepared various fused arenes and heteroarenes with aliphatic chains, such as indolines.[6] However, the preparation of structurally related indanes (X = C) has so far proved problematic, with the yields being generally moderate and the scope very limited. As outlined in Scheme 2-9, this method relies on the ability of xanthates

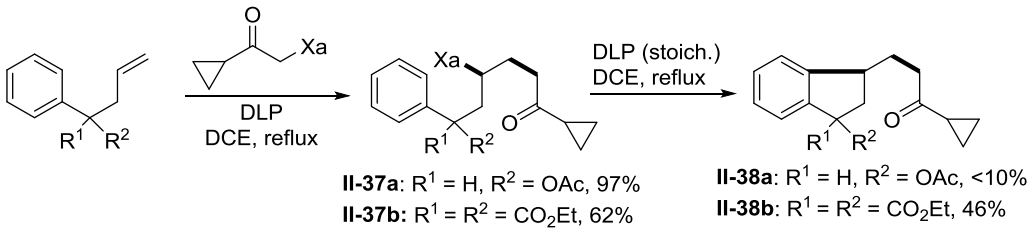
[44] Liu, X. J.; You, S. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 4002.

to mediate both intermolecular addition to alkenes (**II-32→II-33**) and intramolecular cyclization (**II-33→II-36**) to form the cyclopentene ring.



Scheme 2-9: Radical-based route to indanes

For example, upon treatment of xanthate intermediate **II-37a** with stoichiometric DLP, cyclized product **II-38a** was isolated in poor yield from a complex mixture. While placing two carbethoxy groups afforded the indane **II-38b** in useful yield of 46% (Scheme 2-10). In the latter case, the cyclization might be favored by the germinal ester groups *via* Thorpe-Ingold effect.[45]

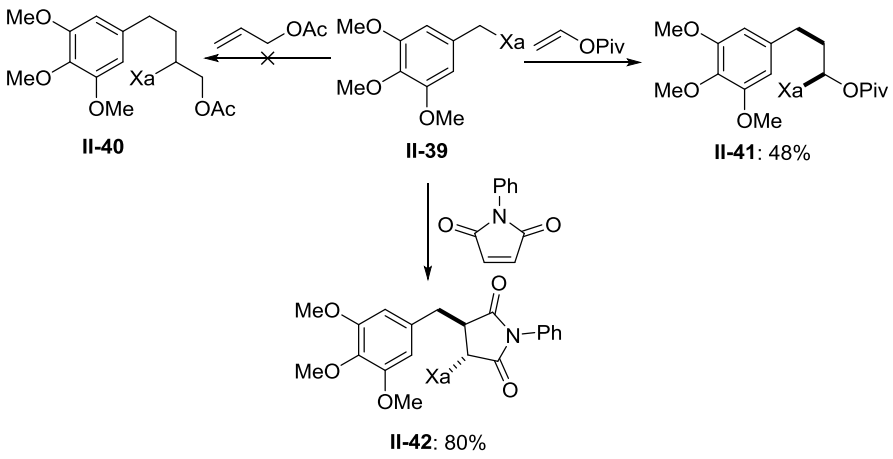


Scheme 2-10: Preparation of indanes

Significant difference in the strain in indolines and indanes could be responsible for this large difference. For instance, *N*-methylindoline is about 4 kcal/mol less strained than indane.[46] The radical cyclization step (**II-33→II-35**, Scheme 2-9) being reversible, the cyclized form **II-35** for indane (X = C) will therefore be disfavored due to increased strain. Moreover, the oxidizing ability of the peroxide is not sufficient to drain the equilibrium toward the penultimate cation intermediate. All these factors render the preparation of indanes difficult. Considering the higher radicophilicity of pyridine, we hoped that this property would compensate for the increased strain and

[45] Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.
[46] Verevkin, S. P.; Emel'yanenko, V. N. *J. Phys. Chem. A* **2011**, *115*, 1992.

provide a more pratical and general preparation of azaindanes **II-36** (X = N). Another considerable advantage concerns the higher efficiency of intermolecular addition of pyridylmethyl xanthates over benzylic xanthates, the latter reacting only with activated and preferentially electrophilic olefins.[47] For example, as illustrated in Scheme 2-11, no adduct **II-40** was obtained for the reaction of xanthate **II-39** with allyl acetate. On the other hand, vinyl acetate, an activated alkene, reacted readily with xanthate **II-39** to furnish **II-41** in a useful yield of 48%. Meanwhile, high yield of **II-42** was obtained for the addition to strongly electrophilic *N*-phenylmaleimide.[48]



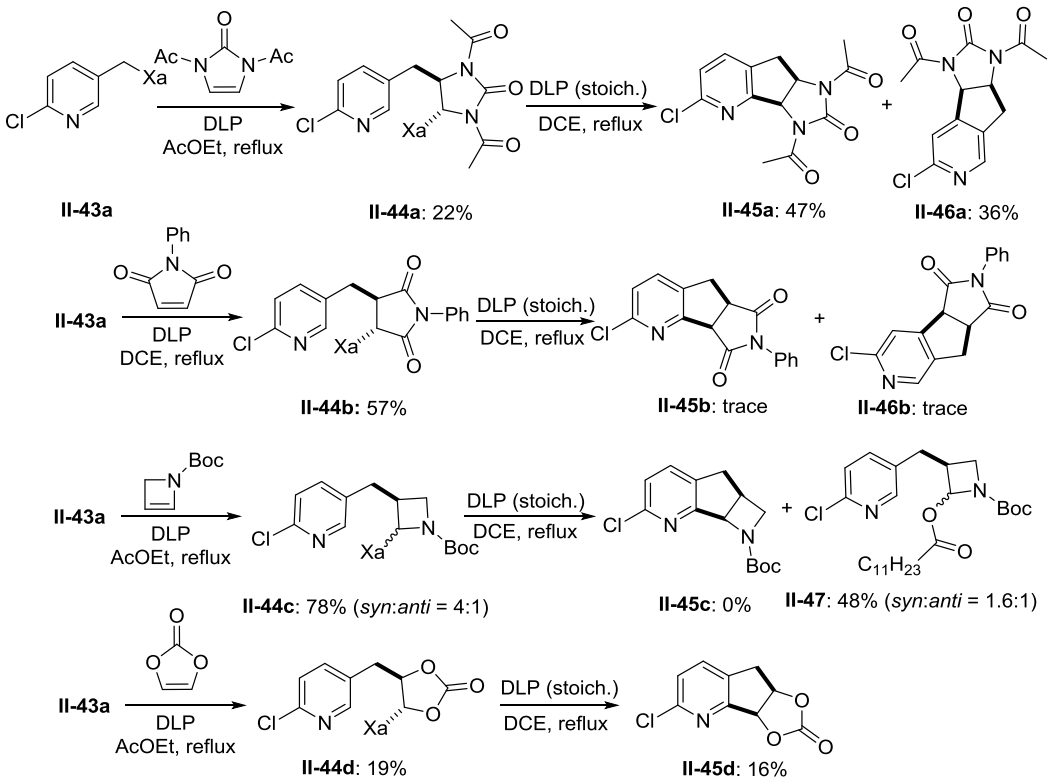
Scheme 2-11: Reaction with benzylic xanthate

2.3.1 Preliminary experiments

During our investigations into the addition of xanthate **II-43a** to *N*, *N*'-diacyl-imidazol-2-one,[30] we found that, upon treatment of the intermediate xanthate **II-44a** with stoichiometric DLP, the cyclized products **II-45a** and **II-46a** were obtained in 47% and 36% yields, respectively. These azaindanes contain a latent *vicinal* diamino motif. In order to extend the scope of applicable olefins, xanthate **II-43a** was initially adopted due to its facile preparation from the reaction of the cheap and commercially available 2-chloro-5-(chloromethyl)pyridine [49] with potassium *O*-ethyl dithiocarbonate. Adduct **II-44b** was easily prepared by trituration (methanol/diethyl

[47] Ferjancic, Z.; Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2008**, 2996.
[48] Guindeuil, S. *Ph.D. Thesis*; Ecole Polytechnique: Palaiseau, **2006**.
[49] 2-Chloro-5-(chloromethyl)pyridine (100 g, 40 £) is commercially available from Fluorochem.

ether) in 57% yield.[47] However, the cyclization step only furnished a trace of the desired products **II-45b** and **II-46b**. Addition of xanthate **II-43a** to Boc-protected azetine afforded efficiently **II-44c** in 78% yield, but again the cyclization failed. Instead, product **II-43** where the xanthate group had been replaced by a laurate group was isolated. Xanthtate **II-44d**, derived from addition of xanthate **II-43a** to vinylidene carbonate, was obtained in only 19% yield, and its cyclization proceeded poorly to afford **II-45d** in 16% yield, along with unidentified products (Scheme 2-12). We therefore assumed that cyclization of **II-44a** was favored by a polarity match between the moderate nucleophilic character of the radical from **II-44a** and the electrophilic pyridine. Considering that the radicophilicity of the pyridine ring could be enhanced upon protonation, discovered many years ago by Minisci *et al.*,[50] we hoped that the cyclization could be more favorable in the presence a strong acid, such as TFA.

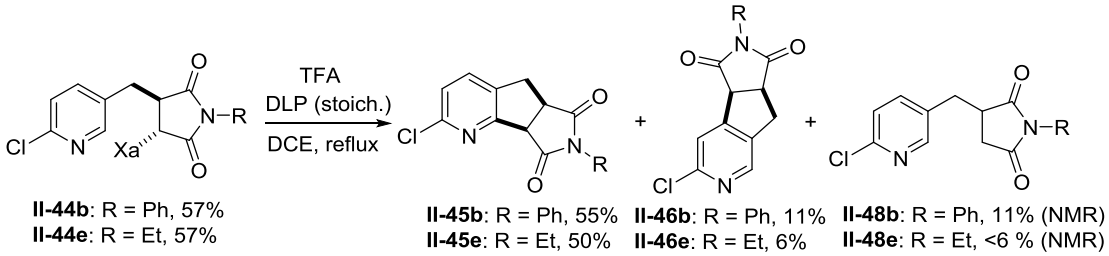


Scheme 2-12: Preliminary results for synthesis of azaindanes

2.3.2 Scope of preparation of azaindanes

[50] (a) Punta, C.; Minisci, F. *Trends Het. Chem.* **2008**, *13*, 1. (b) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990**, *27*, 79. (c) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489.

We were pleased to find that, in the presence of 1.2 equiv of TFA, exposure of adducts **II-44b** and **II-44e** to stoichiometric DLP in refluxing DCE furnished a good combined yield of the corresponding isomeric azaindanes **II-45b** (55%) and **II-46b** (11%), **II-45e** (50%) and **II-46e** (6%), together with a small quantity of simply reduced non-cyclized side-products **II-48b** and **II-48e**. Moreover, both major products **II-45b** and **II-45e** were highly crystalline and precipitated directly from the reaction medium in coincidentally the same yield of 44%, allowing us to easily prepare gram quantities of azaindane **II-45b** (Figure 2-2**)**. Further amounts could be isolated by chromatographic purification of the concentrated filtrate (Scheme 2-13).



Scheme 2-13: First examples of azaindane formation in the presence of TFA

The vinylidene carbonate adduct **II-45d**, unfortunately, seemed unstable to the presence of TFA and gave a dark brown solution containing no detectable desired products. To verify whether this method can also be applied to open-chain alkene traps, we commenced with the addition of **II-43a** to *N*-vinylphthalimide. As for the degenerative addition process, our previous study revealed that xanthate should be used in excess to minimize the formation of oligomers.[19] A quick optimization in terms of equivalents of xanthate indicated 4 equivalents of xanthate **II-43a** gave **II-44f** in higher yield of 57% (Table 2-1). The cyclization of **II-44f** mediated by stoichiometric peroxide afforded the two regioisomers **II-45f** and **II-46f** in high combined yield (77%), while no reduced product **II-48f** was obtained in this particular case (Scheme 2-14). It should be mentioned that without TFA, the reaction proceeded poorly to give the desired products, demonstrating again the importance of the acid.

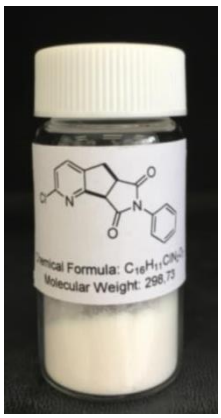
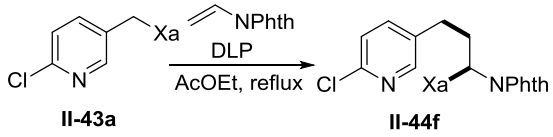


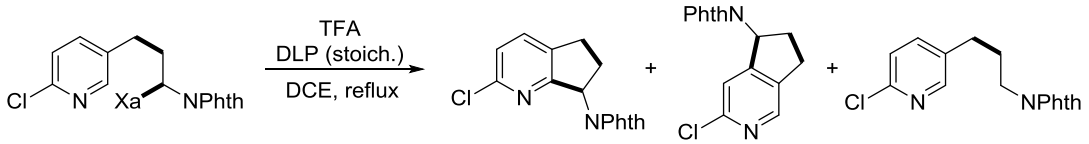
Figure 2-2: **II-45b** (0.92 g)

Table 2-1: Optimization of addition to *N*-vinylphthalimide



II-43a **II-44f**

equivalents of **II-43a**	isolated yield (%)
2	39
3	48
4	57



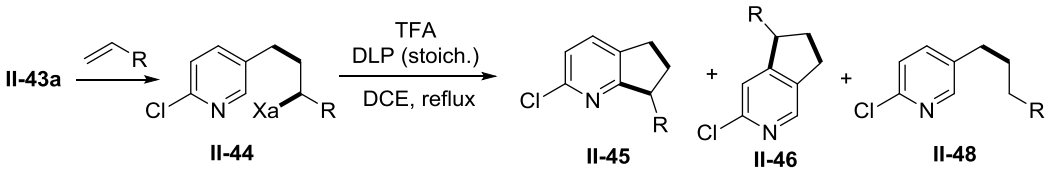
II-44f **II-45f**: 57% **II-46f**: 20% **II-48f**: 0%

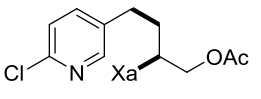
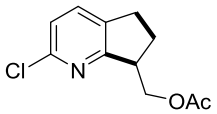
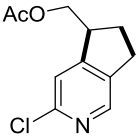
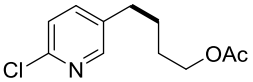
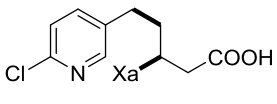
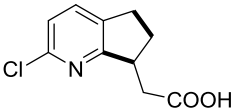
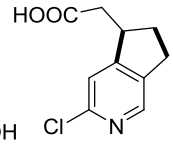
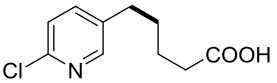
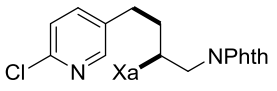
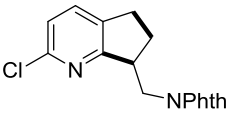
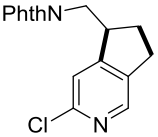
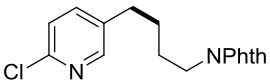
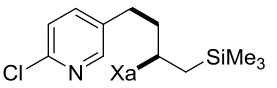
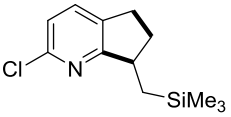
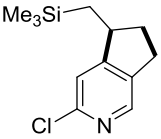
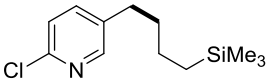
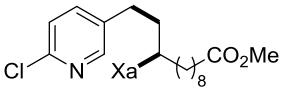
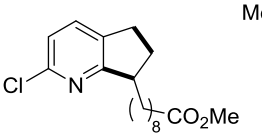
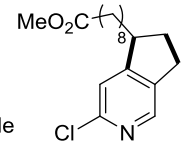
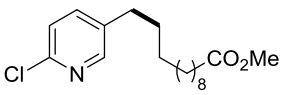
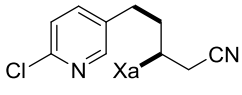
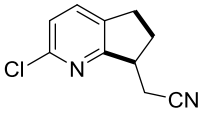
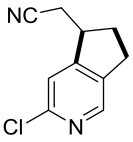
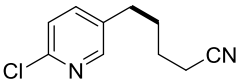
Scheme 2-14: Cyclization of **II-44f**

Intermolecular addition to other olefins delivered the expected adducts **II-44g-p** in variable but useful yields. Treatment of these intermediates furnished the expected azaindanes **II-45** and **II-46** as regioisomers with modest regioselectivity, along with a small amount of reduced noncyclized products **II-48**. As for the cyclization of **II-44l**, for unknown reasons, **II-45l** was isolated from a complex mixture in only 24% yield. Cyclization of xanthate **II-44m** bearing pinacol boronate group proceeded moderately, but the expected products were not isolated pure due to possible hydrolysis. To our dismay, cyclization of **II-44n** with benzoate group, a protected form of the corresponding alcohol, gave a dark brown solution and no desired products were detected. While the addition to allyl trimethylsilane and subsequent cyclization (→**II-44j**→ **II-45j** and **II-46j**) took place in the normal manner, de-silylated azaindanes **II-45o** and **II-46o** were obtained *via* the same sequence starting with vinyl trimethylsilane, resulting from an acid induced proto-desilylation of the expected products **II-51** and **II-52** as shown in Scheme 2-15. Addition of xanthate **II-43a** to ethyl vinyl sulfide afforded **II-44p** in good yield of 62%. However, upon attempted

cyclization, the elimination took place at unexpectedly low temperature[51] and the vinyl sulfide **II-49** was isolated in 16% yield from the reaction mixture, along with other side-products, possibly the regioisomer **II-50** from migration of the double bond (Table 2-2).

Table 2-2: Extension to open-chain alkene partners

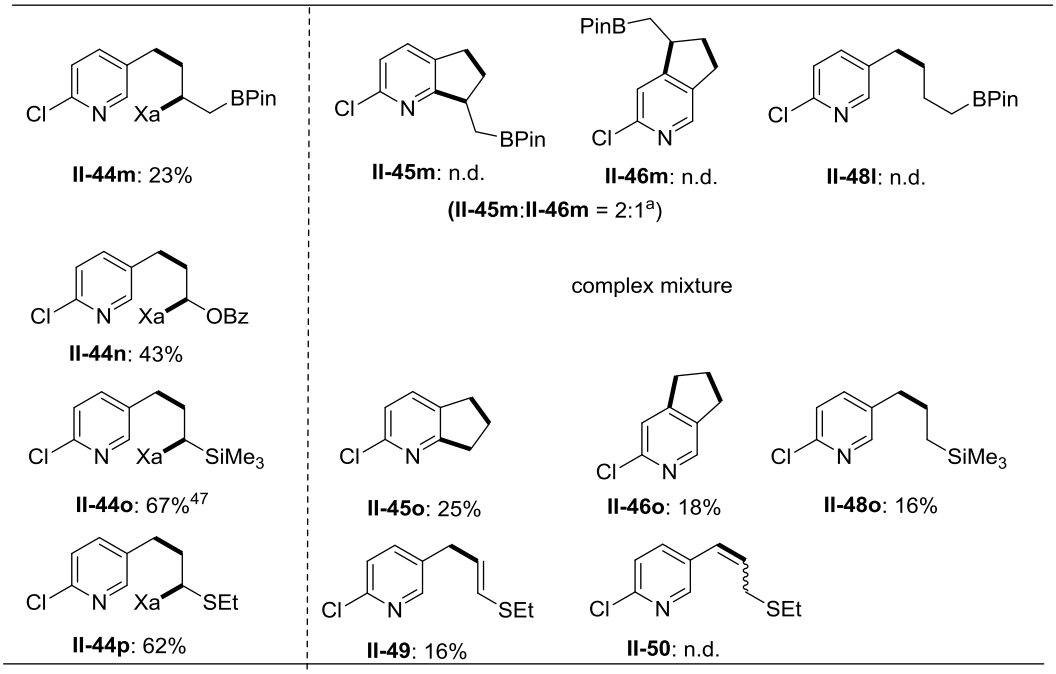


 **II-44g**: 49%	 **II-45g**: 37%	 **II-46g**: 12%[a]	 **II-48g**: 12%[a]
 **II-44h**: 26%	 **II-45h**: 49%	 **II-46h**: 13%	 **II-48h**: <9%
 **II-44i**: 47%	 **II-45i**: 42%	 **II-46i**: 30%	 **II-48i**: 8%
 **II-44j**: 55%	 **II-45j**: 54%	 **II-46j**: 12%	 **II-48j**: 8%[a]
 **II-44k**: 62%[47]	 **II-45k**: 46%	 **II-46k**: 22%	 **II-48k**: <4%
 **II-44l**: 41%	 **II-45l**: 24%	 **II-46l**: n.d.	 **II-48l**: n.d.

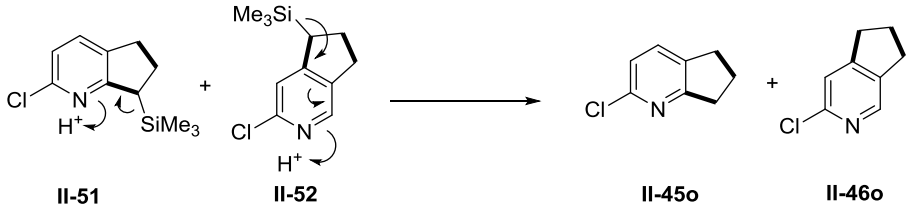
[a] Determined by ^{1}H NMR of the crude products.

[51] Braun, M.-G.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 776.

(continued)



[a] Determined by ^{1}H NMR of the crude products.



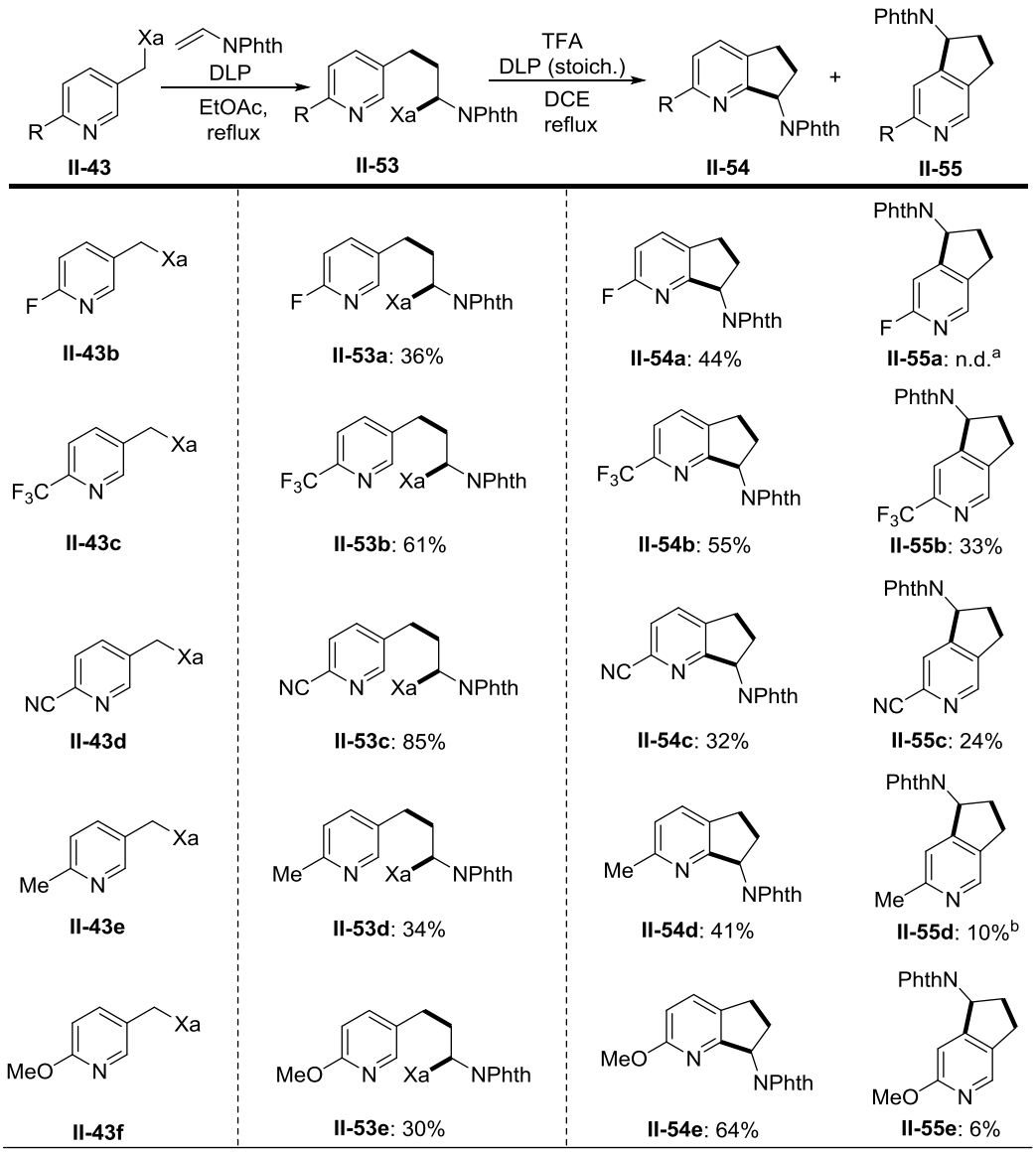
Scheme 2-15: Proto-desilylation of **II-51** and **II-52** to give **II-45o** and **II-46o**

It is worth mentioning that the chlorine atom present allows for further modification through direct or transition-metal-catalyzed cross-coupling. The chlorine atom can also be replaced by other equally useful substituents, including electron-withdrawing fluorine, trifluoromethyl, cyano and electron-donating methyl and methoxy. Xanthates **II-43b-f** could thus be easily prepared from commercially available reagents in no more than three steps (see Experimental Part for details). It should be noted that xanthate **II-43e** decomposed slowly and became brown and stank, probably due to the higher nucleophilicity of its pyridine nitrogen.

Addition of xanthates **II-43b-f** to *N*-vinylphthalimide was then investigated, as shown in Table 2-3. Addition of xanthate **II-43b** containing a mono-fluoro group afforded adduct **II-53a** in a moderate yield of 36%. As for xanthates bearing strong

electron-withdrawing groups (CF_3 for **II-43c** and CN for **II-43d**), yields for the intermolecular additions were substantially higher as compared to those with xanthates containing electron-donating groups (Me for **II-43e** and MeO for **II-43f**). Upon treatment of **II-53** with stoichiometric amount of peroxide, the expected azaindanes **II-54** and **II-55** were delivered. For the ring closure of xanthate **II-53a**, the minor regioisomer **II-55a** could not be easily purified and its yield was not determined. Instead, the dexanthylated product **II-56** was isolated in 7% yield. Azaindanes containing a trifluoromethyl group (**II-54b** and **II-55b**) and a cyano group (**II-54c** and **II-55c**) were obtained in good combined yields, although the regioselectivity is modest in both cases. Cyclization of xanthate adduct **II-53d** generated the corresponding major product **II-54d** in moderate yield of 41%. However, the isolated yield for the minor cyclization product **II-55d** was not determined and a ratio of **II-54d**:**II-55d** = 4:1 was estimated from ^{1}H NMR of the crude products. For the cyclization of xanthate **II-53e**, azaindanes **II-54e** and **II-55e** containing a methoxy group were isolated in a ratio of 10.7:1.

Table 2-3: Addition of xanthates to *N*-vinylphthalimide and subsequent cyclization

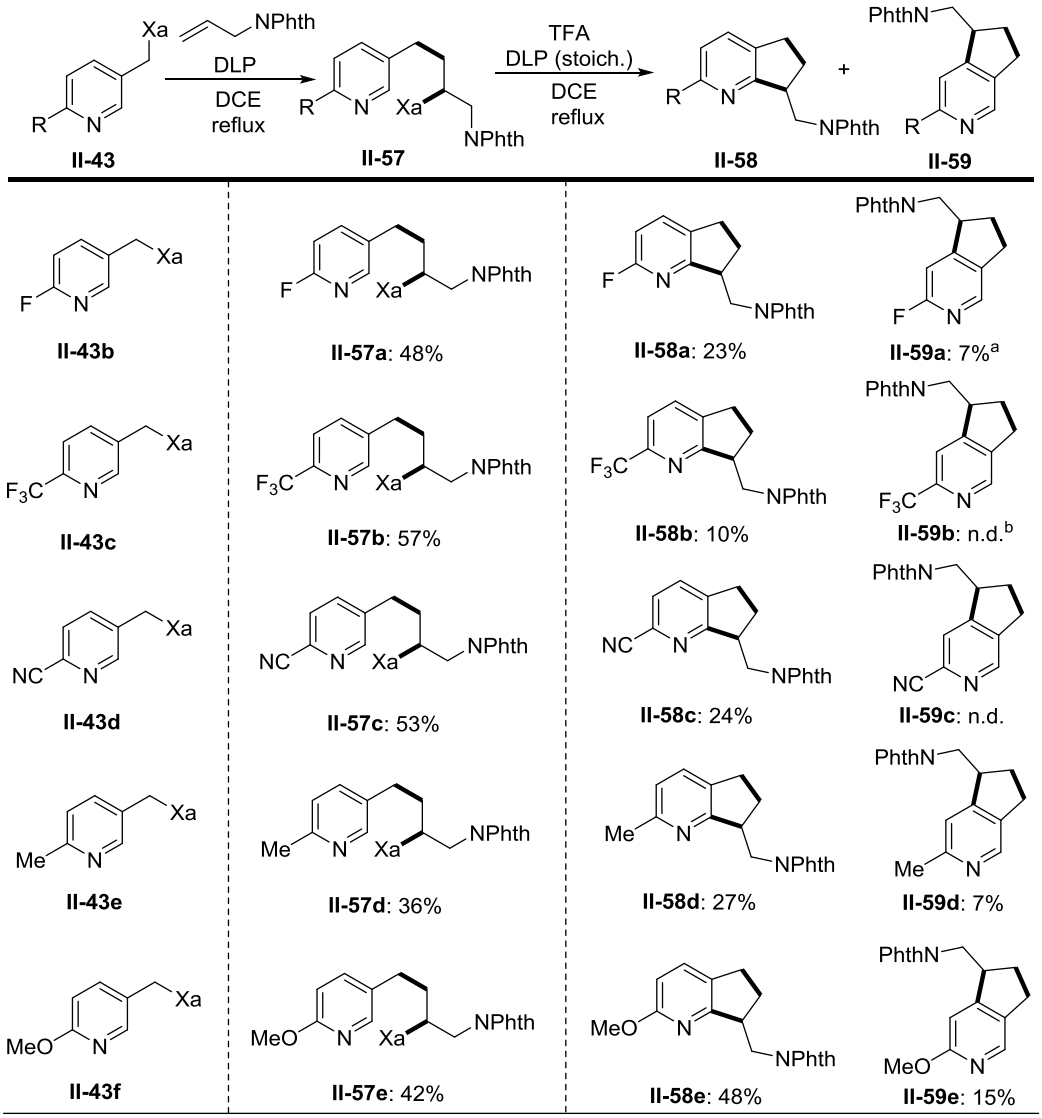


[a] Reduced product **II-56** was isolated in 7% yield. [b] Estimated by ^{1}H NMR of the crude products.

Another typical olefinic partner, *N*-allyl-phthalimide, was also involed in the same sequence (Table 2-4). The corresponding xanthate adducts **II-57a-e** were prepared in moderate to good yields. Mono-fluoro-containing adduct **II-57a** was obtained in 48% yield. Again, additions of pyridine xanthates bearing strong electron-withdrawing groups (**II-43c-d**) to *N*-allylphthalimide are more favorable than additions with xanthates containing electron-donating groups (**II-43e-f**). Besides, while addition of xanthates **II-43c-d** proceeded more efficiently with *N*-vinylphthalimide (61% for adduct **II-53b** and 85% for adduct **II-53c**) than with *N*-allylphthalimide (57% for adduct **II-57b** and 53% for adduct **II-57c**), slightly higher yields were obtained for

additions of xanthates **II-43e-f** to *N*-allylphthalimide (36% for adduct **II-57d** and 42% for adduct **II-57e**, as compared to 34% for adduct **II-53d** and 30% for adduct **II-53e**). As for the cyclization step, azaindanes **II-58** and **II-59** were generated as expected, albeit in lower yields than azaindanes **II-54** and **II-55** derived from *N*-vinylphthalimide.

Table 2-4: Addition of xanthates to *N*-allylphthalimide and subsequent cyclization



[a] Reduced product **II-60** was isolated in 14% yield. [b] Reduced product **II-61** was observed in 15% yield estimated by ^{1}H NMR of the crude products.

A more favorable polarity matching between the in-coming radical and the olefin (also pyridine) is certainly responsible for this difference. For the intermolecular addition, pyridines with lower electron density (**II-43c-d**) reacted more efficiently with electron-rich olefins (both *N*-vinyl- and *N*-allyl-phthalimide). Since a *geminal*

phthalimido group is modestly electron-donating, whereas a *vicinal* phthalimido group exerts a detrimental inductive electron-withdrawing effect, *N*-vinylphthalimide is therefore slightly richer in electron density than *N*-allylphthalimide, which accounts for the higher yields of **II-53b-c** than **II-57b-c**. Since radicals generated from **II-53** are more electron-rich than those from **II-57**, cyclization of **II-53** proceeded therefore in higher efficiency.

In general, there seems to be good to moderate regioselectivities for the cyclization. Take the formation of **II-54** and **II-55** for example. As depicted in Figure 2-3, generally, the cyclization has a preference for C6 over C4. Moreover, electron-withdrawing groups (R = CF_3, CN) resulted in lower regioselectivity (C6:C4 = 5:3 for CF_3, for instance), while electron-donating groups (R = Cl, Me and OMe) gave higher regioselectivity (up to C6:C4 = 10.7:1 for OMe). The regioselectivity matches, to some extent, the trend of Hammett's value (σ-value) of the R group.[52] Several possible reasons might explain these results. Pyridine reacts inherently with nucleophiles at the C2 and C4 position. The innate reactivity of these sites can be further modified by the substituents. Chlorine and methoxy groups were found to act as both *ortho*-activators and *meta*-deactivators, while methyl only activates the *ortho* position. Moreover, reactivity at C6 is strongly influenced by the substituents at the C2 position, with electron-withdrawing groups deactivating C6 position and electron-donating groups activating C6 position.[53] Taking all these factors into account, we can conclude that Cl, Me and OMe at the C2 position activate C6 while deactivating C4; whereas CF_3 and CN deactivate C6 position, thus equalizing the reactivity of C4 and C6 towards nucleophilic radicals. The three-carbon alkyl chain at the C5 position should not be neglected since it also functions as an *ortho* activator, rendering the cyclization process more favorable in all cases (Figure 2-4). The effect of the fluorine atom is more complicated and more experiments should be devised to elucidate its effect on both radical addition and cyclization.

[52] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
[53] O'hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122.

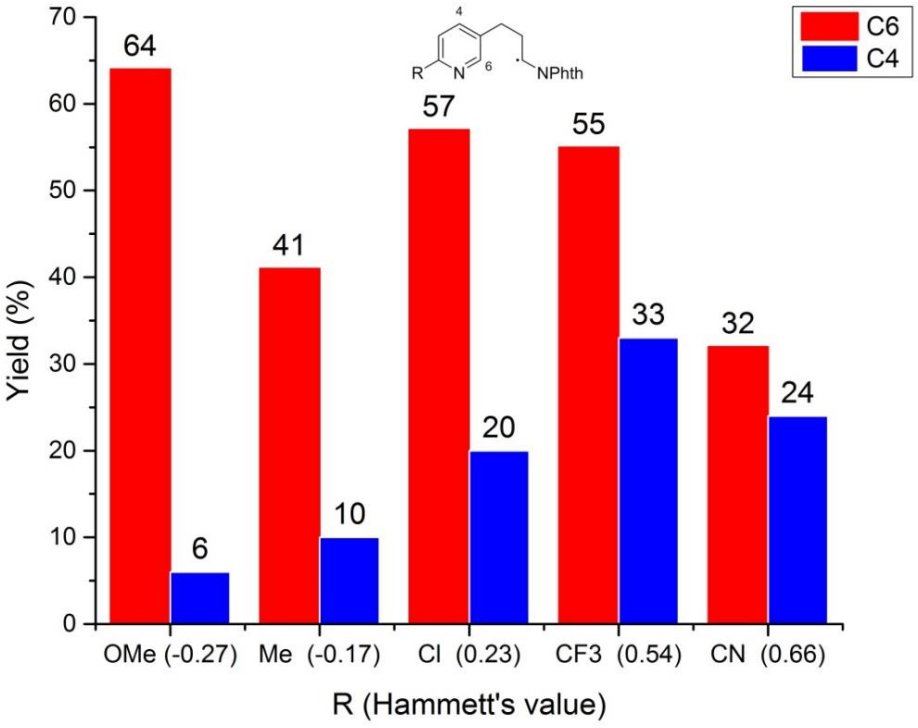


Figure 2-3: Comparison of regioselectivity

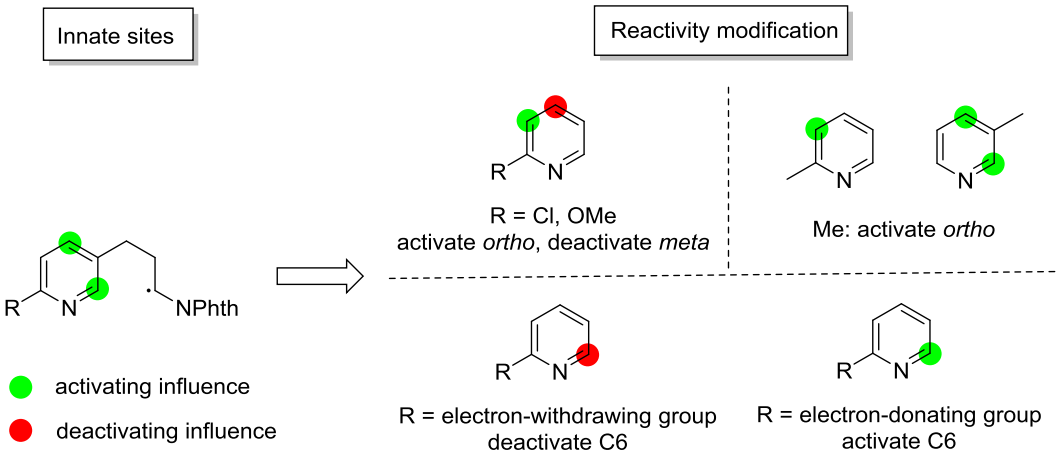
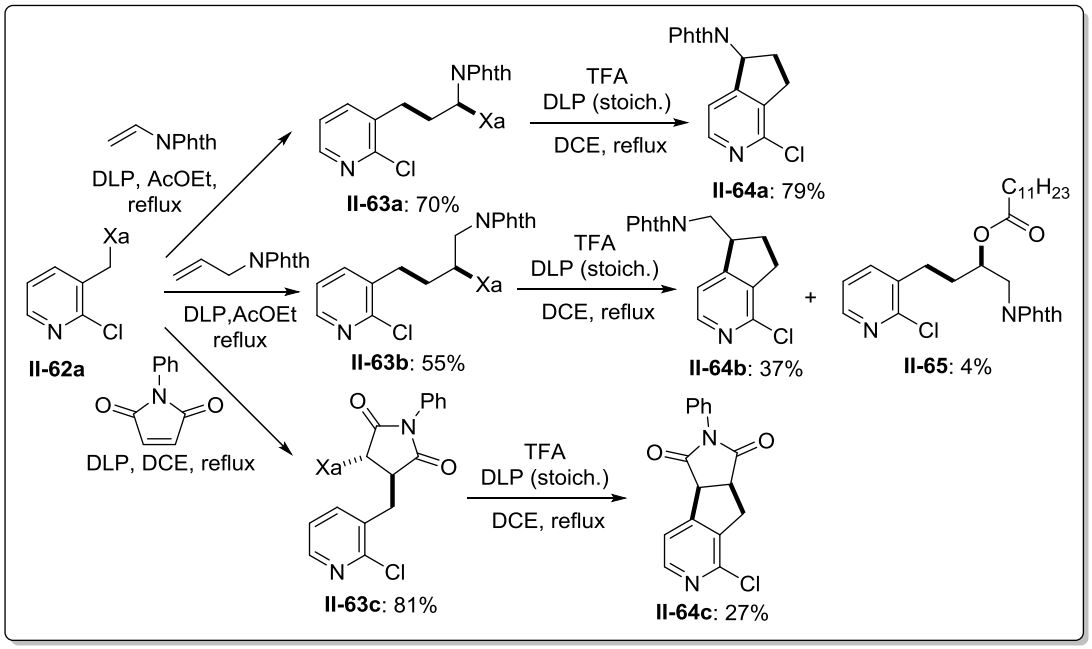


Figure 2-4: Factors controlling regioselectivities

Moving the xanthate group to the β position of the pyridine ring, next to the R group on the α position, as in xanthate **II-62a**, should afford adducts that can cyclize in only one way. Indeed, adducts **II-63a-c** from addition of **II-62a** to *N*-vinyl- and *N*-allyl-phthalimide, and to *N*-phenylmaleimide were obtained in high yield, especially for the addition to electron-poor *N*-phenylmaleimide. Upon exposure to stoichiometric peroxide, ring-closure of these xanthate intermediates provided the desired azaindanes

II-64a-c. In the case of cyclization of **II-63b**, the expected product **II-64b** was obtained in 37% yield, along with 4% of a side-product **II-65**. The tricyclic product **II-63c** was isolated in 21% yield, together with other unidentified side-products. Again, the large difference in yield reflects the untoward effects of a polarity mismatch between the incipient radical and the pyridine nucleus (Scheme 2-16).



Scheme 2-16: Synthesis of cyclopenta[*c*]pyridines

Xanthate analogues of **II-62a** were also easily accessible (see Experimental Part for details). Xanthates **II-62b-f** were then subjected to the addition/cyclization sequence, as depicted in Table 2-5 and Table 2-6. While addition of fluoro-substituted xanthate **II-62b** to *N*-vinyl- and *N*-allyl-phthalimide proceeded moderately to give adducts **II-66a** and **II-70a** in yields of 39% and 49%, respectively, their cyclization proceeded poorly to deliver complex mixtures in both cases and no azaindanes **II-67a** and **II-71a** were observed. The possible reason for this disappointing result is an *ipso* attack of the intermediate radical on the fluorine bearing position.[54] The CF_3-bearing azaindane **II-71b** was surprisingly obtained in 2-times higher yield than that of **II-67b** (72% for **II-71b** *vs.* 36% for **II-67b**). The reason for this is still unclear. The cyanopyridine

[54] For examples of radical *ipso* attacks on fluorinated pyridines, see: (a) Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 3426. (b) Laot, Y.; Petit, L.; Tran, N. D. M.; Zard, S. Z. *Aust. J. Chem.* **2011**, *64*, 416.

adduct **II-66c**, itself obtained in 87% yield, underwent cyclization poorly and gave rise to a complex mixture. Attempt to perform the cyclization without TFA also failed to afford the desire products. The most plausible cause is a faster competing addition of intermediate radical **II-68** onto the nitrile group to give iminyl radical **II-69**, which could then evolve into a myriad of unwanted products. Divergent behavior was observed for the corresponding ester **II-66d**, with the expected azaindane **II-67d** isolated in 75% yield. The plausible reason is that, the nitrile and the carboxylate groups being similar in electron-withdrawing power (σ_{CN} = 0.66, σ_{CO2Me} = 0.45),[52] the latter, however, is a very poor trap for radicals and the desired cyclization step is therefore not interrupted. As explained in Figure 2-4, the OMe group exerts a *meta*-deactivating effect, and the corresponding azaindane **II-67e** was therefore obtained in 44% yield, but a lower yield was obtained for **II-71d** (13%).[55]

[55] Substitution of xanthate group by laurate group was isolated for the cyclization of **II-70d**.

Table 2-5: Synthesis of cyclopenta[*c*]pyridines derived from *N*-vinylphthalimide

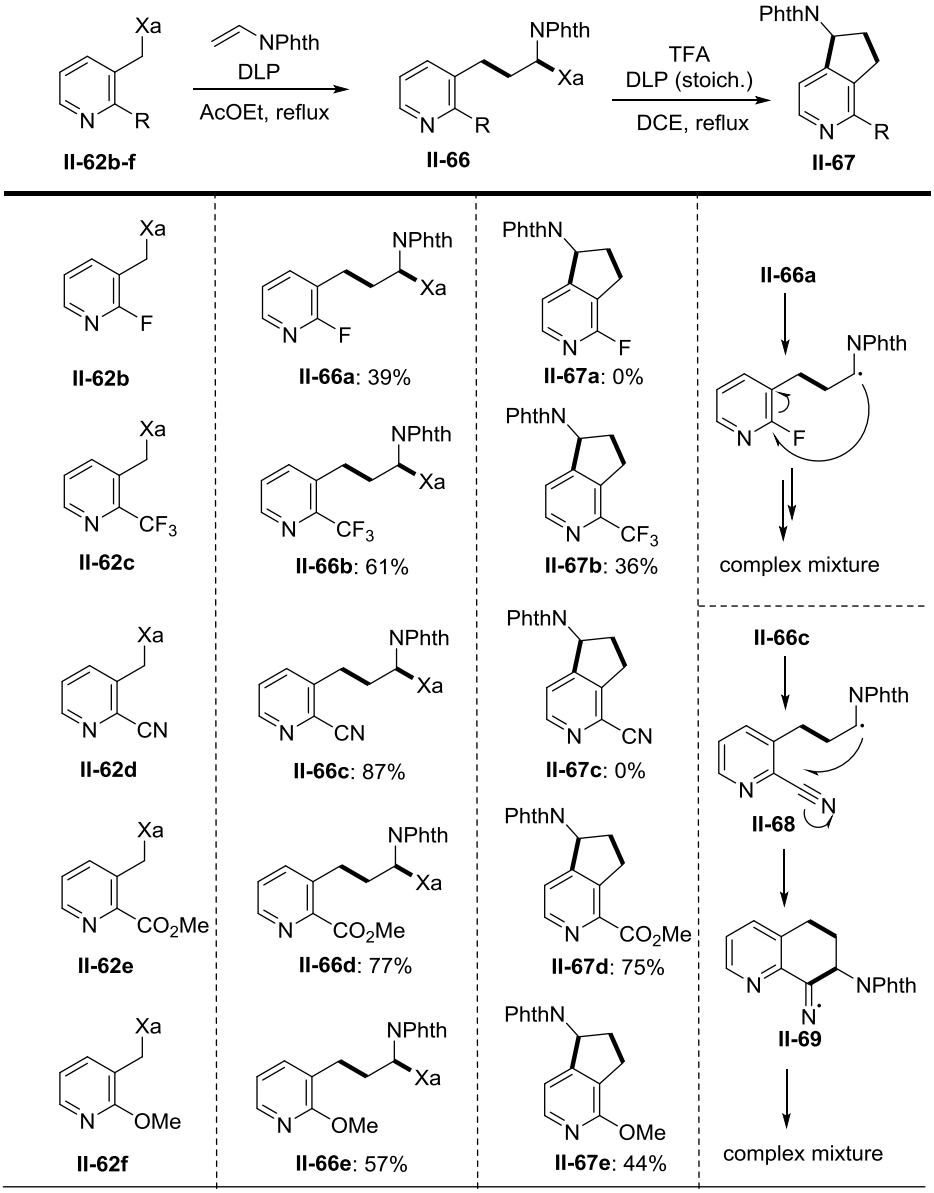
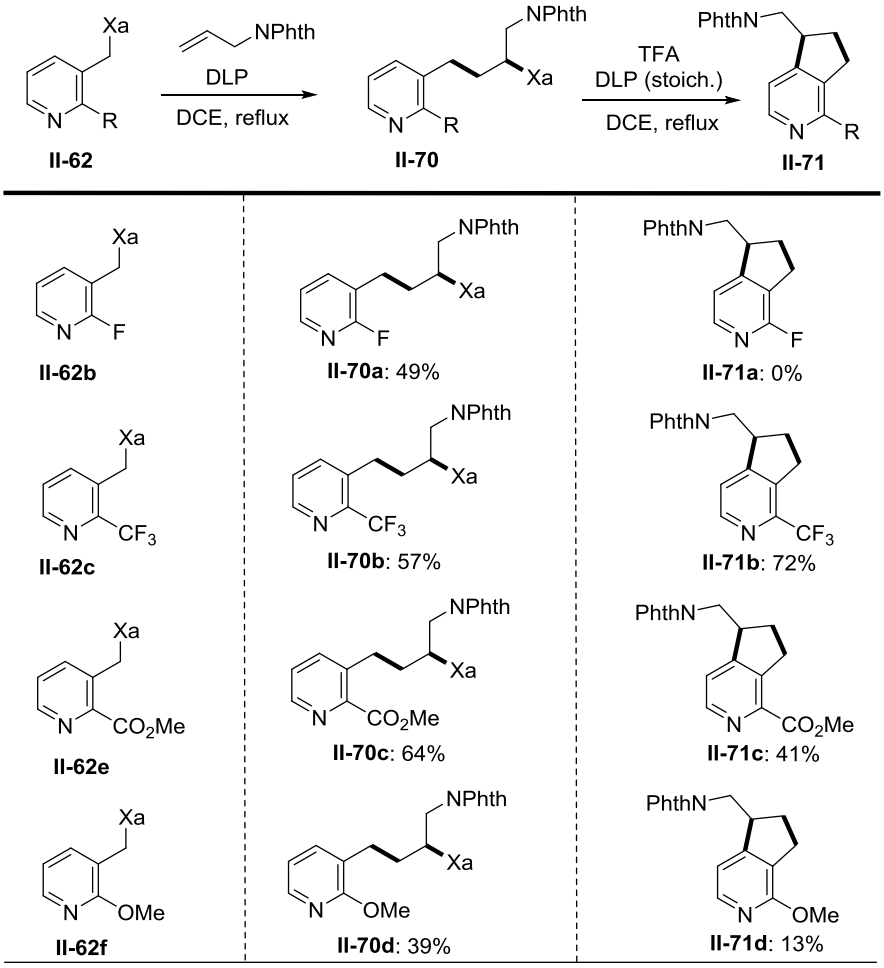


Table 2-6: Synthesis of cyclopenta[*c*]pyridines derived from *N*-allylphthalimide

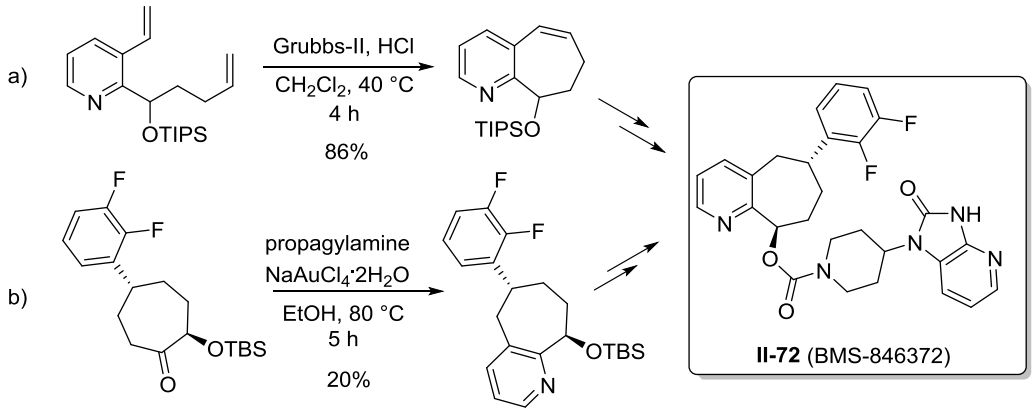


2.3.3 Preparation of cyclohepta[*b*]pyridine

Finally, an exceptional extension of this work, the preparation of cyclohepta[*b*]pyridines, was developed. Cyclohepta[*b*]pyridine is a motif present in several biologically active molecules, most notably **II-72** (BMS-846372), a potent calcitonin gene-related peptide (CGRP) receptor antagonist and a promising drug in antimigraine treatment developed by the Bristol-Myers Squibb Company.[56] Except for cases where formation of the cycloheptane ring was achieved from suitably substituted

[56] Luo, G.; Chen, L.; Conway, C. M.; Denton, R.; Keavy, D.; Gulianello, M.; Huang, Y.; Kostich, W.; Lentz, K. A.; Mercer, S. E.; Schartman, R.; Signor, L.; Browning, M.; Macor, J. E.; Dubowchik, G. M. *ACS Med. Chem. Lett.* **2012**, *3*, 337.

pyridines *via* ring-closing metathesis (for example, Scheme 2-17a),[57] most synthetic methods rely on constructing the pyridine ring from cycloheptanone (for example, Scheme 2-17b)[58] or *via* Kondrat'eva's reaction similar to that in Scheme 2-2.[37,38]



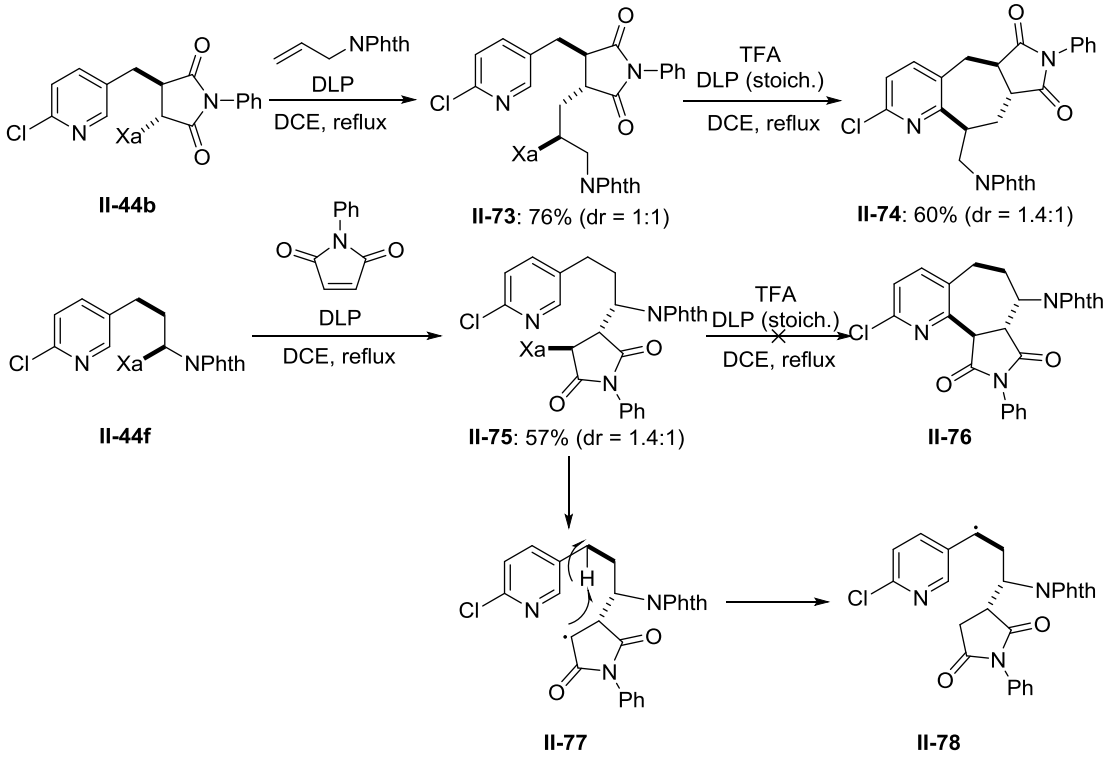
Scheme 2-17: Examples for the preparation of intermediates for **II-72**

As outlined in Scheme 2-18, our method depends on two successive intermolecular additions followed by an intramolecular cyclization. Compound **II-44b**, itself a radical adduct, added efficiently to *N*-allylphthalimide to deliver **II-73** in 76% yield. The intermolecular addition step competes successfully against its cyclization to afford **II-45b** and **II-46b**, demonstrating again that the ring closure is relatively sluggish without TFA. Treatment of **II-73** with stoichiometric peroxide in the presence of TFA afforded cyclohepta[*b*]pyridine **II-74** as the major product in 60% yield. However, one limitation was revealed during our attempt to close adduct **II-75**, which was obtained in 57% yield from addition of **II-44f** to *N*-phenylphthalimide. No substantial product **II-78** was isolated, caused possibly by a preferable 1,5-hydrogen shift transforming intermediate **II-77** into benzylic radical **II-78**, which evolves to give a complex mixture. In the case of **II-73**, the cyclization competes over the internal translocation process due to the *trans* disposition of the two chains across the

[57] For recent examples, see: (a) Desai, L. V.; Hay, M. B.; Leahy, D. K.; Wei, C.; Fanfair, D.; Rosner, T.; Hsiao, Y.; *Tetrahedron* **2013**, *69*, 5677. (b) Leahy, D. K.; Fan, Y.; Desai, L. V.; Chan, C.; Zhu, J.; Luo, G.; Chen, L.; Hanson, R. L.; Sugiyama, M.; Rosner, T.; Cuniere, N.; Guo, Z.; Hsiao, Y.; Gao, Q. *Org. Lett.* **2012**, *14*, 4938. (c) Yoshizumi, T.; Ohno, A.; Tsujita, T.; Takahashi, H.; Okamoto, O.; Hayakawa, I.; Kigoshi, H. *Synthesis* **2009**, 1153.

[58] For recent examples, see: (a) Pan, B.; Liu, B.; Yue, E.; Liu, Q.; Yang, X.; Wang, Z.; Sun, W.-H. *ACS Catal.* **2016**, *6*,1247. (b) Wu, K.; Huang, Z.; Liu, C.; Zhang, H.; Lei, A. *Chem. Commun.* **2015**, *51*, 2286. (c) Srimani, D.; Ben-David, Y.; Milstein, D. *Chem. Commun*. **2013**, *49*, 6632.

rigid 5-membered ring, making the benzylic hydrogen atom inaccessible for hydrogen abstraction.



Scheme 2-18: Modular route to functional cyclohepta[*b*]pyridine

2.4 Further extension

The examples above explored the cyclization onto the innate electrophilic position of the pyridine ring. Cyclization of adducts derived from radicals (**II-80** and **II-81)** onto the C3 and C5 positions would also lead to interesting molecules. Besides, radicals **II-80** and **II-81** were proved to have noticeably higher reactivity over **II-79** due to their increased electrophilic character, presumably resulting from better delocalization toward the more electronegative nitrogen ring.[47] Higher yields should therefore be expected for intermolecular addition with radicals **II-80** and **II-81** (Figure 2-5).

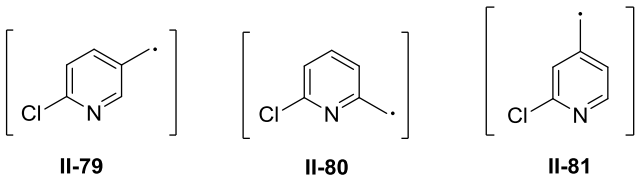
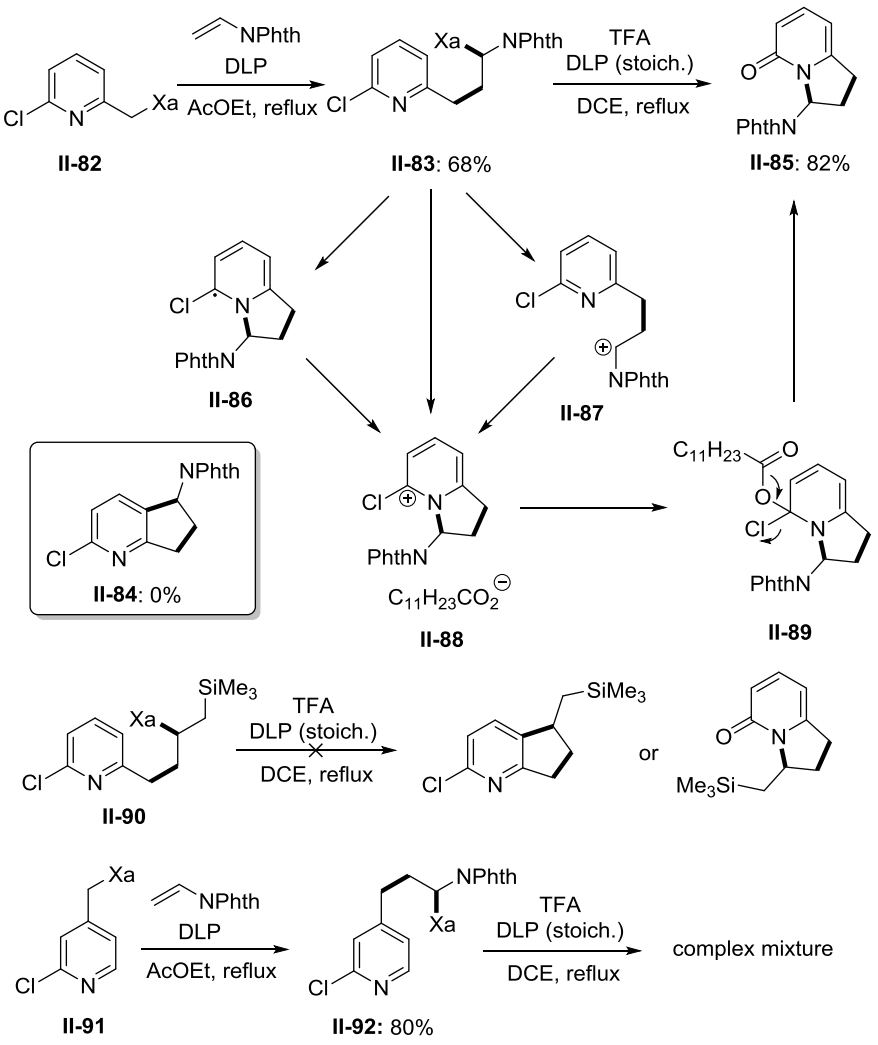


Figure 2-5: Comparison of three chloropyridylmethyl radicals

Indeed, while **II-44f** was afforded in 57% yield from **II-43a**, adducts **II-83** and **II-92** were isolated in substantially higher yields (68% and 80%, respectively) from their corresponding xanthates. However, product **II-84** resulting from cyclization onto the C5 position was not observed. Instead, pyridone **II-85** was isolated in good yield of 82%, possibly *via* the key intermediate **II-88**. This substance could be produced in two possible pathways, either from attack of the radical on the pyridine nitrogen to give radical **II-86**, followed by oxidation, or from departure of the xanthate group to afford cationic species **II-87** followed by subsequent reaction with the pyridine nitrogen. The equilibrium between the ion-pair intermediate **II-88** and neutral species **II-89** is shifted by the final hydrolysis, delivering the observed pyridone **II-85**.[59] To gain an insight into the mechanism, xanthate **II-90**[47] was subjected to the cyclization process. The radical generated from xanthate **II-90** is similar in electron density to that of phthalimide **II-83**, due to inductive electron-donating effect, while elimination of xanthate group is less plausible. However, no desired product was observed either from normal cyclization or attack on the pyridine nitrogen, indicating that the reaction with **II-83** proceeded most probably by an ionic pathway. As for adduct **II-92**, its cyclization gave a complex mixture and no desired product was observed (Scheme 2-19). The results above demonstrated that cyclization in the presence of TFA in reluxing DCE should in principle take place at the inherently reactive sites.

[59] For a radical ring closure on the pyridine nitrogen, see: El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, 4422. For a similar process on pyrimidine, see: Qin, L.; Liu, Z.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 2966.



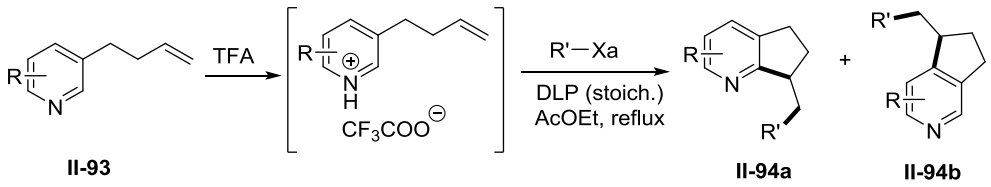
Scheme 2-19: Further extension of cyclization

2.5 Conclusion and perspective

In summary, we have provided a modular approach to the preparation of functionalized azaindanes. This method features mild reaction conditions, high functional group tolerance and useful yields. Azaindanes prepared, together with the intermolecular adducts containing the pyridine nucleus, would be tedious to prepare by conventional ionic chemistry, since many of the polar functional groups incorporated would not be compatible with ionic or organometallic methods. Moreover, the strategic ability and subtlety of the degenerative xanthate transfer process in the assembly of more than one carbon-carbon bonds allows facile construction of richly decorated azaindanes and cyclohepta[*b*]pyridine.

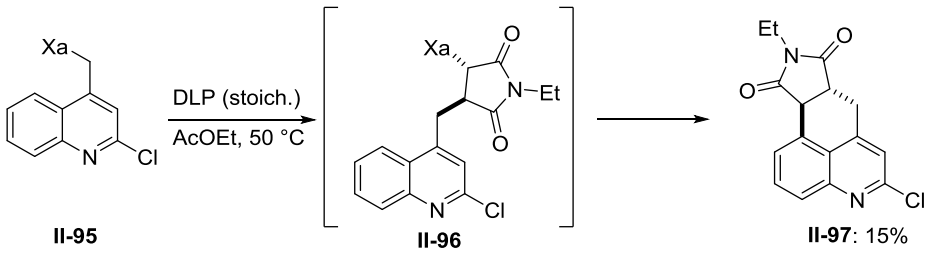
Since the reaction conditions for cyclization is not optimized in terms of yield and regioselectivity, several parameters could be modified to improve the outcome, including solvent, acid additive and number of equivalents, temperature, peroxide and method for the addition of peroxide, etc. Moreover, in order to obtain either regioisomer of **II-45** and **II-46**, we could in principle block the other reactive site with a removable group such as chlorine. The one-pot preparation of azaindanes from pyridylmethyl xanthates also seems promising.

Furthermore, instead of starting with the pyridylmethyl xanthates, this family of compounds can also be accessed from the other way around: the pyridine now bears the olefinic partner. Addition of an external xanthate to the double bond followed by cyclization would also lead to azaindanes **II-94** (Scheme 2-20). Moreover, by altering the chain length, preparation of cycloalkylpyridines other than azaindanes should also be possible. Another advantage is that substituents on C2 position to block the nucleophilicity of the pyridine nitrogen may not be required. The substrate base should therefore be significantly expanded.



Scheme 2-20: Another approach to azaindanes

This chemistry could, in principle, be applied to other heteroaromatics, including pyrazines, pyrimidines, quinolines, isoquinolines, etc. For example, our initial studies revealed that without TFA, tetracyclic product **II-97** could be isolated in one-pot from **II-95** in 15% yield (Scheme 2-21). It is worth investigating this reaction in the presence of TFA.



Scheme 2-21: Preparation of tetracyclic quinoline **II-97**

Chapter 3

Xanthate-Based Radical Alkylation of Pyrazines

3.1 Introduction

Pyrazine (1,4-diazine), together with pyridazine (1,2-diazine) and pyrimidine (1,3-diazine), constitutes the family of diazines, an important class of azahetereocycles. Pyrazines exhibit special properties and are broadly distributed in food industry, fragrances, pharmaceuticals, agrochemicals, etc. For example, 2-*sec*-butyl-3-methoxypyrazine (**III-1**) is present in wines such as Cabernet-Sauvignon[60] and alkylpyrazines are responsible for flavors thermally formed in daily foodstuff, such as coffee, meat and potatoes.[61] The trialkylsubstituted pyrazine (**III-2**) serves as an alarm pheromone in ants.[62] As for drugs, amiloride (**III-3**), a potassium-sparing diuretic, is used in the management of hypertension and congestive heart failure. After more than 20 years' effort in the search for inhibitors of SHP2 phosphatase, a stimulator of cancer growth in its open conformation, researchers at Novartis finally found a potent small molecule SHP099 (**III-4**), which can keep SHP2 in its closed conformation by binding its three active sites (Figure 3-1).[63]

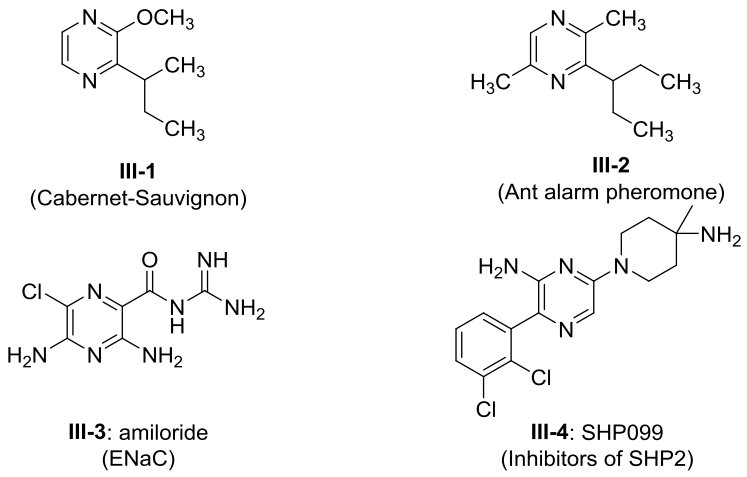


Figure 3-1: Products containing pyrazine scaffold

---

60 Amrani-Hemaimi, M.; Cerny, C.; Fay, L. B. *J. Agric. Food Chem.* **1995**, *43*, 2818.

61 (a) Maga, J. A. *Pyrazine in Foods. An Update*; Furia, T. E., Ed.; CRC Critical Reviews In Food Sciences And Nutrition: Boca Raton, FL, 1982; Vol. 16, pp 1–48. (b) Brophy, J. J.; Cavill, G. W. K. *Heterocycles* **1980**, *14,* 477. (c) Seeman, J. I.; Ennis, D. M.; Secor, H. V.; Claweson, L.; Palen, J. *Chem. Senses* **1989**, *14,* 395.

62 (a) Brown, W. V.; Moore, B. P. *Insect Biochem.* **1979**, *9*, 451. (b) Oldham, N. J.; Morgan, E. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2713.

63 (a) Chen, Y. P.; LaMarche, M. J.; Fekkes, P.; Fortin, P. D. *et al. Nature* **2016**, *535*, 148. (b) Fortanet, J. G.; Chen, C. H. T.; Chen, Y. N. P.; LaMarche, M. J. *et al. J. Med. Chem.* **2016**, *59*, 7773.

3.2 Regioselective Minisci C-H alkylations of pyrazines

Considering the importance of the pyrazine moiety, the development of approaches to highly functionalized pyrazines is therefore desired by both academia and by industry. Conventional methods for the preparation of pyrazines include cyclocondensation,[64] functionalization of cyclohexane derivatives, [65] transition metal catalyzed cross-coupling with halogenopyrazines,[66] and, finally, metalation.[67] Despite these efforts, the pyrazines prepared, however, suffer from limited substitution patterns, harsh reaction conditions, etc. These disadvantages limit their application in the drug discovery process, where building such libraries of compounds by systematic chemical alteration is highly demanded. Yet installation of the substituent at the early stage to achieve small modification of a complex lead molecule is not trivial and challenging.[68] As a result, radical alkylation of heteroarenes, especially by Minisci reactions, has nowadays emerged as a rapid and direct method for the functionalization of heteroarenes, especially in their late-stage modification.

Seminal work for the substitution of heterocycles by Minisci *et al.* in 1971 involves radicals generated from carboxylic acid by silver-catalyzed oxidative decarboxylation.[69] In 1989, they reported alkylation of heteroarene bases with alkyl radicals generated from alkyl iodides with H_2O_2 and $Fe(II)SO_4 \bullet 7H_2O$ in DMSO, in

---

64 For some recent examples of cyclocondensation, see: (a) Matsushita, H.; Lee, S.-H.; Yoshida, K.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *Org. Lett.* **2004**, *6*, 4627. (b) Gnanaprakasam, B.; Zhang, J.; Milstein, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 1468. (c) Palacios, F.; de Retana, A. M. O.; Gil, J. I.; de Munain, R. L. *Org. Lett.* **2002**, *4*, 2405. (d) Loy, N. S. Y.; Kim, S.; Park, C. *Org. Lett.* **2015**, *17*, 395. (e) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376. (f) Matsushita, H.; Lee, S.-H.; Yoshida, K.; Clapham, B.; Koch, G.;Zimmermann, J.; Janda, K. D. *Org. Lett.* **2004**, *6*, 4627.

65 For examples of functionalization of cyclohexane derivatives, see: (a) Mehta, V. P.; Sharma, A.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *J. Org. Chem.* **2008**, *73*, 2382. (b) Mehta, V. P.; Modha, S. G.; Van der Eycken, E. V. *J. Org. Chem.* **2010**, *75*, 976. (c) Modha, S. G.; Trivedi, J. C.; Mehta, V. P.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 846.

66 Wimmer, L.; Rycek, L.; Koley, M.; Schnurch, M. in *Topics of heterocyclic chemistry*, ed. Maes, B.; Cossy, J.; Polanc, S. Springer, Switzerland, **2015**, pp. 1–97.

67 (a) Mosrin, M.; Bresser, T.; Knochel, P. *Org. Lett.* **2009**, *11*, 3406. (b) Monzón, G.; Tirotta, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 10624. (c) Groll, K.; Manolikakes, S. M.; Mollat du Jourdin, X.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.

68 (a) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546. (b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.

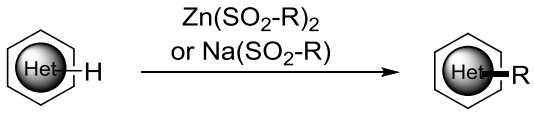
69 Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575.

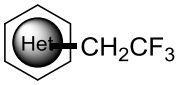
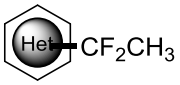
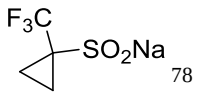
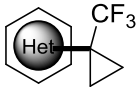
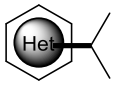
which DMSO serves not only as the solvent but also as Me• precursor.[70] Since then, toolkits for the generation of such radicals have largely expanded. Alkylation with sulfinate salts has been extensively investigated by Baran *et al.* and various fluoro-containing groups, such as $-CF_3$, $-CH_2CF_3$, $-CF_2CH_3$, can be installed regioselectively (Table 3-1). These small groups serve as fluorinated mimics of $-CH_3$, $-CH_2CH_3$, $-OCH_3$, respectively.[71] The reaction is normally accomplished with TBHP in a mixture of organic solvent and water, with an acid additive as for the difluoromethylation (TFA), difluoroethylation ($TsOH•H_2O$ and $ZnCl_2$) and isopropylation (TFA). This type of reaction tolerates a large range of functional groups, including nitriles, free alcohol, free amines, carboxylic acids, ketones, esters. As for trifluoromethylation, zinc sulfinate $Zn(SO_2\text{-}CF_3)_2$ proves to be a superior reagent than its corresponding sodium salt $Na(SO_2\text{-}CF_3)$ (Langlois' reagent)**.**[72] Later in 2014, they reported the generation of radicals from sulfinates by electrochemistry. Under electrochemical initiation, numerous substrates recalcitrant to initiation with peroxides showed improved reactivity and regioselectivity. Besides, the use of stoichiometric peroxide is also circumvented.[73]

---

70 Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224.
71 For a review of alkylation with sulfinates, see: Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 12692.
72 For a detailed study of the effect of the counter-ion, see: Baxter, R. D.; Blackmond, D. G. *Tetrahedron* **2013**, *69*, 5604.
73 O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 11868.

Table 3-1: Sulfinate salts and their corresponding products



Sulfinates	Products
$Zn(SO_2\text{-}CF_3)_2$[53,74] or $Na(SO_2\text{-}CF_3)$[75]	
$Zn(SO_2\text{-}CF_2H)_2$[74,76]	
$Zn(SO_2\text{-}CH_2CF_3)_2$[74]	
$Zn(SO_2\text{-}CH_2F)_2$[74]	
$Na(SO_2\text{-}CF_2CH_3)$[77]	
 78	
$Zn(SO_2\text{-}CH(CH_3)_2)_2$[53, 74]	

As shown in Figure 3-2, by using sulfinates as radical progenitors, several fluoro-containing groups and isopropyl group were installed in good yields. Noteworthy is that pyrazines bearing electron-withdrawing groups gave the *para*-substituted products (**III-5**, **III-8** and **III-10**) as the only regioisomer.

74 Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.
75 Ji, Y.; Brückl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411.
76 Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494.
77 Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949.
78 Gianatassio, R. L.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851.

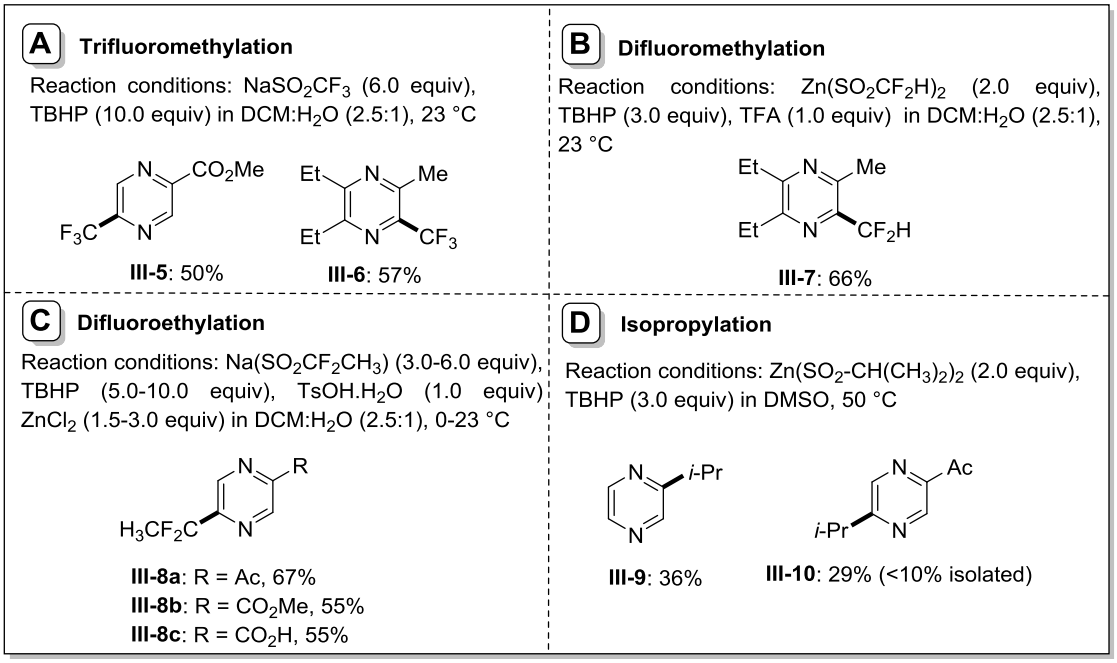


Figure 3-2: Direct functionalization of pyrazines with sulfinates by Baran *et al.*

Other methods enabling the generation of alkyl radicals suitable for C-H alkylation of heteroarenes have also been invented (Figure 3-3). Molander *et al.* firstly adopted alkyltrifluoroborates for alkylation by using $Mn(OAc)_3$ as the oxidant. Cyclobutyl, cyclopentyl, cyclohexyl and isopinocampheyl, among others, were introduced into various heterocyclic bases in good yields.[79] In 2017, they developed a photoredox-catalyzed version of this reaction with Fukuzumi's organophotocatalyst and $K_2S_2O_8$ as the oxidant.[80] Alkyltrifluoroborates can also be replaced by boronic acids. Chen *et al.* have reported photoredox alkylations with boronic acids catalyzed by a ruthenium photocatalyst under oxidation with acetoxybenziodoxole.[81] The reaction proceeded equally well for challenging primary alkyl groups. Under photo-redox conditions, MacMillan,[82] DiRocco,[83] and Barriault (with $[Au_2(dppm)_2]Cl_2$ as photocatalyst)[84] have realized generation of radicals from ether, peroxide and unactivated bromoalkanes, respectively. Very recently, Molander *et al.*

[79] Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.
[80] Matsui, J. K.; Primer, D. N.; and Molander, G. A. *Chem. Sci.* **2017**, *8*, 3512.
[81] Li, G.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2016**, *7*, 6407.
[82] Jin, J.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565.
[83] DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802.
[84] McCallum, T.; Barriault, L. *Chem. Sci.* **2016**, *7*, 4754.

disclosed the formation of alkyl radicals by homolytic cleavage of 1,4-dihydropyridines (DHP). Using $Na_2S_2O_8$ as oxidant, C-H alkylation of heteroarenes proceeded in good yields and high regioselectivity. Attempt to use *N*-methylated DHP as the radical progenitor failed to afford the desired products, indicating that the deprotonation of the $DHP^{+\bullet}$ precedes homolytic cleavage to generate the reactive radical. As a complement to TFA, the proton produced *in situ* serves also as the proton source to activate the heterocycles.[85] Readily available aldehydes have recently been used as the alkyl sources through decarbonylation of the acyl radical.[86] In order to shift the equilibrium from acyl radical to alkyl radical, such reactions require elevated temperature (>100 ℃) in order to favor the extrusion of CO. Unprotected amino acids have recently found application in the alkylation of heteroarenes, as reported by Baxter *et al.* [87] The alkyl radical is generated by *in-situ* Strecker degradation to form the corresponding aldehyde followed by decarbonylation.

Li *et al.* demonstrated a catalyst-free and redox-neutral approach to engender alkyl radicals by homolytic cleavage from appropriate sulfones under photo-irradiation.[88] In general, except for benzyl and methyl groups, other primary, secondary and tertiary alkyls groups can be installed in good yields. Another useful strategy involves alkenes as radical progenitors *via* radical olefin hydrofunctionalization. In Herzon's olefin hydropyridylation, the heteroarene bases have to be first converted into *N*-methoxyheteroarenium salts, which capture the intermediate radical and finally deliver the functionalized products. However, *N*-methoxyheteroarenium salts have to be used in large excess (5.0 equiv) and a stoichiometric cobalt reagent is required.[89] Baran *et al.* have described the conversion of alkenes to radicals with iron (III) salt. The *in-situ* generated radicals were involved in the Minisci alkylations in the presence

---

85 Gutiérrez-Bonet, A.; Remeur, C.; Matsui, J. K.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139*, 12251.

86 (a) Paul, S.; Guin, J. *Chem. - Eur. J.* **2015**, *21*, 17618. (b) Tang, R.-J.; Kang, L.; Yang, L. *Adv. Synth. Catal.* **2015**, *357*, 2055. (c) Bohman, B.; Berntsson, B.; Dixon, R. C. M; Stewart, C. D.; Barrow, R. A. *Org. Lett.* **2014**, *16*, 2787.

87 Mai, D. N.; Baxter, R. D. *Org. Lett.* **2016**, *18*, 3738.

88 Liu, P.; Liu, W.; Li, C. *J. Am. Chem. Soc.* **2017**, *139*, 14315.

89 (a) Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2016**, *138*, 8718. (b) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 5998.

of 2 equivalents of a Lewis acid BEt_3•Et_2O.[90] Last but not the least, as described in Chapter 1, xanthates have also found their application in the alkylation of heteroarenes and this chemistry is still prospering (Figure 3-3).[23-33]

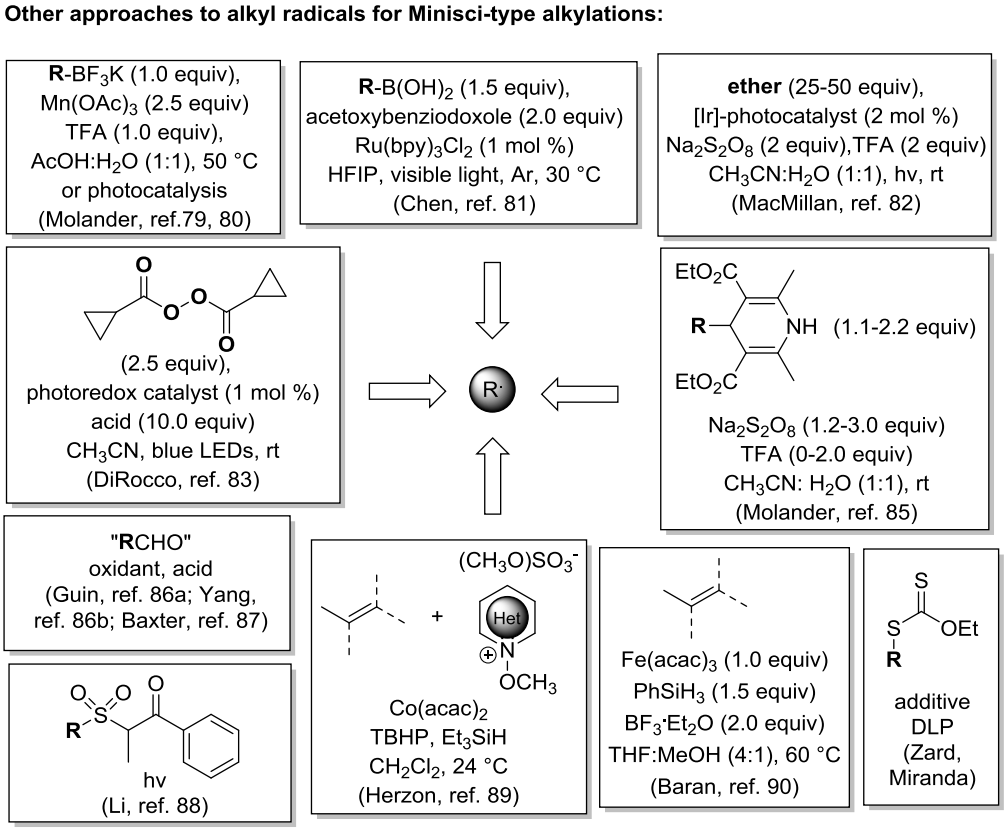
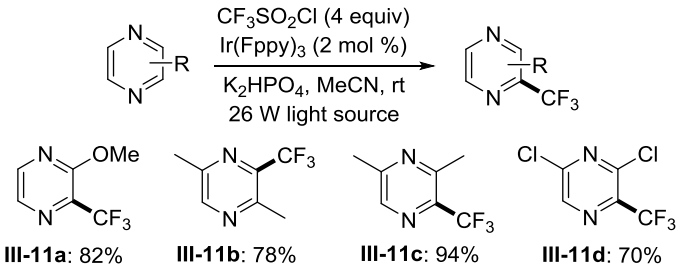


Figure 3-3: "All roads lead to" alkyl radicals

In particular, MacMillan *et al.* reported a photocatalyzed trifluoromethylation with trifluoromethanesulfonyl chloride, as exemplified by the synthesis of trifluoromethylpyrazines **III-10** (Scheme 3-1). The desired products **III-11** were furnished in high yields.[91]

[90] Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 2484.
[91] Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

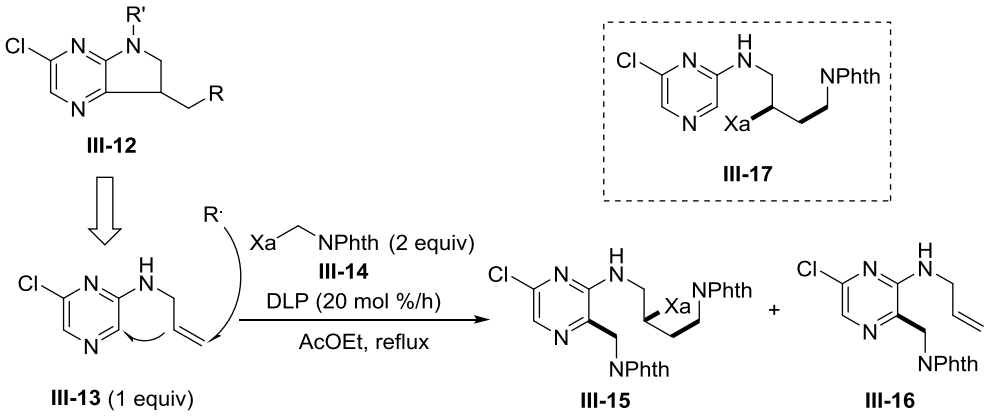


Scheme 3-1: Trifluoromethylation of pyrazines by MacMillan *et al.*

3.3 Xanthate-based intermolecular radical alkylation of pyrazines

3.3.1 Discovery of the intermolecular alkylation of pyrazines

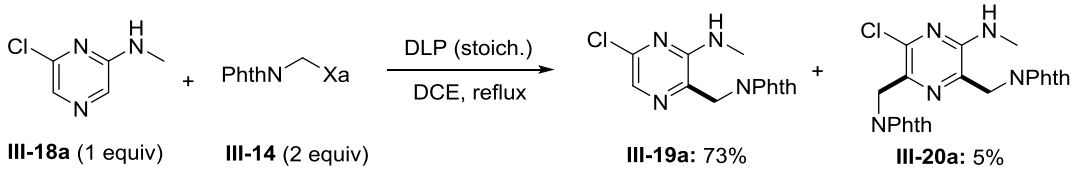
Over the past three decades, xanthate-based radical chemistry has been adopted for the construction of polycyclic molecules through a sequence of intermolecular addition to unactivated alkenes followed by cyclization to aromatics and heteroaromatic scaffolds or in the direct functionalization of indoles, pyrroles, thiophenes, etc.[6] However, molecules containing the pyrazine nucleus have not yet been investigated. In this context, bicyclic molecule **III-12** was targeted, which might be prepared from addition of radical R• to olefin **III-15**, followed by cyclization. However, upon treatment of **III-13** with 2 equivalents of phthalimidomethyl xanthate (**III-14**) in ethyl acetate under reflux, my colleague Dr. Qin observed the formation of product **III-15**, resulting from the simple addition of the xanthate to the olefin and Minisci alkylation, together with alkylated product **III-16** (Scheme 3-2). In the latter product, the terminal and expectedly more reactive olefin was not affected. Indeed, product **III-17** arising from simple degenerative xanthate addition to the alkene was not observed in this case, which implies that addition/oxidation sequence to this particular pyrazine is to some extent more favored than radical xanthate transfer process to the alkene. Direct functionalization of pyrazines by xanthate-based radical chemistry seemed therefore feasible.



Scheme 3-2: Discovery of intermolecular alkylation of pyrazine by Dr. Qin

3.3.2 Scope of alkylation of pyrazines

By simply changing the allyl group of **III-13** to a methyl group, addition of xanthate **III-14** to pyrazine **III-18a** gave the expected product **III-19a** in 73% yield, together with 5% of double addition product **III-20a** (Scheme 3-3). The position of the incorporated phthamimidomethyl group in **III-19a** was confirmed by HMBC- and nOe-NMR experiment. In this case, the base-sensitive xanthate group is compatible with the methylamino group and the little pyrazine nitrogen. Protonation of the pyrazine nitrogen or protection of the extranuclear nitrogen is therefore not necessary.



Scheme 3-3: Addition of phthalimidomethyl xanthate to pyrazine **III-18a**

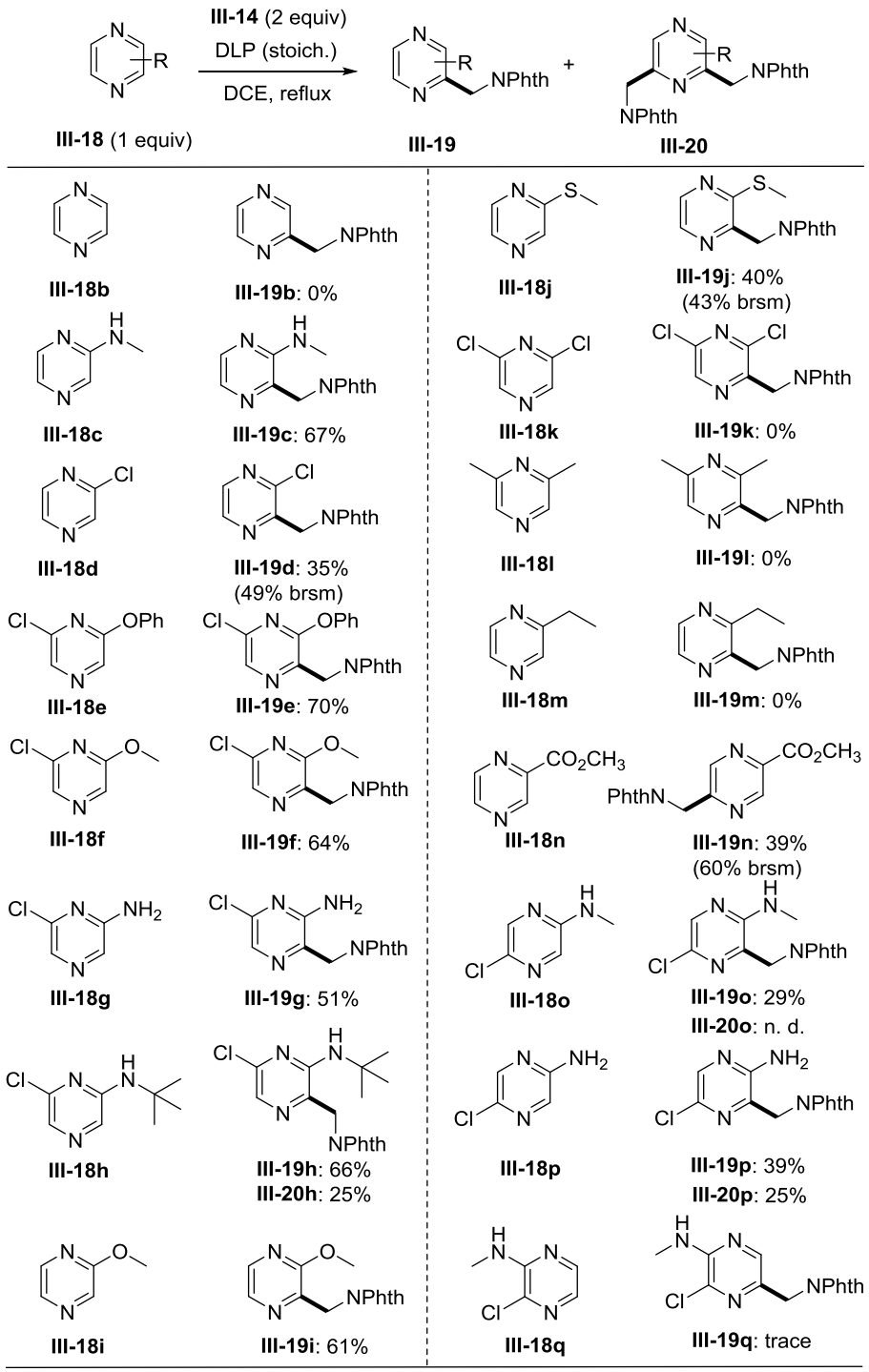
This inspiring result encouraged us to explore the scope of pyrazine substrates (Table 3-2). As for the addition to non-substituted pyrazine, product **III-19b** was not observed, indicating that either the methylamino group or the chlorine atom activates the pyrazine ring. Indeed, **III-19c** with a methylamino group was obtained in 67% yield, while chlorine-bearing product **III-19d** was obtained in 35% percent yield (49% brsm). Electron-donating methylamino group is therefore a better activating group than chlorine. Variation of the electron-donating methylamino group to other groups was then investigated, including phenoxy, methoxy, amino, *tert*-butylamino and the

desired products **III-19e-i** were isolated in good yield. Pyrazine **III-19h** containing a *tert*-butylamino group was obtained in lower ratio compared to pyrazine **III-19a**, probably due to steric hindrance. The *tert*-butylamino group can serve as a protected amino group in the place of Boc, since the protection of amine with Boc failed under routine conditions. The *tert*-butyl group can be in principle removed by treatment with TFA. 2-Thiomethylpyrazine **III-18j** was also successfully involved in the addition to afford **III-19j**, albeit in lower yield (40%). The thiomethyl group can serve as a leaving group in the Liebeskind-Srogl cross-coupling.[92] Unfortunately, addition to 2,6-dichloropyrazine **III-18k** gave no desired product **III-19k**. As for alkylpyrazines **III-18l-m**, reaction to give adducts **III-19l** and **III-19m** were not successful, possibly because of lower electron-donating ability of the alkyl group and poor stabilization of the formed cation thereof. Pyrazine **III-18n** containing an electron-withdrawing group gave exclusively the *para*-substituted product **III-19n** in moderate yield, in accordance with the results of Baran *et al*.[73,74,77]

The other two regioisomers of pyrazine **III-18a** were exposed to the same reaction to further confirm the *ortho*-activation of electron-donating group. From the reaction with pyrazine **III-18o**, product **III-19o** was obtained in 29% yield, while 2-amino-5-chloropyrazine **III-18p** gave pyrazine **III-19p** in 39% yield, together with 25% of double-addition compound **III-20p**, due to the *meta*-deactivating *ortho*-activating chlorine (Figure 2-4, Chapter 2). As for 2,3-disubstituted pyrazine **III-18q**, only a trace of the desired product **III-19q** was observed (Table 3-2).

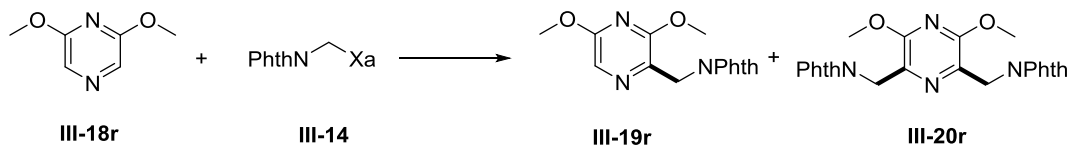
[92] (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (b) Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276.

Table 3-2: Scope of pyrazine substrates



For pyrazines containing two electron-donating groups, as in the case of **III-18r**, by changing the relative equivalents of pyrazine **III-18r** and xanthate **III-14**, mono-substituted product **III-19r** and double addition product **III-20r** could be obtained in variable ratio and in good combined yields (Table 3-3).

Table 3-3: Addition of phthalimidomethyl xanthate to 2,6-dimethoxypyrazine



III-18r III-14 III-19r III-20r

ratio of **III-18r**:**III-14**	**III-19r**: **III-20r** [a]	yield **(III-19r**, **III-20r)** [b]
2:1	8.0:1	55%, 9%
1:2	1:1.5	n. d.
1:3	1:3.4	25%, 50%

[a.] Ratio determined by ^{1}H NMR of the crude products; [b.] Isolated yields.

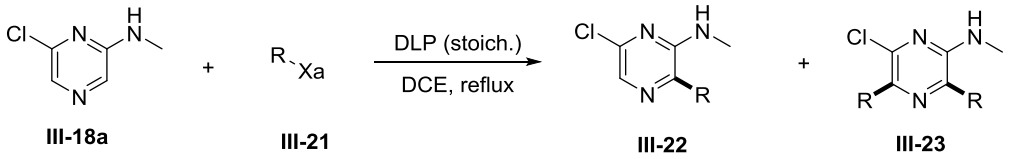
We further explored the substrate scope by reacting pyrazine **III-18a** with various xanthates to access unprecedented structures. As the pyrazine ring is electron-deficient, we anticipated that electron-rich radicals might show higher reactivity than electron-poor radicals due to polarity matching.[93] Radicals substituted by an amide-type nitrogen atom are relatively electron-rich species and could thus add efficiently to pyrazines.

As shown in Table 3-4, secondary phthalimido-containing xanthates were investigated and adducts **III-22a-c** were obtained in good yields (65-73%). Noteworthy is pyrazine **III-22b**, prepared from a trifluoromethyloxadiazomethyl-containing xanthate developed recently in our lab.[94] However, compound **III-22d** bearing a benzoyl group was not observed, possibly due to steric hindrance and too high stability of the captodative radical derived from xanthate **III-21d**. As for the addition with xanthate **III-21e** containing an oxazolidinone motif, the desired product **III-22e** was obtained in 47% yield, while by-product **III-24** was observed in less than 7% yield. Xanthate **III-21e** can undergo thermal elimination of the xanthate group to give an iminium intermediate, which can react with the methylamino group to give side-product **III-24** (Scheme 3-4). Succinimidomethyl- and phenylaminomethyl-xanthates (**III-21f-g)** added equally efficiently to pyrazine **III-18a** and afforded adducts **III-22f-g** in good

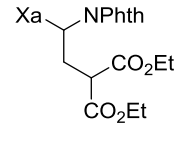
93 Anthore, L.; Zard, S. Z. *Org. Lett.* **2015**, *17*, 3058.
94 Qin, L.; Zard, S. Z. *Org. Lett.* **2015**, *17*, 1577.

yield. Moreover, our recently developed approach to protected 1,2-diamines was also applied in the alkylation process.[30] Alkylated products **III-22h-i** with quite complicated structures were isolated in good yields. Since the electron-withdrawing trifluoromethyl group on the radical center of **III-21j** is not sufficient to negate the electron-donating effect of the nitrogen, the desired addition took place smoothly and the trifluoroethylaminated pyrazine **III-22j** was produced in 73% yield. From a drug development perspective, the trifluoroethylamine group can be regarded as an amide isostere.[33] Gratifyingly, the rather stable benzyl radical added to pyrazine **III-18a** with reasonable efficiency to give adduct **III-22k** in 48% yield. *tert*-Butylpyrazine **III-22l** was also obtained in 36% yield by addition of a *tert*-butyl radical to pyrazine **III-18a**. Unfortunately, compound **III-22m** containing a thiol ether motif was not obtained starting with xanthate **III-21m**, for reasons which are not clear.

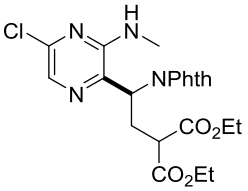
Table 3-4: Scope of electron-rich xanthate substrates



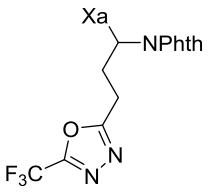
III-18a + **III-21** → **III-22** + **III-23**



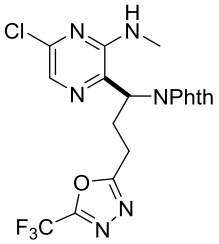
III-21a



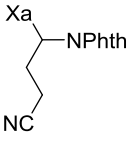
III-22a: 65%



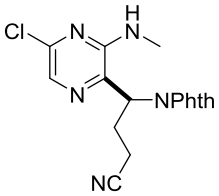
III-21b



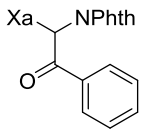
III-22b: 78%



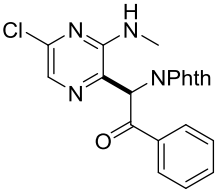
III-21c



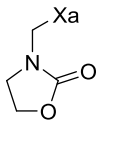
III-22c: 73%
III-23c: 26% (*dr* = 1:1)



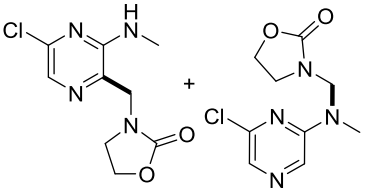
III-21d



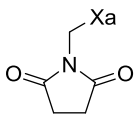
III-22d: 0%



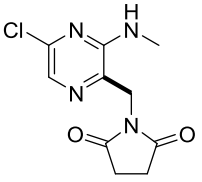
III-21e



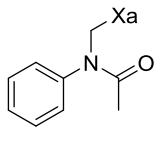
III-22e: 47% **III-24**: <7%



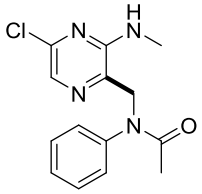
III-21f



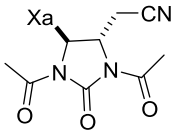
III-22f: 52%
III-23f: 28%



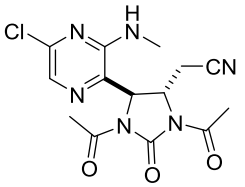
III-21g



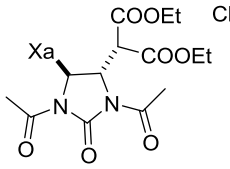
III-22g: 67%



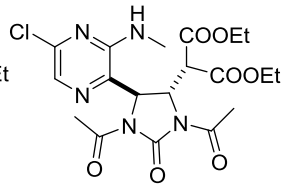
III-21h



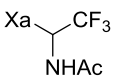
III-22h: 69%



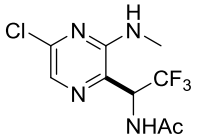
III-21i



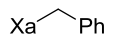
III-22i: 84%
III-23i: 14% (*dr* = 1.0:1.1)



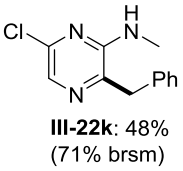
III-21j



III-22j: 74%

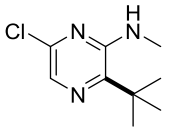


III-21k

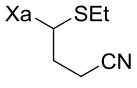


III-22k: 48%
(71% brsm)

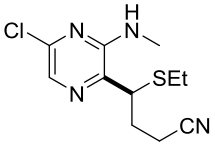
III-21l



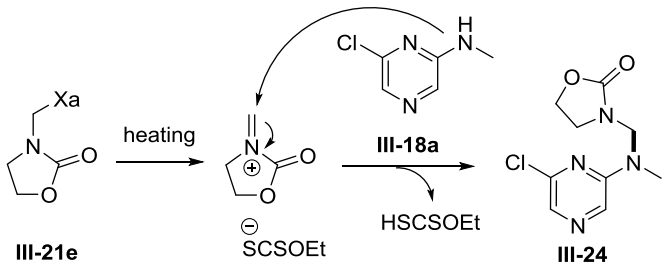
III-22l: 36%



III-21m

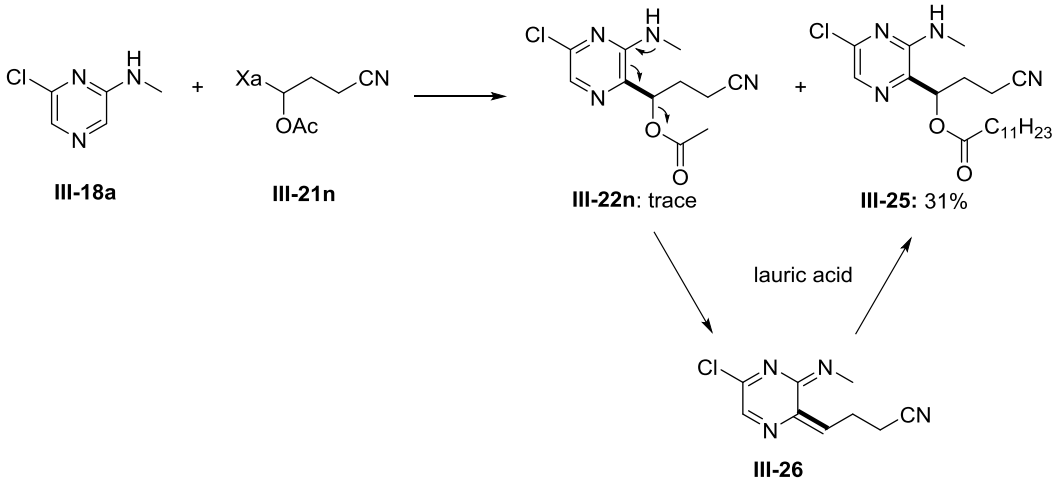


III-22m: 0%



Scheme 3-4: Plausible mechanism for the formation of side-product **III-24**

The mildly nucleophilic *α*-acetoxy substituted radicals should also be eligible for the radical addition in principle. However, addition of xanthate **III-21n** to pyrazine **III-18a** afforded a small amount of the expected product **III-22n**. A careful examination of the reaction mixture revealed the formation of laurate **III-25** in 31% yield. A plausible mechanism involves elimination of the acetate group in initial product **III-22n** with the aid of the methylamino group to give intermediate **III-26**, followed by nucleophilic attack by the lauric acid present in the medium then furnishes compound **III-25** (Scheme 3-5).



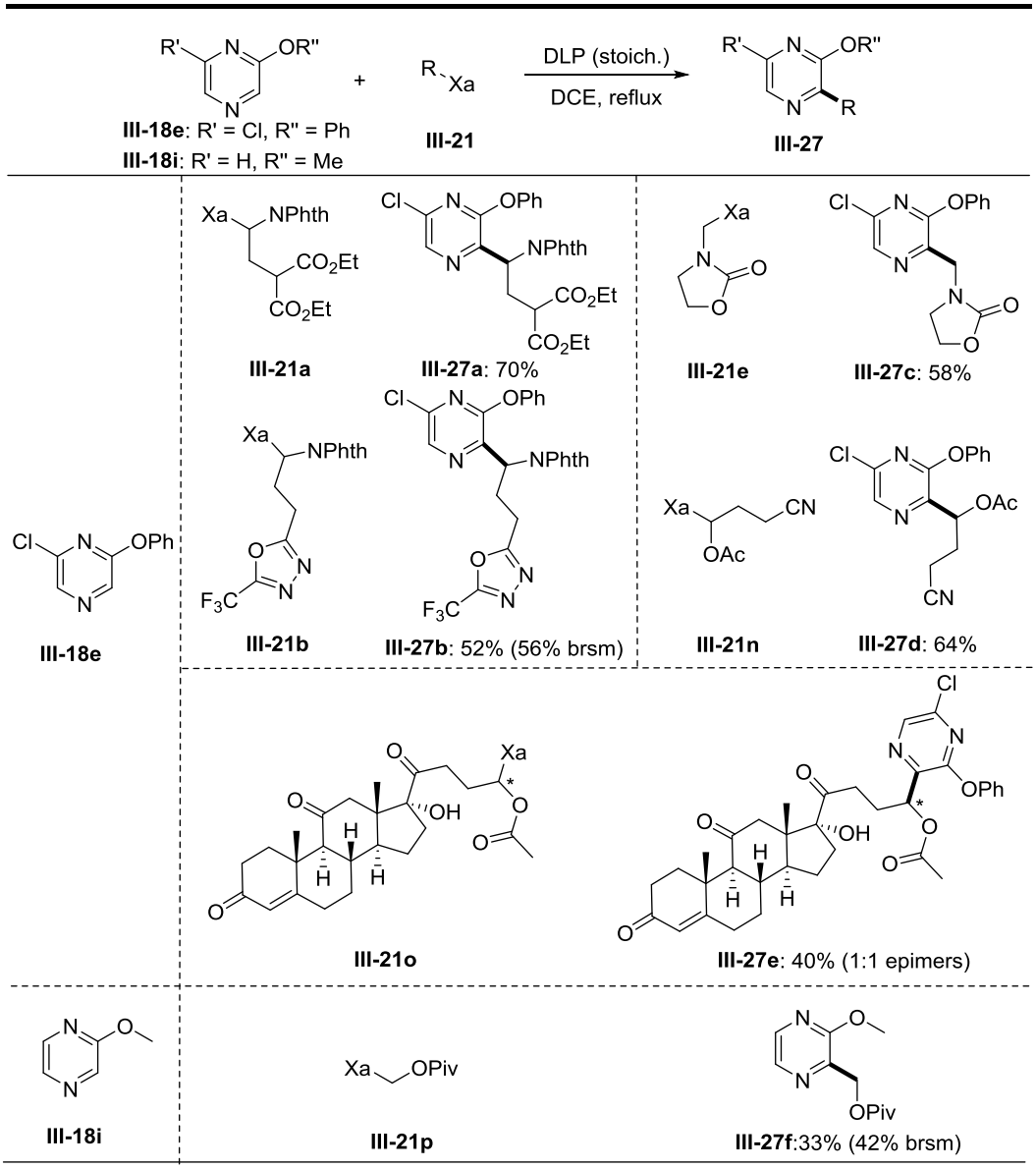
Scheme 3-5: Addition of *α*-acetoxy substituted xanthate **III-21n** to pyrazine **III-18a**

Similarly, addition of different xanthates to phenoxy- and alkoxy-pyrazine was also examined (Table 3-5). Xanthates **III-21a-b** added with similar efficiency to furnish adducts **III-27a-b** in good yields. It should be noted that under the same reaction conditions, xanthates **III-21a-b** were firstly consumed and part of the starting pyrazine was recovered, indicating the slightly lower reactivity of pyrazine **III-18e** compared to 2-chloro-6-methylaminopyrazine **III-18a**. In the absence of the

nucleophilic amino group, the addition of oxazolidinonemethyl radical generated from xanthate **III-21e** afforded smoothly adduct **III-27c** in 58% yield. The power of the xanthate technology can be further illustrated by the formation of highly complex **III-27e**, which arose from the addition of a steroid xanthate **III-21o**. Pivalatomethyl xanthate **III-21p** also proved to be a suitable substrate for this process, as indicated by the formation of product **III-27f**. The relatively low yield (33%) is probably due to the low stability of the in-coming radical.[95]

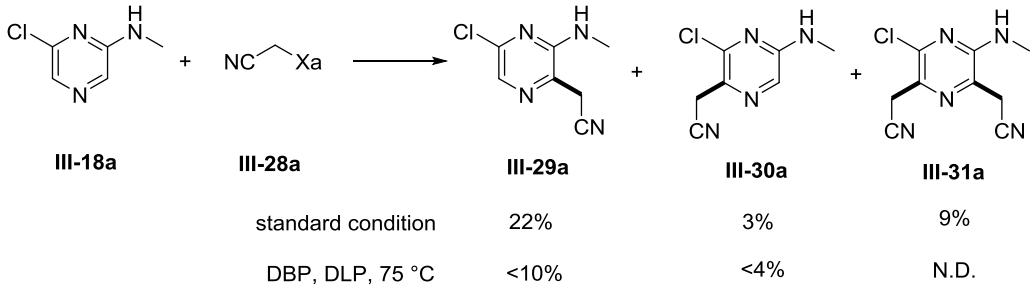
[95] Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279.

Table 3-5: Addition of xanthates to phenoxy- and alkoxy-pyrazine



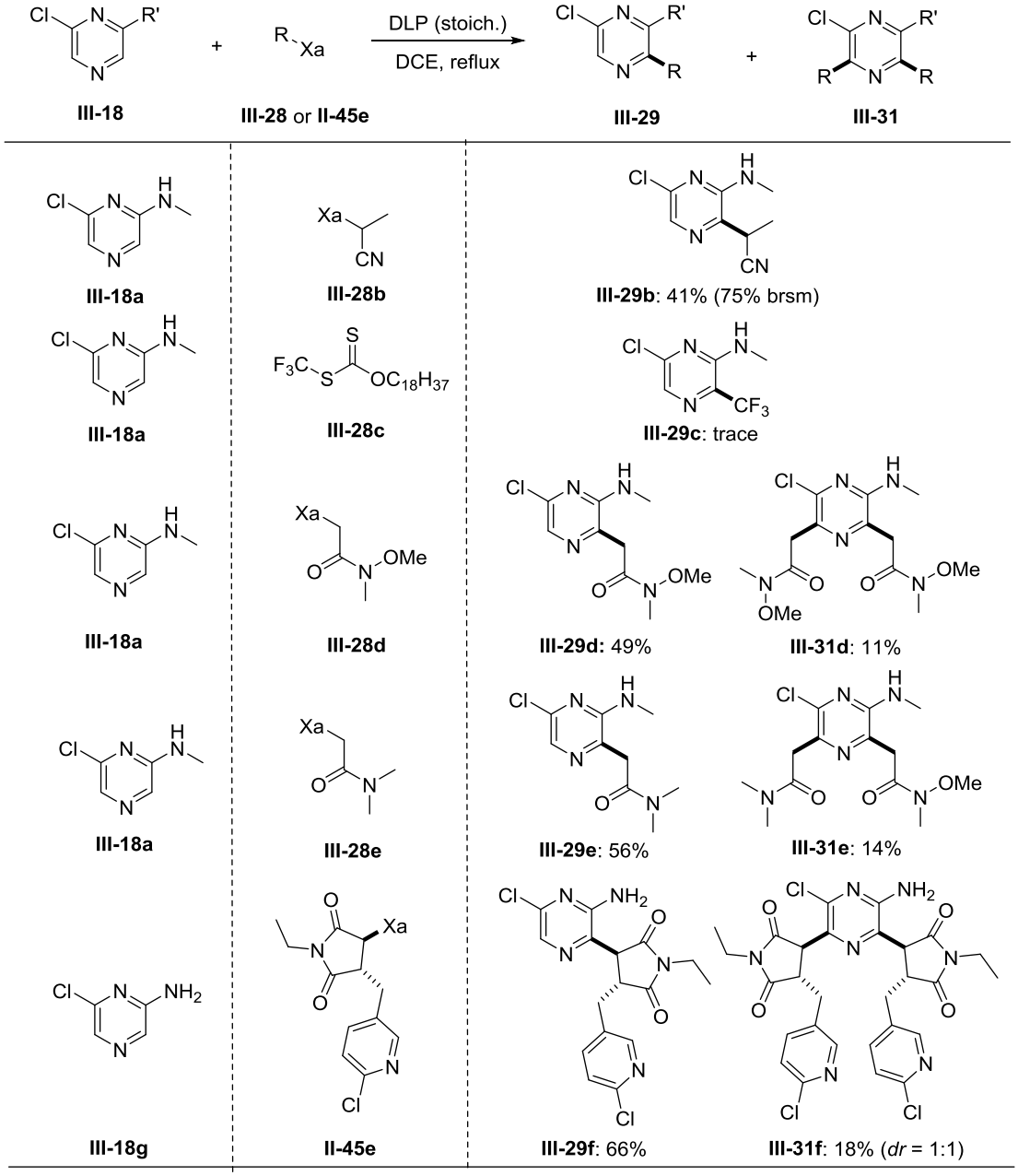
Since the addition proceeded efficiently with xanthates leading to electron-rich radicals, as are the results for most Minisci alkylations methods presented above, we were curious about whether the addition could be achieved with xanthate presursors of electron-poor radicals. Our investigation commenced with the cyanomethyl xanthate **III-28a**. To our disappointment, under different reaction conditions, the solution became dark brown immediately upon addition of DLP and three products were obtained in moderate combined yield (34%). *ortho*-Addition product **III-29a** remained still the major product, while *para*-addition product **III-29b** was isolated in this case in 3% yield. This result implied the poor reactivity of xanthates furnishing

electron-poor radicals towards pyrazines (Scheme 3-6). To our surprise, however, addition of 2-propionitrile xanthate **III-28b** to pyrazine **III-18a** gave adduct **III-29b** cleanly in 41% yield, even though some starting pyrazine **III-18a** was recovered. The reason for this difference in behavior is not presently clear. Trifluoromethyl xanthate **III-28c** was also tested, but only a trace of the trifluoromethylated product **III-29c** was obtained from the complex mixture. Finally, we were surprised to find that reaction of the Weinreb amide, *N*,*O*-dimethyl acetylhydroxamic acid xanthate **III-28d** afforded adduct **III-29d** in 49% yield, with 11% of double addition product **III-31d**. This proved to be also the case for normal amide xanthate (**III-28e**). An unusual example, which underscores the power of the present xanthate chemistry, is the synthesis of molecule **III-29f** containing both a pyridine and a pyrazine. It results from the sequential addition of *S*-pyridylmethyl xanthate **II-43a** (Scheme 2-12, Chapter 2) to *N*-ethylmaleimide to give adduct **II-45e** (Scheme 2-12, Chapter 2), followed by alkylation of pyrazine **III-18g** (Table 3-6).



Scheme 3-6: Addition of cyanomethyl xanthate **III-28a** to pyrazines

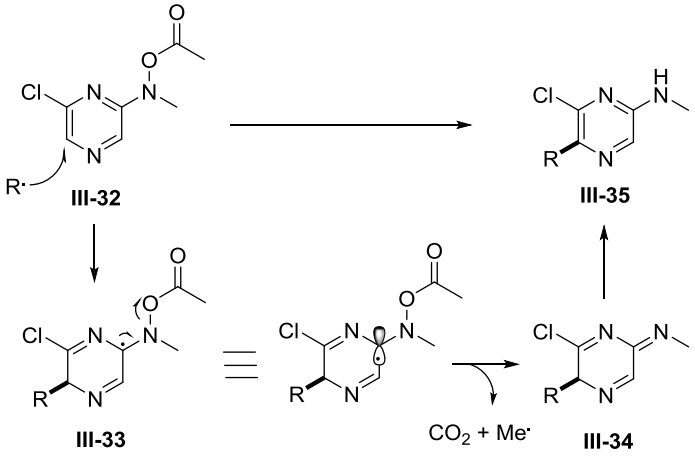
Table 3-6: Addition of electron-deficient radicals to pyrazines



3.3.3 Addition to *N*-acetoxy pyrazine

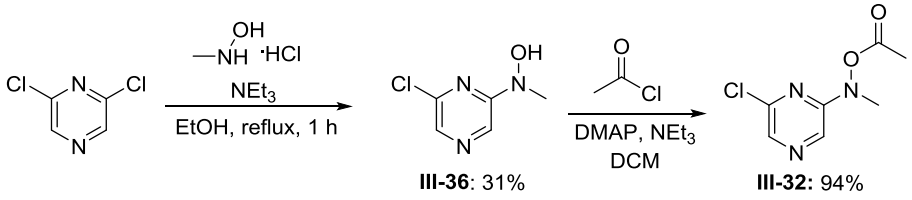
As demonstrated above, functionalization of the *ortho*-position to the electron-donating group or chlorine can be in most cases achieved in good yield. To realize regioselective alkylation on the *para*-position, pyrazine **III-32** containing an *N*-acetoxy group was examined. The intermediate radical **III-33** could in principle undergo a fragmentation of the *N*-OAc bond with the formation of an acetoxy radical.

The latter could extrude CO_2 to give a methyl radical, which could propagate the same radical chain process as $C_{11}H_{23}$•. The resulting intermediate **III-34** could then tautomerize to give the *para*-substituted product **III-35** (Scheme 3-7).



Scheme 3-7: Functionalization of pyrazine by loss of acetoxy group

Pyrazine **III-32** was synthesized in two steps. First, aromatic nucleophilic substitution of *N*-methylhydroxylamine to 2,6-dichloropyrazine gave hydroxylamine **III-36** in 31% yield, although the reaction solution was quite clean. Acetylation furnished **III-32** in 94% yield (Scheme 3-8).

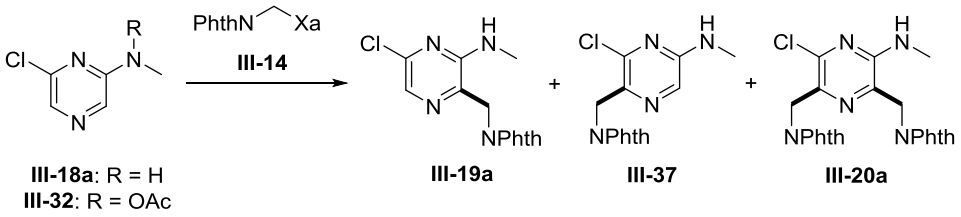


Scheme 3-8: Synthesis of *N*-acetoxy pyrazine **III-32**

Xanthate **III-14** was first tested on this new substrate. However, under standard reaction conditions, no *para*-substituted product **III-37** was obtained, whereas a larger proportion of double alkylation product **III-20a** was observed (entry 2, Table 3-7) in comparison with the reaction with pyrazine **III-18a** (entry 1, Table 3-7). Since this process might be a chain process and stoichiometric peroxide is in principle not required for oxidation, a substoichiometric amount of peroxide might be sufficient for the reaction to go to completion. Dilauroyl peroxide was therefore added in 5 mol % portions into the reaction solution. However, stoichiometric DLP was still required for

the total consumption of pyrazine **III-32** and a similar ratio of pyrazines **III-19a**:**III-20a** was obtained (entry3, Table 3-7). A possible explanation is that the *ortho*-position in pyrazine **III-32** is no longer more preferable considering that *N*-OAc group is much less electron-donating than an amino group. Upon formation of adduct **III-37** (path a), the *ortho*-activating methylamino group is revealed and *ortho*-position becomes again activated. Since phthalimidomethyl radical is a suitable radical for this reaction, a second addition proceeds efficiently. Pyrazine **III-20a** formed *via* path b contributes also to the higher proportion, although to a lesser extent (Figure 3-4).

Table 3-7: Addition of xanthate **III-14** to pyrazine **III-32**



entry	R	**III-19a**:**III-20a**	yield of **III-19a** (%)[b]
1	H (**III-18a**)	21:1	73
2	OAc (**III-32**)	2.6:1 (20 mol % DLP/h)[a]	45
3	OAc (**III-32**)	2.3:1 (5 mol % DLP/h)[a]	41

[a.] Ratio determined by ^{1}H NMR of the crude products; [b.] Isolated yield.

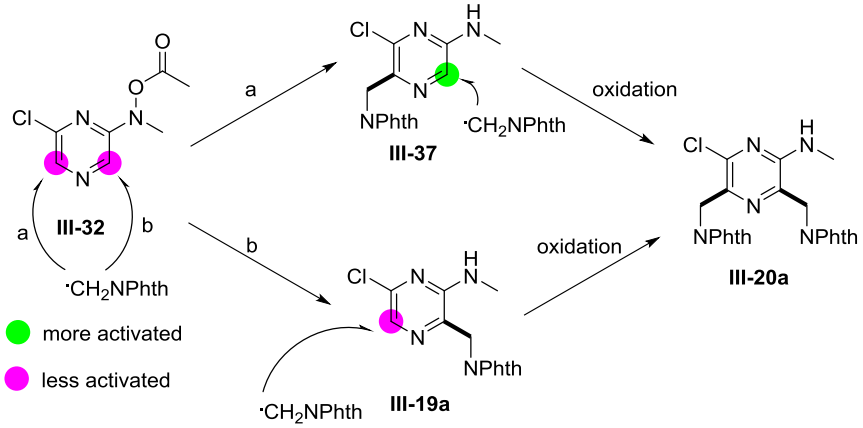
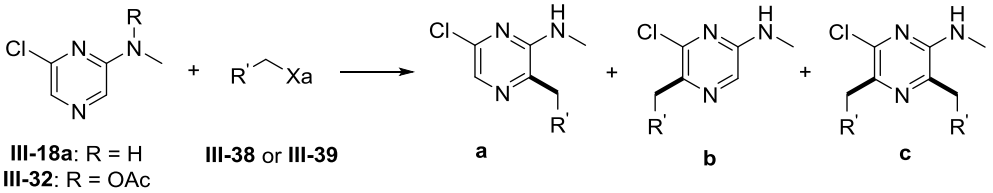


Figure 3-4: Possible explanation for the larger ratio of dialkylated pyrazine **III-20a**

We then attempted to improve the efficiency of the addition using xanthates generating electron-poor radicals. Trifluoromethyl oxadiazomethyl xanthate **III-38** and ethyl α-xanthylacetate **III-39** were tested. In all cases, the reaction solutions turned dark brown and the process proceeded sluggish. With xanthate **III-38**, a small

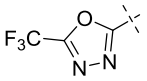
amount of *para*-substituted pyrazine **III-40b** was observed for both pyrazine substrates. Moreover, the same trend was observed: the double alkylated products **III-40c** and **III-41c** were obtained in higher proportion with pyrazine **III-32** (Table 3-8).

Table 3-8: Addition of electron-deficient xanthates to **III-32**



III-18a: R = H
III-32: R = OAc

III-38 or **III-39**

R'	R	**a**: **b**: **c** [a]
 **III-38**	H (**III-18a**)	(**III-40**) 3:1:3
	OAc (**III-32**)	(**III-40**) 3:1:4
 **III-39**	H (**III-18a**)	(**III-41**) 9:1:3
	OAc (**III-32**)	(**III-41**) 9:0:10

[a] Ratio determined by ^{1}H NMR of the crude products.

The reaction of pyrazine **III-32** with xanthate **III-39** was monitored by ^{1}H NMR (Figure 3-5). To observe more closely the evolution of the reaction, it was carried out at 50 ℃ instead of under reflux. After 1 h, pyrazines **III-41a** and **III-41b** were formed in a ratio of 2.6:1.0, as determined by the integration of peaks corresponding to the aromatic protons H1 and H3. Dialkylated pyrazine **III-41c** was not yet formed at this stage. As the reaction proceeded, this ratio increased to 6.3:1.0 after 5 h. After 11 h, pyrazine **III-41b** almost disappeared. Meanwhile, peaks corresponding to dialkylated pyrazine **III-41c** (H5 and H6) became progressively more and more important. These results indicate that most of pyrazine **III-41c** probably formed from compound **III-41b**.

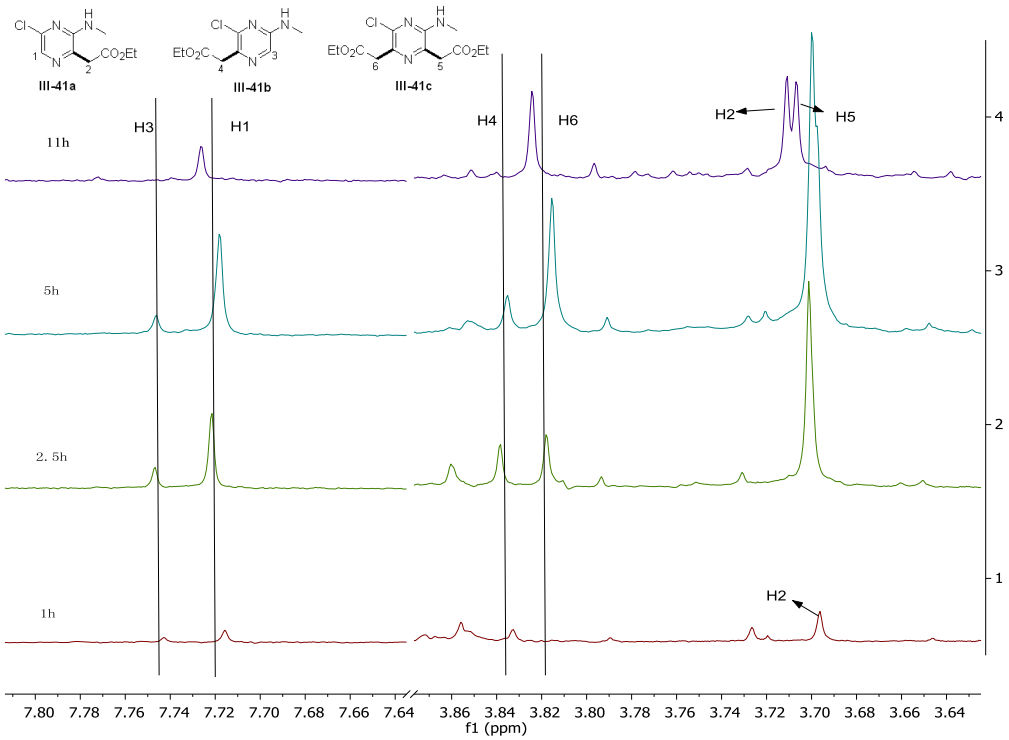
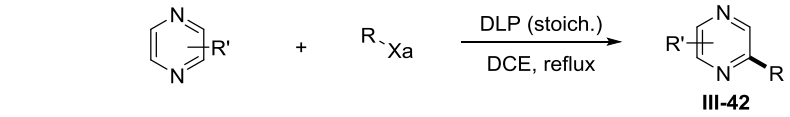


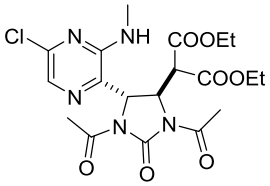
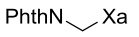
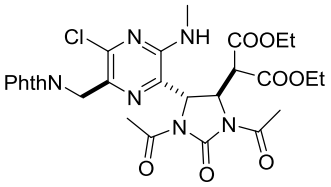
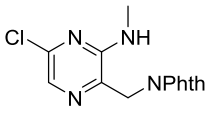
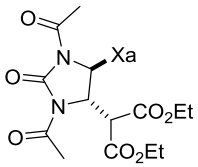
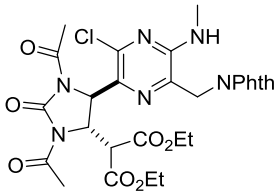
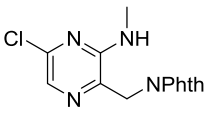
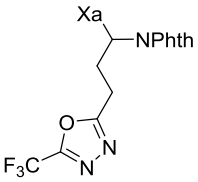
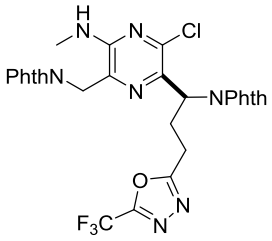
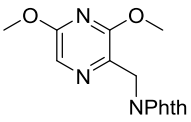
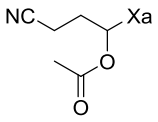
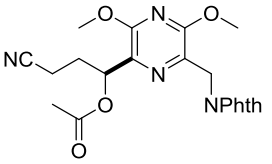
Figure 3-5: Monitoring of the evolution of the reaction of pyrazine **III-32** with xanthate **III-39** (Other peaks are omitted for clarity)

3.3.4 Access to tetrasubstituted pyrazines

Considering that double alkylated products can be formed in variable yields, functionalization of the last position should be therefore feasible by treating mono-alkylated products above with a different xanthate. Addition of xanthate **III-14** to pyrazine **III-22i** gave new pyrazine **III-42a** in 59% yield, while addition of xanthate **III-21i** to pyrazine **III-19a** afforded compound **III-42b** in a yield of 76%. This proves that the sequence of functionalization can be easily tuned as desired. Pyrazine **III-42c** was also obtained in moderate yield (44%) from reaction of xanthate **III-21b** and pyrazine **III-19a**. With an electron-donating group *ortho* to the last available position, the alkylation was quite efficient and pyrazine **III-42d** was obtained in good yield (59%) with no starting material **III-19r** revovered (Table 3-9).

Table 3-9: Access to tetrasubstituted pyrazines

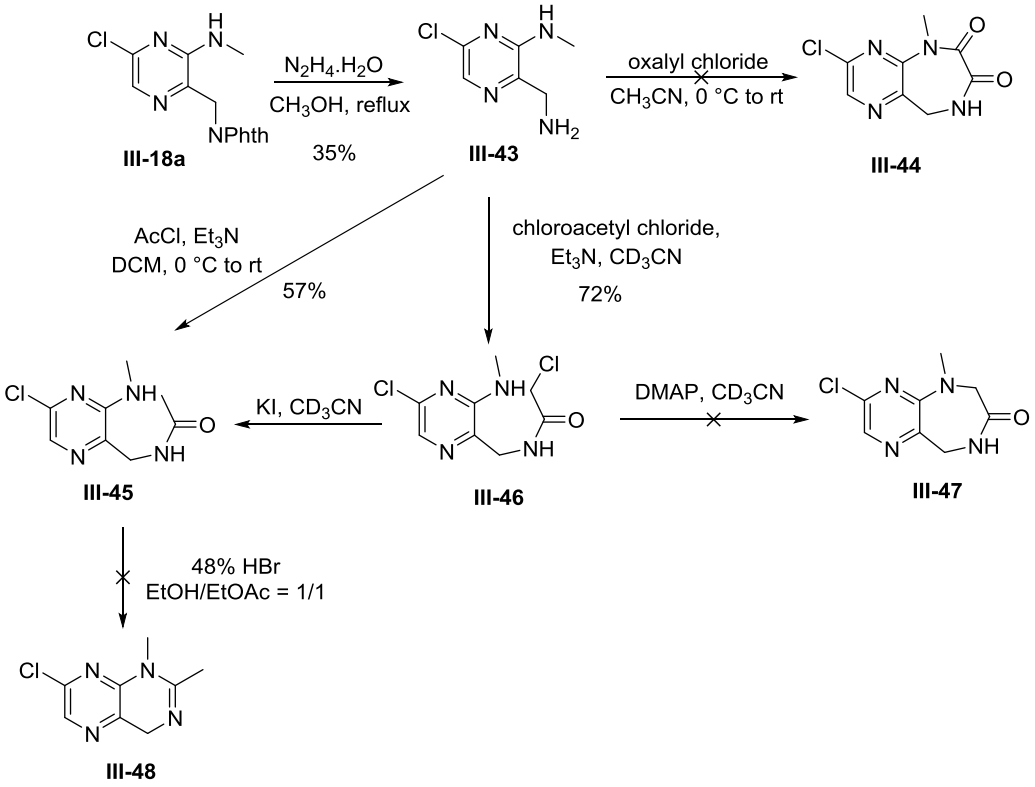


 **III-22i**	 **III-14**	 **III-42a**: 59% (82% brsm)
 **III-19a**	 **III-21i**	 **III-42b**: 76% (83% brsm)
 **III-19a**	 **III-21b**	 **III-42c**: 44% (72% brsm)
 **III-19r**	 **III-21n**	 **III-42d**: 59%

3.3.5 Post-modification

The phthalimido group was then removed with hydrazine to afford the amine **III-43** in 35% yield. Unwanted reactions of hydrazine with the chloropyrazine ring are probably the cause of the moderate yield. Treatment of aminomethyl pyrazine **III-43** with oxalyl chloride in CH_3CN gave no desired product. Benzodiazepinone derivative **III-47** was then targeted. Reaction of pyrazine **III-43** with chloroacetyl chloride afforded chloroacetamide **III-46** in 72% yield. Unfortunately, its cyclization failed either with DMAP, or with KI in CD_3CN. In the latter case, the reduced product **III-45** was isolated. Compound **III-45** could be also prepared from pyrazine **III-43** by acetylation with acetyl chloride. Unfortunately, treatment of this substance with 48%

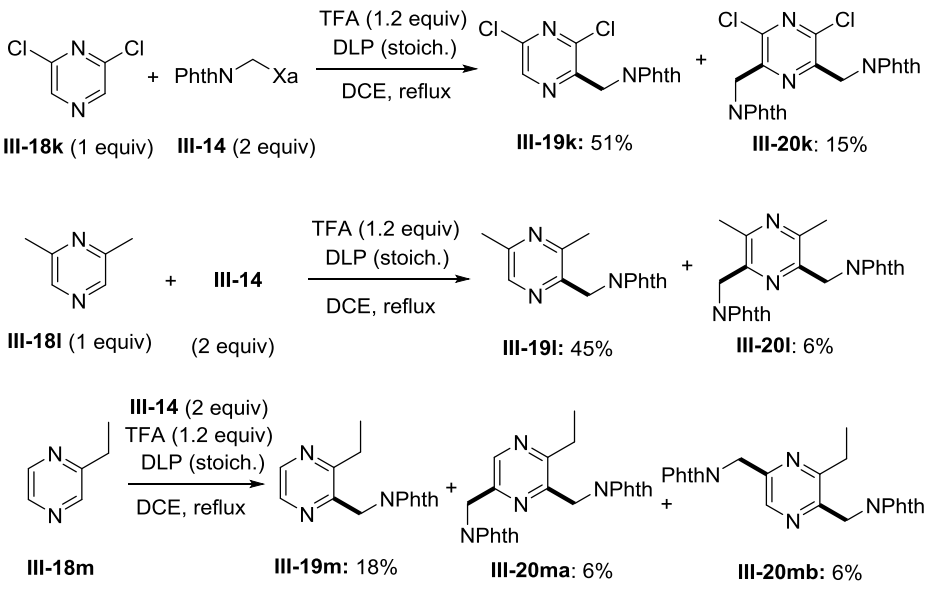
HBr gave no desired cyclized product **III-46** (Scheme 3-9).



Scheme 3-9: Attempts of cyclization of **III-43**

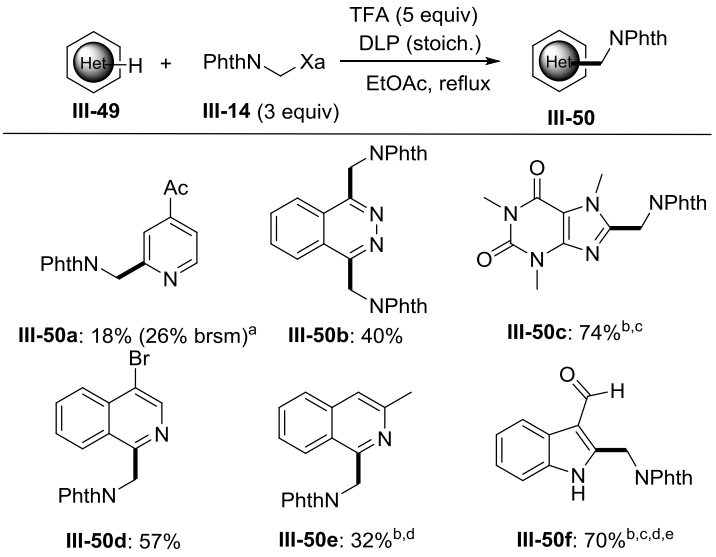
3.4 Further extension

As our knowledge of the Minisci alkylation accumulates, we appreciate the fact that alkylation of electron-deficient heteroarenes can be improved by adding a strong acid. Indeed, we were pleased to find that, in the presence of 1.2 equivalents of TFA, reaction of 2,6-dichloropyrazine **III-18k** or 2,6-dimethylpyrazine **III-18l** with xanthate **III-14** afforded pyrazines **III-19k** and **III-20k** in 51% and 15% yields, and pyrazines **III-19l** and **III-20l** in yields of 45% and 6%, respectively. Reaction of 2-ethylpyrazine **III-18m** with xanthate **III-14** gave monoalkylated **III-19m** in 18% yield, together with 1:1 regioisomers (**III-20ma** and **III-20mb**) from double alkylation (Scheme 3-10). These pyrazine substrates were unreactive in the previous study (Table 3-2).



Scheme 3-10: Reaction of pyrazines in the presence of TFA

This chemistry is not limited to pyrazines. Several other heteroarenes could also be modified under non-optimized reaction conditions. These include pyridine (**III-50a**), phthalazine (**III-50b**), caffeine (**III-50c**), isoquinoline (**III-50d-e**) and indole (**III-50f**). In the case of electron-rich caffeine and indole, no acid was required for the reaction to proceed and the product **III-50f** was obtained in 70% by simple trituration with diethyl ether and recrystallization (Scheme 3-11).

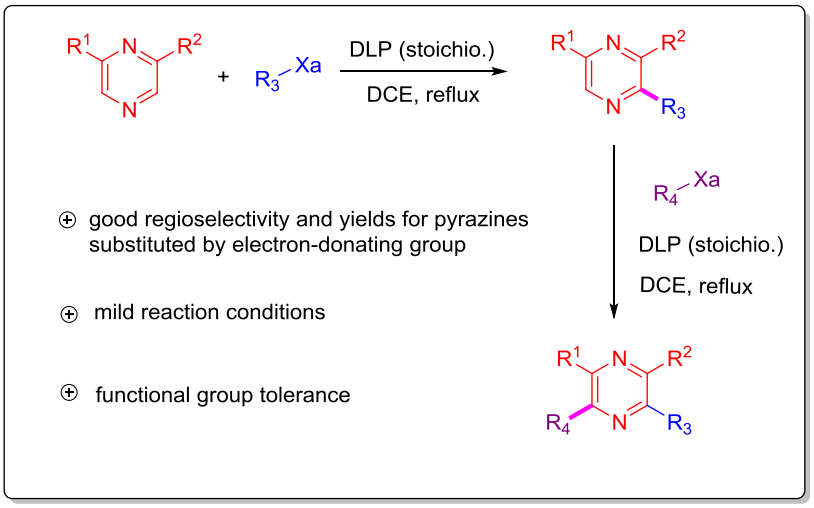


[a] 1.3 equiv of **III-14** was used and the double addition product **III-51** was isolated in 9% yield (14% brsm). [b] No TFA added. [c] DCE was used as solvent. [d] 2.0 equiv of **III-14** was used. [e] the reaction was carried out at 50 °C.

Scheme 3-11: Alkylation of other heteroarenes

3.5 Conclusion and perspective

In summary, we have developed a novel method for the functionalization of pyrazines based on xanthate radical chemistry. This method combines degenerative radical addition to alkenes and Minisci reaction to construct highly functionalized pyrazines. The present methodology can be also applied to other heteroaromatic systems. This approach exhibits good yields, mild metal-free reaction conditions and excellent functional group tolerance (Scheme 3-12). These features provide a practical method for the late-stage functionalization of complex molecules.



Scheme 3-12: General features of the present method

Considering the power of this method, numerous variations could be envisaged. Numerous other combinations of heteroarenes and xanthates are possible including drugs or natural products containing heteroaromatic rings. Our limited efforts to construct adjoining rings have failed but further work should overcome the problem and provide access to novel polycyclic structures.

Chapter 4

Towards an Inexpensive Radical Methylation and Ethylation of Heteroarenes

4.1 Introduction

Being the smallest organic motif, the methyl group plays a key role in many biological phenomena. For example, the difference between uracil (**IV-1**), an RNA nucleobase, and thymine (**IV-2**), a DNA nucleobase, is a tiny methyl group. Methylation of DNA is crucial for many biological processes.[96] Methylation of cysteine in a type of ubiquitin-chain sensory proteins may disrupt its coordinating ability with zinc ion and loses the ubiquitin-chain binding activity.[97] In Nature, *S*-adenosylmethionine (SAM) is found to be responsible for the methylation of biological molecules, including tryptophan, cysteine and uracil, with SAM being the radical or ionic methyl source.[98]

Figure 4-1: Difference of uracil and thymine by one methyl group

The significance of introducing a methyl group is far beyond this chapter. For the contemporary drug discovery process, the late stage functionalization of potential drug candidates has nowadays been raised to prominence. Instead of the traditional *de novo* synthesis, direct modification of advanced intermediates allows rapid diversification of structures and might largely shorten the research timeline. Introduction of small fluorinated groups, including trifluoromethyl, difluoromethyl, difluorethyl groups, are of particular interests due to their enhanced metabolic stability towards oxidation by cytochrome P450 enzyme.[99] However, installation of

---

96 (a) Choy, J.S.; Wei, S.; Lee, J.Y.; Tan, S.; Chu, S.; Lee, T.-H. *J. Am. Chem. Soc.* **2010**, *132*, 1782. (b) Okano, M.; Bell, D.W.; Haber, D.A.; Li, E. *Cell* **1999**, *99*, 247. (c) Jaenisch, R., and Bird, A. *Nat. Genet.* **2003**, *33*, 245.

97 Zhang, L.; Ding, X.; Cui, J.; Xu, H.; Chen, J.; Gong, Y.-N.; Hu, L.; Zhou, Y.; Ge, J.; Lu, Q.; Liu, L.; Chen, S.; Shao, F. *Nature* **2012**, *481*, 204.

98 (a) Zhang, Q.; van der Donk, W. A.; Liu, W. *Acc. Chem. Res.* **2012**, *45*, 555. (b) Fujimori, D. G. *Curr. Opin. Chem. Biol.* **2013**, *17*, 597. (c) Zhou, P.; O'Hagan, D.; Mocek, U.; Zeng, Z.; Yuen, L. D.; Frenzel, T.; Unkefer, C. J.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1989**, *111*, 7274. (d) Kelly, W. L.; Pan, L.; Li, C. *J. Am. Chem. Soc.* **2009**, *131*, 4327.

99 Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

these groups risks the violation of Lipinski's rules[100] in cases where the molecular weight and logP value of the starting compound is already high. For instance, simple trifluoromethylation results in ΔMW = 68 g•mol^{-1} and Δ*c*logP ≈ 0.9. Besides, their physiochemical properties can also be diminished and finally affect other properties.[101] Introduction of a small methyl group (ΔMW = 14 g•mol^{-1} and Δ*c*logP ≈ 0.5) can therefore overcome these disadvantages and provide an effective alternative.[102] Indeed, installation of a seemingly mundane methyl group can result in drastic increase in solubility, bioavailability and metabolic activity of drug candidates[102b] and a so-called "magic methyl effect" culminates.[103] For example, compound **IV-3** and **IV-4** are potent inhibitors of p38α MAP3 kinase while the latter with a methyl group possesses a potency of 208-fold higher than the corresponding non-methylated product **IV-3** (Figure 4-2).[104] Considering the utility and ubiquity of this small alkyl group, approaches to methylation are highly desirable, giving rise to a "call for new C-H methylation reactions".[103] Notably, an important branch in methylation lies in the methylation of heteroarenes.

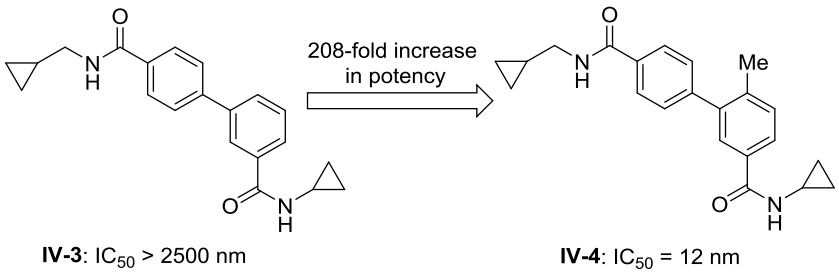


Figure 4-2: Example of the "magic methyl effect"

4.2 Direct methylation of heteroarenes

Conventional methods for access to methylated arenes depend chiefly on directed

100 Lipinski, C. A. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235.
101 *Lipophilicity in Drug Action and Toxicology* (Eds.: V. Pliska, B. Testa, H. Waterbeemd), Wiley-VCH, Weinheim, **2008**.
102 (a) Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489. (b) Barreiro, E.J.; Kümmerle, A.E.; Fraga, C.A.M. *Chem. Rev.* **2011**, *111*, 5215.
103 Schönherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256.
104 Angell, R.; Aston, N. M.; Bamborough, P.; Buckton, J. B.; Cockerill, S.; deBoeck, S. J.; Edwards, C. D.; Holmes, D. S.; Jones, K. L.; Laine, D. I.; Patel, S.; Smee, P. A.; Smith, K. J.; Somers, D. O.; Walker, A. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428.

ortho-metalation.[105] However, these tools demand the pre-installation of directing groups and stoichiometric strong bases (*n*-BuLi, for example). As for the methylation of heteroaromatics by C-H activation, methods are even more limited since the presence of the heteroatom will interfere with the coordination of the catalysts with the directing groups.[106] Despite these difficulties, several strategies have been developed, mainly consisting of metal-mediated methylation, metal-free ionic methylation and most prominently radical methylation (Figure 4-3).[107]

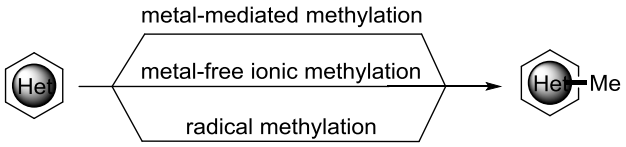


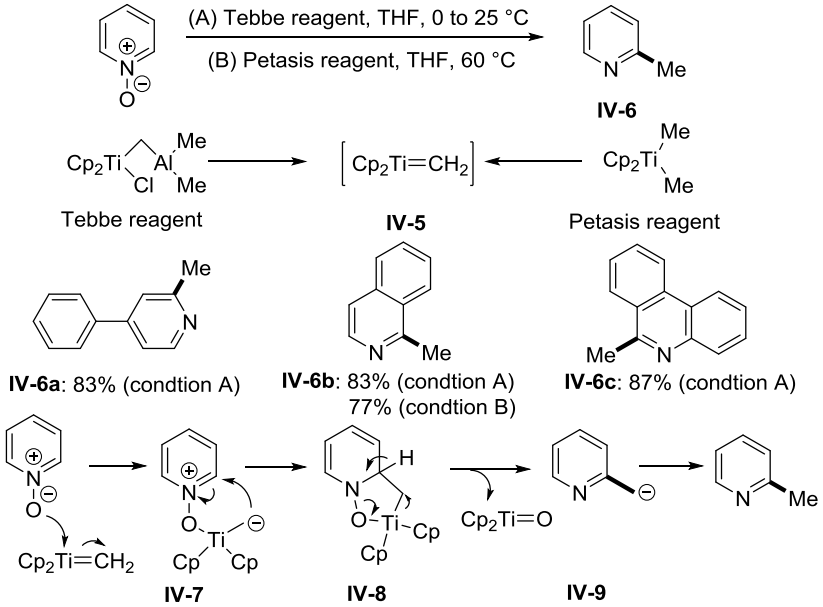
Figure 4-3: Methods for direct methylation of heteroarenes

4.2.1 Metal-mediated methylation of heteroarenes

Substrates for metal-mediated methylation are heteroaromatic *N*-oxides. In 2000, Nicolaou *et al.* developed the methylation *via* deoxygenation of *N*-oxides with titanocene methylidene (**IV-5**) generated from either Tebbe[108] reagent or Petasis[109] reagent.[110] The reaction proceeded excellently with pyridine-derived *N*-oxides, affording methylated products **IV-6** in good yields. For the reaction with isoquinoline *N*-oxide, only one regiosiomer **IV-6b** was observed. Coordination of the oxygen to the titanium species gives intermediate **IV-7**, followed by intramolecular cyclization on heteroarenes to form the metallacycle **IV-8**. This intermediate then breaks down to afford anionic species **IV-9**, driven by hydrogen elimination to release $Cp_2Ti{=}O$. Finally, protonation delivers the methylated product **IV-6** (Scheme 4-1).

---

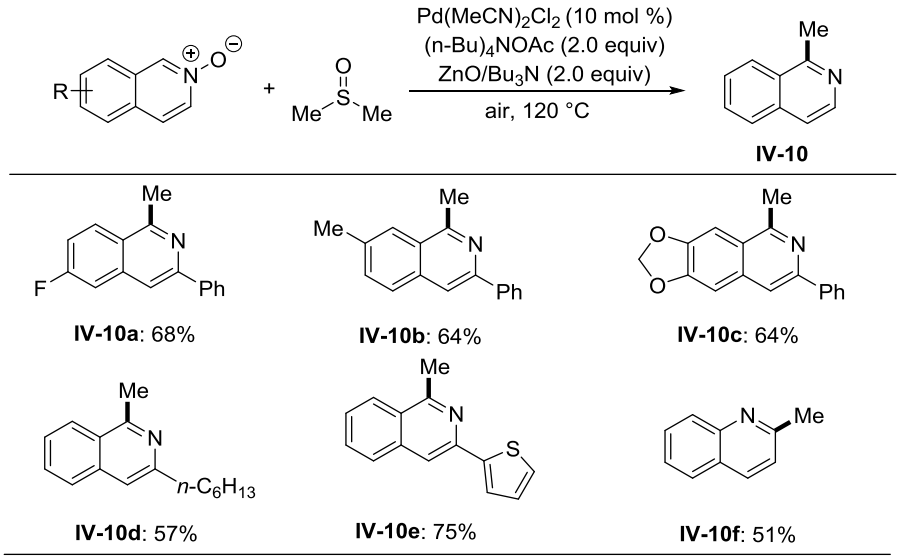
105 Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
106 Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515*, 389.
107 Kim, J.; Cho, S. H. *Synlett* **2016**, *27*, 2525.
108 Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
109 Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
110 Nicolaou, K. C.; Koumbis, A. E.; Snyder, S. A.; Simonsen, K. B. *Angew. Chem. Int. Ed.* **2000**, *39*, 2529.



Scheme 4-1: Methylation with titanocene methylidene

In 2012, Deng *et al.* reported a Pd-catalyzed methylation of isoquinoline *N*-oxides with DMSO as the methyl source.[111] The reaction proceeded with $Pd(MeCN)_2Cl_2$ catalyst, $(n\text{-}Bu)_4NOAc$ as a phase-transfer catalyst and a base (ZnO or Bu_3N) in air at 120 ℃. Various methylated isoquinolines (**IV-10a-e**) and one quinoline (**IV-10f)** were prepared in good yields (Scheme 4-2). The reaction mechanism is not very clear. This method, however, seems limited in regard of heteroarene substrates, since no reaction with other heteroaromatics was presented.

111 Yao, B.; Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H.; Wang, M.-K.; Tang, R.-Y.; Zhang, X.-G.; Deng, C.-L. *Adv. Synth. Catal.* **2012**, *354*, 1890.

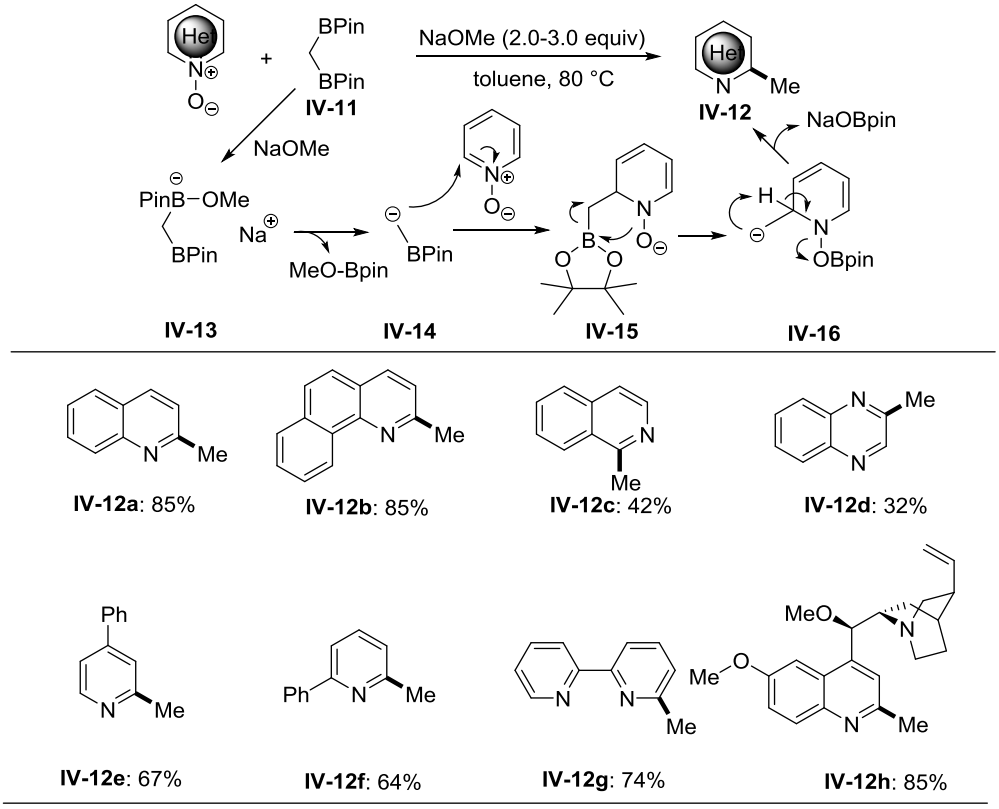


Scheme 4-2: Pd-catalyzed methylation using DMSO as the methyl source

4.2.2 Metal-free ionic methylation of heteroarenes

In 2016, Cho *et al.* disclosed a regioselective methylation of heteroarene *N*-oxides involving bis[(pinacolato)boryl]methane (**IV-11**) as the methyl source.[112] The reaction is applicable to a range of heteroarenes, including quinoline (**IV-12a**), benzo[*h*]quinoline (**IV-12b**), isoquinoline (**IV-12c**), quinoxaline (**IV-12d**), pyridine (**IV-12e-f**) and 2,2'-bipyridine (**IV-12g**). Notably, a methylated 9-*O*-methylquinine (**IV-12h)** was obtained in good yield of 85%. The reaction pathway was proposed as follows: coordination of NaOMe to **IV-11** gives intermediate **IV-13**, followed by cleavage of the C-B bond to generate the α-borylcarbanionic species **IV-14**. Nucleophilic attack of anion **IV-14** at the *ortho* position of *N*-oxides forms intermediate **IV-15**, which undergoes intramolecular boron migration and subsequent proton transfer to afford the methylated product **IV-12** (Scheme 4-3).

[112] Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 9690.

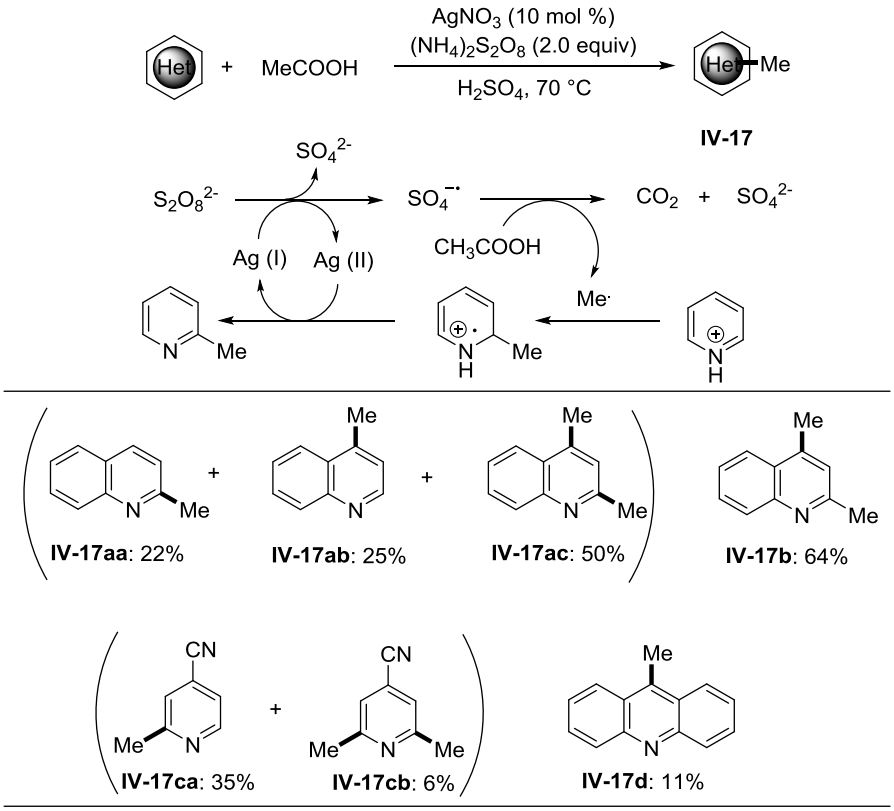


Scheme 4-3: Methylation of heteroarene *N*-oxides with diborylmethane

4.2.3 Radical methylation of heteroarenes

As described in Chapter 3, a broad range of methods are available for the radical alkylation of heteroaromatics (Figure 3-3). Despite these advances, few methods are suitable for the introduction of the small methyl group.

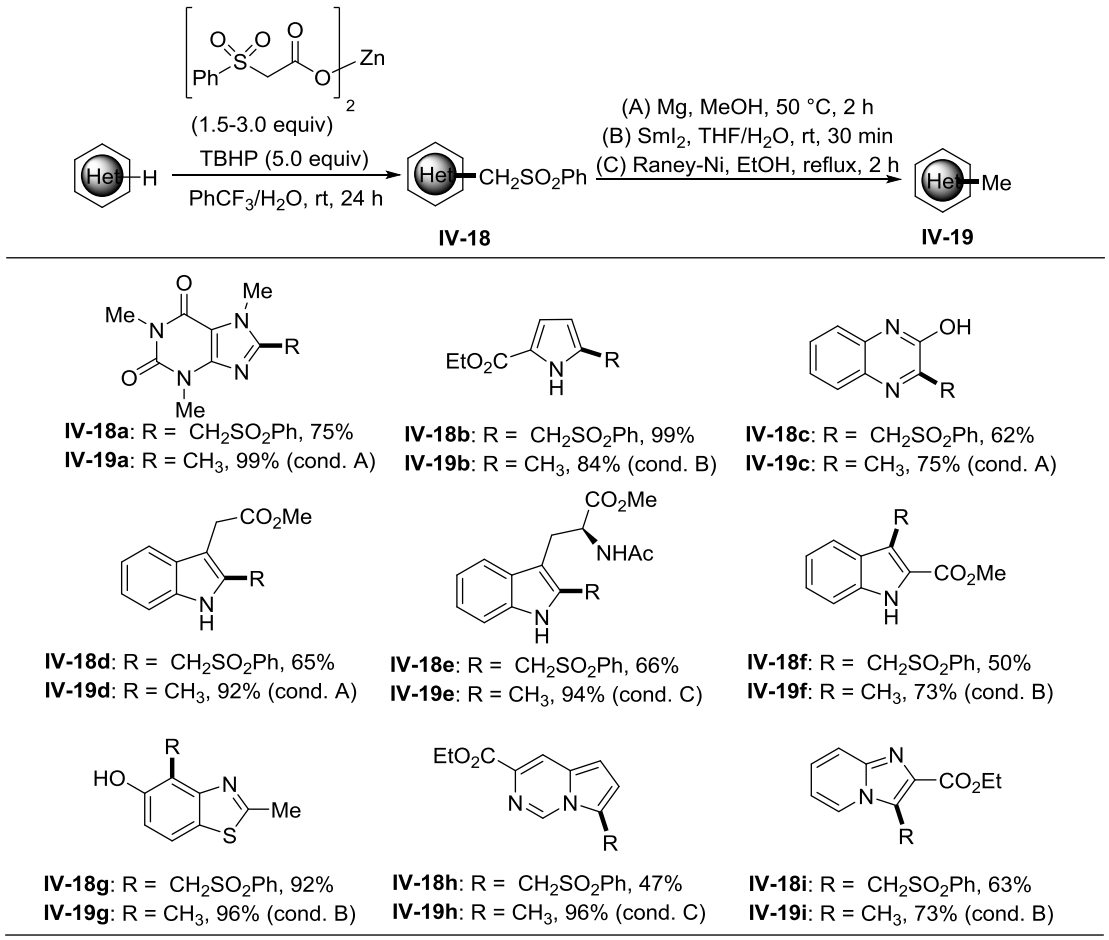
The pioneering work of Minisci *et al.* effected decarboxylative methylation with acetic acid as the methylation reagent.[69] In the methylation of quinoline, three isomers (**IV-17aa**-**ac**) were isolated in good combined yield. In the case of 2-methylquinoline, only one product (**IV-17b**) was obtained in 64% yield. Methylation of 4-cyanopyridine gave the monomethylation product **IV-17ca** and dimethylation product **IV-17cb** in moderate yield. However, methylation of acridine afforded 9-methylacridine **IV-17d** in low yield. Under catalysis of silver nitrate, peroxydisulphate is reduced to give a $SO_4^{\bullet-}$ radical anion, which promotes the decarboxylation of acetic acid to deliver Me•. The methyl radical then adds to the electrophilic position of the protonated heteroarenes and subsequent oxidation by Ag(II) and rearomatization delivers the methylated heteroaromatics (Scheme 4-4).



Scheme 4-4: Silver-catalyzed decarboxylative methylation of heteroarenes

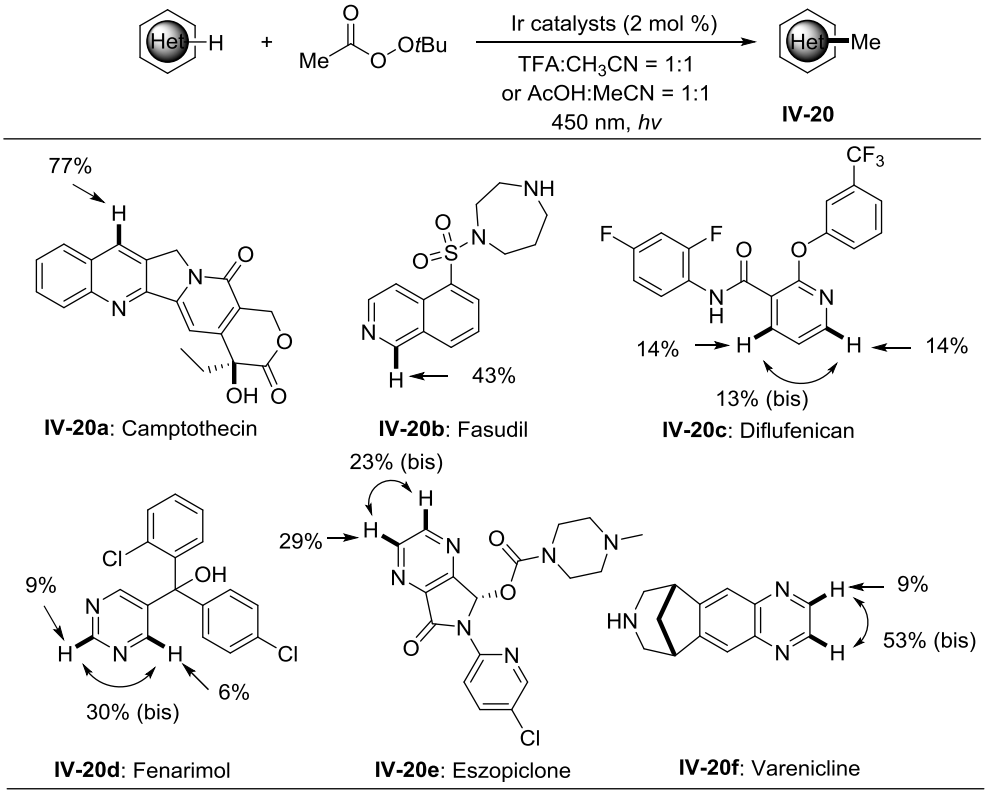
In 2014, Baran *et al.* reported a two-step process involving addition of sulfonylmethyl radicals to heteroarenes followed by desulfonylation.[113] Owing to the electrophilic nature of the radical species, the radical addition took place at the most nucleophilic site of electron-rich heteroarenes, including caffeine (**IV-18a**), pyrrole (**IV-18b**), quinoxaline (**IV-18c**), indoles (**IV-18d-f**), benzothiazole (**IV-18g**), indolizine-type heterocyles (**IV-18h-i**). In the case of azaindoles, imidazoles and benzimidazoles, the reaction proceeded equally well. These intermediates were then involved in the subsequent revelation of methyl group under three different conditions. The resulting methylated products were obtained in good to excellent yields (Scheme 4-5).

[113] Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853.



Scheme 4-5: Addition and desulfonylation for the methylation of heteroaromatics

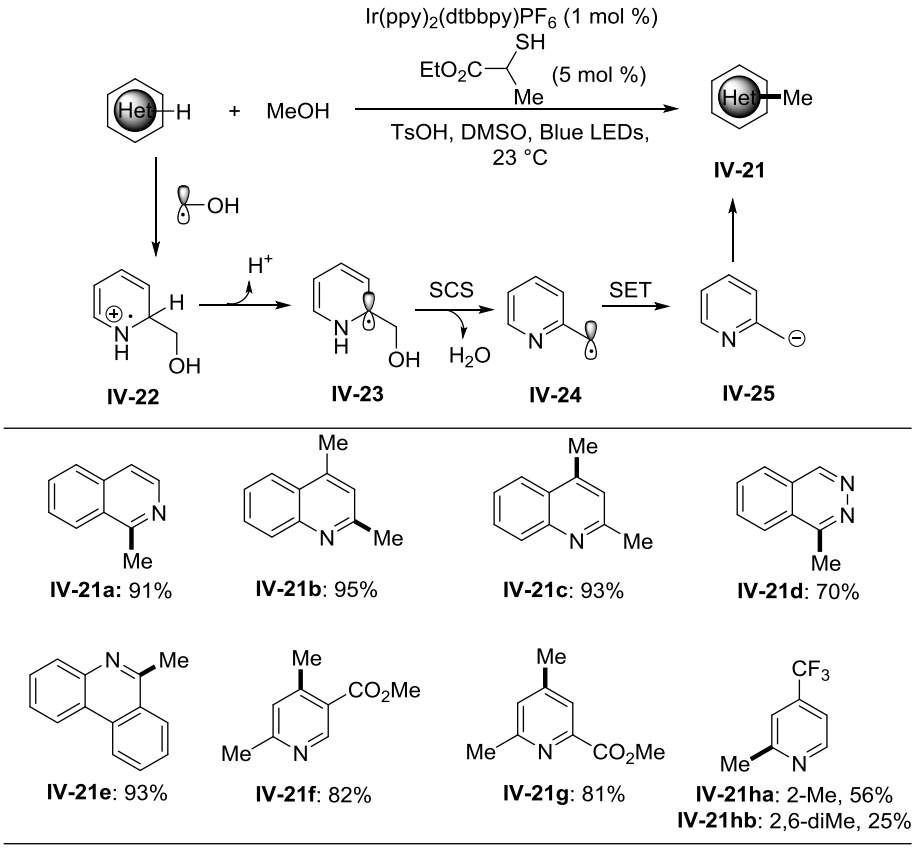
In the same year, DiRocco *et al.* described a photo-redox methylation of biologically active heteroarenes.[83] Several medicinal and agrochemical agents bearing quinoline (**IV-20a**), isoquinoline (**IV-20b**), pyridine (**IV-20c**), pyrimidine (**IV-20d**), pyrazine (**IV-20e**), quinoxaline (**IV-20f**) as core structures were successfully processed by this method (Scheme 4-6). Proton-coupled electron-transfer from the excited-state metal catalyst to *tert*-butylperacetate generates a *tert*-butoxy radical, which undergoes *β*-scission to generate the active Me• radical.



Scheme 4-6: Photo-redox methylation of medicinal and agrochemical agents

In 2015, MacMillan *et al.* developed an alternative method for methylation using readily available methanol as the methyl source.[114] The substrate scope of this transformation is rather wide, since a large range of heteroaromatics can be methylated in good to excellent yield. The presence of the thiol catalyst is essential since it is oxidized by the Ir^{IV} catalyst, generated by the oxidation with a sacrificial amount of heteroarenes, to afford the thiyl radical, which abstracts a hydrogen atom form methanol to form α-oxy radical. The latter attacks the nucleophilic position of the heteroarenes to generate radical cation **IV-22**. Deprotonation of the sufficiently acidic α-C-H bond of intermediate **IV-22** forms the α-amino radical **IV-23**. A spin-center shift (SCS) takes place at this time to give radical **IV-24**. Subsequent SET to Ir^{IV} catalyst and protonation delivers the desired compounds (Scheme 4-7).

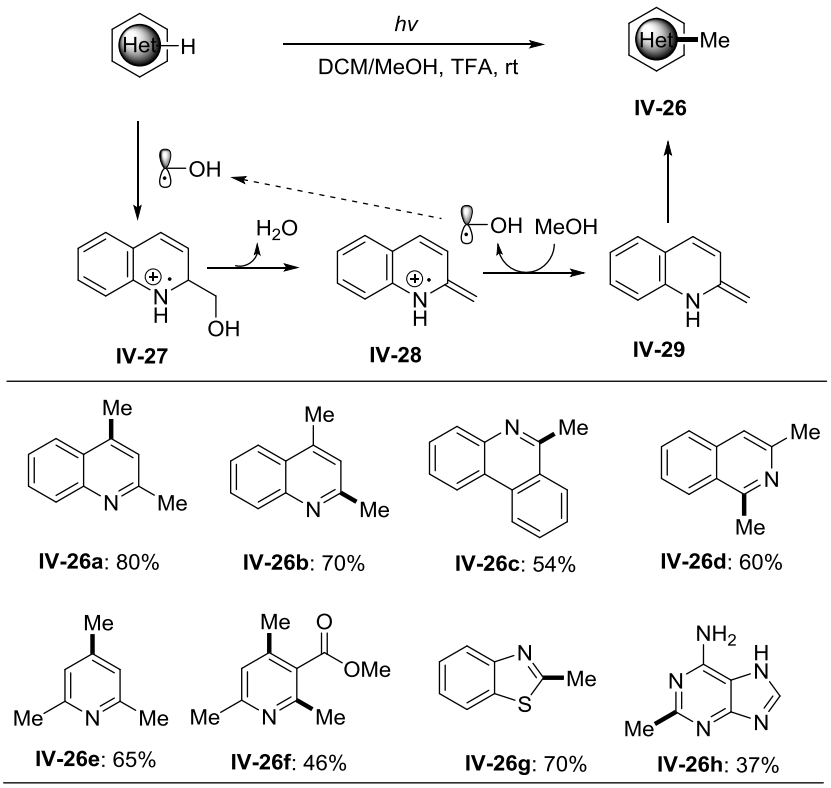
[114] Jin, J.; MacMillan, D. W. C. *Nature* **2015**, *525*, 87.



Scheme 4-7: Methylation of heteroarenes using methanol as the methyl source

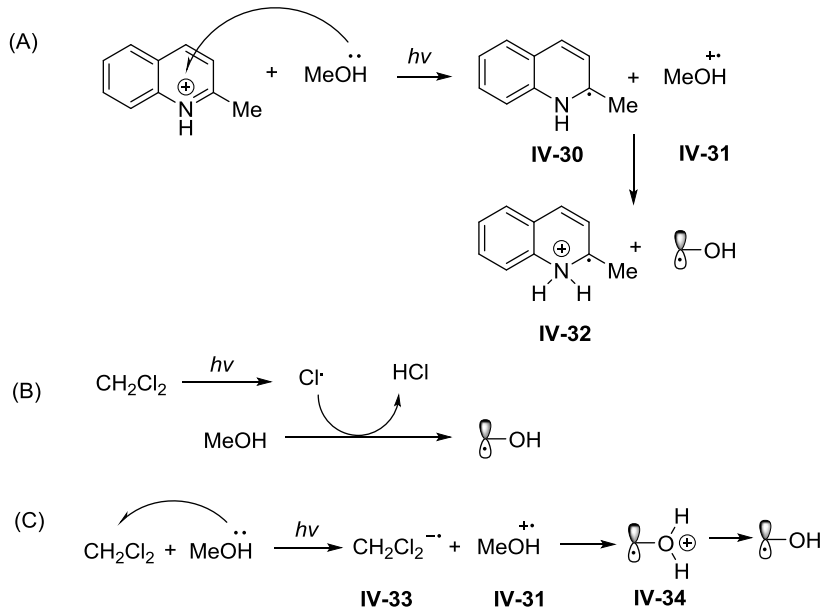
Recently, Li *et al.* described a fascinating method also utilizing methanol as the methylation reagent and solvent without external catalysts.[115] This protocol features the addition of DCM as co-solvent and key promoter. Under photo-irradiation, various methylated heteroarenes, including quinolines (**IV-26a-b**), acridine (**IV-26c**), isoquinoline (**IV-26d**), pyridines (**IV-26e-f**), benzothiazole (**IV-26g**) and purine (**IV-26h**), were prepared in good yields. Then nucleophilic attack of the hydroxymethyl radical onto the protonated heteroarenes forms the radical cation **IV-27**. Upon loss of one molecule of water, intermediate **IV-28** is generated. Abstraction of hydrogen from methanol by the strongly electronegative nitrogen of **IV-28** generates protonated amine of **IV-29**. Proton exchange and tautomerization of **IV-29** delivers the methylated heteroarenes **IV-26** (Scheme 4-8).

[115] Liu, W.; Yang, X.; Zhou, Z.; Li, C. *Chem* **2017**, *2*, 688.



Scheme 4-8: Photo-induced methylation of heteroarenes

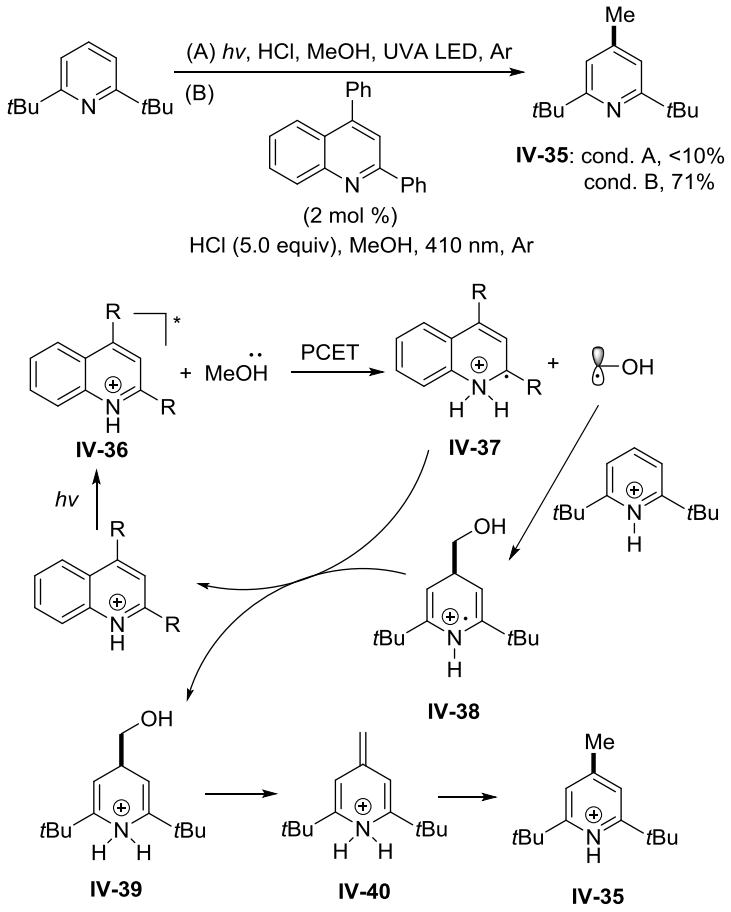
Several pathways for the generation of hydroxymethyl radical were proposed (Scheme 4-9). As demonstrated in pathway A, upon irradiation, electron transfer from methanol to excited-state protonated heteroarene gives the methanol radical cation **IV-31**, together with the intermediate **IV-30**, followed by proton transfer from **IV-31** to **IV-30**, producing the hydroxymethyl radical and protonated radical intermediate **IV-32**. Pathway B describes the formation of the hydroxymethyl radical *via* abstraction of hydrogen by the chlorine radical, which is generated from DCM under UV-irradiation. As for pathway C, electron-transfer from methanol to DCM generates the same radical cation **IV-31.**



Scheme 4-9: Proposed mechanism for the formation of hydroxymethyl radical

Barriault *et al.* reported almost simultaneously a similar process using methanol as the methyl source.[116] Under UVA LED irradiation and in the presence of 5 equivalents of HCl in MeOH, the methylation proceeded readily, affording several methylated heteroarenes in good yield. Mechanistic studies reveal that the single electron transfer from methanol to heteroarene to form methanol radical cation **IV-31** is less plausible due to observed kinetic isotope effect (KIE). Therefore, they proposed that the reaction proceeds through proton-coupled electron transfer promoted by hydrogen bonding between the excited-state heteroarene and methanol, affording **IV-37** (equivalent to **IV-32** in Scheme 4-9) and hydroxymethyl radical. Addition of the latter to protonated heteroarenes affords intermediate **IV-38**, which might be reduced by **IV-37** to generate protonated amino alcohol **IV-39** and regenerate the ground state heteroaromatics. The heteroarenes serve as both the catalyst and the reagent. This mechanism is further proved by methylation of heteroarenes of which the absorption is beyond the UVA region. Using 2.0 mol % of 2,4-diphenylquinoline as catalyst, the reaction proceeded well to afford pyridine **IV-35** in 71% yield, while the absence of the catalyst resulted in less than 10% conversion of the starting material (Scheme 4-10).

[116] McCallum, T.; Pitre, S. P.; Morin, M.; Scaiano, J. C.; Barriault, L. *Chem. Sci.* **2017**, *8*, 7412.

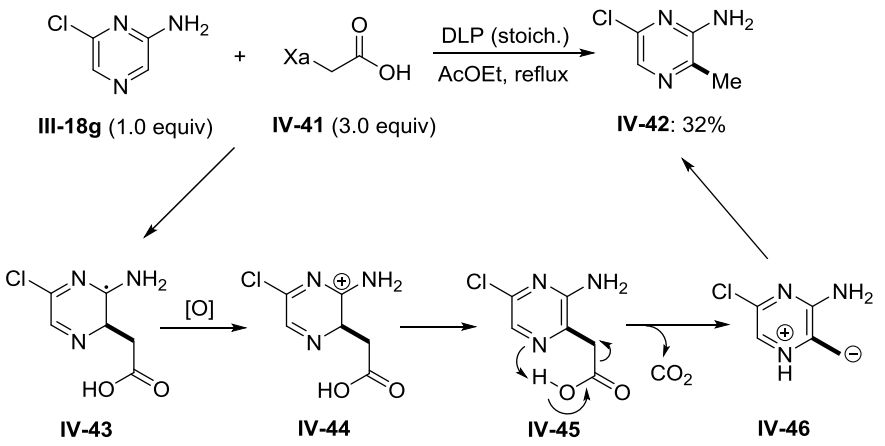


Scheme 4-10: Photochemical methylation using methanol as the methyl source

4.3 Xanthate-based radical methylation of heteroarenes

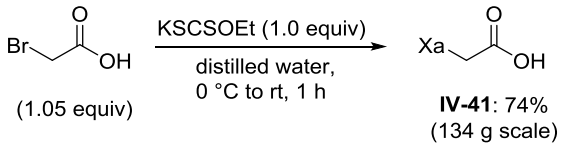
4.3.1 Discovery of a new methylation process

Over the course of our study in the alkylation of pyrazines, we were surprised to find that heating 1.0 equivalent of **III-18g** (Table 3-2, Chapter 3) with 3.0 equivalents of xanthate **IV-41** in refluxing ethyl acetate afforded methylated product **IV-42** in 32% yield. Upon initiation, the carboxymethyl radical generated from xanthate **IV-41** adds to pyrazine **III-18g** to form radical intermediate **IV-43**. Oxidation followed by rearomatization gives unstable arylacetic acid **IV-45**, which undergoes spontaneous decarboxylation and tautomerization to deliver the final product **IV-42** (Scheme 4-11).



Scheme 4-11: Discovery of the methylation of pyrazine **III-18g**

If this method proves to be general for other heteroarenes, methylation involving xanthate **IV-42** as the methyl source will offer an inexpensive and practical method for the late-stage functionalization of complex molecules. The nicely crystalline xanthate **IV-42** was prepared in 134 g scale (0.74 mol) by simply adding potassium *O*-ethyl xanthate to a solution of bromoacetic acid in water, followed by filtration and recrystallization from ethyl acetate/cyclohexane. Considering the price of goods, the cost for **IV-41** is almost negligible.[117]

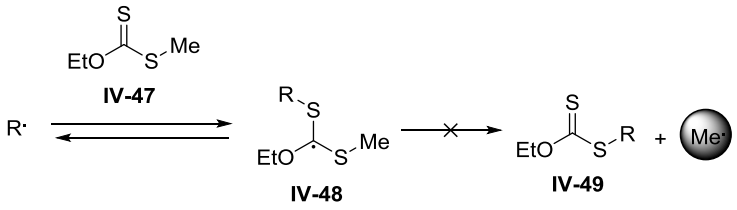


Scheme 4-12: Preparation of xanthate **IV-41**

Moreover, despite the fact that xanthates can mediate the formation of numerous radical types, the direct generation of unstabilized methyl radical is not accessible for obvious reasons inherent to the addition-fragmentation process (Scheme 1-2, Chapter 1). Thus, starting from *S*-methyl xanthate **IV-47**, fragmentation of adduct **IV-48** from addition of radical R• will not afford the highly unstable Me• radical (435 kJ•mol^{-1}) (Scheme 4-13). In stark contrast, as for xanthate **IV-41**, the corresponding carboxymethyl radical is relatively stable due to conjugation with the carbonyl group

[117] Bromoacetic acid (185.50 EUR/2 kg on November 10th, 2017) is commercially available from Sigma-Aldrich.

and can be readily generated in the addition-fragmentation process. Therefore, xanthate **IV-41** may provide a new route for the introduction of methyl group.



Scheme 4-13: Direct generation of a methyl radical

4.3.2 Substrate scope for the addition of xanthate IV-41

Encouraged by this inspiring result, we then investigated the scope of heteroarenes (Table 4-1). Methylation of caffeine **IV-50a** under the same reaction conditions proceeded readily to afford methylated caffeine **IV-51a** in 65% yield. In this case, the decarboxylation took place spontaneously. This is not the case for imidazopyridine **IV-50b**, of which the reaction afforded the non-decarboxylated acid **IV-51b** in excellent yield of 90%, which was isolated by simple filtration and recrystallization from methanol. It is worth noting that the solubility of the product is decreased by the introduction of the acetic acid group and, in favorable cases, the products precipitated directly from the reaction medium, facilitating the purification process (for those isolated by filtration and subsequent recrystallization, the products are highlighted with a box in Table 4-1).

Several other indolizine-type heteroarenes were tested. For unknown reasons, imidazopyrimidine **IV-50c** reacted sluggishly with xanthate **IV-41** and despite several attempts to optimize the reaction conditions, compound **IV-51c** was isolated in only 16% yield. In fact, the reaction evolved quite fast and the heteroarene **IV-50c** was totally consumed. Imidazopyridazine **IV-50d** was found to be a competent substrate for this method, since the desired product **IV-51d** was obtained in 49% yield by simple filtration and recrystallization from methanol. A slightly higher yield of 58% was obtained after purification by column chromatography on silica gel. Phenylimidazothiazole **IV-50e** behaved as expected, delivering product **IV-51e** in 58% yield by filtration and recrystallization from acetic acid. Benefiting from the high crystallinity of adduct **IV-51e**, 2.0 g of the product **IV-51e** was easily prepared and

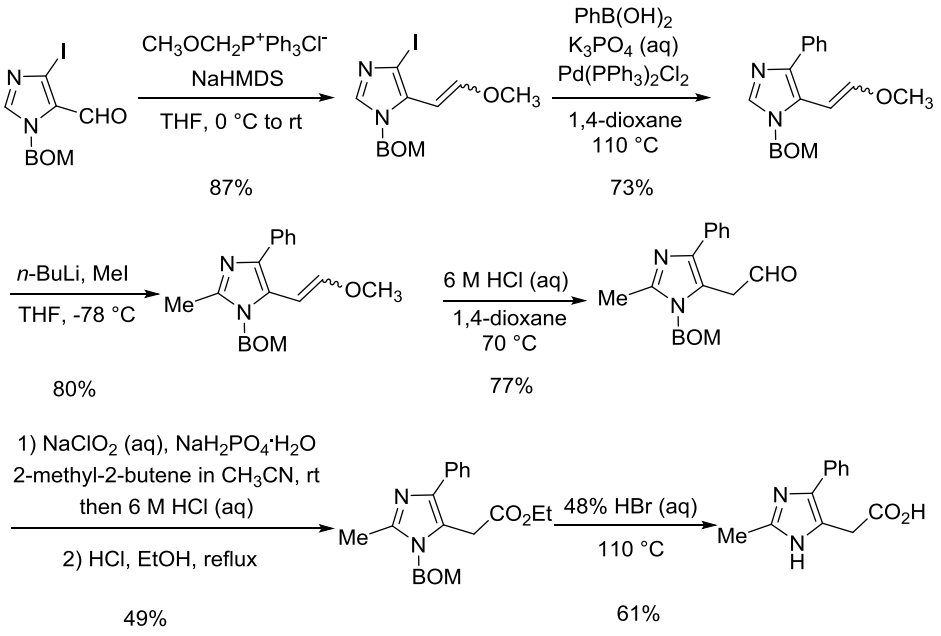
isolated as a white powder (Table 4-1).

Since the carboxymethyl radical is electrophilic in nature, it should in principle add to electron-rich indoles and pyrroles. For unknown reasons, the reaction with 3-substituted indole **IV-50f** under standard reaction conditions gave **IV-51f** in only 13% yield. Reaction at 60 ℃ gave a slightly higher yield of 29%. In contrast, after a brief optimization (Table 4-2), the reaction of 2-substituted indole **IV-50g** and 1.5 equivalents of xanthate **IV-41** in refluxing DCE gave the desired indole **IV-51g** in 60% (1.42 g) after filtration and recrystallization from ethanol. Pyrrole **IV-50h** was also modified by this process and the desired carboxylic acid **IV-51h** was obtained in 38% yield (Table 4-1).

Imidazoles are also suitable substrates for this method (Table 4-1). For example, reaction of 1-methyl-4-nitroimidazole **IV-50i** afforded two regioisomers **IV-51ia** and **IV-51ib**. The former, a carboxylic acid, is highly crystalline and was isolated in 40% yield by simple filtration, followed by short column chromatography to remove the black color. Imidazole **IV-51ib** resulted from addition of xanthate **IV-41** to the C3 position of the imidazole ring and spontaneous decarboxylation. Functionalization of the cheap 4-methyl-2-phenylimidazole[118] afforded readily imidazole-5-acetic acid **IV-51j** in 45% yield. The preparation of imidazole-5-acetic acid derivatives by traditional method has proved to be tedious in the past, involving a sequence of Wittig reaction, Suzuki cross-coupling, methylation, hydrolysis, oxidation, esterification and deprotection (Scheme 4-14).[119]

[118] 4-Methyl-2-phenylimidazole (51.70 EUR/25 g on November 10th, 2017) is commercially available from Sigma-Aldrich.

[119] Madsen, C.; Jensen, A. a.; Liljefors, T.; Kristiansen, U.; Nielsen, B.; Hansen, C. P.; Larsen,M.; Ebert, B.; Bang-Andersen, B.; Krogsgaard-Larsen, P.; Frølund, B. *J. Med. Chem.* **2007**, *50*, 4147.

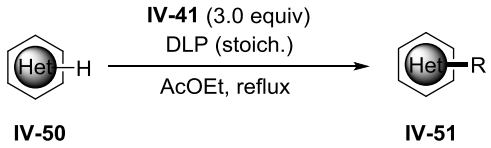


Scheme 4-14: Reported preparation of imidazole-5-acetic acid

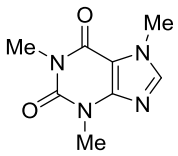
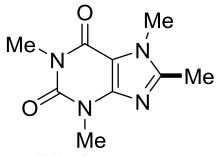
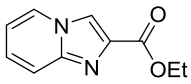
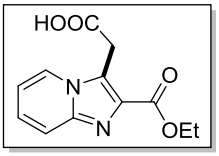
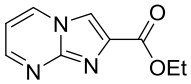
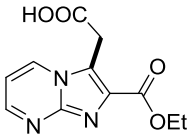
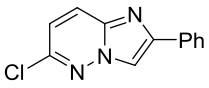
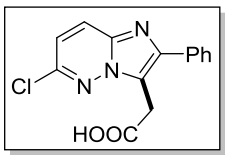
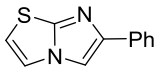
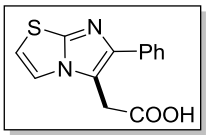
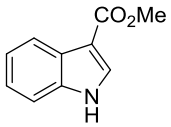
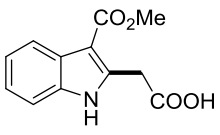
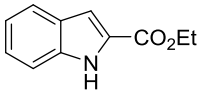
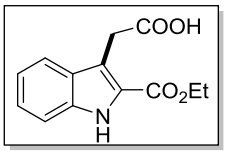
Benzothiazole **IV-50k** reacted poorly with xanthate **IV-41**, and after 6 h, a large proportion of the starting material remained unreacted. When the C2 position of the benzothiazole is blocked, as in the case of benzothiazoles **IV-50l** and **IV-50m**, the corresponding products **IV-51l**, **IV-51ma** and **IV-51mb** are obtained in moderate yields. Interestingly, the regioselectivity is not the same. The addition of xanthate **IV-41** to benzothiazole **IV-50l** took place at the C4 position, directed probably by the electron-donating acetamido group, while the carboxymethyl group was introduced at the C7 position of benzothiazole **IV-50m**, *ortho* to the ethoxy group. A small amount (5%) of disubstituted product **IV-51mb** was also isolated, probably promoted by the weak electron-donating SMe group. The structure of these products was confirmed by nOe NMR experiments. Finally, based on the results of Miranda *et al.*,[120] flavone **IV-50n** reacted slowly with xanthate **IV-41** and compound **IV-51n** was isolated in 28% yield (Table 4-1).

[120] Mijangos, M. V.; González-Marrero, J.; Miranda, L.D.; Vincent-Ruz, P.; Lujan-Montelongo, A.; Olivera-Díaz, D.; Bautista, E.; Ortega, A.; Campos-González, M. L.; Gamez-Montaño, R. *Org Biomol Chem.* **2012**, *10*, 2946.

Table 4-1: Scope of heteroaromatics



IV-50 **IV-51**

Heteroarene	Variation from standard reaction conditions	Product
 **IV-50a**	no	 **IV-51a**: 65%
 **IV-50b**	no	 **IV-51b**: 90%
 **IV-50c**	**IV-41** (1.5 equiv)	 **IV-51c**: 16%
 **IV-50d**	with several drops of DCE as co-solvent	 **IV-51d**: 49% (58% by column)
 **IV-50e**	DCE as solvent	 **IV-51e**: 58% (80% on 10 mmol scale)
 **IV-50f**	reaction at 60 °C	 **IV-51f**: 29%
 **IV-50g**	**IV-41** (1.5 equiv)	 **IV-51g**: 60%

(Continued)

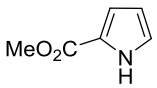
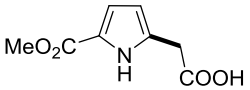
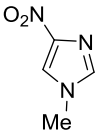
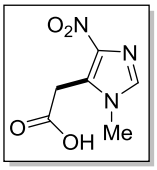
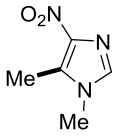
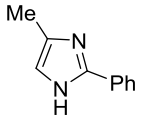
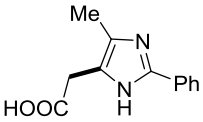
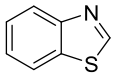
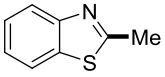
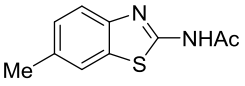
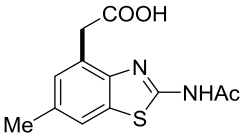
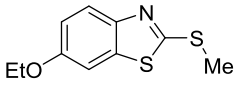
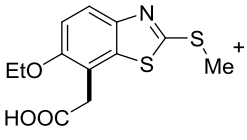
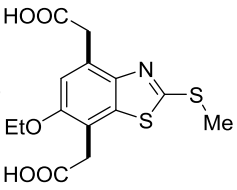
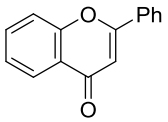
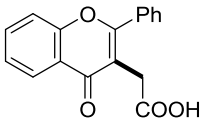
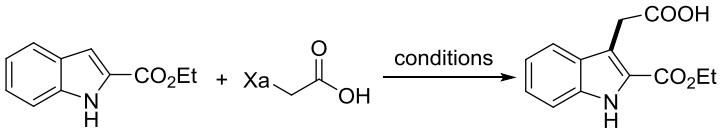
 **IV-50h**	DCE as solvent	 **IV-51h**: 38%
 **IV-50i**	no	 **IV-51ia**: 40% +  **IV-51ib**: 4%
 **IV-50j**	no	 **IV-51j**: 45%
 **IV-50k**	no	 **IV-50k**:**IV-51k** = 2.5:1 (determined by ^{1}H NMR of crude products)
 **IV-50l**	methyl benzoate as solvent	 **IV-51l**: 26% (59% brsm)
 **IV-50m**	no	 **IV-51ma**: 17% +  **IV-51mb**: 5%
 **IV-50n**	no	 **IV-51n**: 28%

Table 4-2: Optimization of addition to indole **IV-50g**



IV-50g **IV-41** **IV-51g**

conditions	yield[a]
IV-41 (3.0 equiv), AcOEt	<42%[b]
IV-41 (1.2 equiv), AcOEt	<47%[b]
IV-41 (1.2 equiv), DCE	39% (~15% RSM)
IV-41 (1.5 equiv), DCE	60%

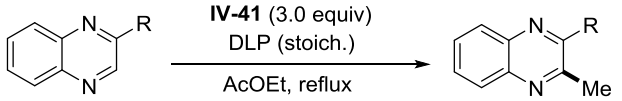
a: yield by filtration; b: product was not pure.

We uncovered some limitations in regard of the heteroarene substrates. Quinoxaline **IV-52a**, which worked well in Baran's method,[113] was first tested in our methylation process. Since it is not soluble in ethyl acetate or DCE, the reaction was carried out in acetic acid at 80 ℃. However, the desired product **IV-53a** was isolated in only 5% yield, together with other unidentified compounds. Attempts to accomplish the methylation with other solvents or peroxide such as DTBP were also fruitless, affording suspensions containing no desired product. Careful examination of the mixture excluded the formation of carboxylic acid **IV-54**, resulting from addition of carboxymethyl radical to other positions available on the benzene ring. In view of the low melting point of xanthate **IV-41** (52-53 ℃), the reaction was attempted under solvent-free conditions. In this case, the desired product **IV-53a** was also formed in a small amount (Table 4-3).

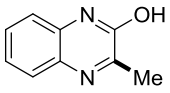
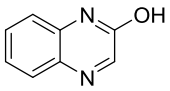
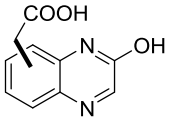
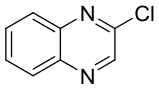
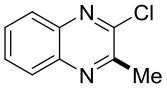
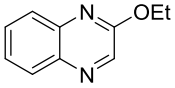
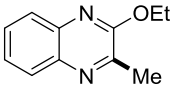
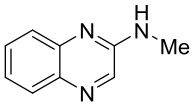
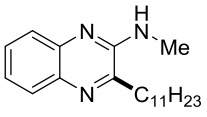
The hydroxyl group was then replaced by a chlorine atom. The conversion of the starting quinoxaline **IV-52b** was relatively low and quinoxaline **IV-53b** was obtained in about 6% yield. To increase the electron density of the C3 position of the quinoxaline ring, quinoxaline **IV-52c** containing an ethoxy group was subjected to the methylation reaction. Indeed, the yield for the desired product **IV-53c** increased. But due to the close polarity of the starting quinoxaline **IV-52c** and the methylated product **IV-53c**, the purification proved troublesome. Finally, in the hope of further increase the electron density of the C3 position, a methylamino group was introduced. However, for the reaction of quinoxaline **IV-53c** containing a methylamino group,

product **IV-53d** substituted by $C_{11}H_{23}$ chain, produced from DLP during the initiation process, was observed as the major product but, due to the difficulty in purification, its yield was not determined. In this case, a small amount of the starting material was also recovered (Table 4-3).

Table 4-3: Attempts for methylation of quinoxalines



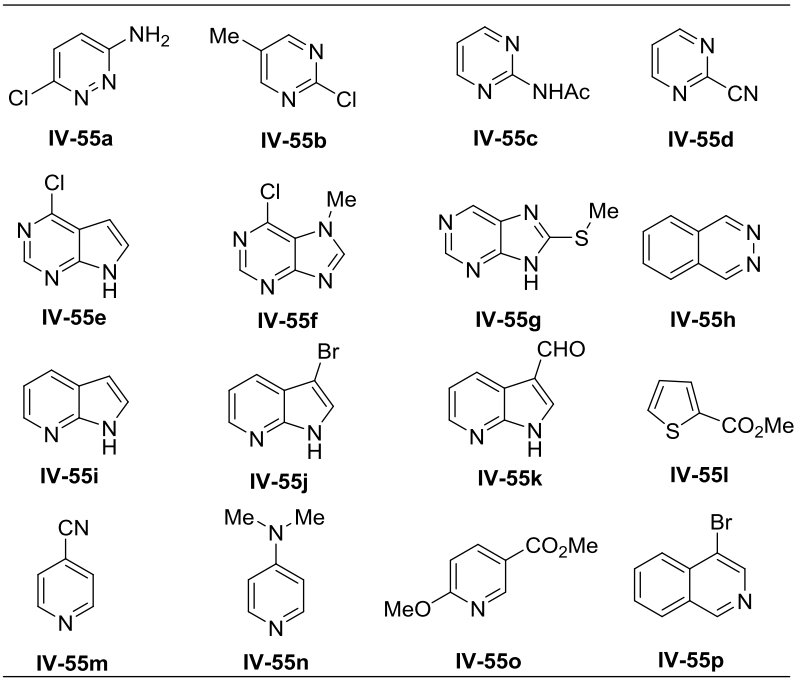
IV-52 → **IV-53**

Quinoxaline	Variation from standard reaction conditions	Product
	DLP, AcOH, 80 °C	 **IV-53a**: 5%
 **IV-52a**	isoamyl acetate, DTBP, 80 °C	black suspension, trace
	$PhCF_3$, DLP, 80 °C	black suspension, insoluble side-product
	methyl benzoate, DLP, 80 °C	orange suspension, insoluble side-product
	neat, DLP, 80 °C	redish brown solution trace
 **IV-54**		
 **IV-52b**	no	 **IV-53b**: ~6% (72% RSM)
 **IV-52c**	no	 **IV-53c**: <20% (contaminated by SM)
 **IV-52d**	no	 **IV-53d**

Other heteroarenes, including pyridazine (**IV-55a**), pyrimidines (**IV-55b-d**), purine-type bases (**IV-55e-g**), phthalazine (**IV-55h**), azaindoles (**IV-55i-k**), pyrrole (**IV-55l**), pyridines (**IV-55m-o**) and isoquinoline (**IV-55p**), as listed in Table 4-4, were found to be inappropriate for this method. A possible reason is that carboxymethyl radical generated from xanthate **IV-41** behaves as an electrophilic radical and the

addition is not favorable due to polarity mismatch.

Table 4-4: Substrates that showed low or no reactivity towards alkylations



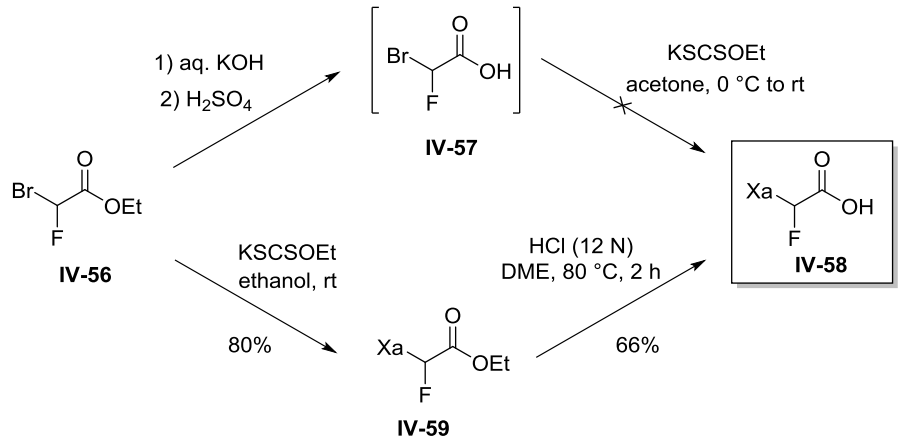
4.3.3 Introduction of fluoroacetic acid group to heteroarenes

An interesting extension of this work is the introduction of the valuable fluoromethyl group, which is considered as an isostere of methyl, hydroxymethyl (CH_2OH) and methoxymethyl (CH_2OCH_3) groups.[121] However, existing methods for the introduction of fluoromethyl group are quite limited, one of which was reported by Baran *et al.* utilizing zinc monofluoromethanesulfinate.[74]

Fluoromethylation could be achieved in principle by utilizing fluoroacetic acid xanthate **IV-58**. The most common method for the preparation of xanthates is the nucleophilic substitution of a leaving group (normally a halogen atom) with potassium *O*-ethyl xanthate. Hydrolysis of the commercially available ethyl bromofluoroacetate **IV-56** afforded carboxylic acid **IV-57**.[122] However, treatment of the acid **IV-57** with potassium *O*-ethyl xanthate gave a complex mixture. By taking advantage of our

[121] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
[122] Boussac, H.; Crassous, J.; Dutasta, J.-P.; Grosvalet, L.; Thozet, A. *Tetrahedron: Asymmetry* **2002**, *13*, 975.

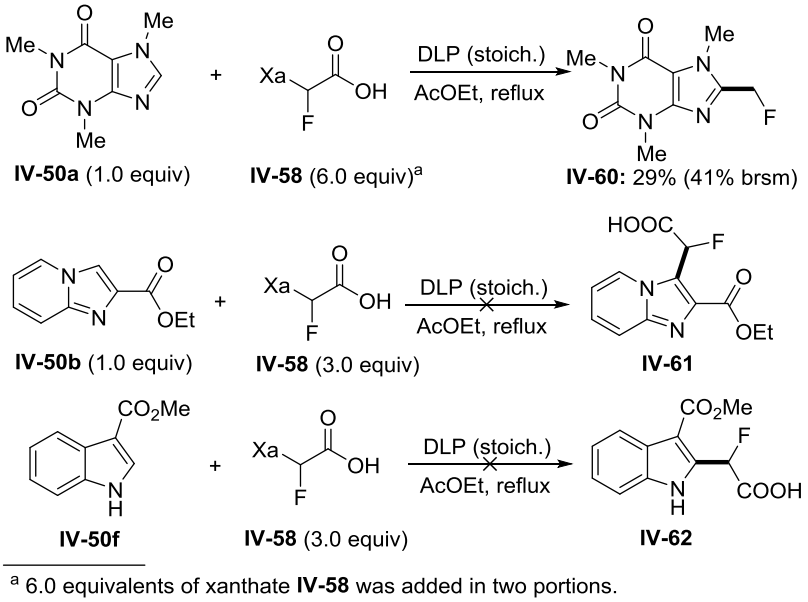
empirical observations that the xanthate group is remarkably resistant to acidic hydrolysis, an alternative route was conceived. Xanthate **IV-59** was first prepared from ester **IV-56** by the literature method[123] and subjected to hydrolysis with aqueous HCl. Cleavage of the ester group in **IV-59** took place readily to deliver carboxylic acid xanthate **IV-58** in 66% yield (Scheme 4-15).



Scheme 4-15: Preparation of fluoroacetic acid xanthate **IV-58**

With fluoro-containing xanthate **IV-58** in hand, we then tested briefly its reactivity. Gratifyingly, the fluoromethylation proved possible, as indicated by the fluoromethylation of caffeine **IV-60** in 29% yield (41% brsm). To our disappointment, the addition of xanthate **IV-58** to imidazopyridine (**IV-50b**) and indole (**IV-50f**) failed in both cases (Scheme 4-16). The reasons for these negative results are still not clear but further efforts will be devoted to investigate the scope and limitations of this modification.

[123] Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, *71*, 2352.



a 6.0 equivalents of xanthate **IV-58** was added in two portions.

Scheme 4-16: Introduction of a fluoromethyl group

4.3.4 Introduction of 2-propionic acid group to heteroarenes

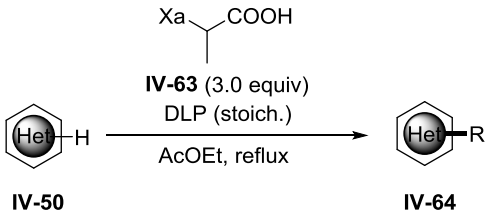
In order to expand the generality of our approach for the methylation and introduction of carboxymethyl group, more substituted carboxylic acid xanthates were tested. The extension commenced with the introduction of a propionic acid group into heteroarenes. The resulting arylpropionic acids belong to the most important class of nonsteroidal antiinflammatory drugs and have been the object of a vast synthetic effort.[124] The propionic acid derived xanthate **IV-63** was prepared in 44% yield by reaction of 2-bromopropionic acid with potassium *O*-ethyl xanthate, followed by trituration of the crude product with pentane.

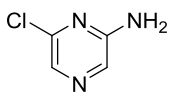
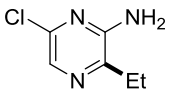
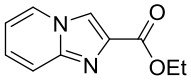
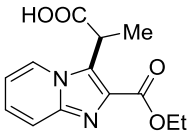
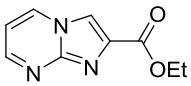
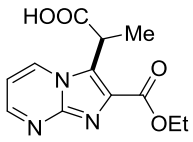
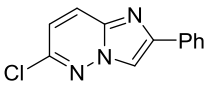
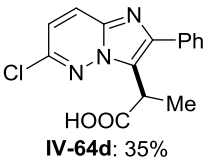
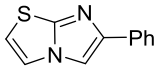
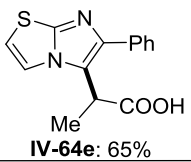
Xanthate **IV-63** was therefore subjected to the addition to several heteroarenes in Table 4-1. And the results are listed in Table 4-5. To our delight, the radical addition to pyrazine **III-18g** and subsequent decarboxylation proceeded readily to afford pyrazine **IV-64a** in 74% yield, more than twice the yield for methylation (32% for **IV-42**). This is probably due to the relatively higher nucleophilicity of the radical generated from xanthate **IV-63** as compared to the carboxymethyl radical derived from xanthate **IV-41**. Indolizine-type systems also gave good to moderate yields of the

[124] Landoni, M. F.; Soraci, A. *Curr. Drug Metab.* **2001**, *2*, 37.

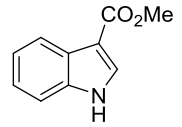
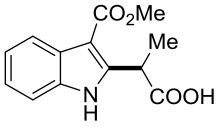
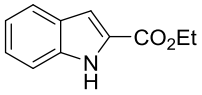
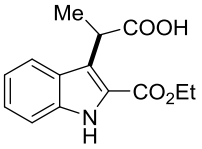
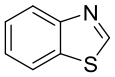
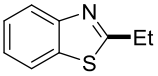
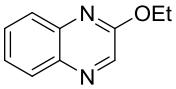
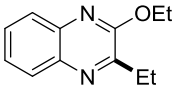
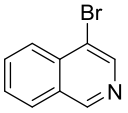
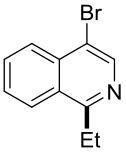
corresponding carboxylic acids **IV-64b-e**. Reaction of 3-substituted indole **IV-50f** gave rise to indole **IV-64f** in higher yield than the corresponding carboxymethylated product **IV-51f** (29% yield, Table 4-1). 2-Ethylbenzothiazole **IV-64h** was isolated in 22% yield in the reaction starting from benzothiazole **IV-50k**, a higher yield than the preparation of **IV-51k**. The same reaction pattern was observed for 2-ethoxyquinoxaline **IV-54c** and the product **IV-64i** was isolated in 53% yield. Finally, the reaction involving 4-bromoisoquinoline **IV-55p** gave rise to 1-ethyl-4-bromoisoquinoline **IV-64j** in 34% yield. However, caffeine (**IV-50a**), pyrrole (**IV-50h**) and flavone (**IV-50n**) showed a lower reactivity towards xanthate **IV-63**.

Table 4-5: Scope of heteroarenes for the introduction of 2-propionic acid group



Heteroarene	Variation from standard reaction conditions	Product
 **III-18g**	no	 **IV-64a**: 74%
 **IV-50b**	3.0 equiv of **IV-63** was added in two portions	 **IV-64b**: 45%
 **IV-50c**	no	 **IV-64c**: 33%
 **IV-50d**	6.0 equiv of **IV-63** was added in two portions	 **IV-64d**: 35%
 **IV-50e**	DCE as solvent	 **IV-64e**: 65%

(Continued)

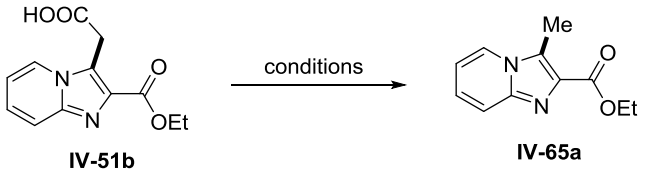
 **IV-50f**	3.0 equiv of **IV-63** was added in two portions, DCE as solvent	 **IV-64f**: 59%
 **IV-50g**	2.4 equiv of **IV-63** was added in two portions, DCE as solvent	 **IV-64g**: 80%
 **IV-50k**	no	 **IV-64h**: 22% (50% brsm)
 **IV-52c**	no	 **IV-64i**: 53%
 **IV-55p**	1.2 equiv of TFA wa added, DCE as solvent	 **IV-64j**: 34%

4.3.5 Microwave-assisted decarboxylation of heteroareneacetic acids

To unveil the methyl group from the acetic acid, decarboxylation was attempted on **IV-51b** (Table 4-6). Neat thermolysis or heating in an inert solvent such as *tert*-butylbenzene afforded the desired decarboxylated product **IV-65a**, albeit in moderate yields. Amii *et al.* reported in 2011 a decarboxylation of 2-aryl-2,2-difluoroacetic acid with KF in DMF to give difluoromethylated arenes.[125] Under these conditions, product **IV-65a** was indeed formed but the yield, 34%, was similar. Finally, we were pleased to find that heating **IV-51b** in *N*-dimethylacetamide (DMA) in a microwave oven at 180 ℃ for 10 min afforded methylated product **IV-65a** in 88% yield.

[125] Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560.

Table 4-6: Decarboxylation of acid **IV-51b**

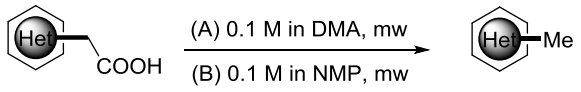


IV-51b **IV-65a**

conditions	results
neat, 165-170 °C, 20 min	black solid, 33% yield
tert-butylbenzene, 0.1 M, reflux	34% yield, insoluble by-products
DMF, 170-190 °C, KF sealed tube, 3 h	black solution, 34% yield
mw, DMA, 180 °C, 10 min	88% yield

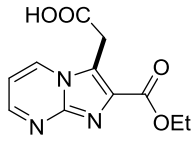
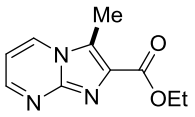
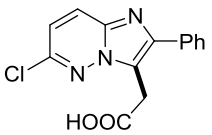
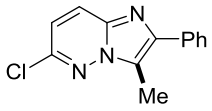
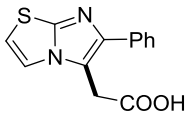
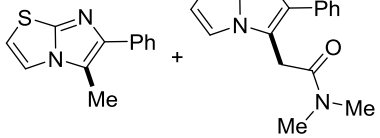
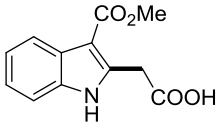
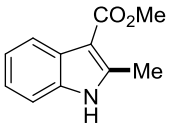
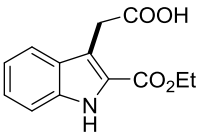
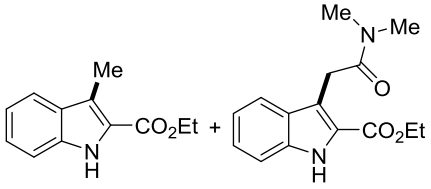
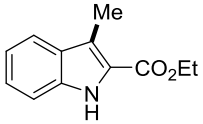
As compiled in Table 4-7, adducts **IV-51c-g** were also subjected to the microwave-assisted decarboxylation process. Decarboxylation of compounds **IV-51c-d** and **IV-51f** proceeded smoothly and the corresponding methylated indolizines **IV-65b-c** and methylated indole **IV-65e** were isolated in good yield. However, as for the decarboxylation of compounds **IV-51e** and **IV-51g**, we found that, in addition to the expected decarboxylated products **IV-65d** and **IV-65f**, side-products **IV-66** and **IV-67**, resulting from a competing transamidation of carboxylic acids **IV-51e** and **IV-51g** with the solvent DMA, were isolated in 46% and 44% yield, respectively. We hoped therefore the formation of the undesired amide could be avoided by utilizing a more robust solvent *N*-methylpyrrolidone (NMP). Indeed, indole **IV-65f** was obtained as the only product in a higher yield of 66% by heating indole **IV-51g** in NMP at 230 ℃ for 70 min.

Table 4-7: Decarboxylation reveals the methyl group



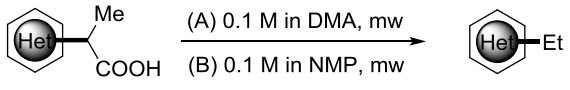
IV-51: R = H

IV-65

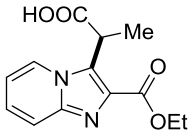
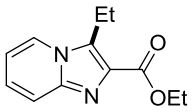
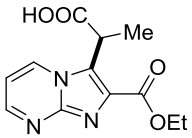
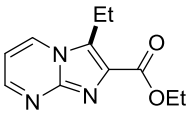
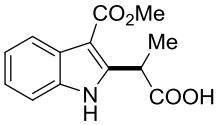
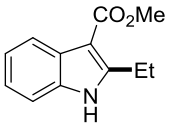
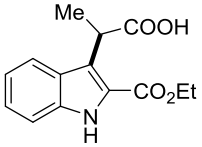
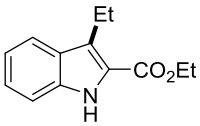
IV-51	Reaction conditions	Products
 **IV-51c**	condition A DMA, 180 °C, 10 min	 **IV-65b**: 72%
 **IV-51d**	condition A DMA, 180 °C, 20 min, then 200 °C, 50 min	 **IV-65c**: 58%
 **IV-51e**	condition A DMA, 200 °C, 70 min, then 220 °C, 10 min	 **IV-65d**: 43% **IV-66**:46%
 **IV-51f**	condition A DMA, 180 °C, 10 min, then 200 °C, 10 min	 **IV-65e**: 79%
 **IV-51g**	condition A DMA, 220 °C, 30 min	 **IV-65f**: 39% **IV-67**: 44%
	condition B NMP, 230 °C, 70 min	 **IV-65f**: 66%

Decarboxylation of arylpropionic acids **IV-64** was also attempted (Table 4-8). Imidazopyridine **IV-68a**, imidazopyrimidine **IV-68b** and ethyl 2-ethyl-3-indolecarboxylate **IV-68c** were obtained in good yield. Decarboxylation of indole **IV-64g** took place at relatively high temperature and NMP had to be used as the solvent. The desired ethylated product **IV-68d** was therefore isolated in 61% yield.

Table 4-8: Decarboxylation reveals the ethyl group



IV-64 **IV-68**

IV-64	Reaction conditions	Products
 **IV-64b**	condition A DMA, 180 °C, 10 min	 **IV-68a**: 72%
 **IV-64c**	condition A DMA, 180 °C, 10 min	 **IV-68b**: 71%
 **IV-64f**	condition A DMA, 180 °C, 10 min	 **IV-68c**: 81%
 **IV-64g**	condition B NMP, 260 °C, 60 min	 **IV-68d**: 61%

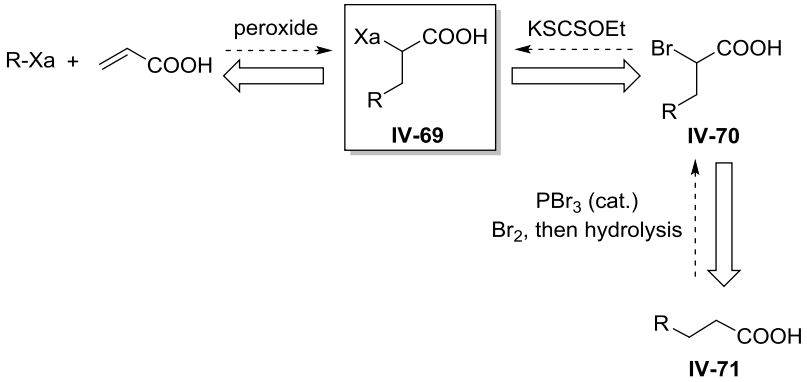
4.4 Conclusion and perspective

In summary, we have uncovered a practical method for the installation of the methyl group and other medicinally related alkyl groups using benign and inexpensive xanthates. This approach is quite efficient in many cases and can be easily conducted on gram scale. Moreover, the carboxylic acid intermediates are also of great potential in the drug development process.

However, the scope in respect of heteroarenes has not yet been fully expanded, especially regarding the introduction of the fluoromethyl group. Since the efficiency of radical addition seems quite sensitive to the functional groups on the heteroarenes, further work should be devoted to provide a better comprehension of the present approach. Moreover, since the aim of the work is to provide an expedient tool for the late-stage functionalization of pharmaceutical leads and drug candidates, the

methylation of biologically important substrates, such as tryptophan and Maxalt (rizatriptan), should be examined.

Apart from the introduction of methyl, ethyl and fluoromethyl groups, more substituted alkyl groups should in principle be easily introduced in a similar manner. Carboxylic acid xanthate **IV-69** could be accessed by two routes, either by radical addition of xanthates to acrylic acid or by substitution of α-bromoacids **IV-70**. Several of the latter are commercially available and others can be prepared by the Hell-Volhard-Zelinsky reaction from the readily available carboxylic acid **IV-71** (Scheme 4-17).

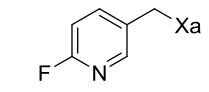


Scheme 4-17: Access to more substituted carboxylic acid xanthates

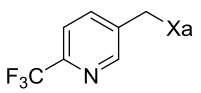
Experimental Part

Summary of Molecules Cited in Experimental Part

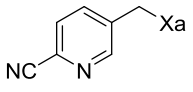
Chapter 2: Modular Route to Azaindanes



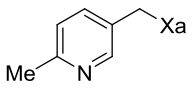
II-43b



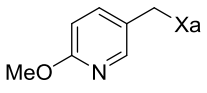
II-43c



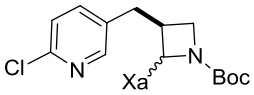
II-43d



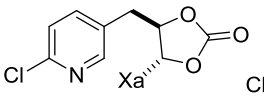
II-43e



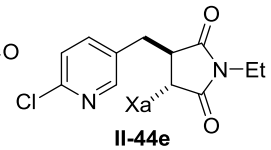
II-43f



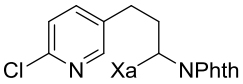
II-44c



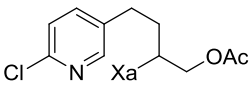
II-44d



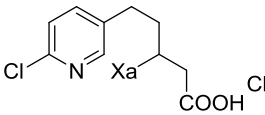
II-44e



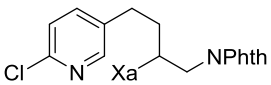
II-44f



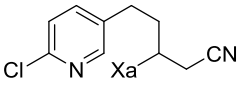
II-44g



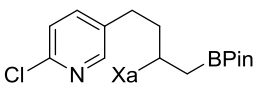
II-44h



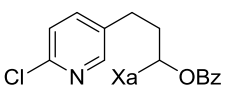
II-44i



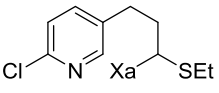
II-44l



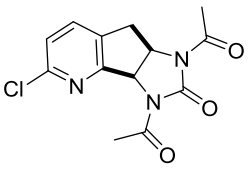
II-44m



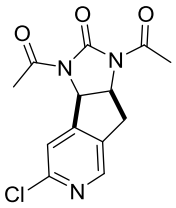
II-44n



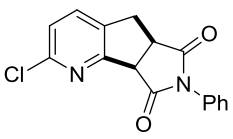
II-44p



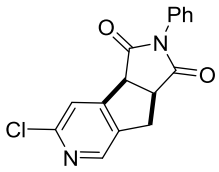
II-45a



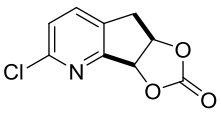
II-46a



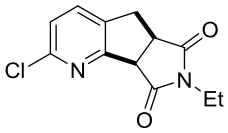
II-45b



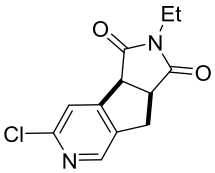
II-46b



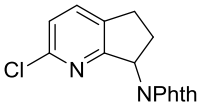
II-45d



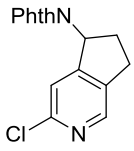
II-45e



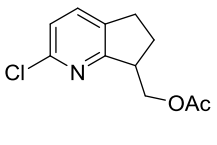
II-46e



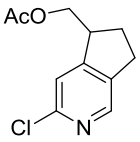
II-45f



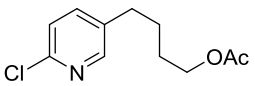
II-46f



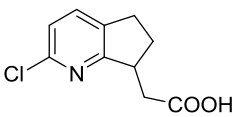
II-45g



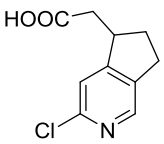
II-46g



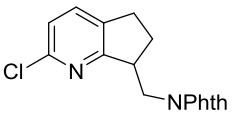
II-48g



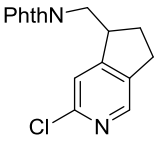
II-45h



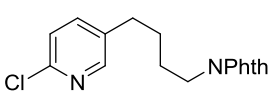
II-46h



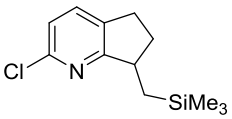
II-45i



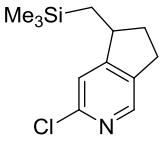
II-46i



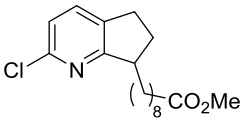
II-48i



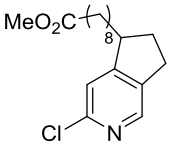
II-45j



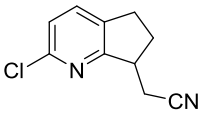
II-46j



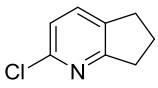
II-45k



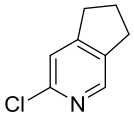
II-46k



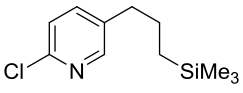
II-45l



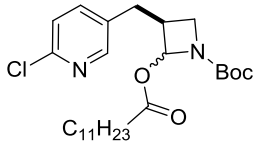
II-45o



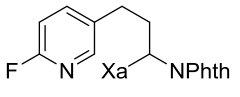
II-46o



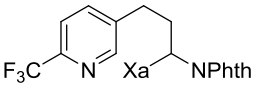
II-48o



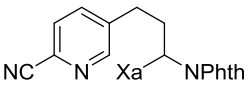
II-47



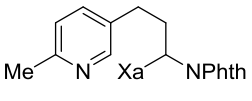
II-53a



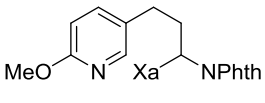
II-53b



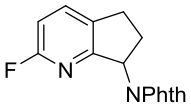
II-53c



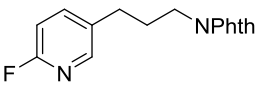
II-53d



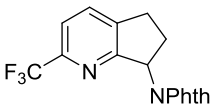
II-53e



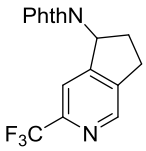
II-54a



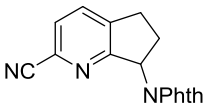
II-56



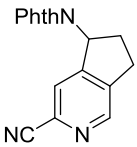
II-54b



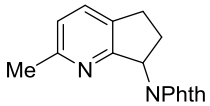
II-55b



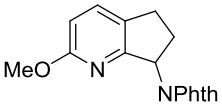
II-54c



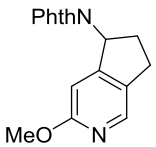
II-55c



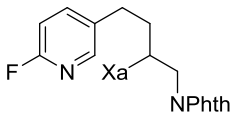
II-54d



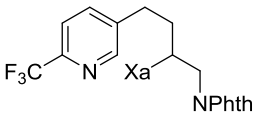
II-54e



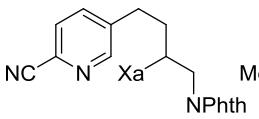
II-55e



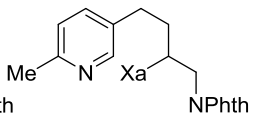
II-57a



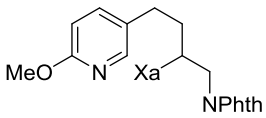
II-57b



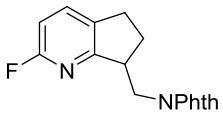
II-57c



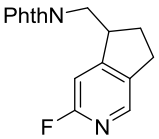
II-57d



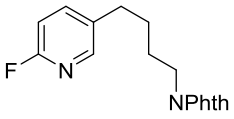
II-57e



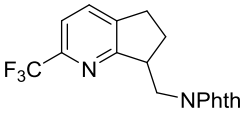
II-58a



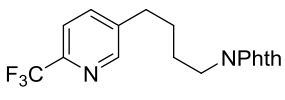
II-59a



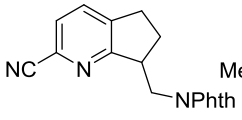
II-60



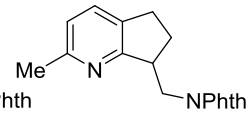
II-58b



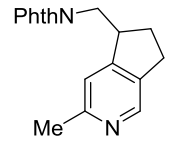
II-61



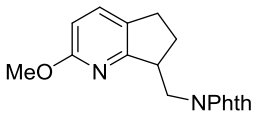
II-58c



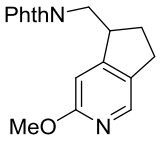
II-58d



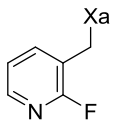
II-59d



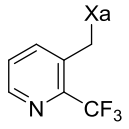
II-58e



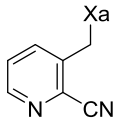
II-59e



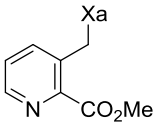
II-62b



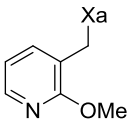
II-62c



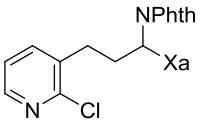
II-62d



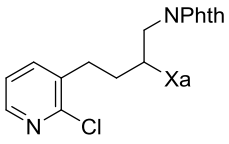
II-62e



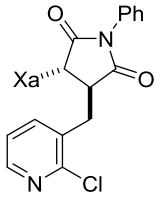
II-62f



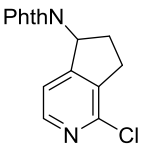
II-63a



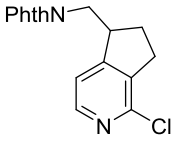
II-63b



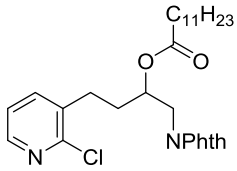
II-63c



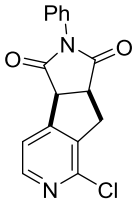
II-64a



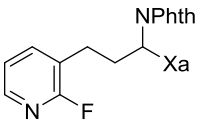
II-64b



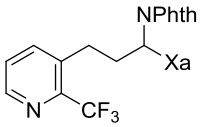
II-65



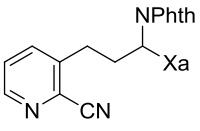
II-64c



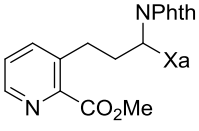
II-66a



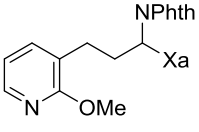
II-66b



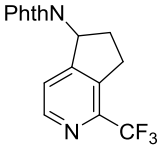
II-66c



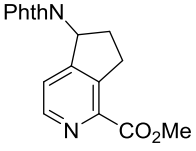
II-66d



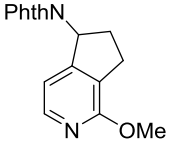
II-66e



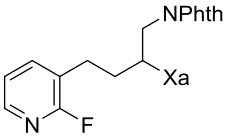
II-67b



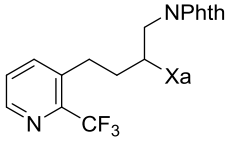
II-67d



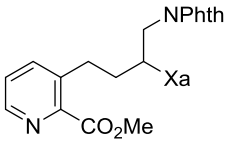
II-67e



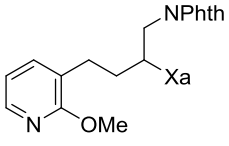
II-70a



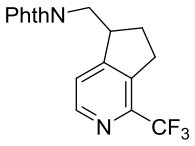
II-67b



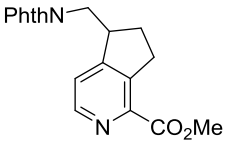
II-67c



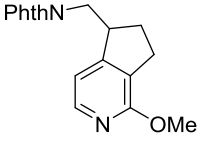
II-67d



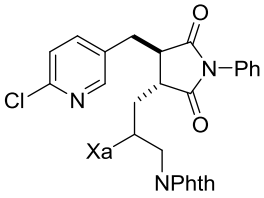
II-71b



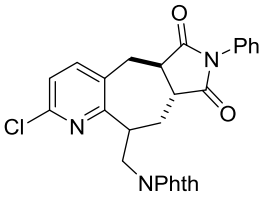
II-71c



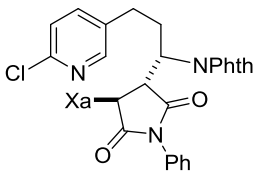
II-71d



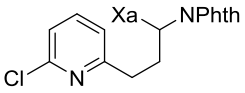
II-73



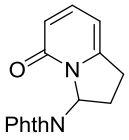
II-74



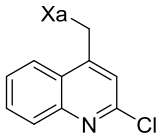
II-75



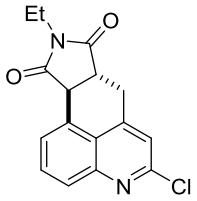
II-83



II-85

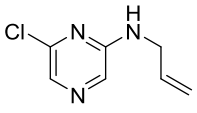


II-95

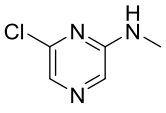


II-97

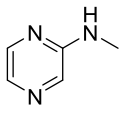
Chapter 3: Xanthate-Based Radical Alkylation of Pyrazines



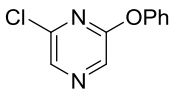
III-13



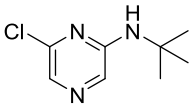
III-18a



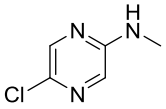
III-18c



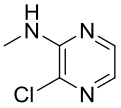
III-18e



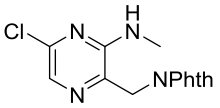
III-18h



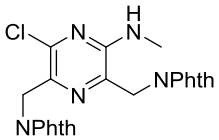
III-18o



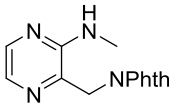
III-18q



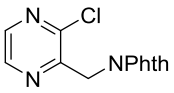
III-19a



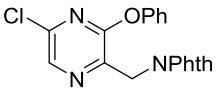
III-20a



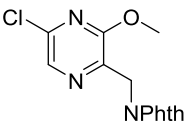
III-19c



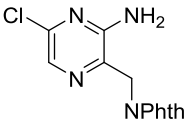
III-19d



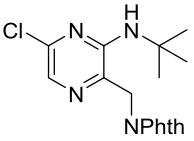
III-19e



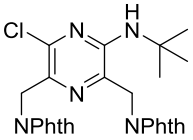
III-19f



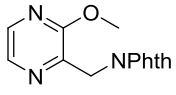
III-19g



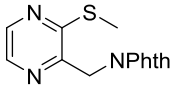
III-19h



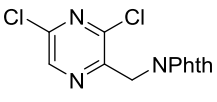
III-20h



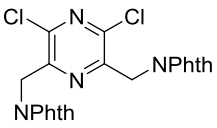
III-19i



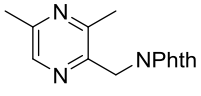
III-19j



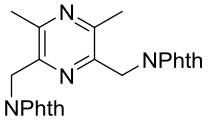
III-19k



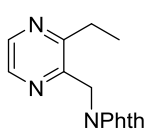
III-20k



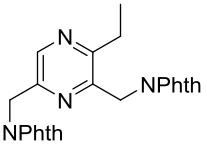
III-19l



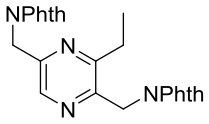
III-20l



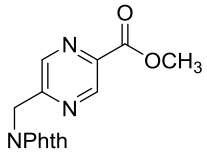
III-19m



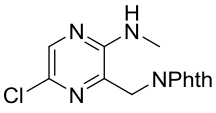
III-20ma



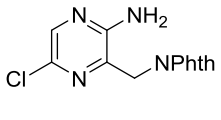
III-20mb



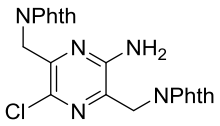
III-19n



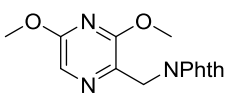
III-19o



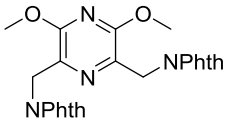
III-19p



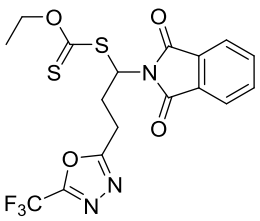
III-20p



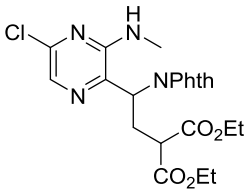
III-19r



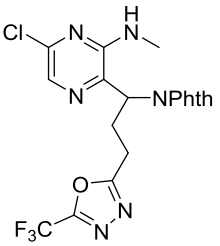
III-20r



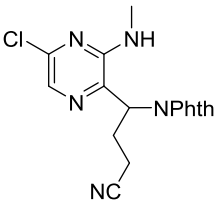
III-21b



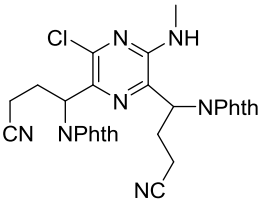
III-22a



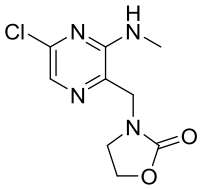
III-22b



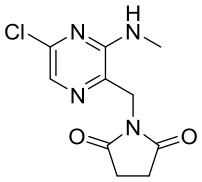
III-22c



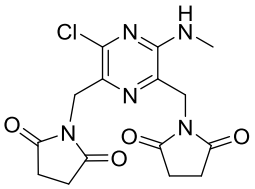
III-23c



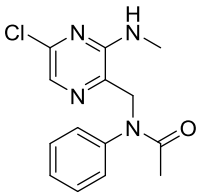
III-22e



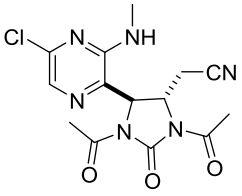
III-22f



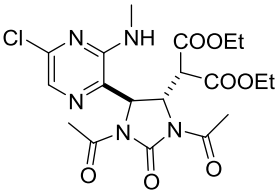
III-23f



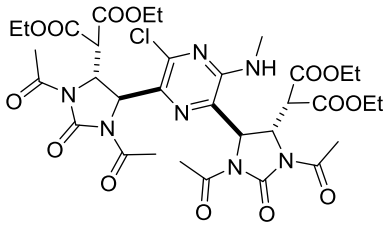
III-22g



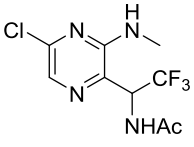
III-22h



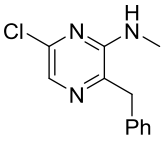
III-22i



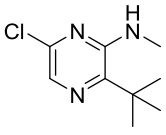
III-23i



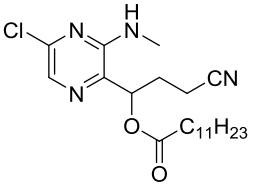
III-22j



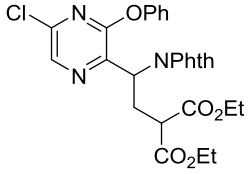
III-22k



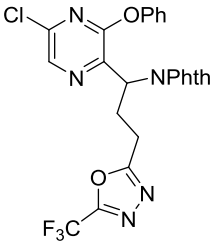
III-22l



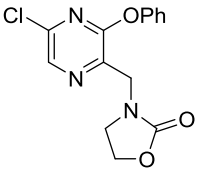
III-25



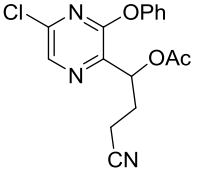
III-27a



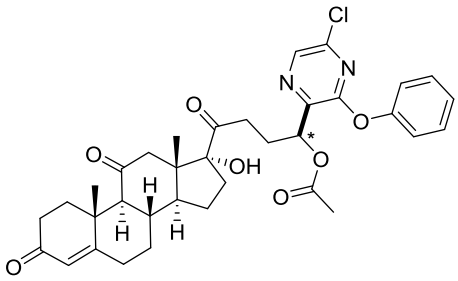
III-27b



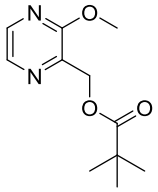
III-27c



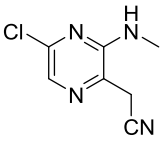
III-27d



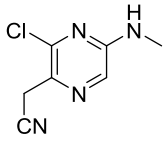
III-27e



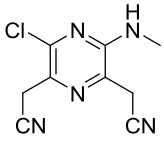
III-27f



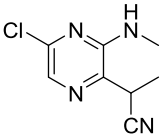
III-29a



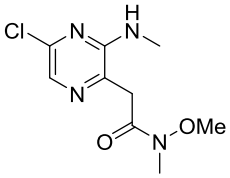
III-30a



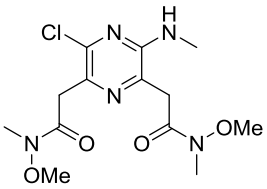
III-31a



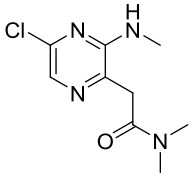
III-29b



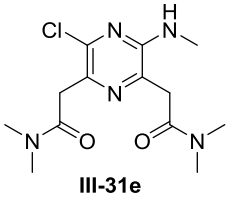
III-29d



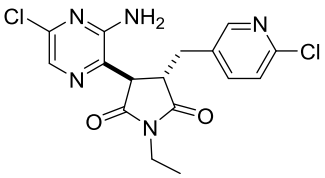
III-31d



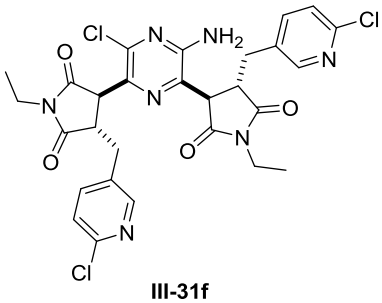
III-29e



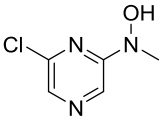
III-31e



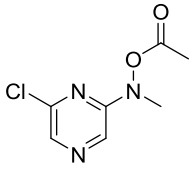
III-29f



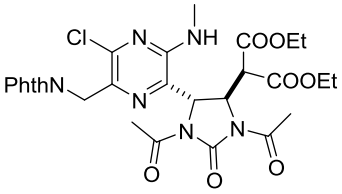
III-31f



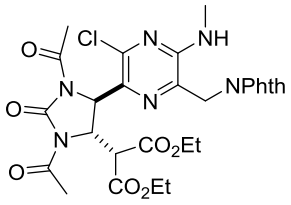
III-36



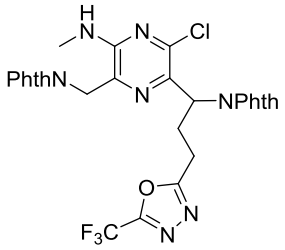
III-32



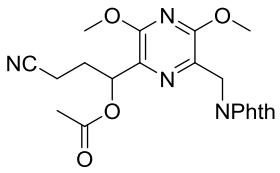
III-42a



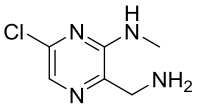
III-42b



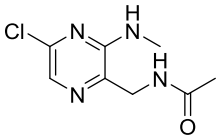
III-42c



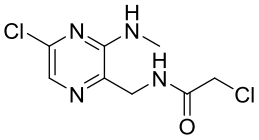
III-42d



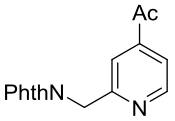
III-43



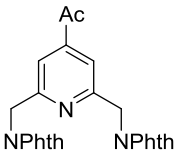
III-45



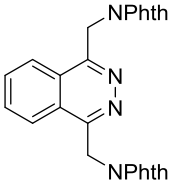
III-46



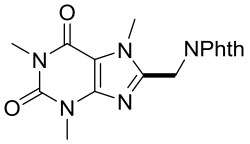
III-50a



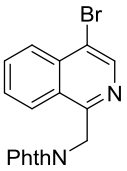
III-51



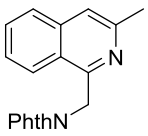
III-50b



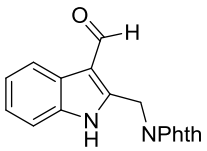
III-50c



III-50d

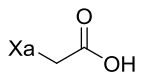


III-50e

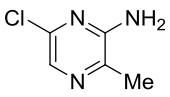


III-50f

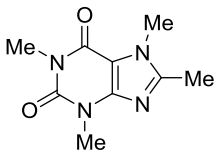
Chapter 4: Towards an Inexpensive Radical Methylation and Ethylation of Heteroarenes



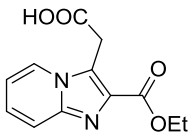
IV-41



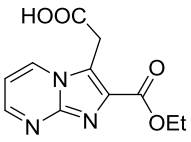
IV-42



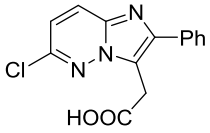
IV-51a



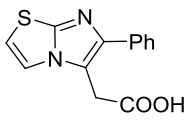
IV-51b



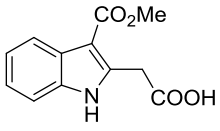
IV-51c



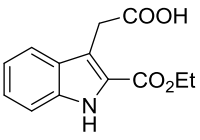
IV-51d



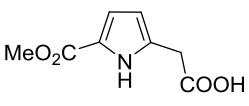
IV-51e



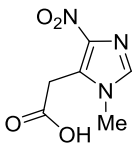
IV-51f



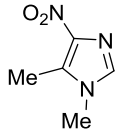
IV-51g



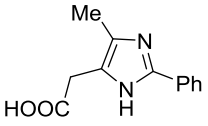
IV-51h



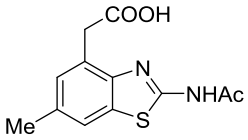
IV-51ia



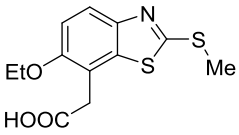
IV-51ib



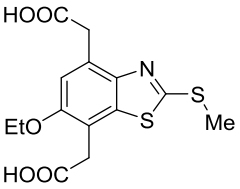
IV-51j



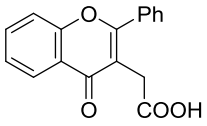
IV-51l



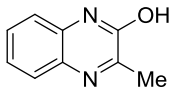
IV-51ma



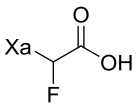
IV-51mb



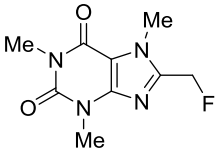
IV-51n



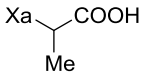
IV-53a



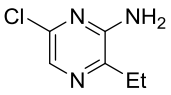
IV-58



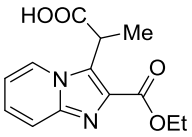
IV-60



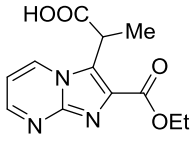
IV-63



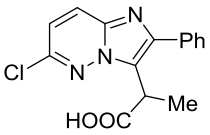
IV-64a



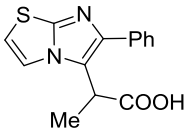
IV-64b



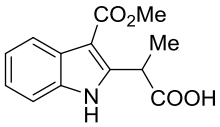
IV-64c



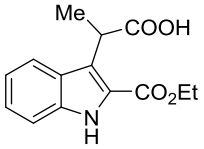
IV-64d



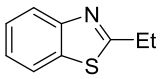
IV-64e



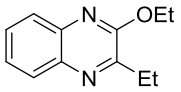
IV-64f



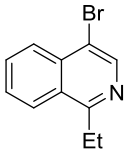
IV-64g



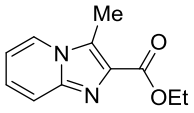
IV-64h



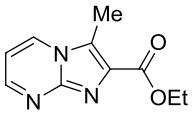
IV-64i



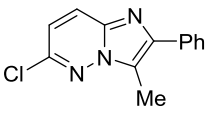
IV-64j



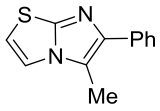
IV-65a



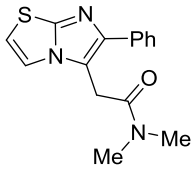
IV-65b



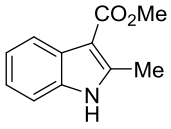
IV-65c



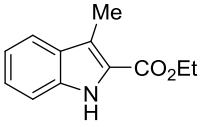
IV-65d



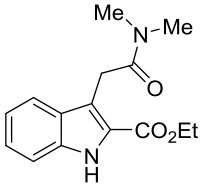
IV-66



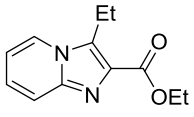
IV-65e



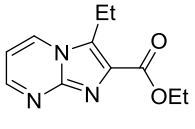
IV-65f



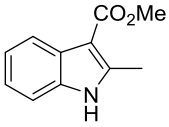
IV-67



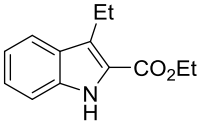
IV-68a



IV-68b



IV-68c



IV-68d

General Experimental Methods

All reactions were carried out under dry, oxygen free nitrogen. Thin Layer Chromatography (TLC) was performed on alumina plates precoated with silica gel (Merck silica gel, 60 F_{254}), which were visualized by the quenching of UV fluorescence when applicable (max = 254 nm and/or 366 nm) and/or by staining with anisadehyde in acidic ethanol solution and/or $KMnO_4$ in basic water followed by heating. Flash chromatography was carried out on Kieselgel 60 (40-63 μm). Petroleum ether refers to the fraction of petroleum boiling between 40 ℃ and 60 ℃. Infrared spectra were recorded as solutions in $CDCl_3$ using CaF_2 cells or as solids in Nujol using CaF_2 cells on a Perkin-Elmer Spectrum Two. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at ambient temperature on a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^{1}H 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 MHz. Chemical shifts (H, C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: δ_H= 7.27 and δ_C= 77.1; DMSO: δ_H = 2.50 and δ_C = 39.5; CD_3COCD_3, δ_H = 2.05 and δ_C = 29.8; CD_3OD: δ_H = 3.31 and δ_C = 49.0). High-resolution mass spectra were recorded by electron impact ionization (EI) on a JMS-GCmateII mass spectrometer. The quoted masses are accurate to ± 5 ppm. Microwave assisted decarboxylation was performed using an Anton Paar® Monowave 300 microwave reactor.

Experimental Procedures and Spectroscopic Data

Chapter 2: Modular Route to Azaindanes

General procedures

General procedure A for the xanthate radical addition

A solution of xanthate (2.0 to 4.0 equiv) and olefin (1.0 equiv) in 1,2-dichloroethane or ethyl acetate (1.0 M according to xanthate) was refluxed under nitrogen for 10 min. DLP was added portionwise (2.5 mol %) per hour until the total consumption of the olefin. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel.

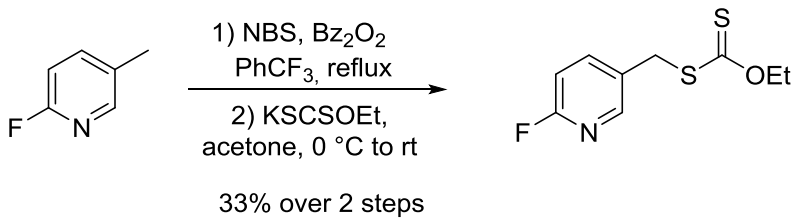
General procedure B for the xanthate radical addition

A solution of xanthate (1.0 equiv) and olefin (3.0 to 4.0 equiv) in 1,2-dichloroethane (1.0 M according to xanthate) was refluxed under nitrogen for 10 min. DLP was added portionwise (5 mol %) per hour until the total consumption of the olefin. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel.

General procedure C for the xanthate radical cyclization

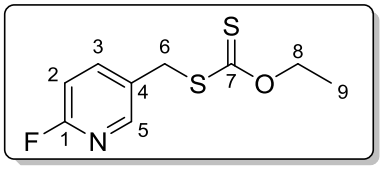
A solution of xanthate (1.0 equiv) and TFA (1.2 equiv) in 1,2-dichloroethane (0.1 M according to xanthate) was refluxed under nitrogen for 10 min. DLP was added portionwise (20 mol %) per hour until the total consumption of the xanthate. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel.

O-Ethyl *S*-((6-fluoropyridin-3-yl)methyl) carbonodithioate (II-43b)



2-Fluoro-5-methylpyridine (5.56 g, 50.0 mmol, 1.0 equiv), NBS (10.68 g, 60.0 mmol, 1.2 equiv) and Bz_2O_2 (2.42 g, 10.0 mmol, 0.2 equiv) in $PhCF_3$ (50 mL) was refluxed under N_2 for 1 h. The suspension was cooled down to room temperature and the solid was removed by filtration and to the filtrate was added dichloromethane. Sat. aqueous K_2CO_3 was added and the organic phase was separated. The aqueous phase was extracted by dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 10:1 to 5:1) to give 5-(bromomethyl)-2-fluoropyridine (3.41 g, 17.9 mmol).

Potassium *O*-ethylxanthate (3.01 g, 18.8 mmol, 1.05 equiv) was added portionwise to a solution of 5-(bromomethyl)-2-fluoropyridine in acetone (36 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 10:1 to 8:1) to give the desired product **II-43b** as a light yellow oil (3.79 g, 16.4 mmol, 33% yield over 2 steps).



Chemical Formula: $C_9H_{10}FNOS_2$
Molecular Weight: 231,30

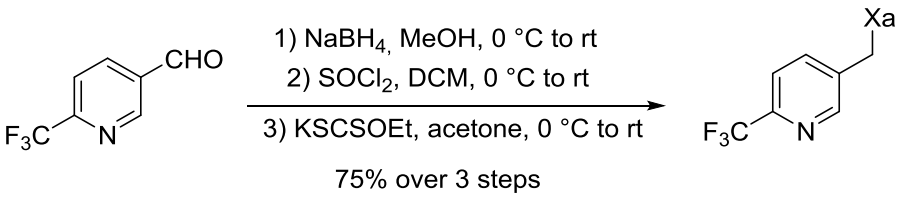
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (dt, J = 2.9, 0.8 Hz, 1H, H_5), 7.79 (ddd, J = 8.4, 7.6, 2.6 Hz, 1H, H_3), 6.89 (ddd, J = 8.5, 3.0, 0.6 Hz, 1H, H_2), 4.65 (q, J = 7.1 Hz, 2H, H_8), 4.34 (s, 2H, H_6), 1.42 (t, J = 7.1 Hz, 3H, H_9).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.0 (C_7), 163.1 (d, J = 238.1 Hz, C_1), 147.9 (d, J = 14.9 Hz, C_5), 141.8 (d, J = 8.0 Hz, C_3), 130.1 (d, J = 4.7 Hz, C_4), 109.6 (d, J = 37.4 Hz, C_2), 70.6 (C_8), 36.5 (d, J = 1.4 Hz, C_6), 13.9 (C_9).

IR (v, cm^{-1}, $CDCl_3$) 2987, 2941, 2900, 1601, 1487, 1406, 1391, 1366, 1251, 1229, 1149, 1112, 1051, 1026.

HRMS (EI+) calculated for $C_9H_{10}FNOS_2$: 231.0188; Found: 231.0190.

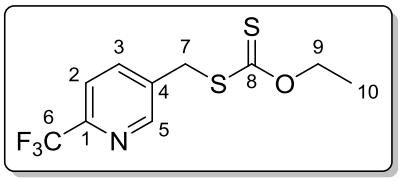
O-Ethyl *S*-((6-(trifluoromethyl)pyridin-3-yl)methyl) carbonodithioate (II-43c)



Into solution of 6-(trifluoromethyl)pyridine-3-carboxaldehyde (2.63 g, 15.0 mmol, 1.0 equiv) in MeOH (75 mL) was added at 0 ℃ $NaBH_4$ (1.13 g, 30.0 mmol, 2.0 equiv). The mixture was allowed to warm up slowly to room temperature and stirred for 3 h. Sat. aqueous NH_4Cl was then added and the mixture was extracted with EtOAc for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (6-(trifluoromethyl)-pyridin-3-yl)methanol as a colorless oil (2.60 g, 14.7 mmol, 98% yield), which was directly used in the next step.

(6-(Trifluoromethyl)-pyridin-3-yl)methanol was dissolved in 45 mL dichloromethane and the solution was then cooled down to 0 ℃. Thionyl chloride (3.49 g, 2.1 mL, 29.4 mmol, 2.0 equiv) was then added dropwise into the solution above and the mixture was refluxed overnight. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and then neutralized with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 5-(chloromethyl)-2-(trifluoromethyl)pyridine as a light yellow oil (2.51 g, 12.8 mmol, 87% yield), which was directly used in the next step.

Potassium *O*-ethylxanthate (2.16 g, 13.5 mmol, 1.05 equiv) was added portionwise to a solution of 5-(chloromethyl)-2-(trifluoromethyl)pyridine in acetone (25.6 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) afforded product **II-43c** as a white solid (3.16 g, 11.2 mmol, 83% yield).



Chemical Formula: $C_{10}H_{10}F_3NOS_2$
Molecular Weight: 281,31

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.72 (d, J = 2.1 Hz, 1H, H_5), 7.91 – 7.85 (m, 1H, H_3), 7.64 (dd, J = 8.2, 0.8 Hz, 1H, H_2), 4.65 (q, J = 7.1 Hz, 2H, H_9), 4.41 (s, 2H, H_7), 1.42 (t, J = 7.1 Hz, 3H, H_{10}).

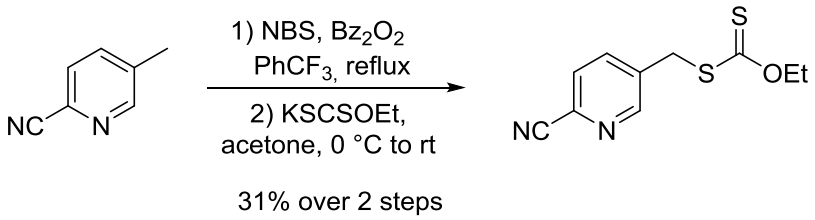
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.5 (C_8), 150.5 (C_5), 147.3 (q, J = 34.7 Hz, C_1), 137.9 (C_3), 136.0 (C_4), 121.6 (q, J = 272.2 Hz, CF_3), 120.4 (q, J = 2.7 Hz, C_2), 70.9 (C_9), 36.8 (C_7), 13.9 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 1337, 1229, 1185, 1149, 1113, 1088, 1049, 1029.

HRMS (EI+) calculated for $C_{10}H_{10}F_3NOS_2$: 281.0156; Found: 281.0165.

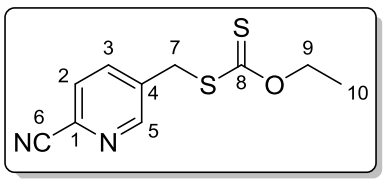
mp : 49-50 ℃

S-((6-Cyanopyridin-3-yl)methyl) *O*-ethyl carbonodithioate (II-43d)



5-Methylpyridine-2-carbonitrile (1.96 g, 16.6 mmol, 1.0 equiv), NBS (3.55 g, 19.9 mmol, 1.2 equiv) and Bz_2O_2 (804 mg, 3.3 mmol, 0.2 equiv) in $PhCF_3$ (50 mL) was refluxed under N_2 for 2 h. The suspension was cooled down to room temperature and the solid was removed by filtration and to the filtrate was added dichloromethane. Sat. aqueous K_2CO_3 was added and the organic phase was separated. The aqueous phase was extracted by dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 10:1 to 4:1) afforded a mixture of the starting compound (2.9 mmol estimated by ^{1}H NMR of the mixture, 349 mg) and the brominated product (8.4 mmol estimated by ^{1}H NMR of the mixture, 1.65 g).

Potassium *O*-ethylxanthate (2.01 g, 12.6 mmol, 1.5 equiv) was added portionwise to a solution of 5-(bromomethyl)picolinonitrile in acetone (16 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization of the residue from ethyl acetate afforded the desired product **II-43d** as a white solid (1.21 g, 5.1 mmol, 31% yield over two steps).



Chemical Formula: $C_{10}H_{10}N_2OS_2$
Molecular Weight: 238,32

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.75 – 8.68 (m, 1H, H_5), 7.85 (ddt, J = 8.0, 2.3, 0.7 Hz, 1H, H_3), 7.65 (dd, J = 8.0, 0.8 Hz, 1H, H_2), 4.64 (q, J = 7.1 Hz, 2H, H_9), 4.40 (s, 2H, H_7), 1.41 (t, J = 7.1 Hz, 3H, H_{10}).

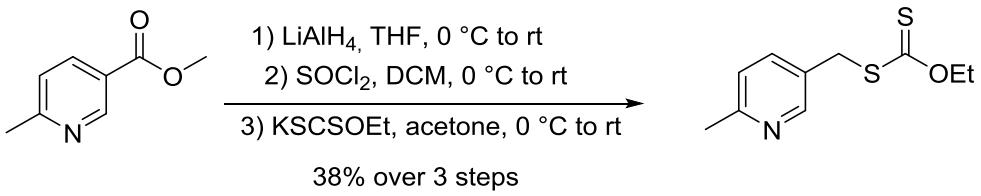
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.3 (C_8), 151.7 (C_5), 137.4 (C_3), 136.9 (C), 132.8 (C), 128.3 (C_2), 117.2 (C_6), 71.0 (C_9), 36.9 (C_7), 13.9 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2988, 1567, 1471, 1387, 1365, 1232, 1150, 1112, 1049, 1026.

HRMS (EI+) calculated for $C_{10}H_{10}N_2OS_2$: 238.0235; Found: 238.0234.

mp : 78-79 ℃

_O_-Ethyl _S_-((6-methylpyridin-3-yl)methyl) carbonodithioate (II-43e)

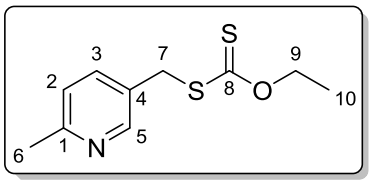


Into a suspension of $LiAlH_4$ (1.71 g, 45.0 mmol, 1.5 equiv) in dry THF (60 mL) at 0 ℃ was added dropwise a solution of methyl 6-methylnicotinate (4.54 g, 30.0 mmol, 1.0 equiv) in dry THF (10 mL). The mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The reaction mixture was quenched with sat. aqueous Na_2SO_4 at 0 ℃. The mixture was filtered over a pad of Celite, and the solid washed with ethyl acetate. The organic layer of filtrate was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (6-methylpyridin-3-yl)methanol (2.12 g, 17.2 mmol), which was used without further purification.

(6-Methylpyridin-3-yl)methanol was dissolved in 50 mL dichloromethane and the solution was then cooled down to 0 ℃. Thionyl chloride (4.10 g, 2.5 mL, 34.4 mmol, 2.0 equiv) was then added dropwise into the solution above and the mixture was allowed to warm up to room temperature and stirred overnight. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and then neutralized with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 5-(chloromethyl)-2-methylpyridine (2.20 g, 15.5 mmol), which was used without further purification.

Potassium _O_-ethylxanthate (2.61 g, 16.3 mmol, 1.05 equiv) was added portionwise to a solution of 5-(chloromethyl)-2-methylpyridine in acetone (50 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic

extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 7:3 to 1:1) afforded product **II-43e** as an orange oil (2.62 g, 11.5 mmol, 38% yield over 3 steps), which decomposed slowly to give a brown oil.



Chemical Formula: $C_{10}H_{13}NOS_2$
Molecular Weight: 227,34

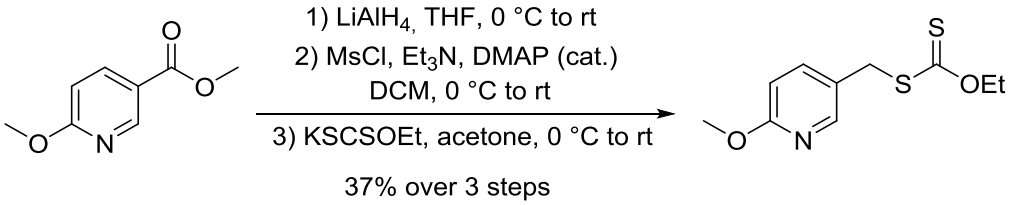
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.49 (d, J = 2.3 Hz, 1H, H_5), 7.58 (dd, J = 8.0, 2.4 Hz, 1H, H_3), 7.12 (d, J = 8.0 Hz, 1H, H_2), 4.66 (q, J = 7.1 Hz, 2H, H_9), 4.32 (s, 2H, H_7), 2.55 (s, 3H, H_6), 1.43 (t, J = 7.1 Hz, 3H, H_{10}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.4 (C_8), 157.8 (C_1), 149.6 (C_5), 136.9 (C_3), 128.9 (C_4), 123.2 (C_2), 70.4 (C_9), 37.3 (C_7), 24.3 (C_6), 13.9 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 2927, 1603, 1570, 1491, 1444, 1389, 1298, 1224, 1148, 1112, 1051, 1031.

HRMS (EI+) calculated for $C_{10}H_{13}NOS_2$: 227.0439; Found: 227.0431.

_O_-Ethyl _S_-((6-methoxypyridin-3-yl)methyl) carbonodithioate (II-43f)



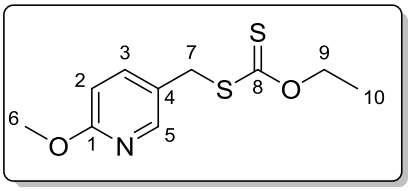
Into a suspension of $LiAlH_4$ (854 mg, 22.5 mmol, 1.5 equiv) in dry THF (15 mL) at 0 ℃ was added dropwise a solution of methyl 6-methoxynicotinate (2.51 g, 15.0 mmol, 1.0 equiv) in dry THF (10 mL). The mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The reaction mixture was treated with ethyl acetate at 0 ℃, followed by dropwise addition of water. The mixture was filtered over a pad of Celite, and the solid washed with ethyl acetate. The organic layer of filtrate was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (6-methoxypyridin-3-yl)methanol as a colorless oil (1.56 g, 11.2 mmol), which was used without further purification.

To a solution of (6-methoxypyridin-3-yl)methanol in 75 mL dichloromethane was added at 0 ℃ triethylamine (2.27 g, 3.1 mL, 22.4 mmol, 2.0 equiv) and a catalytic amount of 4-(dimethylamino)pyridine, followed by methanesulfonyl chloride (1.55 g, 1.0 mL, 13.5 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight, and then it was quenched by the addition of ice. The mixture was further diluted with dichloromethane, and the organic layer was washed with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/diethyl ether = 5:1) to give 5-(chloromethyl)-2-methoxypyridine as a colorless oil (960 mg, 6.1 mmol).[126] **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.14 (d, J = 2.6 Hz, 1H), 7.62 (dd, J = 8.6, 2.5 Hz, 1H), 6.75 (dd, J = 8.6, 0.7 Hz, 1H), 4.55 (s, 2H), 3.94 (s, 3H).

---

[126] Kozikowski, A. P.; Xia, Y.; Reddy, E. R.; Tuckmantel, W.; Hanin, I.; Tang, X. C. *J. Org. Chem.* **1991**, *56*, 4636.

Potassium *O*-ethylxanthate (1.46 g, 9.1 mmol, 1.5 equiv) was added portionwise to a solution of 5-(chloromethyl)-2-methoxypyridine in acetone (12 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:1) to give the desired product **II-43f** as a colorless oil (1.35 g, 5.5 mmol, 37% yield over 3 steps).



Chemical Formula: $C_{10}H_{13}NO_2S_2$
Molecular Weight: 243,34

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.19 – 8.10 (m, 1H, H_5), 7.55 (dd, J = 8.5, 2.6 Hz, 1H, H_3), 6.70 (dd, J = 8.5, 0.7 Hz, 1H, H_2), 4.65 (q, J = 7.1 Hz, 2H, H_9), 4.29 (s, 2H, H_7), 3.92 (s, 3H, H_6), 1.42 (t, J = 7.1 Hz, 3H, H_{10}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.7 (C_8), 163.8 (C_1), 147.1 (C_5), 139.5 (C_3), 124.5 (C_4), 111.1 (C_2), 70.3 (C_9), 53.6 (C_6), 37.2 (C_7), 13.9 (C_{10}).

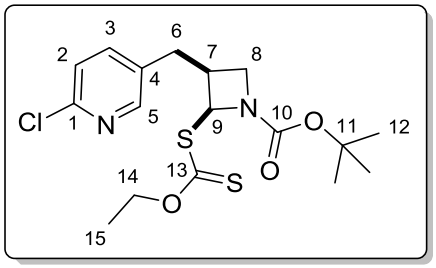
IR (v, cm^{-1}, $CDCl_3$) 3015, 2986, 2948, 2902, 1611, 1573, 1493, 1463, 1445, 1388, 1311, 1293, 1249, 1227, 1208, 1149, 1113, 1052, 1027.

HRMS (EI+) calculated for $C_{10}H_{13}NO_2S_2$: 243.0388; Found: 243.0394.

tert-Butyl 3-((6-chloropyridin-3-yl)methyl)-2-((ethoxycarbonothioyl)thio)-azetidine-1-carboxylate (II-44c)

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (460 mg, 1.86 mmol, 2.0 equiv), *N*-Boc-azetine (192 mg, 1.24 mmol, 1.0 equiv) with several drops of 2,6-lutidine in ethyl acetate (1.9 mL), and needed 2 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:1 to 1:1) afforded **II-44c** (389 mg, 0.97 mmol, 78% yield) as a 1:4 diastereoisomer.

Minor diastereoisomer (***syn***):



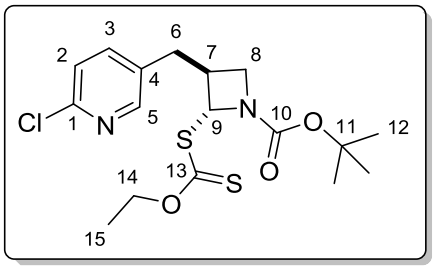
Chemical Formula: $C_{17}H_{23}ClN_2O_3S_2$
Molecular Weight: 402,95

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (d, J = 2.5 Hz, 1H), 7.44 (dd, J = 8.2, 2.6 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.17 (d, J = 7.4 Hz, 1H), 4.57 (qd, J = 7.0, 1.0 Hz, 2H), 3.93 (t, J = 8.1 Hz, 1H), 3.55 (dd, J = 8.3, 5.4 Hz, 1H), 3.30 (dtt, J = 10.9, 7.9, 5.6 Hz, 1H), 3.05 (dd, J = 14.4, 5.7 Hz, 1H), 2.89 (dd, J = 14.5, 10.4 Hz, 1H), 1.42 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.9 (C_{13}), 155.1 (C_{10}), 149.9 (C_1), 149.8 (C_5), 139.1 (C_3), 133.1 (C_4), 124.3 (C_2), 81.1 (C_{11}), 72.7 (C_9), 69.9 (C_{14}), 52.6 (C_8), 35.2 (C_7), 33.5 (C_6), 28.4 (C_{12}), 13.9 (C_{15}).

HRMS (EI+) calculated for $C_{17}H_{23}ClN_2O_3S_2$: 402.0839, M-Xa: $C_{14}H_{18}ClN_2O_2$: 281.1057; Found: 281.1045.

Major diastereoisomer (***anti***):

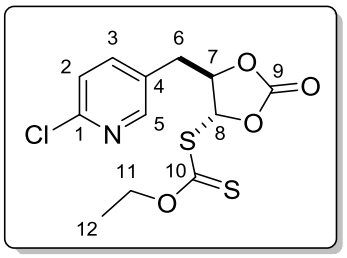


Chemical Formula: $C_{17}H_{23}ClN_2O_3S_2$
Molecular Weight: 402,95

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.23 (d, J = 2.5 Hz, 1H, H_5), 7.48 (dd, J = 8.3, 2.5 Hz, 1H, H_3), 7.26 – 7.23 (m, 1H, H_2), 5.76 (d, J = 4.0 Hz, 1H, H_9), 4.67 – 4.57 (m, 2H, H_{14}), 3.94 (t, J = 7.8 Hz, 1H, H_{8a}), 3.53 (dd, J = 8.2, 4.7 Hz, 1H, H_{8b}), 3.23 (dd, J = 13.4, 5.2 Hz, 1H, H_{6a}), 3.01 – 2.86 (m, 2H, H_{6a} and H_7), 1.41 (t, J = 7.2 Hz, 3H, H_{15}), 1.41 (s, 9H, H_{12}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.7 (C_{13}), 154.8 (C_{10}), 150.1 (C_1), 149.7 (C_5), 139.0 (C_3), 132.7 (C_4), 124.3 (C_2), 81.1 (C_{11}), 72.9 (C_9), 69.9 (C_{14}), 51.5 (C_8), 40.2 (C_7), 35.8 (C_6), 28.3 (C_{12}), 13.9 (C_{15}).

_S_-(5-((6-Chloropyridin-3-yl)methyl)-2-oxo-1,3-dioxolan-4-yl) _O_-ethyl carbonodithioate (II-44d)

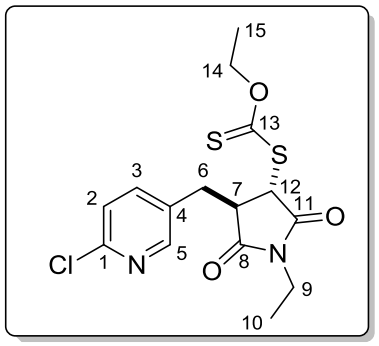


Chemical Formula: $C_{12}H_{12}ClNO_4S_2$
Molecular Weight: 333,8010

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (642 mg, 2.59 mmol) and vinylene carbonate (669 mg, 7.77 mmol) in ethyl acetate (2.6 mL), and needed 18 h for the reaction to go to completion. Flash chromatography on silica gel (dichloromethane/diethyl ether = 20:1) afforded product **II-44d** as a light brown oil (167 mg, 0.50 mmol, 19% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.30 (d, J = 2.5 Hz, 1H, H_5), 7.60 (dd, J = 8.3, 2.5 Hz, 1H, H_3), 7.33 (d, J = 8.1 Hz, 1H, H_2), 6.16 (d, J = 5.6 Hz, 1H, H_8), 4.85 (ddd, J = 7.3, 5.6, 4.6 Hz, 1H, H_7), 4.68 (qd, J = 7.2, 1.0 Hz, 2H, H_{11}), 3.22 (dd, J = 14.9, 4.5 Hz, 1H, H_{6a}), 3.14 (dd, J = 14.9, 7.3 Hz, 1H, H_{6b}), 1.44 (t, J = 7.1 Hz, 3H, H_{12}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 207.0 (C_{10}), 152.3 (C_9), 151.3 (C_2), 150.3 (C_5), 140.0 (C_3), 128.3 (C_4), 124.7 (C_2), 85.9 (C_8), 80.4 (C_7), 71.6 (C_{11}), 35.9 (C_6), 13.7 (C_{11}).
IR (ν, cm^{-1}, $CDCl_3$) 2987, 2940, 1823, 1590, 1566, 1464, 1387, 1367, 1359, 1291, 1250, 1143, 1111, 1048, 1007.
HRMS (EI+) calculated for $C_{12}H_{12}ClNO_4S_2$: 332.9896; Found: 332.9885.

(4-((6-Chloropyridin-3-yl)methyl)-1-ethyl-2,5-dioxopyrrolidin-3-yl) O-ethyl carbonodithioate (II-44e)

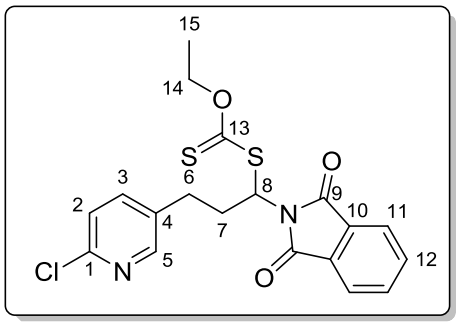


Chemical Formula: $C_{15}H_{17}ClN_2O_3S_2$
Molecular Weight: 372,88

A magnetically stirred solution of the *N*-ethylmaleimide (503 mg, 4.02 mmol, 1.0 equiv) and xanthate **II-43a** (1.99 g, 8.04 mmol, 2.0 equiv) in DCE (8.0 mL) was refluxed for 15 min under a flow of nitrogen. DLP (5 mol %) was then added to the refluxing solution and the olefin was totally consumed in 60 min. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure. The crude product was triturated with diethyl ether to give product **II-44e** as a white solid (852 mg, 2.28 mmol, 57% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.26 (d, J = 2.6 Hz, 1H), 7.54 (dd, J = 8.1, 2.6 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 4.63 (m, 2H, H_{14}), 4.10 (d, J = 6.5 Hz, 1H, H_{12}), 3.57 (q, J = 7.2 Hz, 2H, H_9), 3.40 (q, J = 6.2 Hz, 1H, H_7), 3.20 (d, J = 6.0 Hz, 2H, H_6), 1.39 (t, J = 7.1 Hz, 3H, H_{15}), 1.14 (t, J = 7.2 Hz, 3H, H_{10}).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 210.1 (C_{13}), 175.7 (C=O), 172.2 (C=O), 150.9 (C), 150.6 (CH), 140.0 (CH), 130.8 (C), 124.5 (CH), 71.4 (C_{14}), 49.5 (C_{12}), 47.7 (C_7), 34.8 (C_9), 31.3 (C_6), 13.8 (C_{15}), 13.0 (C_{10}).
IR (ν, cm^{-1}, $CDCl_3$) 2985, 2941, 1782, 1711, 1602, 1588, 1565, 1462, 1444, 1401, 1380, 1350, 1226, 1111, 1047.
HRMS (EI+) calculated for $C_{15}H_{17}ClN_2O_3S_2$: 372.0369; Found: 372.0351.
mp: 122-123 ℃

_S_-(3-(6-Chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl) _O_-ethyl carbonodithioate (II-44f)

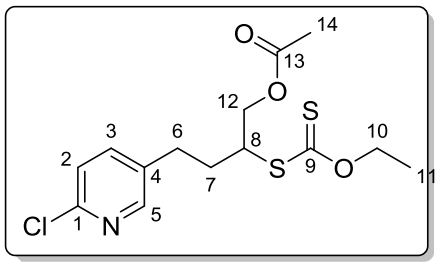


Chemical Formula: $C_{19}H_{17}ClN_2O_3S_2$
Molecular Weight: 420,93

According to the general procedure A, the reaction was carried out with xanthate **II-43a** (991 mg, 4.00 mmol) and *N*-vinylphthalimide (173 mg, 1.00 mmol) in ethyl acetate (4.0 mL), and needed 19 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:2 to 1:1) afforded product **II-44f** as a light yellow oil (228 mg, 0.57 mmol, 57% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.17 (d, J = 2.5 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.79 – 7.71 (m, 2H), 7.47 (dd, J = 8.2, 2.5 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 6.28 (dd, J = 9.0, 6.5 Hz, 1H, H_8), 4.61 (q, J = 7.1 Hz, 2H, H_{14}), 2.83 – 2.73 (m, 1H, H_{6a}), 2.72 – 2.57 (m, 2H, H_{6b} and H_{7a}), 2.50 – 2.40 (m, 1H, H_{7b}), 1.38 (t, J = 7.1 Hz, 3H, H_{15}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{13}), 166.9 ($2C_9$), 149.6 (C_5 and C_1), 138.8 (C_3), 134.7 (2CH), 134.2 (C_4), 131.5 ($2C_{10}$), 124.1 (C_2), 123.8 (2CH), 70.7 (C_{14}), 57.2 (C_8), 34.2 (C_7), 29.5 (C_6), 13.8 (C_{15}).
IR (ν, cm^{-1}, $CDCl_3$) 2985, 2930, 1780, 1720, 1461, 1380, 1360, 1333, 1235, 1111, 1048.
HRMS (EI+) calculated for $C_{19}H_{17}ClN_2O_3S_2$: 420.0369, M-Xa: $C_{16}H_{12}ClN_2O_2$: 299.0587; Found: 299.0581.

4-(6-Chloropyridin-3-yl)-2-((ethoxycarbonothioyl)thio)butyl acetate (II-44g)

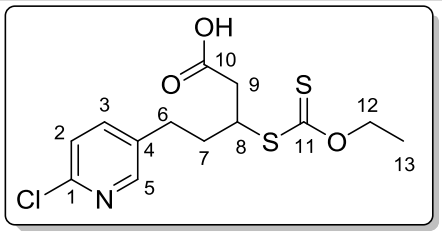


Chemical Formula: $C_{14}H_{18}ClNO_3S_2$
Molecular Weight: 347,87

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (743 mg, 3.00 mmol) and allylacetate (1.20 g, 12.00 mmol) in ethyl acetate (3.0 mL), and needed 18 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 3:1) afforded product **II-44g** as a light yellow oil (637 mg, 1.83 mmol, 61% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 (dd, J = 2.6, 0.7 Hz, 1H, H_5), 7.50 – 7.44 (m, 1H, H_3), 7.28 – 7.23 (m, 1H, H_2), 4.64 (q, J = 7.1 Hz, 2H, H_{10}), 4.34 – 4.22 (m, 2H, H_{12}), 3.95 (ddt, J = 9.3, 6.1, 5.1 Hz, 1H, H_8), 2.83 (ddd, J = 14.9, 9.8, 5.4 Hz, 1H, H_{6a}), 2.73 (ddd, J = 14.1, 9.8, 6.7 Hz, 1H, H_{6b}), 2.12 – 2.01 (m, 1H, H_{7a}), 2.07 (s, 3H, H_{14}), 1.93 (dtd, J = 14.6, 9.6, 5.4 Hz, 1H, H_{7b}), 1.42 (t, J = 7.1 Hz, 3H, H_{11}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.7 (C_9), 170.8 (C_{13}), 149.7 (C_5), 149.6 (C_1), 138.9 (C_3), 135.2 (C_4), 124.2 (C_2), 70.6 (C_{10}), 65.5 (C_{12}), 48.9 (C_8), 32.2 (C_7), 29.5 (C_6), 21.0 (C_{14}), 13.9 (C_{11}).
IR (v, cm^{-1}, $CDCl_3$) 2985, 2941, 1741, 1588, 1566, 1461, 1384, 1365, 1230, 1138, 1111, 1052, 1029.
HRMS (EI+) calculated for $C_{14}H_{18}ClNO_3S_2$: 347.0417; Found: 347.0415.

5-(6-Chloropyridin-3-yl)-3-((ethoxycarbonothioyl)thio)pentanoic acid (II-44h)



Chemical Formula: $C_{13}H_{16}ClNO_3S_2$
Molecular Weight: 333,85

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (496 mg, 2.00 mmol) and 3-butenoic acid (516 mg, 6.00 mmol) in ethyl acetate (2.0 mL), and needed 15 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 6:1 to 4:1 with 1% CH_3COOH by volume) followed by further purification (toluene/CH_3COOH = 5:1) afforded product **II-44h** as a colorless oil (171 mg, 0.51 mmol, 26% yield).

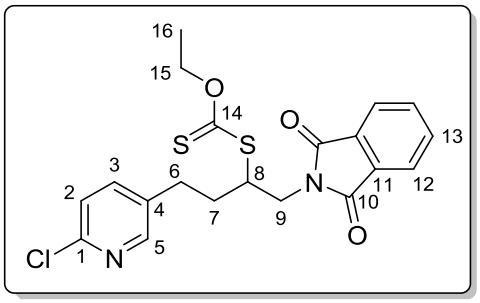
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.30 (dd, J = 2.5, 0.7 Hz, 1H, H_5), 7.51 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.29 – 7.24 (m, 1H, H_2), 4.65 (qd, J = 7.1, 0.9 Hz, 2H, H_{11}), 4.05 (ddt, J = 9.4, 8.2, 4.7 Hz, 1H, H_8), 2.95 (dd, J = 16.7, 4.8 Hz, 1H, H_{9a}), 2.90 – 2.70 (m, 3H, H_6 and H_{9b}), 2.20 – 2.09 (m, 1H, H_{7a}), 2.02 (dtd, J = 14.6, 9.7, 5.3 Hz, 1H, H_{7b}), 1.42 (t, J = 7.1 Hz, 3H, H_{13}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.0 (C_{11}), 175.4 (C_{10}), 149.5 (C_5), 149.2 (C_1), 139.4 (C_3), 135.5 (C_4), 124.3 (C_2), 70.4 (C_{12}), 45.9 (C_8), 39.3 (C_9), 34.5 (C_7), 29.8 (C_6), 13.9 (C_{13}).

IR (v, cm^{-1}, $CDCl_3$) 2987, 2939, 2866, 1746, 1713, 1588, 1566, 1461, 1387, 1226, 1137, 1111, 1053.

HRMS (EI+) calculated for $C_{13}H_{16}ClNO_3S_2$: 333.0260, M-Xa: $C_{10}H_{11}ClNO_2$: 212.0478; Found: 212.0473.

_S_-(4-(6-Chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)butan-2-yl) O-ethyl carbonodithioate (II-44i)



Chemical Formula: $C_{20}H_{19}ClN_2O_3S_2$
Molecular Weight: 434,95

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (496 mg, 2.00 mmol) and *N*-allylphthalimide (1.12 g, 6.00 mmol) in 1,2-dichloroethane (2.0 mL), and needed 12 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:1 to 3:1) followed by further purification (toluene/ethyl acetate = 6:1) afforded product **II-44i** as a white solid (407 mg, 0.94 mmol, 47% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 (dd, J = 2.6, 0.7 Hz, 1H, H_5), 7.89 – 7.81 (m, 2H), 7.77 – 7.70 (m, 2H), 7.48 (dd, J = 8.2, 2.6 Hz, 1H, H_3), 7.23 (dd, J = 8.1, 0.7 Hz, 1H, H_2), 4.59 (m, 2H, H_{15}), 4.15 (dtd, J = 8.6, 7.1, 5.1 Hz, 1H, H_8), 4.05 – 3.94 (m, 2H, H_9), 2.91 (ddd, J = 15.0, 10.2, 5.2 Hz, 1H, H_{6a}), 2.76 (ddd, J = 14.0, 10.2, 6.3 Hz, 1H, H_{6b}), 2.03 (dddd, J = 14.4, 10.2, 6.4, 5.1 Hz, 1H, H_{7a}), 1.98 – 1.86 (m, 1H, H_{7b}), 1.40 (t, J = 7.1 Hz, 3H, H_{16}).

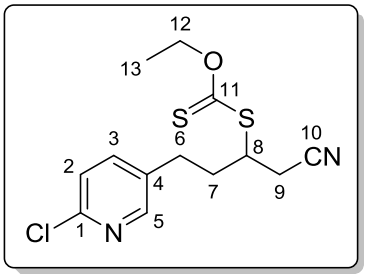
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.2 (C_{14}), 168.2 ($2C_{10}$), 149.8 (C_5), 149.5 (C_1), 139.0 (C_3), 135.3 (C_4), 134.4 (2CH), 131.9 ($2C_{11}$), 124.2 (C_2), 123.6 (2CH), 70.5 (C_{15}), 49.0 (C_8), 40.9 (C_9), 33.3 (C_7), 29.4 (C_6), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2938, 1774, 1717, 1588, 1566, 1462, 1431, 1394, 1364, 1335, 1227, 1111, 1050.

HRMS (EI+) calculated for $C_{20}H_{19}ClN_2O_3S_2$: 434.0526, M-Xa: $C_{17}H_{14}ClN_2O_2$: 313.0744; Found: 313.0747.

mp: 96-97 ℃

S-(4-(6-Chloropyridin-3-yl)-1-cyanobutan-2-yl) *O*-ethyl carbonodithioate (II-40l)



Chemical Formula: $C_{13}H_{15}ClN_2OS_2$
Molecular Weight: 314,85

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (372 mg, 1.50 mmol) and allyl cyanide (302 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 15 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 10:1 to 4:1) afforded product **II-44l** as a light yellow oil (135 mg, 0.43 mmol, 29% yield).

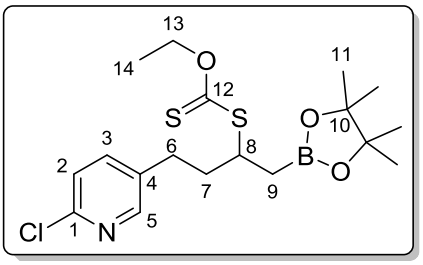
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (dd, J = 2.5, 0.8 Hz, 1H, H_5), 7.48 (dd, J = 8.2, 2.6 Hz, 1H, H_3), 7.26 (dd, J = 8.2, 0.7 Hz, 1H, H_2), 4.65 (qd, J = 7.1, 0.8 Hz, 2H, H_{12}), 3.90 – 3.79 (m, 1H, H_8), 2.95 – 2.81 (m, 3H, H_9 and H_{6a}), 2.74 (ddd, J = 14.2, 9.1, 7.3 Hz, 1H H_{6b}), 2.20 – 2.03 (m, 2H, H_7), 1.43 (t, J = 7.1 Hz, 3H, H_{13}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.8 (C_{11}), 150.0 (C_1), 149.6 (C_5), 138.8 (C_3), 134.4 (C_4), 124.3 (C_2), 116.9 (C_{10}), 70.9 (C_{12}), 45.9 (C_8), 33.6 (C_7), 29.4 (C_6), 24.2 (C_9), 13.9 (C_{13}).

IR (ν, cm^{-1}, $CDCl_3$) 2989, 2940, 2864, 1588, 1566, 1461, 1420, 1386, 1365, 1291, 1233, 1149, 1137, 1111, 1052, 1026, 1002.

HRMS (EI+) calculated for $C_{13}H_{15}ClN_2OS_2$: 314.0314; Found: 314.0324.

_S_-(4-(6-Chloropyridin-3-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-44m)



Chemical Formula: $C_{18}H_{27}BClNO_3S_2$
Molecular Weight: 415,80

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (372 mg, 1.50 mmol) and allylboronic acid pinacol ester (756 mg, 4.50 mmol) in ethyl acetate (1.5 mL), and needed 13 h for the reaction to go to completion. Flash chromatography on silica gel (toluene/ethyl acetate = 15:1) afforded product **II-44m** as a colorless oil (144 mg, 0.35 mmol, 23% yield).

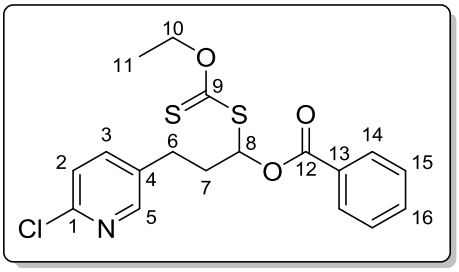
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (d, J = 2.5 Hz, 1H, H_5), 7.47 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.23 (d, J = 8.1 Hz, 1H, H_2), 4.63 (q, J = 7.1 Hz, 2H, H_{13}), 3.98 – 3.87 (m, 1H, H_8), 2.80 – 2.64 (m, 2H, H_6), 2.01 (td, J = 8.3, 6.8 Hz, 2H, H_7), 1.40 (t, J = 7.1 Hz, 3H, H_{14}), 1.37 – 1.27 (m, 2H, H_9), 1.23 (d, J = 1.9 Hz, 12H, H_{11}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 214.2 (C_{12}), 149.7 (C_5), 149.2 (C_1), 139.0 (C_3), 136.0 (C_4), 124.0 (C_2), 83.7 (C_{10}), 69.8 (C_{13}), 47.1 (C_8), 37.5 (C_7), 29.7 (C_6), 24.95 (CH_3), 24.93 (CH_3), 13.9 (C_{14}) (C9 not observed).

IR (ν, cm^{-1}, $CDCl_3$) 2983, 2936, 1587, 1566, 1461, 1382, 1366, 1331, 1217, 1143, 1110, 1051.

HRMS (EI+) calculated for $C_{18}H_{27}BClNO_3S_2$: 415.1214; Found: 415.1204.

3-(6-Chloropyridin-3-yl)-1-((ethoxycarbonothioyl)thio)propyl benzoate (II-44n)



Chemical Formula: $C_{18}H_{18}ClNO_3S_2$
Molecular Weight: 395,92

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (2.48 g, 10.0 mmol) and vinyl benzoate (2.96 g, 2.77 mL, 20.0 mmol) in ethyl acetate (10.0 mL), and needed 14 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 4:1 to 3:1) afforded product **II-44n** as a light yellow oil (1.70 g, 4.3 mmol, 43% yield).

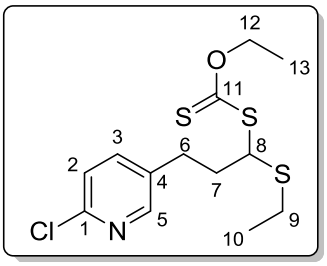
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (dd, J = 2.5, 0.8 Hz, 1H, H_5), 8.06 – 7.96 (m, 2H, H_{14}), 7.59 (ddt, J = 7.9, 7.0, 1.4 Hz, 1H, H_{16}), 7.54 – 7.42 (m, 3H, $2H_{15}$ and H_3), 7.27 – 7.22 (m, 1H, H_2), 6.91 (t, J = 6.4 Hz, 1H, H_8), 4.60 (qd, J = 7.1, 2.1 Hz, 2H, H_{10}), 2.90 – 2.76 (m, 2H, H_6), 2.45 – 2.29 (m, 2H, H_7), 1.34 (t, J = 7.1 Hz, 3H, H_{11}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 290.6 (C_9), 165.2 (C_{12}), 149.71 (C_1), 149.69 (C_5), 138.9 (C_3), 134.6 (C_4), 133.8 (C_{16}), 130.0 (C_{14}), 129.1 (C_{13}), 128.7 (C_{15}), 124.2 (C_2), 80.7 (C_8), 70.6 (C_{10}), 35.5 (C_7), 28.4 (C_6), 13.7 (C_{11}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2938, 1774, 1718, 1566, 1431, 1411, 1395, 1364, 1227, 1111, 1050.

HRMS (EI+) calculated for $C_{18}H_{18}ClNO_3S_2$: 395.0417, M-Xa: $C_{15}H_{13}ClNO_2$: 274.0635; Found: 274.0631.

_S_-(3-(6-Chloropyridin-3-yl)-1-(ethylthio)propyl) _O_-ethyl carbonodithioate (II-44p)



Chemical Formula: $C_{13}H_{18}ClNOS_3$
Molecular Weight: 335,92

According to the general procedure B, the reaction was carried out with xanthate **II-43a** (743 mg, 3.00 mmol) and ethyl vinyl sulfide (794 mg, 9.00 mmol) in ethyl acetate (3.0 mL), and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 20:1 to 15:1) afforded product **II-44p** as a yellow oil (629 mg, 1.87 mmol, 62% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (d, J = 2.4 Hz, 1H, H_5), 7.51 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.27 – 7.23 (m, 1H, H_2), 4.69 (dd, J = 8.6, 5.0 Hz, 1H, H_8), 4.61 (q, J = 7.1 Hz, 2H, H_{12}), 2.93 – 2.79 (m, 2H, H_6), 2.73 (dq, J = 12.6, 7.8, 7.3 Hz, 1H, H_{9a}), 2.63 (dq, J = 12.7, 7.4 Hz, 1H, H_{9b}), 2.35 (dddd, J = 14.3, 9.4, 7.1, 5.0 Hz, 1H, H_{7a}), 2.16 (dtd, J = 14.2, 8.9, 5.4 Hz, 1H, H_{7b}), 1.39 (t, J = 7.1 Hz, 3H, H_{13}), 1.27 (t, J = 7.4 Hz, 3H, H_{10}).

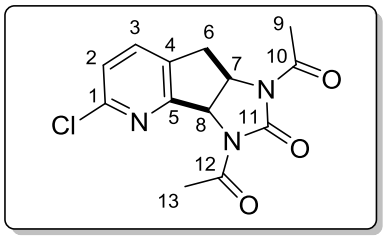
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 214.1 (C_{11}), 149.8 (C_5), 149.5 (C_1), 139.1 (C_3), 135.0 (C_4), 124.0 (C_2), 70.1 (C_{12}), 54.8 (C_8), 37.2 (C_7), 29.7 (C_{11}), 26.1 (C_6), 14.7 (C_{10}), 13.9 (C_{13}).

IR (v, cm^{-1}, $CDCl_3$) 2980, 2931, 1587, 1566, 1459, 1385, 1290, 1266, 1222, 1139, 1109, 1049.

HRMS (EI+) calculated for $C_{13}H_{18}ClNOS_3$: 335.0239; Found: 335.0232.

1,1'-(5-Chloro-2-oxo-8,8a-dihydroimidazo[4',5':4,5]cyclopenta[1,2-*b*]pyridine-1,3(2*H*,3a*H*)-diyl)bis(ethan-1-one) (II-45a)

According to the general procedure C (no TFA added), the reaction was carried out with xanthate **II-44a** (164 mg, 0.39 mmol) in 3.9 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 3/1 to 1/1) afforded product **II-45a** as a white solid (54 mg, 0.18 mmol, 47% yield) and product **II-46a** as a white solid (41 mg, 0.14 mmol, 36% yield).



Chemical Formula: $C_{13}H_{12}ClN_3O_3$
Molecular Weight: 293,71

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.53 (dt, J = 7.9, 1.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 5.89 (d, J = 8.5 Hz, 1H, H_8), 4.92 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H, H_7), 3.45 (ddd, J = 18.2, 6.9, 1.1 Hz, 1H, H_{6a}), 3.25 (dt, J = 18.3, 1.1 Hz, 1H, H_{6b}), 2.60 (s, 3H, H_9 or H_{13}), 2.53 (s, 3H, H_9 or H_{13}).

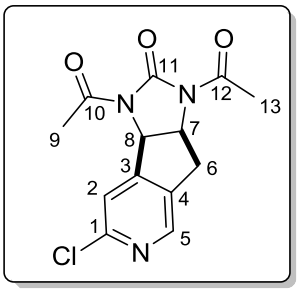
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 171.6, 169.9, 159.5, 152.0, 151.9, 136.1 (CH), 132.7, 125.0 (CH), 57.7 (C_8), 53.9 (C_7), 35.2 (C_6), 25.0 (C_9 or C_{13}), 24.8 (C_9 or C_{13}).

IR (ν, cm^{-1}, $CDCl_3$) 2962, 2928, 2856, 1757, 1704, 1431, 1364, 1304, 1265, 1233, 1187.

HRMS (EI+) calculated for $C_{13}H_{12}ClN_3O_3$: 293.0567; Found: 293.0573.

mp: 172-173 ℃

1,1'-(5-Chloro-2-oxo-8,8a-dihydroimidazo[4',5':3,4]cyclopenta[1,2-*c*]pyridine-1,3(2*H*,3a*H*)-diyl)bis(ethan-1-one) (II-46a)



Chemical Formula: $C_{13}H_{12}ClN_3O_3$
Molecular Weight: 293,71

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (d, J = 1.3 Hz, 1H), 7.65 (s, 1H), 5.76 (d, J = 8.8 Hz, 1H, H_8), 4.97 (ddd, J = 8.8, 7.6, 2.3 Hz, 1H, H_7), 3.56 (ddd, J = 18.5, 7.7, 1.2 Hz, 1H, H_{6a}), 3.23 (dd, J = 18.3, 2.3 Hz, 1H, H_{6b}), 2.59 (s, 3H, H_9 or H_{13}), 2.55 (s, 3H, H_9 or H_{13}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 171.3, 171.2, 151.7, 151.3, 150.7, 146.8 (CH), 135.7, 123.1 (CH), 58.4 (C_8), 54.8 (C_7), 36.3 (C_6), 24.9 (C_9 or C_{13}), 24.7 (C_9 or C_{13}).

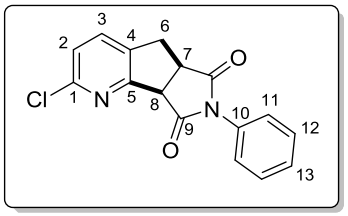
IR (ν, cm^{-1}, $CDCl_3$) 2962, 2928, 2856, 1757, 1704, 1431, 1364, 1304, 1265, 1233, 1187.

HRMS (EI+) calculated for $C_{13}H_{12}ClN_3O_3$: 293.0567; Found: 293.0573.

mp: 224-226 ℃

2-Chloro-7-phenyl-5a,8a-dihydropyrrolo[3',4':4,5]cyclopenta[1,2-*b*]pyridine-6,8(5*H*,7*H*)-dione (II-45b)

According to the general procedure C, the reaction was carried out with xanthate **II-44b** (210 mg, 0.50 mmol) and TFA (68 mg, 46 μL, 0.60 mmol) in 5.0 mL 1,2-dichloroethane and needed 9 h to go to completion. Recrystallization from ethyl acetate gave 66 mg (0.22 mmol) of the **II-45b** as a white solid. The mother liquor was evaporated and flash chromatography on silica gel (petroleum ether/diethyl ether/dichloromethane =3:3:4) gave product **II-45b** (16 mg, 0.05 mmol, 11%) and an analytical sample of product **II-46b** (11% yield by NMR estimation).



Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,7260

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.59 (dt, J = 8.1, 1.1 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.39 – 7.34 (m, 1H), 7.29 (dd, J = 8.1, 0.8 Hz, 1H), 7.27 – 7.26 (m, 1H), 7.24 (t, J = 1.4 Hz, 1H), 4.56 (dt, J = 8.3, 0.9 Hz, 1H, H_8), 3.89 (td, J = 8.3, 5.1 Hz, 1H, H_7), 3.52 – 3.47 (m, 2H, H_6).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 178.1 (C=O), 172.9 (C=O), 157.4 (C), 151.8 (C), 136.0 (CH), 133.8 (C), 131.8 (C), 129.2 (CH), 128.8 (CH), 126.5 (CH), 124.4 (CH), 52.3 (C_8), 42.4 (C_7), 32.2 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3071, 3050, 2934, 2864, 1738, 1719, 1599, 1583, 1571, 1499, 1429, 1376, 1241, 1190, 1166, 1127, 1088.

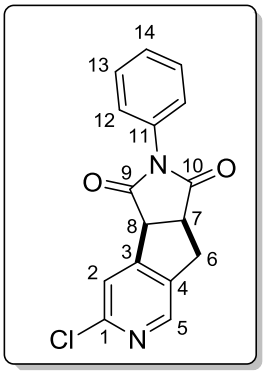
HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0512.

mp: 223-224 ℃

Gram-scale synthesis of II-45b:

According to the general procedure C, the reaction was carried out with xanthate **II-44b** (3.16 g, 7.5 mmol) and TFA (1.03g, 0.69 mL, 9.0 mmol) in 75 mL 1,2-dichloroethane and needed 9 h to go to completion. Trituration with ethyl acetate (10 mL) gave **II-45b** (0.92 g, 3.1 mmol, 41% yield) as a white powder.

5-Chloro-2-phenyl-8,8a-dihydropyrrolo[3',4':3,4]cyclopenta[1,2-*c*]pyridine-1,3(2*H*,3a*H*)-dione (II-46b)



Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,73

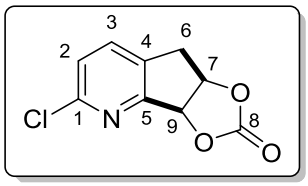
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.36 (d, J = 1.0 Hz, 1H), 7.61 (t, J = 1.0 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.38 (m, 1H), 7.25 – 7.20 (m, 2H), 4.51 (dd, J = 8.4, 1.0 Hz, 1H, H_8), 3.90 (td, J = 8.4, 4.9 Hz, 1H, H_7), 3.57 – 3.51 (m, 2H, H_6).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 177.7 (C=O), 174.1 (C=O), 150.6 (C), 149.8 (C), 146.5 (CH), 136.5 (C), 131.5 (C), 129.4 (CH), 129.1 (CH), 126.4 (CH), 121.1 (CH), 51.5 (C_8), 44.1 (C_7), 32.4 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 3066, 2934, 1783, 1718, 1593, 1499, 1466, 1379, 1359, 1187, 1153.

HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0514.

5-Chloro-3a,8a-dihydro-8*H*-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyridin-2-one (II-45d)



Chemical Formula: $C_9H_6ClNO_3$
Molecular Weight: 211,60

The reaction was carried out with xanthate **II-44d** (167 mg, 0.50 mmol) in 3.9 mL 1,2-dichloroethane and needed 6 h to go to completion. The solvent was removed under reduced pressure. Flash chromatography on silica gel (gradient of dichloromethane/ethyl acetate = 4/1 to 2/1) afforded **II-45d** (17 mg, 0.08 mmol, 16% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3CN) 7.79 – 7.75 (m, 1H, H_3), 7.43 (d, J = 8.2 Hz, 1H, H_2), 5.89 (d, J = 6.9 Hz, 1H, H_9), 5.50 (td, J = 6.7, 1.3 Hz, 1H, H_7), 3.40 (ddd, J = 18.4, 6.4, 1.1 Hz, 1H, H_{6a}), 3.25 (dt, J = 18.5, 1.2 Hz, 1H, H_{6b}).

^{13}C NMR (δ, ppm) (100 MHz, CD_3CN) 157.9 (C_5), 155.4 (C_8), 152.1 (C_1), 138.5 (C_3), 135.4 (C_2), 126.7 (C_4), 82.9 (C_9), 79.5 (C_7), 36.1 (C_6).

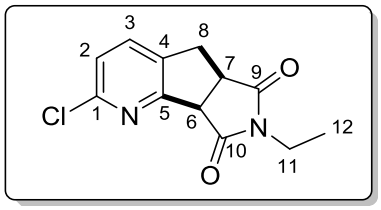
IR (ν, cm^{-1}, nujol) 1779, 1669, 1154, 1056.

HRMS (EI+) calculated for $C_9H_6ClNO_3$: 211.0036; Found: 211.0041.

mp: 186-188 ℃

2-Chloro-7-ethyl-5a,8a-dihydropyrrolo[3',4':4,5]cyclopenta[1,2-*b*]pyridine-6,8(5*H*,7*H*)-dione (II-45e)

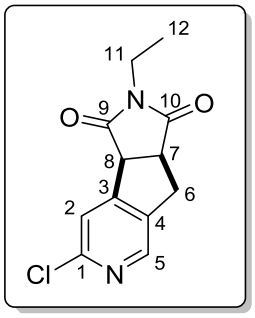
According to the general procedure C, the reaction was carried out with xanthate **II-44e** (186 mg, 0.50 mmol) and TFA (68 mg, 46 μL, 0.60 mmol) in 5.0 mL 1,2-dichloroethane and needed 6 h to go to completion. Recrystallization from ethyl acetate gave 55 mg (0.22 mmol) of product **II-45e** as a white solid. The mother liquor was evaporated and flash chromatography on silica gel (gradient of diethyl ether/dichloromethane = 1:20 to 1:15) gave 18 mg (0.07 mmol) of 1:1 mixture of product **II-45e** (9 mg, 0.03 mmol, 6% yield) and an analytical sample of product **II-46e** (6% yield by NMR estimation).



Chemical Formula: $C_{12}H_{11}ClN_2O_2$
Molecular Weight: 250,68

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.53 (dt, J = 8.1, 1.0 Hz, 1H, H_3), 7.23 (dd, J = 8.1, 0.8 Hz, 1H, H_2), 4.38 (dd, J = 8.2, 0.9 Hz, 1H, H_6), 3.68 (td, J = 8.4, 4.9 Hz, 1H, H_7), 3.53 (qd, J = 7.2, 1.2 Hz, 2H, H_{11}), 3.40 – 3.35 (m, 2H, H_8), 1.13 (t, J = 7.2 Hz, 3H, H_{12}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 178.8 (C_9 or C_{10}), 173.8 (C_9 or C_{10}), 157.5 (C), 151.6 (C), 135.9 (C_3), 133.7 (C), 124.2 (C_2), 52.2 (C_6), 42.2 (C_7), 34.4 (C_{11}), 31.8 (C_8), 13.1 (C_{12}).
IR (ν, cm^{-1}, $CDCl_3$) 2984, 2941, 1780, 1706, 1583, 1571, 1445, 1429, 1393, 1379, 1351, 1226, 1175, 1127, 1090, 1010.
HRMS (EI+) calculated for $C_{12}H_{11}ClN_2O_2$: 250.0509; Found: 250.0510.
mp: 190-191 ℃

Bis(ethan-1-one)5-Chloro-2-ethyl-8,8a-dihydropyrrolo[3',4':3,4]cyclopenta[1,2-c] pyridine-1,3(2*H*,3a*H*)-dione (II-46e)



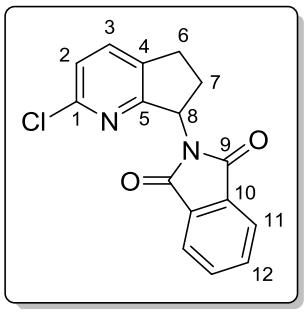
Chemical Formula: $C_{12}H_{11}ClN_2O_2$
Molecular Weight: 250,68

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.29 (d, J = 1.0 Hz, 1H, H_5), 7.53 (s, 1H, H_2), 4.33 (dd, J = 8.2, 0.9 Hz, 1H, H_8), 3.70 (td, J = 8.4, 4.9 Hz, 1H, H_7), 3.53 – 3.48 (m, 2H, H_{11}), 3.43 – 3.40 (m, 2H, H_6), 1.11 (t, J = 7.2 Hz, 3H, H_{12}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 178.4 (C_9 or C_{10}), 174.9 (C_9 or C_{10}), 150.3 (C), 149.9 (C), 146.4 (C_5), 136.5 (C), 121.0 (C_2), 51.5 (C_8), 43.9 (C_7), 34.5 (C_{11}), 31.9 (C_6), 13.0 (C_{12}).

2-(2-Chloro-6,7-dihydro-5*H*-cyclopenta[b]pyridin-7-yl)isoindoline-1,3-dione (II-45f)

According to the general procedure C, the reaction was carried out with xanthate **II-44f** (221 mg, 0.55 mmol) and TFA (75 mg, 50 μL, 0.66 mmol) in 5.5 mL 1,2-dichloroethane and needed 6 h to go to completion. Recrystallization from ethyl acetate gave 50 mg (0.17 mmol, 30% yield) of the **II-45f** as a white solid. The mother liquor was evaporated and flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:5 to 3:7) gave product **II-45f** (44 mg, 0.15 mmol, 27% yield) and a product **II-46f** (33 mg, 0.11 mmol, 20% yield).



Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,73

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.83 – 7.78 (m, 2H), 7.73 – 7.68 (m, 2H), 7.55 (dt, J = 8.1, 1.0 Hz, 1H, H_3), 7.17 (dd, J = 8.0, 0.8 Hz, 1H, H_2), 5.77 (ddd, J = 9.2, 7.5, 0.8 Hz, 1H, H_8), 3.26 – 3.19 (m, 1H, H_{7a}), 3.01 – 2.90 (m, 1H, H_{7b}), 2.63 (dtd, J = 12.9, 9.0, 3.7 Hz, 1H, H_{6a}), 2.44 (ddt, J = 13.3, 9.6, 7.6 Hz, 1H, H_{6b}).

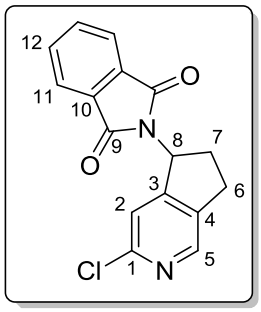
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.9 ($2C_9$), 161.2 (C_5), 150.3 (C_1), 135.9 (C_4), 135.4 (C_3), 134.1 (2CH), 132.2 ($2C_{10}$), 123.4 (2CH), 123.2 (C_2), 54.1 (C_8), 29.0 (C_6), 28.0 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2956, 1772, 1716, 1577, 1469, 1426, 1391, 1367, 1171, 1123, 1109, 1090, 1021.

HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0511.

mp: 169-170 ℃

2-(3-Chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)isoindoline-1,3-dione (II-46f)



Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,73

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.33 (s, 1H, H_5), 7.86 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 7.05 (s, 1H, H_2), 5.81 (t, J = 8.4 Hz, 1H, H_8), 3.32 (ddd, J = 16.3, 8.5, 4.7 Hz, 1H, H_{7a}), 3.00 (dt, J = 16.3, 8.2 Hz, 1H, H_{7b}), 2.65 – 2.50 (m, 2H, H_6).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.6 ($2C_9$), 153.6 (C), 149.4 (C), 146.1 (C_5), 138.5 (C), 134.5 (2CH), 131.9 ($2C_{10}$), 123.7 (2CH), 119.2 (C_2), 53.7 (C_8), 30.3 (C_6), 28.3 (C_7).

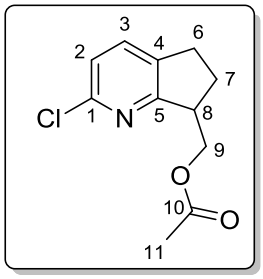
IR (v, cm^{-1}, $CDCl_3$) 2958, 1772, 1717, 1599, 1568, 1468, 1387, 1359, 1105, 1070, 1089.

HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0516.

mp: 143-144 ℃

(2-Chloro-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-yl)methyl acetate (II-45g)

According to the general procedure C, the reaction was carried out with xanthate **II-44g** (345 mg, 0.76 mmol) and TFA (104 mg, 70 μL, 0.91 mmol) in 7.6 mL 1,2-dichloroethane and needed 9 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:5 to 1:4) gave product **II-45g** as a colorless oil (64 mg, 0.28 mmol, 37% yield) and 42 mg of 1:1 mixture of product **II-46g** (12% yield by NMR) and reduced product **II-48g** (12% yield by NMR), which can be partially separated on silica gel (14-40 μm) to give analytical samples.



Chemical Formula: $C_{11}H_{12}ClNO_2$
Molecular Weight: 225,67

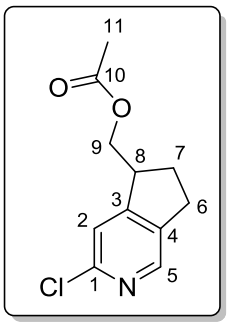
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.46 (dt, J = 7.9, 1.0 Hz, 1H, H_3), 7.10 (dd, J = 8.0, 0.8 Hz, 1H, H_2), 4.52 (dd, J = 11.0, 4.5 Hz, 1H, H_{9a}), 4.25 (dd, J = 11.0, 7.2 Hz, 1H, H_{9b}), 3.46 (dtd, J = 8.2, 6.8, 4.4 Hz, 1H, H_8), 2.99 – 2.79 (m, 2H, H_6), 2.35 (dtd, J = 13.2, 8.7, 5.7 Hz, 1H, H_{7a}), 2.04 – 1.92 (m, 1H, H_{7b}), 2.02 (s, 3H, H_{11}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 171.2 (C_{10}), 164.8 (C_5), 149.8 (C_1), 136.3 (C_4), 135.0 (C_3), 122.3 (C_2), 66.1 (C_9), 44.8 (C_8), 28.6 (C_6), 27.4 (C_7), 21.0 (C_{11}).

IR (v, cm^{-1}, $CDCl_3$) 2954, 1736, 1586, 1572, 1458, 1442, 1424, 1384, 1365, 1252, 1170, 1121, 1066, 1038.

HRMS (EI+) calculated for $C_{11}H_{12}ClNO_2$: 225.0557, M-CH_3CO_2: 165.0340; Found: 165.0354.

(3-Chloro-6,7-dihydro-5H-cyclopenta[*c*]pyridin-5-yl)methyl acetate (II-46g)

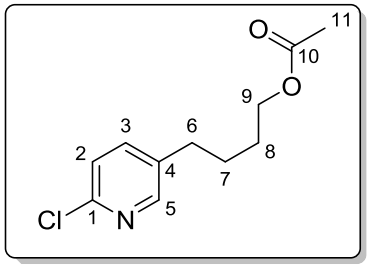


Chemical Formula: $C_{11}H_{12}ClNO_2$
Molecular Weight: 225,67

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.23 (d, J = 1.0 Hz, 1H, H_5), 7.24 (s, 1H, H_2), 4.27 (dd, J = 11.1, 6.3 Hz, 1H, H_{9a}), 4.17 (dd, J = 11.0, 6.9 Hz, 1H, H_{9b}), 3.47 (p, J = 7.1 Hz, 1H, , H_8), 3.02 – 2.83 (m, 2H, H_6), 2.34 (dtd, J = 13.6, 8.3, 5.4 Hz, 1H, H_{7a}), 2.09 (s, 3H, H_{11}), 1.91 (ddt, J = 13.1, 8.7, 7.2 Hz, 1H, H_{7b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 171.0 (C_{10}), 156.8 (C), 149.8 (C), 145.5 (C_5), 139.5 (C), 120.3 (C_2), 65.9 (C_9), 44.2 (C_8), 29.1 (C_7), 28.4 (C_6), 21.0 (C_{11}).

4-(6-Chloropyridin-3-yl)butyl acetate (II-48g)



Chemical Formula: $C_{11}H_{14}ClNO_2$
Molecular Weight: 227,69

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 – 8.18 (m, 1H, H_5), 7.47 (ddd, J = 8.1, 2.5, 0.6 Hz, 1H, H_3), 7.25 (dd, J = 8.4, 0.9 Hz, 1H, H_2), 4.11 – 4.05 (m, 2H, H_9), 2.67 – 2.59 (m, 2H, H_6), 2.04 (s, 3H, H_{11}), 1.72 – 1.64 (m, 4H, H_7 and H_8).

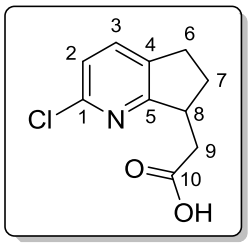
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 171.3 (C_{10}), 149.7 (C_5), 149.3 (C), 138.8 (C_3), 136.2 (C), 124.1 (C_2), 64.1 (C_9), 31.9 (C_6), 28.2 (C_7 or C_8), 27.5 (C_7 or C_8), 21.1 (C_{11}).

IR (ν, cm^{-1}, $CDCl_3$) 2946, 1732, 1588, 1566, 1460, 1386, 1368, 1250, 1138, 1108, 1051, 1025.

HRMS (EI+) calculated for $C_{11}H_{14}ClNO_2$: 227.0713; Found: 227.0721.

2-(2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)acetic acid (II-45h)

According to the general procedure C, the reaction was carried out with xanthate **II-44h** (148 mg, 0.44 mmol) and TFA (60 mg, 40 μL, 0.53 mmol) in 4.4 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:3 with 1% CH_3COOH by volume as additive) gave product **II-45h** as a white solid (46 mg, 0.22 mmol, 49% yield) and product **II-46h** as a white solid (12 mg, 0.06 mmol, 13% yield).



Chemical Formula: $C_{10}H_{10}ClNO_2$
Molecular Weight: 211,65

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.51 (d, J = 8.0 Hz, 1H, H_3), 7.14 (d, J = 7.9 Hz, 1H, H_2), 3.65 – 3.49 (m, 1H, H_8), 3.07 (dd, J = 16.1, 6.2 Hz, 1H, H_{9a}), 2.99 – 2.80 (m, 2H, H_6), 2.58 – 2.50 (m, 2H, H_{6a} and H_{9b}), 1.81 (dq, J = 13.0, 9.1 Hz, 1H, H_{6b}).

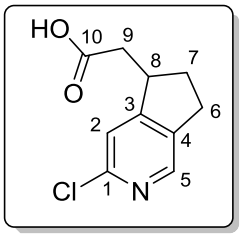
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.5 (C_{10}), 166.5 (C_5), 149.2 (C_1), 136.0 (C_4), 135.5 (C_3), 122.4 (C_2), 41.3 (C_8), 38.9 (C_9), 31.2 (C_7), 28.6 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 2971, 2650, 1729, 1583, 1445, 1434, 1422, 1302, 1280, 1173, 1123, 1106.

HRMS (EI+) calculated for $C_{10}H_{10}ClNO_2$: 211.0400; Found: 211.0397.

mp: 77-78 ℃

2-(3-Chloro-6,7-dihydro-5*H*-cyclopenta[c]pyridin-5-yl)acetic acid (II-46h)



Chemical Formula: $C_{10}H_{10}ClNO_2$
Molecular Weight: 211,65

^{1}H NMR (δ, ppm) (400 MHz, DMSO-d_6) 8.23 (s, 1H, H_5), 7.39 (s, 1H, H_2), 3.46 (qd, J = 8.1, 5.3 Hz, 1H, H_8), 2.97 – 2.74 (m, 3H, H_6 and H_{9a}), 2.43 (dd, J = 16.3, 8.7 Hz, 1H, H_{9b}), 2.34 (dtd, J = 12.4, 8.0, 4.3 Hz, 1H, H_{7a}), 1.72 (dq, J = 12.6, 8.4 Hz, 1H, H_{7b}).

^{13}C NMR (δ, ppm) (100 MHz, DMSO-d_6) 173.1 (C_{10}), 159.7 (C_1), 147.8 (C_3), 145.1 (C_5), 139.6 (C_4), 119.6 (C_2), 40.7 (C_8), 37.8 (C_9), 32.1 (C_7), 27.8 (C_6).

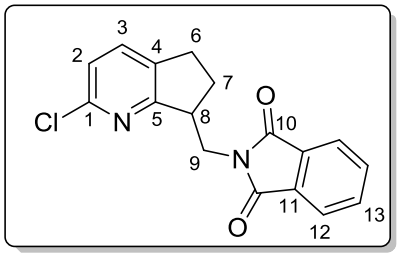
IR (ν, cm^{-1}, nujol) 1704, 1601, 1557, 1413, 1362, 1298.

HRMS (EI+) calculated for $C_{10}H_{10}ClNO_2$: 211.0400; Found: 211.0398.

mp: decomposed at 215 ℃.

2-((2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)methyl)isoindoline-1,3-dione (II-45i)

According to the general procedure C, the reaction was carried out with xanthate **II-44i** (382 mg, 0.88 mmol) and TFA (120 mg, 81 μL, 1.05 mmol) in 8.8 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:2 to 1:1) gave the following products:



Chemical Formula: $C_{17}H_{13}ClN_2O_2$
Molecular Weight: 312,75

II-45i (116 mg, 0.37 mmol, 42% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 (dd, J = 5.4, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H, H_3), 7.09 (dd, J = 7.9, 0.8 Hz, 1H, H_2), 4.14 (dd, J = 13.5, 7.0 Hz, 1H, H_{9a}), 3.84 (dd, J = 13.5, 8.9 Hz, 1H, H_{9b}), 3.70 (ddd, J = 15.3, 8.5, 6.6 Hz, 1H, H_8), 2.98 (ddd, J = 16.7, 8.9, 5.9 Hz, 1H, H_{6a}), 2.88 – 2.77 (m, 1H, H_{6b}), 2.28 (dtd, J = 13.0, 8.5, 5.7 Hz, 1H, H_{7a}), 1.95 (ddt, J = 12.9, 8.7, 6.3 Hz, 1H, H_{7b}).

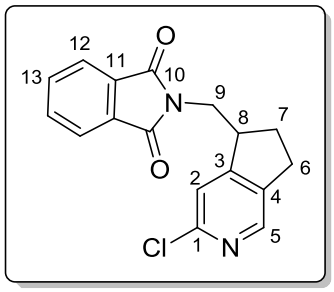
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.7 ($2C_{10}$), 165.6 (C_5), 149.7 (C_2), 135.9 (C_4), 135.0 (C_3), 134.0 (2CH), 132.3 ($2C_{11}$), 123.4 (2CH), 122.3 (C_2), 43.8 (C_8), 41.0 (C_9), 28.32 (C_6 or C_7), 28.27 (C_6 or C_7).

IR (v, cm^{-1}, $CDCl_3$) 2947, 1772, 1715, 1571, 1437, 1424, 1393, 1363, 1335, 1170, 1121, 1101, 1089, 1033.

HRMS (EI+) calculated for $C_{17}H_{13}ClN_2O_2$: 312.0666; Found: 312.0661.

mp: 140-141 ℃

2-((3-Chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-46i)



Chemical Formula: $C_{17}H_{13}ClN_2O_2$
Molecular Weight: 312,75

II-46i (83 mg, 0.27 mmol, 30% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.24 (s, 1H, H_5), 7.88 (dd, J = 5.4, 3.1 Hz, 2H), 7.79 – 7.72 (m, 2H), 7.25 (s, 1H, H_2), 3.93 (dd, J = 13.6, 5.5 Hz, 1H, H_{9a}), 3.81 (dd, J = 13.6, 9.3 Hz, 1H, H_{9b}), 3.66 (ddd, J = 14.5, 8.6, 5.9 Hz, 1H, H_8), 3.07 – 2.96 (m, 1H, H_{6a}), 2.90 – 2.78 (m, 1H, H_{6b}), 2.24 (dtd, J = 13.1, 8.2, 6.0 Hz, 1H, H_{7a}), 1.99 (ddt, J = 12.8, 8.5, 6.3 Hz, 1H, H_{7b}).

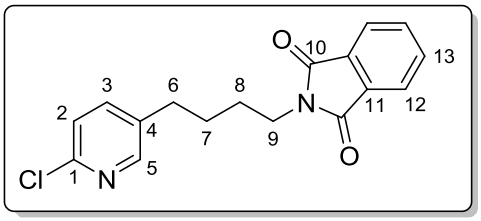
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{10}$), 156.8 (C_3), 149.3 (C_1), 145.6 (C_5), 139.4 (C_4), 134.4 (2CH), 132.0 ($2C_{11}$), 123.6 (2CH), 120.2 (C_2), 44.3 (C_8), 40.9 (C_9), 30.3 (C_7), 28.1 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 2940, 1773, 1716, 1597, 1561, 1469, 1434, 1396, 1361, 1338, 1293, 1190, 1173, 1102, 1072, 1031.

HRMS (EI+) calculated for $C_{17}H_{13}ClN_2O_2$: 312.0666; Found: 312.0665.

mp: 134-135 ℃

2-(4-(6-Chloropyridin-3-yl)butyl)isoindoline-1,3-dione (II-48i)



Chemical Formula: $C_{17}H_{15}ClN_2O_2$
Molecular Weight: 314,77

Reduced product **II-48i** (23 mg, 0.07 mmol, 8% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 – 8.18 (m, 1H, H_5), 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.46 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.23 (dd, J = 8.2, 0.7 Hz, 1H, H_2), 3.72 (t, J = 6.9 Hz, 2H, H_9), 2.65 (t, J = 7.5 Hz, 2H, H_6), 1.78 – 1.69 (m, 2H), 1.69 – 1.60 (m, 2H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.6 ($2C_{10}$), 149.7 (C_5), 149.2 (C_1), 138.9 (C_3), 136.2 (C_4), 134.1 (2CH), 132.2 ($2C_{11}$), 124.1 (C_2), 123.4 (2CH), 37.6 (C_9), 31.8 (C_6), 28.4 (C_7 or C_8), 28.2 (C_7 or C_8).

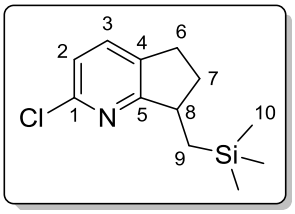
IR (v, cm^{-1}, $CDCl_3$) 2945, 2964, 1771, 1712, 1462, 1439, 1397, 1375, 1108, 1037, 1025.

HRMS (EI+) calculated for $C_{17}H_{15}ClN_2O_2$: 314.0822; Found: 314.0805.

mp: 140-141 ℃

2-Chloro-7-((trimethylsilyl)methyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (II-45j)

According to the general procedure C, the reaction was carried out with xanthate **II-44j** (225 mg, 0.62 mmol) and TFA (85 mg, 57 μL, 0.75 mmol) in 6.2 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:20 to 1:10) gave the following products:



Chemical Formula: $C_{12}H_{18}ClNSi$
Molecular Weight: 239,82

II-45j (81 mg, 0.34 mmol, 54% yield, colorless oil)

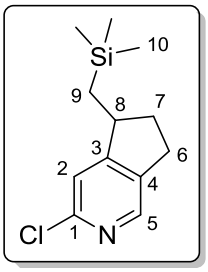
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.41 (dd, J = 7.9, 1.1 Hz, 1H, C_3), 7.04 (dd, J = 7.9, 0.9 Hz, 1H, C_2), 3.15 (dtd, J = 11.6, 8.3, 3.1 Hz, 1H, H_8), 2.92 – 2.72 (m, 2H, H_6), 2.39 (dtd, J = 12.6, 7.9, 3.7 Hz, 1H, H_{7a}), 1.67 (dt, J = 12.7, 8.8 Hz, 1H, H_{7b}), 1.53 (dd, J = 14.7, 3.1 Hz, 1H, H_{9a}), 0.61 (dd, J = 14.7, 11.7 Hz, 1H, H_{9b}), 0.07 (s, 9H, H_{10}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 170.8 (C_5), 149.6 (C_1), 134.9 (C_4), 134.6 (C_3), 121.2 (C_2), 42.0 (C_8), 33.1 (C_7), 28.7 (C_6), 21.5 (C_9), -0.6 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2956, 2855, 1586, 1568, 1419, 1261, 1249, 1166, 1119.

HRMS (EI+) calculated for $C_{12}H_{18}ClNSi$: 239.0897; Found: 239.0896.

3-Chloro-5-((trimethylsilyl)methyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (II-46j)



Chemical Formula: $C_{12}H_{18}ClNSi$
Molecular Weight: 239,82

II-46j (18 mg, 0.08 mmol, 12% yield, colorless oil)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.17 (s, 1H, H_5), 7.13 (s, 1H, H_2), 3.18 – 3.07 (m, 1H, H_8), 2.90 (ddd, J = 16.0, 8.7, 3.0 Hz, 1H, H_{6a}), 2.80 (dt, J = 16.3, 8.6 Hz, 1H, H_{6b}), 2.38 (dtd, J = 12.5, 7.6, 3.0 Hz, 1H, H_{7a}), 1.63 (dq, J = 12.5, 9.3 Hz, 1H, H_{7b}), 1.19 (dd, J = 14.5, 3.3 Hz, 1H, H_{9a}), 0.66 (dd, J = 14.6, 11.6 Hz, 1H, H_{9b}), 0.09 (s, 9H, H_{10}).

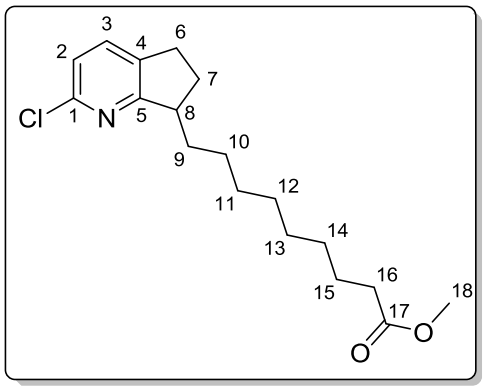
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 163.4 (C_3), 149.2 (C_1), 144.9 (C_5), 138.5 (C_4), 119.3 (C_2), 41.4 (C_8), 35.3 (C_7), 28.8 (C_6), 21.9 (C_9), -0.6 (C_{10}).

IR (v, cm^{-1}, $CDCl_3$) 2956, 2899, 2870, 1595, 1560, 1464, 1439, 1355, 1298, 1263, 1250, 1140, 1075.

HRMS (EI+) calculated for $C_{12}H_{18}ClNSi$: 239.0897; Found: 239.0902.

Methyl 9-(2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)nonanoate (II-45k)

According to the general procedure C, the reaction was carried out with xanthate **II-44k** (368 mg, 0.82 mmol) and TFA (113 mg, 76 μL, 0.99 mmol) in 8.2 mL 1,2-dichloroethane and needed 9 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:10 to 1:3) gave product **II-45k** (123 mg, 0.38 mmol, 46% yield) as a white solid and product **II-46k** (60 mg, 0.19 mmol, 22% yield) as a colorless oil.



Chemical Formula: $C_{18}H_{26}ClNO_2$
Molecular Weight: 323,86

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.41 (dt, J = 8.0, 1.1 Hz, 1H, H_3), 7.04 (dd, J = 7.9, 0.8 Hz, 1H, H_2), 3.65 (s, 3H, H_{18}), 3.07 (q, J = 8.1 Hz, 1H, H_8), 2.92 – 2.73 (m, 2H), 2.38 – 2.25 (m, 3H), 2.01 (dtd, J = 11.2, 7.7, 7.1, 4.5 Hz, 1H), 1.75 (ddt, J = 12.8, 8.9, 7.3 Hz, 1H), 1.60 (dq, J = 11.7, 7.2 Hz, 2H), 1.43 – 1.24 (m, 11H).

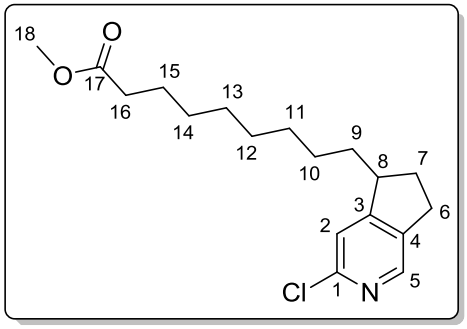
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 174.5 (C_{17}), 169.2 (C_5), 149.5 (C_1), 135.6 (C_4), 134.7 (C_3), 121.4 (C_2), 51.6 (C_{18}), 45.6 (C_8), 34.2 (CH_2), 34.0 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.34 (CH_2), 29.25 (CH_2), 28.6 (CH_2), 27.6 (CH_2), 25.1 (CH_2).

IR (ν, cm^{-1}, $CDCl_3$) 2931, 2857, 1731, 1587, 1569, 1458, 1439, 1420, 1264, 1199, 1168, 1120.

HRMS (EI+) calculated for $C_{18}H_{26}ClNO_2$: 323.1652; Found: 323.1657.

mp: 59-60 ℃

Methyl 9-(3-chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)nonanoate (II-46k)



Chemical Formula: $C_{18}H_{26}ClNO_2$
Molecular Weight: 323,86

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.18 (d, J = 1.0 Hz, 1H, H_5), 7.12 (t, J = 0.9 Hz, 1H, H_2), 3.66 (s, 3H, H_{18}), 3.12 – 3.02 (m, 1H, H_8), 2.90 (ddd, J = 16.0, 8.6, 4.5 Hz, 1H), 2.80 (dtd, J = 16.2, 8.1, 1.1 Hz, 1H), 2.37 – 2.27 (m, 3H), 1.83 – 1.67 (m, 2H), 1.67 – 1.52 (m, 3H), 1.45 – 1.28 (m, 10H).

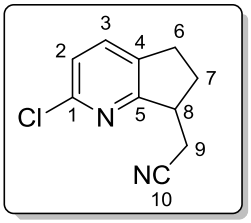
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 174.4 (C_{17}), 161.1 (C_3), 149.0 (C_1), 145.1 (C_5), 139.3 (C_4), 119.7 (C_2), 51.6 (C_{18}), 45.0 (C_8), 34.2 (CH_2), 34.1 (CH_2), 32.4 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 27.5 (CH_2), 25.1 (CH_2).

IR (v, cm^{-1}, $CDCl_3$) 2930, 2857, 1731, 1596, 1559, 1464, 1438, 1356, 1265, 1199, 1175, 1069.

HRMS (EI+) calculated for $C_{18}H_{26}ClNO_2$: 323.1652; Found: 323.1639.

2-(2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)acetonitrile (II-45l)

According to the general procedure C, the reaction was carried out with xanthate **II-44l** (237 mg, 0.75 mmol) and TFA (103 mg, 69 μL, 0.90 mmol) in 7.5 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:2 to 1:1) gave the product **II-45l** as a colorless oil (35 mg, 0.18 mmol, 24% yield).



Chemical Formula: $C_{10}H_9ClN_2$
Molecular Weight: 192,65

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.51 (dt, J = 8.0, 1.0 Hz, 1H, H_3), 7.15 (dd, J = 8.0, 0.9 Hz, 1H, H_2), 3.53 – 3.42 (m, 1H, H_8), 3.06 – 2.99 (m, 1H), 2.98 (d, J = 4.2 Hz, 1H), 2.90 (dtt, J = 16.5, 8.4, 1.0 Hz, 1H), 2.71 (dd, J = 16.9, 8.0 Hz, 1H), 2.57 (dtd, J = 13.2, 8.4, 3.8 Hz, 1H), 2.02 (ddt, J = 13.2, 9.1, 8.2 Hz, 1H).

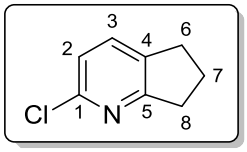
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 164.1 (C_5), 150.2 (C_1), 135.8 (C_4), 135.4 (C_3), 122.9 (C_2), 118.4 (C_{10}), 41.7 (C_8), 29.7 (CH_2), 28.4 (CH_2), 21.5 (CH_2).

IR (ν, cm^{-1}, $CDCl_3$) 2956, 2931, 2856, 1585, 1573, 1442, 1424, 1171, 1122.

HRMS (EI+) calculated for $C_{10}H_9ClN_2$: 192.0454; Found: 192.0453.

2-Chloro-6,7-dihydro-5H-cyclopenta[*b*]pyridine (II-45o)

According to the general procedure C, the reaction was carried out with xanthate **II-44o** (278 mg, 0.80 mmol) and TFA (109 mg, 73 μL, 0.96 mmol) in 8.0 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:20 to 1:10) gave the following products:



Chemical Formula: C_8H_8ClN
Molecular Weight: 153,61

II-45o (31 mg, 0.20 mmol, 25% yield, white solid).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.44 (m, 1H, H_3), 7.06 (dd, J = 7.9, 0.9 Hz, 1H, H_2), 2.99 (t, J = 7.7 Hz, 2H, H_6), 2.95 – 2.86 (m, 2H, H_8), 2.14 (p, J = 7.6 Hz, 2H, H_7).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 166.6 (C_5), 149.3 (C_1), 135.9 (C_4), 134.6 (C_3), 121.2 (C_2), 34.2 (C_6), 30.2 (C_8), 23.3 (C_7).

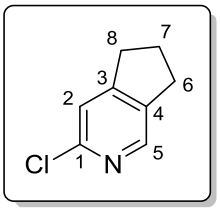
IR (ν, cm^{-1}, $CDCl_3$) 2962, 1588, 1570, 1436, 1419, 1169, 1120, 1081.

HRMS (EI+) calculated for C_8H_8ClN: 153.0345; Found: 153.0341.

mp: 62-64 ℃(lit.[127]: 70-71 ℃)

[127] Thompson, W. *J. Am. Chem. Soc.* **1931**, *53*, 3160.

3-Chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (II-46o)



Chemical Formula: C_8H_8ClN
Molecular Weight: 153,61

II-46o (22 mg, 0.14 mmol, 20% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.23 – 8.16 (m, 1H), 7.18 (d, J = 1.1 Hz, 1H), 2.95 – 2.85 (m, 4H), 2.13 (p, J = 7.6 Hz, 2H).

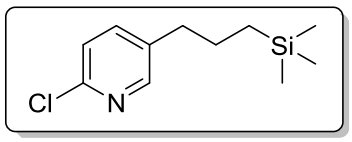
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 157.6, 148.9, 145.1, 139.5, 120.4, 32.7, 29.7, 25.5.

IR (ν, cm^{-1}, $CDCl_3$) 2959, 1598, 1561, 1464, 1434, 1358, 1300, 1239, 1185, 1068.

HRMS (EI+) calculated for C_8H_8ClN: 153.0345; Found: 153.0346.

mp: 69-70 ℃

2-Chloro-5-(3-(trimethylsilyl)propyl)pyridine (II-48o)



Chemical Formula: $C_{11}H_{18}ClNSi$
Molecular Weight: 227,81

Reduced product **II-48o** (29 mg, 0.13 mmol, 16% yield, colorless oil)

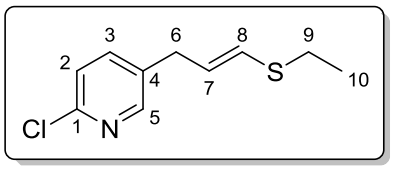
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 – 8.17 (m, 1H), 7.48 – 7.42 (m, 1H), 7.23 (dd, J = 8.1, 0.7 Hz, 1H), 2.60 (t, J = 7.5 Hz, 2H), 1.65 – 1.53 (m, 2H), 0.57 – 0.44 (m, 2H), -0.03 (s, 9H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 149.8, 149.0, 139.0, 136.8, 123.9, 36.1, 25.9, 16.4, -1.6.

IR (ν, cm^{-1}, $CDCl_3$) 2955, 2931, 2860, 1587, 1566, 1461, 1383, 1249, 1138, 1113, 1026.

HRMS (EI+) calculated for $C_{11}H_{18}ClNSi$: 227.0897; Found: 227.0908.

(*E*)-2-Chloro-5-(3-(ethylthio)allyl)pyridine (II-49)



Chemical Formula: $C_{10}H_{12}ClNS$
Molecular Weight: 213,72

According to the general procedure, the reaction was carried out with xanthate **II-44p** (235 mg, 0.70 mmol) and TFA (96 mg, 64 μL, 0.84 mmol) in 7.0 mL 1,2-dichloroethane and was stopped after 7 h. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:20 to 1:15) gave product **II-49** as a yellow oil (24 mg, 0.11 mmol, 16% yield).

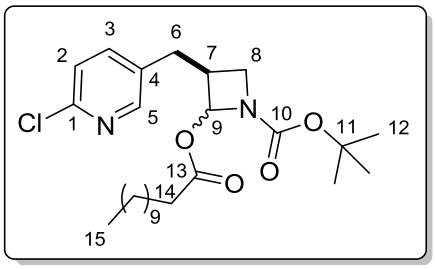
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (dd, J = 2.5, 0.7 Hz, 1H, H_5), 7.48 – 7.44 (m, 1H, H_3), 7.27 – 7.23 (m, 1H, H_2), 6.04 (dt, J = 15.0, 1.4 Hz, 1H, H_8), 5.63 (dt, J = 15.0, 6.8 Hz, 1H, H_7), 3.39 (dt, J = 6.9, 0.9 Hz, 2H, H_6), 2.68 (q, J = 7.4 Hz, 2H, H_9), 1.28 (t, J = 7.4 Hz, 3H, H_{10}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 149.7 (C_5), 149.5 (C_1), 139.1 (C_3), 134.5 (C_4), 126.5 (C_8), 125.6 (C_7), 124.1 (C_2), 35.8 (C_6), 26.6 (C_9), 14.6 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2976, 2930, 2874, 1586, 1566, 1460, 1383, 1266, 1210, 1137, 1109, 1050, 1026.

HRMS (EI+) calculated for $C_{10}H_{12}ClNS$: 213.0379; Found: 213.0378.

tert-Butyl 3-((6-chloropyridin-3-yl)methyl)-2-(dodecanoyloxy)azetidine-1-carboxylate (II-47)



Chemical Formula: $C_{26}H_{41}ClN_2O_4$
Molecular Weight: 481.07

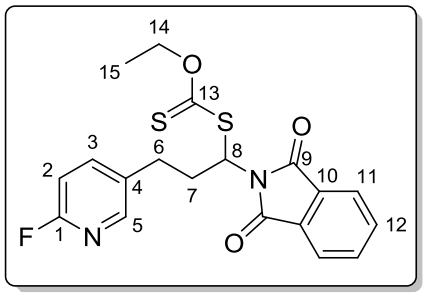
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (2H), 7.46 (dd, J = 8.2, 2.5 Hz, 1H, 1st dia), 7.41 (dd, J = 8.2, 2.5 Hz, 1H, 2nd dia), 7.26 – 7.25 (m, 1H, 1st dia), 7.24 (d, J = 2.6 Hz, 1H, 2nd dia), 6.46 (d, J = 6.4 Hz, 1H, 2nd dia), 6.06 (d, J = 3.3 Hz, 1H, 1st dia), 3.87 (t, J = 7.9 Hz, 1H, 1st dia), 3.78 (t, J = 7.9 Hz, 1H, 2nd dia), 3.52 (dd, J = 8.1, 5.2 Hz, 1H, 2nd dia), 3.39 (dd, J = 8.0, 5.4 Hz, 1H, 1st dia), 3.13 (dd, J = 14.4, 6.0 Hz, 1H, 1st dia), 3.08 – 2.98 (m, 1H, 2nd dia), 2.93 – 2.78 (m, 2H, 1st dia and 2nd dia), 2.66 (tdd, J = 7.8, 5.6, 3.5 Hz, 1H, 1st dia), 2.42 – 2.25 (m, 4H, 1st dia and 2nd dia), 1.61 (t, J = 7.2 Hz, 4H, 1st dia and 2nd dia), 1.43 (s, 9H, 1st dia), 1.42 (s, 9 H, 2nd dia), 1.33 – 1.20 (m, 32H, 1st dia and 2nd dia), 0.868 (t, J = 6.9, 3H, , 1st dia), 0.866 (t, J = 6.9, 3H, , 2nd dia).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 172.7, 172.5, 155.0, 154.9, 150.1, 149.9, 149.7, 149.6, 139.0, 138.78, 133.1, 132.9, 124.3, 87.2, 83.3, 81.03, 80.93, 50.1, 49.1, 39.4, 35.4, 34.4, 33.5, 32.0, 30.7, 29.7, 29.6, 29.5, 29.4, 29.25, 29.19, 28.4, 24.9, 24.9, 22.8, 14.3.

IR (ν, cm^{-1}, $CDCl_3$) 2957, 2929, 2856, 1707, 1588, 1566, 1462, 1393, 1370, 1346, 1258, 1144, 1111.

HRMS (EI+) calculated for $C_{26}H_{41}ClN_2O_4$: 480.2755; Found: not found.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(6-fluoropyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-53a)



Chemical Formula: $C_{19}H_{17}FN_2O_3S_2$
Molecular Weight: 404,47

According to the general procedure A, the reaction was carried out with xanthate **II-43b** (1.39 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and needed 17 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of toluene/ethyl acetate = 10:1) afforded product **II-53a** as a light yellow oil (218 mg, 0.54 mmol, 36% yield).

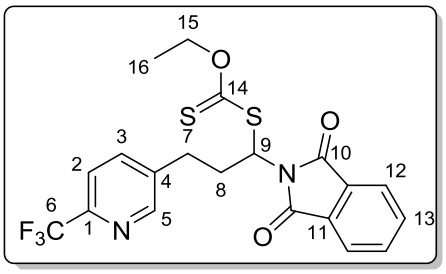
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.99 (dt, J = 2.7, 0.9 Hz, 1H, H_5), 7.88 – 7.81 (m, 2H), 7.79 – 7.71 (m, 2H), 7.64 – 7.57 (m, 1H, H_3), 6.81 (ddd, J = 8.4, 3.0, 0.7 Hz, 1H, H_2), 6.29 (dd, J = 9.0, 6.7 Hz, 1H, H_8), 4.62 (q, J = 7.1 Hz, 2H, H_{14}), 2.84 – 2.56 (m, 3H, H_6 and H_{7a}), 2.51 – 2.40 (m, 1H, H_{7b}), 1.38 (t, J = 7.1 Hz, 3H, H_{15}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{13}), 166.9 ($2C_9$), 162.6 (d, J = 236.4 Hz, C_1), 147.4 (d, J = 14.4 Hz, C_5), 141.1 (d, J = 7.7 Hz, C_3), 134.6 (2CH), 132.9 (d, J = 4.5 Hz, C_4), 131.6 ($2C_{10}$), 123.8 (2CH), 109.4 (d, J = 37.2 Hz, C_2), 70.7 (C_{13}), 57.3 (C_8), 34.5 (C_7), 29.3 (d, J = 1.1 Hz, C_6), 13.8 (C_{13}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2939, 2867, 1780, 1720, 1601, 1486, 1395, 1380, 1362, 1333, 1241, 1111, 1048.

HRMS (EI+) calculated for $C_{19}H_{17}FN_2O_3S_2$: 404.0665, M-Xa: $C_{16}H_{12}FN_2O_2$: 283.0883; Found: 283.0878.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(6-(trifluoromethyl)pyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-53b)



Chemical Formula: $C_{20}H_{17}F_3N_2O_3S_2$
Molecular Weight: 454,48

According to the general procedure A, the reaction was carried out with xanthate **II-43c** (1.69 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and needed 9 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 6:1 to 4:1) afforded product **II-53b** as a colorless oil (418 mg, 0.92 mmol, 61% yield).

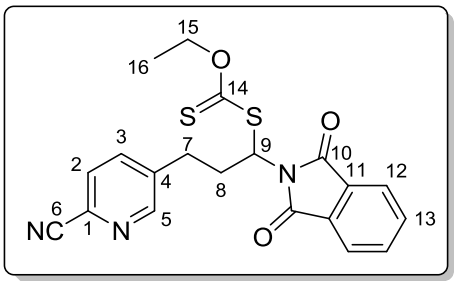
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.52 (d, J = 2.1 Hz, 1H, H_5), 7.86 – 7.79 (m, 2H), 7.75 (dt, J = 5.2, 3.5 Hz, 2H), 7.70 – 7.65 (m, 1H, H_3), 7.53 (dd, J = 8.1, 0.8 Hz, 1H, H_2), 6.30 (dd, J = 9.2, 6.4 Hz, 1H, H_9), 4.62 (q, J = 7.1 Hz, 2H, H_{15}), 2.90 (ddd, J = 14.4, 8.6, 6.1 Hz, 1H, H_{7a}), 2.84 – 2.75 (m, 1H, H_{7b}), 2.70 (dtd, J = 14.0, 8.9, 6.8 Hz, 1H, H_{8a}), 2.50 (ddt, J = 13.0, 8.7, 6.1 Hz, 1H, H_{8b}), 1.37 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{14}), 166.9 ($2C_{10}$), 150.2 (C_5), 146.5 (q, J = 34.5 Hz, C_1), 138.7 (C_4), 137.1 (C_3), 134.7 (2CH), 131.5 ($2C_{11}$), 123.8 (2CH), 121.6 (q, J = 272.3 Hz, CF_3), 120.2 (q, J = 2.8 Hz, C_2), 70.8 (C_{15}), 57.3 (C_9), 34.1 (C_8), 30.2 (C_7), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2985, 2939, 1780, 1720, 1470, 1380, 1362, 1337, 1230, 1183, 1147, 1111, 1089, 1049.

HRMS (EI+) calculated for $C_{20}H_{17}F_3N_2O_3S_2$: 454.0633, M-Xa: $C_{17}H_{12}F_3N_2O_2$: 333.0851; Found: 333.0845.

_S_-(3-(6-cyanopyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl) _O_-ethylcarbonodithioate (II-53c)



Chemical Formula: $C_{20}H_{17}N_3O_3S_2$
Molecular Weight: 411,49

According to the general procedure A, the reaction was carried out with xanthate **II-43d** (949 mg, 4.00 mmol) and *N*-vinylphthalimide (173 mg, 1.00 mmol) in ethyl acetate (4.0 mL), and needed 11 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 2:1) afforded product **II-53c** as a white powder (349 mg, 0.85 mmol, 85% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.52 (d, J = 1.5 Hz, 1H, H_5), 7.87 – 7.81 (m, 2H), 7.77 (dt, J = 5.2, 3.5 Hz, 2H), 7.65 (dd, J = 8.0, 2.2 Hz, 1H, H_3), 7.56 (dd, J = 8.0, 0.9 Hz, 1H, H_2), 6.29 (dd, J = 9.3, 6.5 Hz, 1H, H_9), 4.62 (q, J = 7.1 Hz, 2H, H_{15}), 2.89 (ddd, J = 14.8, 8.8, 6.2 Hz, 1H, H_{7a}), 2.79 (ddd, J = 14.5, 8.6, 6.5 Hz, 1H, H_{7b}), 2.69 (dtd, J = 14.1, 8.9, 6.6 Hz, 1H, H_{8a}), 2.50 (ddt, J = 14.0, 8.7, 6.3 Hz, 1H, H_{8b}), 1.38 (t, J = 7.1 Hz, 3H, H_{16}).

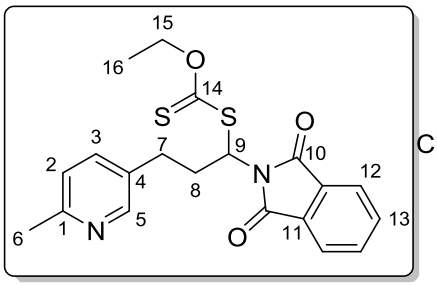
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{14}), 166.9 ($2C_{10}$), 151.5 (C_5), 139.7 (C_1), 136.7 (C_3), 134.8 (2CH), 132.0 (C_4), 131.4 ($2C_{11}$), 128.2 (C_2), 123.9 (2CH), 117.2 (C_6), 70.9 (C_{15}), 57.3 (C_9), 33.9 (C_8), 30.4 (C_7), 13.9 (C_{16}).

IR (v, cm^{-1}, $CDCl_3$) 2985, 2938, 1780, 1720, 1470, 1380, 1361, 1333, 1230, 1111, 1049.

HRMS (EI+) calculated for $C_{20}H_{17}N_3O_3S_2$: 411.0711, M-Xa: $C_{17}H_{12}N_3O_2$: 290.0930; Found: 290.0924.

mp: 93-94 ℃

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(6-methylpyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-53d)



Chemical Formula: $C_{20}H_{20}N_2O_3S_2$
Molecular Weight: 400,51

According to the general procedure A, the reaction was carried out with xanthate **II-43e** (1.36 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and no evolvement for the reaction after 19 h. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:2 to 1:3) afforded product **II-53d** as a light brown oil (203 mg, 0.51 mmol, 34% yield).

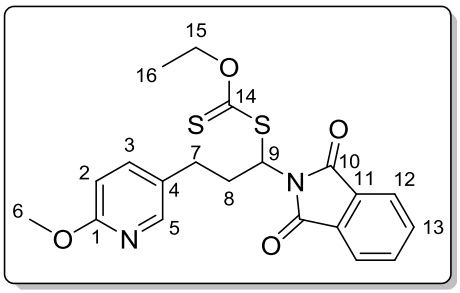
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.27 (d, J = 2.4 Hz, 1H, H_5), 7.87 – 7.80 (m, 2H), 7.76 – 7.70 (m, 2H), 7.37 (dd, J = 8.0, 2.4 Hz, 1H, H_3), 7.01 (d, J = 7.9 Hz, 1H, H_2), 6.28 (dd, J = 8.8, 6.6 Hz, 1H, H_9), 4.61 (q, J = 7.1 Hz, 2H, H_{15}), 2.76 (ddd, J = 16.1, 9.6, 5.9 Hz, 1H, H_{7a}), 2.70 – 2.57 (m, 2H, H_{7b} and H_{8a}), 2.49 – 2.38 (m, 1H, H_{8b}), 2.43 (s, 3H, H_6), 1.38 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.9 (C_{14}), 166.9 ($2C_{10}$), 156.5 (C_1), 149.1 (C_5), 136.2 (C_3), 134.5 (2CH), 132.1 (C_4), 131.6 ($2C_{11}$), 123.8 (2CH), 123.0 (C_2), 70.7 (C_{15}), 57.4 (C_9), 34.3 (C_8), 29.9 (C_7), 24.1 (C_6), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2928, 1780, 1720, 1603, 1490, 1470, 1380, 1361, 1333, 1232, 1111, 1048.

HRMS (EI+) calculated for $C_{20}H_{20}N_2O_3S_2$: 400.0915, M-Xa: $C_{17}H_{15}N_2O_2$: 279.1134; Found: 279.1133.

_S_-(1-(1,3-dioxoisoindolin-2-yl)-3-(6-methoxypyridin-3-yl)propyl) O-ethyl carbonodithioate (II-53e)



Chemical Formula: $C_{20}H_{20}N_2O_4S_2$
Molecular Weight: 416,51

According to the general procedure A, the reaction was carried out with xanthate **II-43f** (1.67 g, 6.87 mmol) and *N*-vinylphthalimide (297 mg, 1.72 mmol) in ethyl acetate (6.9 mL), and needed 15 h for the reaction to go to completion. Flash chromatography on silica gel (ethyl acetate/toluene = 1:10) afforded product **II-53e** as a colorless oil (217 mg, 0.52 mmol, 30% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.91 (dd, J = 2.5, 0.7 Hz, 1H, H_5), 7.86 – 7.80 (m, 2H), 7.77 – 7.70 (m, 2H), 7.38 (dd, J = 8.5, 2.6 Hz, 1H, H_3), 6.61 (dd, J = 8.5, 0.7 Hz, 1H, H_2), 6.31 – 6.23 (m, 1H, H_9), 4.61 (q, J = 7.1 Hz, 2H, H_{15}), 3.83 (s, 3H, H_6), 2.76 – 2.66 (m, 1H, H_{7a}), 2.66 – 2.54 (m, 2H, H_{7b} and H_{8a}), 2.47 – 2.34 (m, 1H, H_{8b}), 1.38 (t, J = 7.1 Hz, 3H, H_{16}).

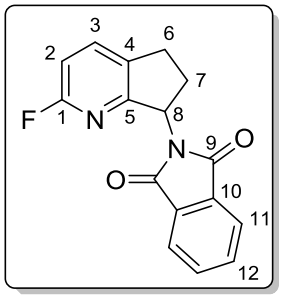
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.9 (C_{14}), 166.9 ($2C_{10}$), 163.0 (C_1), 146.2 (C_5), 138.8 (C_3), 134.5 (2CH), 131.6 ($2C_{11}$), 127.8 (C_4), 123.7 (2CH), 110.7 (C_2), 70.6 (C_{15}), 57.3 (C_9), 53.4 (C_6), 34.4 (C_8), 29.4 (C_7), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2984, 2947, 1780, 1720, 1610, 1493, 1391, 1380, 1361, 1333, 1291, 1229, 1111, 1048, 1029.

HRMS (EI+) calculated for $C_{20}H_{20}N_2O_4S_2$: 416.0864, M-Xa: $C_{17}H_{15}N_2O_3$: 295.1083; Found: 295.1092.

2-(2-Fluoro-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-yl)isoindoline-1,3-dione (II-54a)

According to the general procedure C, the reaction was carried out with xanthate **II-53a** (190 mg, 0.47 mmol) and TFA (64 mg, 43 μL, 0.56 mmol) in 4.7 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:3 to 2:3) gave the following products:



Chemical Formula: $C_{16}H_{11}FN_2O_2$
Molecular Weight: 282,27

Product **II-54a** (58 mg, 0.21 mmol, 44% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.81 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 – 7.64 (m, 3H), 6.78 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H, H_2), 5.76 (t, J = 8.5 Hz, 1H, H_8), 3.28 – 3.16 (m, 1H, H_{6a}), 3.04 – 2.88 (m, 1H, H_{6b}), 2.65 (dtd, J = 12.6, 8.9, 3.5 Hz, 1H, H_{7a}), 2.51 (ddt, J = 13.3, 9.5, 7.7 Hz, 1H, H_{7b}).

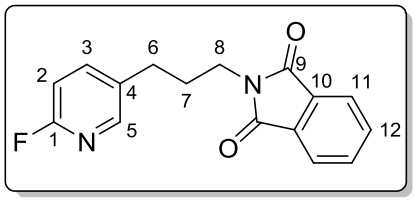
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.9 ($2C_9$), 163.8 (d, J = 237.8 Hz, C_1), 158.8 (d, J = 13.4 Hz, C_5), 137.6 (d, J = 8.2 Hz, C_3), 134.2 (d, J = 4.3 Hz, C_4), 134.1 (2CH), 132.2 ($2C_{10}$), 123.4 (2CH), 108.4 (d, J = 37.3 Hz, C_2), 54.0 (C_8), 29.1 (C_7), 27.8 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2955, 1771, 1716, 1601, 1459, 1420, 1390, 1369, 1265, 1227, 1109, 1090.

HRMS (EI+) calculated for $C_{16}H_{11}FN_2O_2$: 282.0805; Found: 282.0802.

mp: 128-129 ℃

2-(3-(6-fluoropyridin-3-yl)propyl)isoindoline-1,3-dione (II-56)



Chemical Formula: $C_{16}H_{13}FN_2O_2$
Molecular Weight: 284,29

Reduced product **II-56** (10 mg, 0.04 mmol, 7% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.05 (d, J = 2.5 Hz, 1H, H_5), 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.64 (td, J = 8.0, 2.6 Hz, 1H, H_3), 6.84 (dd, J = 8.4, 2.9 Hz, 1H, H_2), 3.75 (t, J = 7.0 Hz, 2H, H_8), 2.72 – 2.64 (m, 2H, H_6), 2.07 – 1.96 (m, 2H, H_7).

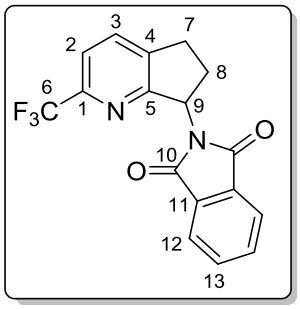
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_9$), 162.5 (d, J = 235.8 Hz, C_1), 147.2 (d, J = 14.3 Hz, C_5), 141.0 (d, J = 7.7 Hz, C_3), 134.2 (2CH), 134.0 (d, J = 4.5 Hz, C_4), 132.1 ($2C_{10}$), 123.4 (2CH), 109.3 (d, J = 37.2 Hz, C_2), 37.5 (C_8), 29.9 (C_7), 29.5 (d, J = 1.1 Hz, C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2947, 1774, 1713, 1601, 1485, 1439, 1396, 1373, 1253, 1031.

HRMS (EI+) calculated for $C_{16}H_{13}FN_2O_2$: 284.0961; Found: 284.0967.

2-(2-(Trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)isoindoline-1,3-dione (II-54b)

According to the general procedure C, the reaction was carried out with xanthate **II-53b** (364 mg, 0.80 mmol) and TFA (110 mg, 73 μL, 0.96 mmol) in 8.0 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/toluene = 1:20) gave the following products:



Chemical Formula: $C_{17}H_{11}F_3N_2O_2$
Molecular Weight: 332,28

II-54b (146 mg, 0.44 mmol, 55% yield, white powder)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 – 7.68 (m, 3H), 7.52 (d, J = 7.9 Hz, 1H, H_2), 5.83 (t, J = 8.4 Hz, 1H, H_9), 3.33 (ddd, J = 16.9, 9.5, 3.7 Hz, 1H, H_{8a}), 3.05 (dt, J = 16.7, 8.3 Hz, 1H, H_{8b}), 2.67 (ddt, J = 13.0, 9.0, 4.5 Hz, 1H, H_{7a}), 2.49 (ddt, J = 13.3, 9.4, 7.7 Hz, 1H, H_{7b}).

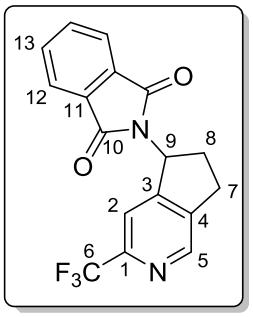
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.9 ($2C_{10}$), 161.7 (C_5), 147.2 (q, J = 34.2 Hz, C_1), 140.5 (C_4), 134.2 (2CH), 133.7 (C_3), 132.2 ($2C_{11}$), 123.5 (2CH), 121.8 (q, J = 272.2 Hz, CF_3), 119.6 (q, J = 2.9 Hz, C_2), 54.0 (C_9), 28.9 (C_7), 28.5 (C_8).

IR (v, cm^{-1}, $CDCl_3$) 2958, 1772, 1717, 1594, 1469, 1391, 1371, 1348, 1313, 1256, 1181, 1160, 1145, 1110, 1091.

HRMS (EI+) calculated for $C_{17}H_{11}F_3N_2O_2$: 332.0773; Found: 332.0769.

mp: 180-181 ℃

2-(3-(Trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)isoindoline-1,3-dione (II-55b)



Chemical Formula: $C_{17}H_{11}F_3N_2O_2$
Molecular Weight: 332,28

II-55b (88 mg, 0.26 mmol, 33% yield, white powder)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.68 (s, 1H, H_5), 7.86 (dd, J = 5.4, 3.1 Hz, 2H), 7.80 – 7.73 (m, 2H), 7.41 (s, 1H, H_2), 5.89 (t, J = 8.3 Hz, 1H, H_9), 3.44 (ddd, J = 16.6, 9.3, 4.3 Hz, 1H, H_{8a}), 3.10 (dt, J = 16.5, 8.1 Hz, 1H, H_{8b}), 2.70 – 2.51 (m, 2H, H_7).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.6 ($2C_{10}$), 151.6 (C_3), 147.0 (C_5), 146.8 (q, J = 34.2 Hz, C_1), 142.7 (C_4), 134.6 (2CH), 131.8 ($2C_{11}$), 123.8 (2CH), 121.8 (q, J = 272.2 Hz, C_6), 115.7 (q, J = 2.7 Hz, C_2), 53.9 (C_9), 29.9 (C_7), 29.1 (C_8).

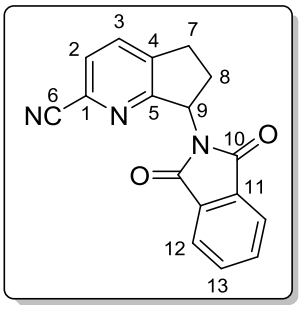
IR (ν, cm^{-1}, $CDCl_3$) 2960, 1771, 1717, 1609, 1470, 1409, 1387, 1369, 1324, 1266, 1178, 1144, 1105, 1067.

HRMS (EI+) calculated for $C_{17}H_{11}F_3N_2O_2$: 332.0773; Found: 332.0771.

mp: 212-213 ℃

7-(1,3-Dioxoisoindolin-2-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-2-carbonitrile (II-54c)

According to the general procedure C, the reaction was carried out with xanthate **II-53c** (205 mg, 0.50 mmol) and TFA (68 mg, 46 μL, 0.60 mmol) in 5.0 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/diethyl ether = 25:1 to 10:1) gave the following products:



Chemical Formula: $C_{17}H_{11}N_3O_2$
Molecular Weight: 289,29

II-54c (47 mg, 0.16 mmol, 32% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 – 7.70 (m, 3H), 7.55 (dd, J = 7.8, 0.7 Hz, 1H, H_2), 5.82 (t, J = 8.7 Hz, 1H, H_9), 3.34 (dddd, J = 17.3, 9.5, 3.5, 1.0 Hz, 1H, H_{8a}), 3.07 (dtd, J = 17.2, 8.7, 1.2 Hz, 1H, H_{8b}), 2.72 – 2.61 (m, 1H, H_{7a}), 2.53 (ddt, J = 13.3, 9.5, 8.1 Hz, 1H, H_{7b}).

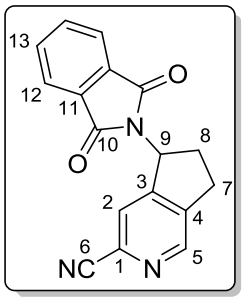
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.8 ($2C_{10}$), 163.0 (C_5), 141.4 (C_1), 134.3 (2CH), 133.6 (C_3), 132.2 (C_4), 132.1 ($2C_{11}$), 127.8 (C_2), 123.6 (2CH), 117.7 (C_6), 53.9 (C_9), 28.8 (C_8), 28.5 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2959, 1772, 1717, 1602, 1578, 1470, 1443, 1390, 1370, 1107.

HRMS (EI+) calculated for $C_{17}H_{11}N_3O_2$: 289.0851; Found: 289.0841.

mp: 171-172 ℃

5-(1,3-Dioxoisoindolin-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-3-carbonitrile (II-55c)



Chemical Formula: $C_{17}H_{11}N_3O_2$
Molecular Weight: 289,29

II-55c (34 mg, 0.12 mmol, 24% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.67 (d, J = 0.9 Hz, 1H, H_5), 7.89 – 7.84 (m, 2H), 7.78 (td, J = 5.2, 2.1 Hz, 2H), 7.44 (t, J = 0.9 Hz, 1H, H_2), 5.87 (ddd, J = 8.9, 7.6, 0.9 Hz, 1H, H_9), 3.43 (ddd, J = 17.0, 9.3, 4.0 Hz, 1H, H_{8a}), 3.11 (dt, J = 16.7, 8.2 Hz, 1H, H_{8b}), 2.64 (ddt, J = 13.1, 8.9, 4.5 Hz, 1H, H_{7a}), 2.55 (ddt, J = 13.3, 9.2, 7.6 Hz, 1H, H_{7b}).

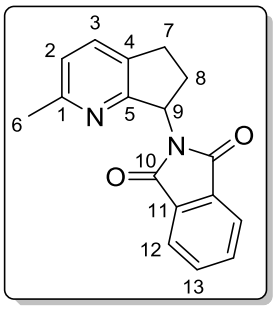
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.5 ($2C_{10}$), 151.3 (C_3), 148.2 (C_5), 143.7 (C_1), 134.7 (2CH), 132.0 (C_4), 131.7 ($2C_{11}$), 123.8 (2CH), 123.7 (C_2), 117.5 (C_6), 53.7 (C_9), 29.8 (C_8), 29.4 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2960, 1771, 1718, 1599, 1567, 1470, 1387, 1367, 1104, 1088.

HRMS (EI+) calculated for $C_{17}H_{11}N_3O_2$: 289.0851; Found: 289.0840.

mp: 163-164 ℃

2-(2-Methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)isoindoline-1,3-dione (II-54d)



Chemical Formula: $C_{17}H_{14}N_2O_2$
Molecular Weight: 278,31

According to the general procedure C, the reaction was carried out with xanthate **II-53d** (188 mg, 0.47 mmol) and TFA (64 mg, 43 μL, 0.56 mmol) in 4.7 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 2:3 to 1:0) gave **II-54d** as a white powder (54 mg, 0.19 mol, 41% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.81 (dd, J = 5.4, 3.1 Hz, 2H), 7.69 (dd, J = 5.5, 3.1 Hz, 2H), 7.53 – 7.43 (m, 1H, H_3), 6.98 (d, J = 7.8 Hz, 1H, H_2), 5.82 – 5.71 (m, 1H, H_9), 3.27 – 3.15 (m, 1H, H_{7a}), 2.93 (dt, J = 16.0, 8.0 Hz, 1H, H_{7b}), 2.60 (dtd, J = 13.0, 9.0, 3.9 Hz, 1H, H_{8a}), 2.44 (s, 3H, H_6), 2.43 – 2.34 (m, 1H, H_{8b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.1 ($2C_{10}$), 159.7 (C_5), 157.3 (C_1), 134.0 (2CH), 133.7 (C_4), 133.0 (C_3), 132.4 ($2C_{11}$), 123.3 (2CH), 122.4 (C_2), 54.7 (C_9), 29.0 (C_8), 28.2 (C_7), 24.3 (C_6).

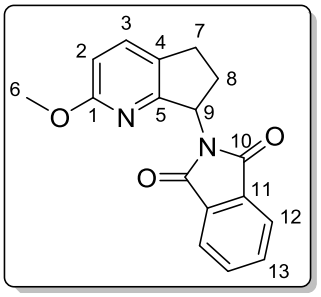
IR (ν, cm^{-1}, $CDCl_3$) 2955, 1771, 1714, 1598, 1461, 1391, 1367, 1172, 1110, 1090.

HRMS (EI+) calculated for $C_{17}H_{14}N_2O_2$: 278.1055; Found: 278.1046.

mp: 180-181 ℃

2-(2-Methoxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)isoindoline-1,3-dione (II-54e)

According to the general procedure C, the reaction was carried out with xanthate **II-53e** (207 mg, 0.50 mmol) and TFA (68 mg, 46 μL, 0.60 mmol) in 5.0 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:2 to 1:1) gave the following products:



Chemical Formula: $C_{17}H_{14}N_2O_3$
Molecular Weight: 294,31

II-54e (94 mg, 0.32 mmol, 64% yield, white powder)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 – 7.78 (m, 2H), 7.71 (dd, J = 5.5, 3.1 Hz, 2H), 7.47 (dt, J = 8.4, 0.9 Hz, 1H, H_3), 6.58 (dd, J = 8.3, 0.9 Hz, 1H, H_2), 5.76 – 5.67 (m, 1H, H_9), 3.73 (s, 3H, H_6), 3.22 – 3.10 (m, 1H, H_{7a}), 2.96 – 2.81 (m, 1H, H_{7b}), 2.59 (dddd, J = 13.0, 9.2, 8.6, 3.7 Hz, 1H, H_{8a}), 2.46 (ddt, J = 13.2, 9.4, 7.3 Hz, 1H, H_{8b}).

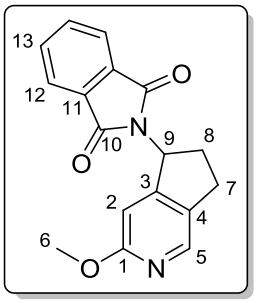
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.2 ($2C_{10}$), 164.4 (C), 157.3 (C), 135.4 (C_3), 134.0 (2CH), 132.3 ($2C_{11}$), 129.0 (C_4), 123.3 (2CH), 109.5 (C_2), 54.8 (C_9), 53.6 (C_6), 28.8 (C_8), 27.8 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 2981, 2955, 2864, 1771, 1714, 1605, 1584, 1477, 1423, 1416, 1391, 1369, 1307, 1258, 1172, 1109, 1089, 1027.

HRMS (EI+) calculated for $C_{17}H_{14}N_2O_3$: 294.1004; Found: 294.1002.

mp: 137-138 ℃

2-(3-Methoxy-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)isoindoline-1,3-dione (II-55e)



Chemical Formula: $C_{17}H_{14}N_2O_3$
Molecular Weight: 294,31

II-55e (9 mg, 0.03 mmol, 6% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.08 (d, J = 1.1 Hz, 1H, C_5), 7.87 – 7.80 (m, 2H), 7.76 – 7.71 (m, 2H), 6.44 (d, J = 1.0 Hz, 1H, C_2), 5.77 (td, J = 8.5, 1.2 Hz, 1H, C_9), 3.87 (s, 3H, C_6), 3.23 (ddd, J = 15.6, 7.0, 5.2 Hz, 1H, C_{7a}), 2.93 (ddd, J = 16.1, 8.9, 7.7 Hz, 1H, C_{7b}), 2.59 – 2.50 (m, 2H, C_8).

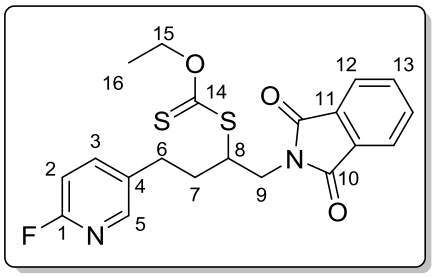
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.8 ($2C_{10}$), 163.5 (C), 153.5 (C), 142.6 (C_5), 134.3 (2CH), 132.2 (C), 132.0 (C), 123.6 (2CH), 105.1 (C_2), 54.0 (C_9), 53.8 (C_6), 30.6 (C_8), 27.8 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2949, 1771, 1716, 1621, 1483, 1384, 1370, 1322, 1113, 1028.

HRMS (EI+) calculated for $C_{17}H_{14}N_2O_3$: 294.1004; Found: 294.1011.

mp: 137-138 ℃

_S_-(1-(1,3-dioxoisoindolin-2-yl)-4-(6-fluoropyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-57a)



Chemical Formula: $C_{20}H_{19}FN_2O_3S_2$
Molecular Weight: 418,50

According to the general procedure B, the reaction was carried out with xanthate **II-43b** (347 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 11 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of toluene/ethyl acetate = 10:1) afforded product **II-57a** as a light yellow oil (300 mg, 0.72 mmol, 48% yield).

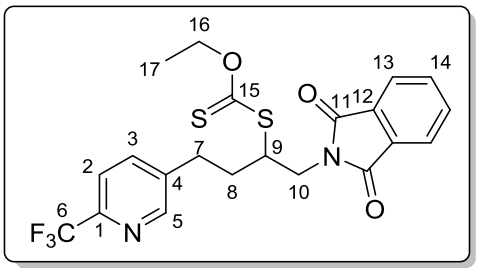
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.07 – 8.00 (m, 1H, H_5), 7.89 – 7.81 (m, 2H), 7.77 – 7.70 (m, 2H), 7.65 – 7.57 (m, 1H, H_3), 6.84 (ddd, J = 8.3, 3.0, 0.7 Hz, 1H, H_2), 4.66 – 4.52 (m, 2H, H_{15}), 4.15 (dtd, J = 8.5, 7.1, 5.1 Hz, 1H, H_8), 4.06 – 3.93 (m, 2H, H_9), 2.91 (ddd, J = 15.0, 10.1, 5.3 Hz, 1H, H_{6a}), 2.77 (ddd, J = 14.1, 10.2, 6.4 Hz, 1H, H_{6b}), 2.04 (dddd, J = 14.4, 10.2, 6.4, 5.1 Hz, 1H, H_{7a}), 1.92 (dddd, J = 14.1, 10.2, 8.6, 5.3 Hz, 1H, H_{7b}), 1.40 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.2 (C_{14}), 168.2 ($2C_{10}$), 162.6 (d, J = 236.1 Hz, C_1), 147.3 (d, J = 14.4 Hz, C_5), 141.2 (d, J = 7.6 Hz, C_3), 134.4 (2CH), 133.9 (d, J = 4.5 Hz, C_4), 131.9 ($2C_{11}$), 123.6 (2CH), 109.4 (d, J = 37.2 Hz, C_2), 70.5 (C_{15}), 48.9 (C_8), 40.9 (C_9), 33.5 (C_7), 29.2 (C_6), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2938, 2865, 1774, 1718, 1601, 1485, 1470, 1431, 1395, 1364, 1335, 1294, 1252, 1226, 1112, 1050, 1003.

HRMS (EI+) calculated for $C_{20}H_{19}FN_2O_3S_2$: 418.0821, M-Xa: $C_{17}H_{14}FN_2O_2$: 297.1039; Found: 297.1041.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-57b)



Chemical Formula: $C_{21}H_{19}F_3N_2O_3S_2$
Molecular Weight: 468,51

According to the general procedure B, the reaction was carried out with xanthate **II-43c** (217 mg, 0.77 mmol) and *N*-allylphthalimide (433 mg, 2.31 mmol) in 1,2-dichloroethane (0.77 mL), and needed 8 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:1 to 4:1) afforded product **II-57b** as a white powder (205 mg, 0.44 mmol, 57% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.55 (d, J = 2.1 Hz, 1H, H_5), 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.73 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 – 7.67 (m, 1H, H_3), 7.58 (dd, J = 8.0, 0.8 Hz, 1H, H_2), 4.58 (qq, J = 6.9, 3.6 Hz, 2H, H_{16}), 4.16 (dtd, J = 8.5, 7.1, 5.1 Hz, 1H, H_9), 4.07 – 3.94 (m, 2H, H_{10}), 3.01 (ddd, J = 15.1, 10.3, 5.2 Hz, 1H, H_{7a}), 2.86 (ddd, J = 14.0, 10.4, 6.2 Hz, 1H, H_{7b}), 2.14 – 2.02 (m, 1H, H_{8a}), 1.95 (dddd, J = 14.1, 10.5, 8.5, 5.3 Hz, 1H, H_{8b}), 1.38 (t, J = 7.1 Hz, 3H, H_{17}).

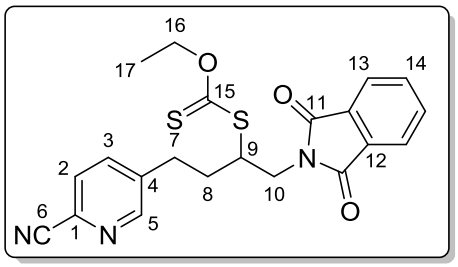
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.1 (C_{15}), 168.2 ($2C_{11}$), 150.3 (C_5), 146.4 (q, J = 34.4 Hz, C_1), 139.8 (C_4), 137.2 (C_3), 134.4 (2CH), 131.8 ($2C_{12}$), 123.6 (2CH), 121.7 (q, J = 272.2 Hz, CF_3), 120.3 (q, J = 2.7 Hz, C_2), 70.5 (C_{16}), 49.0 (C_9), 40.8 (C_{10}), 33.1 (C_8), 30.0 (C_7), 13.8 (C_{17}).

IR (v, cm^{-1}, $CDCl_3$) 2938, 1774, 1718, 1431, 1394, 1337, 1227, 1183, 1147, 1089, 1050.

HRMS (EI+) calculated for $C_{21}H_{19}F_3N_2O_3S_2$: 468.0789; Found: 468.0780.

mp: 114-115 ℃

_S_-(4-(6-Cyanopyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-57c)



Chemical Formula: $C_{21}H_{19}N_3O_3S_2$
Molecular Weight: 425,52

According to the general procedure B, the reaction was carried out with xanthate **II-43d** (356 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 11 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 7:3) afforded product **II-57c** as a light yellow oil (340 mg, 0.80 mmol, 53% yield).

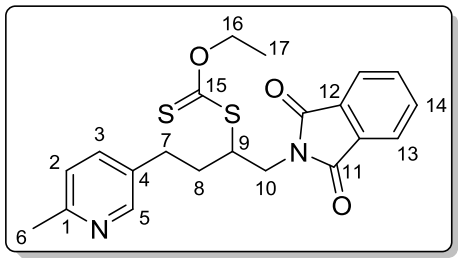
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.56 (dd, J = 2.2, 0.9 Hz, 1H, H_5), 7.88 – 7.81 (m, 2H), 7.77 – 7.71 (m, 2H), 7.67 (dd, J = 8.0, 2.2 Hz, 1H, H_3), 7.61 (dd, J = 8.0, 0.9 Hz, 1H, H_2), 4.59 (qd, J = 7.1, 2.4 Hz, 2H, H_{16}), 4.15 (dtd, J = 8.3, 7.0, 5.2 Hz, 1H, H_9), 4.06 – 3.94 (m, 2H, H_{10}), 3.01 (ddd, J = 14.1, 10.2, 5.4 Hz, 1H, H_{7a}), 2.87 (ddd, J = 14.0, 10.2, 6.2 Hz, 1H, H_{7b}), 2.07 (dddd, J = 14.3, 10.2, 6.2, 5.2 Hz, 1H, H_{8a}), 2.02 – 1.90 (m, 1H, H_{8b}), 1.40 (t, J = 7.1 Hz, 3H, H_{17}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.0 (C_{15}), 168.2 ($2C_{11}$), 151.6 (C_5), 140.8 (C_1), 136.9 (C_3), 134.4 (2CH), 131.9 (C_4), 131.8 ($2C_{12}$), 128.4 (C_2), 123.7 (2CH), 117.4 (C_6), 70.6 (C_{16}), 49.0 (C_9), 40.7 (C_{10}), 33.0 (C_8), 30.3 (C_7), 13.8 (C_{17}).

IR (v, cm^{-1}, $CDCl_3$) 2986, 2937, 2866, 1774, 1718, 1568, 1470, 1431, 1394, 1364, 1335, 1227, 1112, 1050.

HRMS (EI+) calculated for $C_{21}H_{19}N_3O_3S_2$: 425.0868, M-Xa: $C_{18}H_{14}N_3O_2$: 304.1086; Found: 304.1099.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(6-methylpyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-57d)



Chemical Formula: $C_{21}H_{22}N_2O_3S_2$
Molecular Weight: 414,54

According to the general procedure B, the reaction was carried out with xanthate **II-43e** (341 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 15 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 3:1 to 1:3) afforded product **II-57d** as a light orange oil (226 mg, 0.55 mmol, 36% yield).

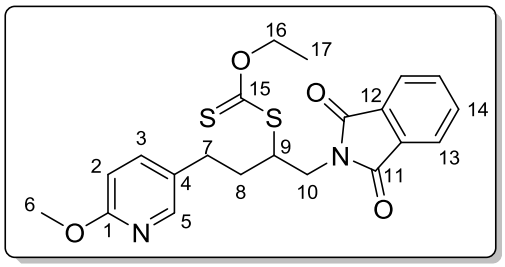
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (d, J = 2.4 Hz, 1H, H_5), 7.85 (dd, J = 5.4, 3.0 Hz, 2H), 7.77 – 7.69 (m, 2H), 7.39 (dd, J = 8.0, 2.4 Hz, 1H, H_3), 7.05 (d, J = 7.9 Hz, 1H, H_2), 4.66 – 4.52 (m, 2H, H_{16}), 4.16 (dtd, J = 8.7, 7.2, 5.0 Hz, 1H, H_9), 4.05 – 3.93 (m, 2H, H_{10}), 2.88 (ddd, J = 15.0, 10.2, 5.2 Hz, 1H, H_{7a}), 2.72 (ddd, J = 13.9, 10.3, 6.3 Hz, 1H, H_{7b}), 2.50 (s, 3H, H_6), 2.08 – 1.97 (m, 1H, H_{8a}), 1.97 – 1.86 (m, 1H, H_{8b}), 1.40 (t, J = 7.1 Hz, 3H, H_{17}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.4 (C_{15}), 168.3 ($2C_{11}$), 156.3 (C_1), 149.3 (C_5), 136.4 (C_3), 134.3 (2CH), 133.2 (C_4), 131.9 ($2C_{12}$), 123.6 (2CH), 123.1 (C_2), 70.4 (C_{16}), 49.1 (C_9), 41.1 (C_{10}), 33.6 (C_8), 29.9 (C_7), 24.1 (C_6), 13.8 (C_{17}).

IR (ν, cm^{-1}, $CDCl_3$) 2929, 1774, 1718, 1603, 1491, 1431, 1394, 1363, 1226, 1112, 1050.

HRMS (EI+) calculated for $C_{21}H_{22}N_2O_3S_2$: 414.1072; Found: 414.1078.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(6-methoxypyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-57e)



Chemical Formula: $C_{21}H_{22}N_2O_4S_2$
Molecular Weight: 430,54

According to the general procedure B, the reaction was carried out with xanthate **II-43f** (486 mg, 2.00 mmol) and *N*-allylphthalimide (1.12 g, 6.00 mmol) in 1,2-dichloroethane (2.0 mL), and needed 17 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 6:1 to 3:1) afforded product **II-57e** as a colorless oil (358 mg, 0.83 mmol, 42% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.97 (s, 1H, H_5), 7.90 – 7.81 (m, 2H), 7.78 – 7.69 (m, 2H), 7.40 (dd, J = 8.5, 2.4 Hz, 1H, H_3), 6.66 (d, J = 8.5 Hz, 1H, H_2), 4.66 – 4.52 (m, 2H, H_{16}), 4.15 (dtd, J = 8.7, 7.1, 5.0 Hz, 1H, H_9), 4.05 – 3.93 (m, 2H, H_{10}), 3.90 (s, 3H, H_6), 2.84 (ddd, J = 14.8, 10.1, 5.2 Hz, 1H, H_{7a}), 2.68 (ddd, J = 14.0, 10.1, 6.4 Hz, 1H, H_{7b}), 2.00 (dddd, J = 15.1, 10.2, 6.4, 5.0 Hz, 1H, H_{8a}), 1.95 – 1.84 (m, 1H, H_{8b}), 1.40 (t, J = 7.1 Hz, 3H, H_{17}).

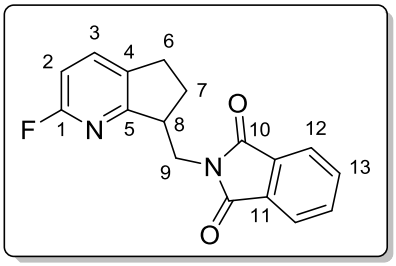
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.5 (C_{15}), 168.3 ($2C_{11}$), 163.0 (C_1), 146.3 (C_5), 139.0 (C_3), 134.3 (2CH), 131.9 ($2C_{12}$), 128.9 (C_4), 123.6 (2CH), 110.8 (C_2), 70.4 (C_{16}), 53.5 (C_6), 49.0 (C_9), 41.1 (C_{10}), 33.7 (C_8), 29.3 (C_7), 13.8 (C_{17}).

IR (v, cm^{-1}, $CDCl_3$) 2984, 2946, 1774, 1718, 1610, 1493, 1432, 1393, 1363, 1290, 1225, 1112, 1050, 1031.

HRMS (EI+) calculated for $C_{21}H_{22}N_2O_4S_2$: 430.1021, M-Xa: $C_{18}H_{17}N_2O_3$: 309.1239; Found: 309.1238.

2-((2-Fluoro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)methyl)isoindoline-1,3-dione (II-58a)

According to the general procedure C, the reaction was carried out with xanthate **II-57a** (286 mg, 0.68 mmol) and TFA (93 mg, 63 μL, 0.82 mmol) in 6.8 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:4) gave the following products:



Chemical Formula: $C_{17}H_{13}FN_2O_2$
Molecular Weight: 296,30

II-58a (46 mg, 0.16 mmol, 23% yield) as a white solid

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, J = 5.4, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.61 – 7.53 (m, 1H, H_3), 6.70 (ddd, J = 8.2, 2.1, 0.8 Hz, 1H, H_2), 4.14 (dd, J = 13.6, 6.7 Hz, 1H, H_{9a}), 3.83 (dd, J = 13.6, 9.0 Hz, 1H, H_{9b}), 3.72 – 3.60 (m, 1H, H_8), 3.03 – 2.90 (m, 1H, H_{6a}), 2.82 (dt, J = 15.8, 7.5 Hz, 1H, H_{6b}), 2.30 (dtd, J = 13.0, 8.5, 5.5 Hz, 1H, H_{7a}), 1.98 (ddt, J = 12.9, 8.8, 6.4 Hz, 1H, H_{7b}).

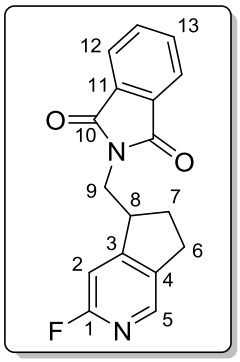
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.7 ($2C_{10}$), 163.5 (d, J = 236.2 Hz, C_1), 163.2 (d, J = 13.7 Hz, C_5), 137.0 (d, J = 8.2 Hz, C_3), 134.3 (d, J = 4.3 Hz, C_4), 134.1 (2CH), 132.3 ($2C_{11}$), 123.4 (2CH), 107.3 (d, J = 37.4 Hz, C_2), 43.8 (C_8), 41.0 (C_9), 28.7 (C_7), 28.1 (d, J = 0.6 Hz, C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2944, 2855, 1772, 1715, 1600, 1455, 1438, 1395, 1363, 1337, 1264, 1190, 1102, 1089, 1035.

HRMS (EI+) calculated for $C_{17}H_{13}FN_2O_2$: 296.0961; Found: 296.0956.

mp: 160-161 ℃

2-((3-Fluoro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-59a)



Chemical Formula: $C_{17}H_{13}FN_2O_2$
Molecular Weight: 296,30

II-59a (15 mg, 0.05 mmol, 7% yield, white solid)

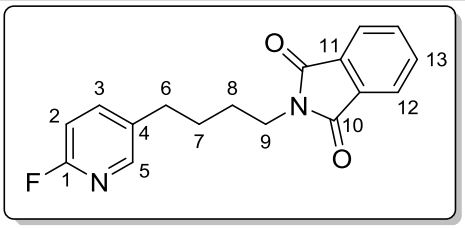
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.05 – 8.00 (m, 1H, H_5), 7.88 (dd, J = 5.5, 3.0 Hz, 2H), 7.79 – 7.73 (m, 2H), 6.82 (d, J = 2.8 Hz, 1H, H_2), 3.95 (dd, J = 13.6, 5.7 Hz, 1H, H_{9a}), 3.83 (dd, J = 13.6, 9.1 Hz, 1H, H_{9b}), 3.68 (ddd, J = 14.7, 8.4, 6.1 Hz, 1H, H_8), 3.07 – 2.95 (m, 1H, H_{6a}), 2.90 – 2.78 (m, 1H, H_{6b}), 2.28 (dtd, J = 13.0, 8.2, 6.0 Hz, 1H, H_{7a}), 2.01 (ddt, J = 12.8, 8.4, 6.3 Hz, 1H, H_{7b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{10}$), 163.1 (d, J = 234.2 Hz, C_1), 159.2 (d, J = 7.7 Hz, C_3), 142.8 (d, J = 15.8 Hz, C_5), 137.8 (d, J = 15.8 Hz, C_4), 134.4 (2CH), 132.0 ($2C_{11}$), 123.6 (2CH), 105.3 (d, J = 39.2 Hz, C_2), 44.3 (d, J = 3.1 Hz, C_8), 40.9 (C_9), 30.8 (C_7), 27.8 (d, J = 1.2 Hz, C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2940, 1773, 1716, 1613, 1583, 1474, 1435, 1397, 1362, 1343, 1309, 1188, 1032.

HRMS (EI+) calculated for $C_{17}H_{13}FN_2O_2$: 296.0961; Found: 296.0951.

2-(4-(6-Fluoropyridin-3-yl)butyl)isoindoline-1,3-dione (II-60)



Chemical Formula: $C_{17}H_{15}FN_2O_2$
Molecular Weight: 298,32

Reduced product **II-60** (28 mg, 0.09 mmol, 14% yield, white powder)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.01 (d, J = 2.4 Hz, 1H, H_5), 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.59 (td, J = 8.0, 2.5 Hz, 1H, H_3), 6.84 (dd, J = 8.3, 2.9 Hz, 1H, H_2), 3.72 (t, J = 6.9 Hz, 2H, H_9), 2.65 (t, J = 7.5 Hz, 2H, H_6), 1.78 – 1.69 (m, 2H, H_7 or H_8), 1.69 – 1.60 (m, 2H, H_7 or H_8).

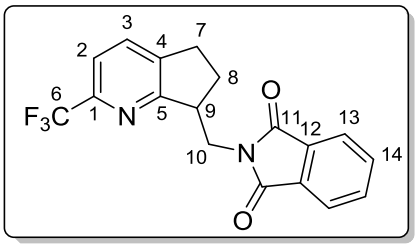
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.6 ($2C_{10}$), 162.5 (d, J = 235.4 Hz), 147.1 (d, J = 14.2 Hz), 141.1 (d, J = 7.6 Hz), 134.1 (2CH), 132.2 ($2C_{11}$), 123.4 (2CH), 109.2 (d, J = 37.1 Hz), 37.6 (C_9), 31.6 (d, J = 1.1 Hz), 28.6 (C_7 or C_8), 28.2 (C_7 or C_8).

IR (ν, cm^{-1}, $CDCl_3$) 2944, 2864, 1772, 1712, 1600, 1485, 1469, 1439, 1397, 1375, 1364, 1252, 1189, 1124, 1037, 1026.

HRMS (EI+) calculated for $C_{17}H_{15}FN_2O_2$: 298.1118; Found: 298.1184.

2-((2-(Trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)methyl)isoindoline-1,3-dione (II-58b)

According to the general procedure C, the reaction was carried out with xanthate **II-57b** (183 mg, 0.39 mmol) and TFA (53 mg, 36 μL, 0.47 mmol) in 3.9 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:4) gave a 1.5:1 mixture of **II-58b** and reduced product **II-61**.



Chemical Formula: $C_{18}H_{13}F_3N_2O_2$
Molecular Weight: 346,31

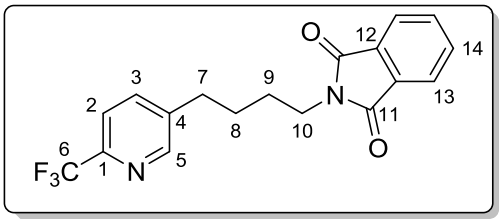
II-58b (10% yield by NMR estimation)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 – 7.81 (m, 2H), 7.74 – 7.71 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H, H_3), 7.41 (d, J = 7.8 Hz, 1H, H_2), 4.10 (dd, J = 13.4, 8.4 Hz, 1H, H, H_{10a}), 3.88 (dd, J = 13.4, 7.9 Hz, 1H, H_{10b}), 3.79 (td, J = 8.2, 5.7 Hz, 1H, H_9), 3.09 (dt, J = 15.5, 7.8 Hz, 1H, H_{7a}), 2.94 (dt, J = 16.6, 7.6 Hz, 1H, H_{7b}), 2.37 (dtd, J = 13.0, 8.5, 6.1 Hz, 1H, H_{8a}), 2.05 – 1.92 (m, 1H, H_{8b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.7 ($2C_{11}$), 165.9 (C_5), 146.5 (q, J = 34.3 Hz, C_1), 140.7 (q, J = 0.7 Hz, C_4), 133.9 (2CH), 133.2 (C_3), 132.3 ($2C_{12}$), 123.3 (2CH), 121.8 (q, J = 272.0 Hz, CF_3), 118.8 (q, J = 2.8 Hz, C_2), 43.0 (C_9), 40.7 (C_{10}), 28.8 (C_7), 28.1 (C_8).

HRMS (EI+) calculated for $C_{18}H_{13}F_3N_2O_2$: 346.0929; Found: 346.0926.

2-(4-(6-(Trifluoromethyl)pyridin-3-yl)butyl)isoindoline-1,3-dione (II-61)



Chemical Formula: $C_{18}H_{15}F_3N_2O_2$
Molecular Weight: 348,33

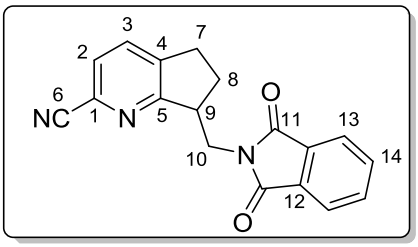
Reduced product **II-61** (15% yield by NMR estimation)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.54 (d, J = 2.1 Hz, 1H, H_5), 7.86 – 7.81 (m, 2H), 7.74 – 7.71 (m, 2H), 7.67 (dd, J = 8.1, 2.1 Hz, 1H, H_3), 7.59 (d, J = 8.0 Hz, 1H, H_2), 3.74 (t, J = 6.4 Hz, 2H, H_{10}), 2.75 (t, J = 7.5 Hz, 2H, H_7), 1.81 – 1.63 (m, 4H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{11}$), 150.3 (C_5), 146.1 (q, J = 34.3 Hz, C_1), 140.7 (q, J = 0.7 Hz, C_4), 137.1 (C_3), 134.1 (2CH), 132.1 ($2C_{12}$), 123.4 (2CH), 121.8 (q, J = 272.0 Hz, CF_3), 120.3 (q, J = 2.7 Hz, C_2), 37.5 (C_{10}), 32.4 (C_7), 28.23 (CH_2), 28.2 (CH_2).

HRMS (EI+) calculated for $C_{18}H_{15}F_3N_2O_2$: 348.1086; Found: 348.1080.

7-((1,3-Dioxoisoindolin-2-yl)methyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-2-carbonitrile (II-58c)



Chemical Formula: $C_{18}H_{13}N_3O_2$
Molecular Weight: 303,32

According to the general procedure C, the reaction was carried out with xanthate **II-57c** (318 mg, 0.75 mmol) and TFA (103 mg, 69 μL, 0.90 mmol) in 7.5 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl /toluene = 1:20 to 1:10) afforded product **II-58c** (55 mg, 0.18 mmol, 24% yield) as white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.91 – 7.84 (m, 2H), 7.78 – 7.71 (m, 2H), 7.62 (dt, J = 7.7, 1.1 Hz, 1H, H_3), 7.46 (dd, J = 7.7, 0.6 Hz, 1H, H_2), 4.14 (dd, J = 13.5, 7.5 Hz, 1H, H_{10a}), 3.86 (dd, J = 13.5, 8.4 Hz, 1H, H_{10b}), 3.75 (qd, J = 8.0, 6.1 Hz, 1H, H_9), 3.10 (dddd, J = 17.3, 8.8, 5.7, 1.2 Hz, 1H, H_{7a}), 2.95 (dddd, J = 17.1, 8.7, 6.5, 1.2 Hz, 1H, H_{7b}), 2.35 (dtd, J = 13.2, 8.5, 5.7 Hz, 1H, H_{8a}), 1.99 (ddt, J = 13.1, 8.8, 6.5 Hz, 1H, H_{8b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.7 ($2C_{11}$), 167.1 (C_5), 141.9 (C_1), 134.2 (2CH), 133.1 (C_3), 132.2 ($2C_{12}$), 131.6 (C_4), 127.2 (C_2), 123.5 (2CH), 117.7 (C_6), 43.6 (C_9), 40.7 (C_{10}), 29.2 (C_7), 28.0 (C_8).

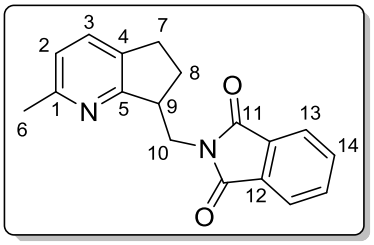
IR (ν, cm^{-1}, $CDCl_3$) 2943, 1773, 1715, 1602, 1469, 1438, 1395, 1364, 1100, 1032.

HRMS (EI+) calculated for $C_{18}H_{13}N_3O_2$: 303.1008; Found: 303.0998.

mp: 186-187 ℃

2-((2-Methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)methyl)isoindoline-1,3-dione (II-58d)

According to the general procedure C, the reaction was carried out with xanthate **II-57d** (210 mg, 0.51 mmol) and TFA (69 mg, 47 μL, 0.61 mmol) in 5.1 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/ethyl acetate = 15:1 to 3:1) gave the following products:



Chemical Formula: $C_{18}H_{16}N_2O_2$
Molecular Weight: 292,34

II-58d (40 mg, 0.14 mmol, 27% yield)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, J = 5.4, 3.0 Hz, 2H), 7.75 – 7.68 (m, 2H), 7.37 (dt, J = 7.6, 1.0 Hz, 1H, H_3), 6.89 (d, J = 7.7 Hz, 1H, H_2), 4.11 (dd, J = 13.5, 7.2 Hz, 1H, H_{10a}), 3.83 (dd, J = 13.5, 8.8 Hz, 1H, H_{10b}), 3.67 (qd, J = 8.2, 5.6 Hz, 1H, H_9), 2.97 (ddd, J = 15.3, 8.1, 6.0 Hz, 1H, H_{7a}), 2.80 (ddd, J = 15.7, 8.7, 5.9 Hz, 1H, H_{7b}), 2.32 (s, 3H, H_6), 2.24 (dtd, J = 13.0, 8.5, 6.2 Hz, 1H, H_{8a}), 1.91 (ddt, J = 13.0, 8.6, 5.7 Hz, 1H, H_{8b}).

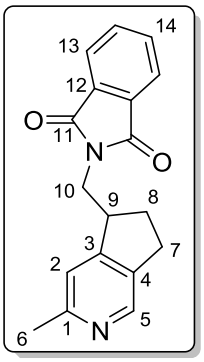
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.8 ($2C_{11}$), 164.2 (C_5), 156.5 (C_1), 133.9 (2CH), 133.7 (C_4), 132.7 (C_3), 132.5 ($2C_{12}$), 123.3 (2CH), 121.4 (C_2), 43.8 (C_9), 41.4 (C_{10}), 28.5 (C_7), 28.2 (C_8), 24.0 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2945, 2857, 1772, 1713, 1591, 1469, 1456, 1438, 1394, 1362, 1334, 1189, 1173, 1101, 1089, 1036.

HRMS (EI+) calculated for $C_{18}H_{16}N_2O_2$: 292.1212; Found: 292.1220.

mp: 124-125 ℃

2-((3-Methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-59d)



Chemical Formula: $C_{18}H_{16}N_2O_2$
Molecular Weight: 292,34

II-59d (10 mg, 0.03 mmol, 7% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.37 (s, 1H, H_5), 7.87 (dd, J = 5.4, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 7.09 (s, 1H, H_2), 3.93 (dd, J = 13.6, 5.3 Hz, 1H, H_{10a}), 3.78 (dd, J = 13.5, 9.6 Hz, 1H, H_{10b}), 3.62 (ddd, J = 14.8, 8.9, 5.7 Hz, 1H, H_9), 3.00 (ddd, J = 15.0, 8.4, 6.0 Hz, 1H, H_{7a}), 2.87 – 2.77 (m, 1H, H_{7b}), 2.51 (s, 3H, H_6), 2.18 (dtd, J = 13.1, 8.2, 6.0 Hz, 1H, H_{8a}), 1.93 (ddt, J = 12.7, 8.5, 6.2 Hz, 1H, H_{8b}).

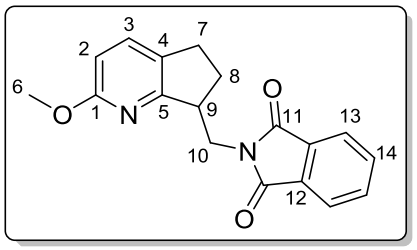
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.6 ($2C_{11}$), 156.2 (C), 153.7 (C), 145.3 (C_5), 137.1 (C_4), 134.3 (2CH), 132.1 ($2C_{12}$), 123.5 (2CH), 119.1 (C_2), 44.3 (C_9), 41.3 (C_{10}), 30.1 (CH_2), 28.3 (CH_2), 24.4 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 2937, 2857, 1772, 1716, 1611, 1485, 1469, 1435, 1397, 1362, 1337, 1189, 1100, 1032.

HRMS (EI+) calculated for $C_{18}H_{16}N_2O_2$: 292.1212; Found: 292.1198.

2-((2-Methoxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)methyl)isoindoline-1,3-dione (II-58e)

According to the general procedure C, the reaction was carried out with xanthate **II-57e** (320 mg, 0.74 mmol) and TFA (102 mg, 68 μL, 0.89 mmol) in 7.4 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:3) gave the following products:



Chemical Formula: $C_{18}H_{16}N_2O_3$
Molecular Weight: 308,34

II-58e (109 mg, 0.35 mmol, 48% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (ddd, J = 5.4, 3.1, 1.0 Hz, 2H), 7.71 (ddd, J = 5.5, 3.0, 1.0 Hz, 2H), 7.37 (dt, J = 8.3, 0.9 Hz, 1H, H_3), 6.48 (dd, J = 8.3, 0.9 Hz, 1H, H_2), 4.11 (dd, J = 13.5, 8.3 Hz, 1H, H_{10a}), 3.84 – 3.76 (m, 1H, H_{10b}), 3.69 – 3.60 (m, 1H, H_9), 3.50 (s, 3H, H_6), 2.97 – 2.86 (m, 1H, H_{7a}), 2.76 (ddd, J = 15.3, 8.7, 6.1 Hz, 1H, H_{7b}), 2.35 – 2.24 (m, 1H, H_{8a}), 1.90 (ddt, J = 12.9, 8.7, 6.1 Hz, 1H, H_{8b}).

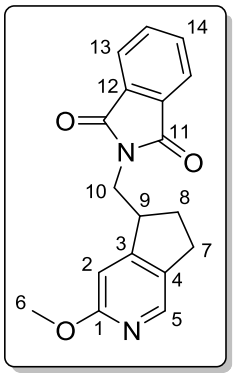
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.7 ($2C_{11}$), 163.8 (C_1), 161.8 (C_5), 135.1 (C_3), 133.9 (2CH), 132.5 ($2C_{12}$), 128.9 (C_4), 123.3 (2CH), 108.8 (C_2), 52.9 (C_6), 43.2 (C_9), 41.4 (C_{10}), 28.6 (C_8), 28.1 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 2938, 2858, 1772, 1714, 1598, 1473, 1438, 1421, 1396, 1362, 1303, 1102, 1090, 1029.

HRMS (EI+) calculated for $C_{18}H_{16}N_2O_3$: 308.1161; Found: 308.1155.

mp: 103-104 ℃

2-((3-Methoxy-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-59e)



Chemical Formula: $C_{18}H_{16}N_2O_3$
Molecular Weight: 308,34

II-59e (35 mg, 0.11 mmol, 15% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.99 (d, J = 1.1 Hz, 1H, H_5), 7.86 (dd, J = 5.4, 3.0 Hz, 2H), 7.77 – 7.71 (m, 2H), 6.63 (s, 1H, H_2), 3.97 – 3.86 (m, 4H, H_6 and H_{10a}), 3.77 (dd, J = 13.5, 9.5 Hz, 1H, H_{10b}), 3.67 – 3.56 (m, 1H, H_9), 3.00 – 2.90 (m, 1H, H_{7a}), 2.82 – 2.72 (m, 1H, H_{7b}), 2.18 (dtd, J = 12.8, 8.1, 6.0 Hz, 1H, H_{8a}), 1.92 (ddt, J = 12.8, 8.3, 6.3 Hz, 1H, H_{8b}).

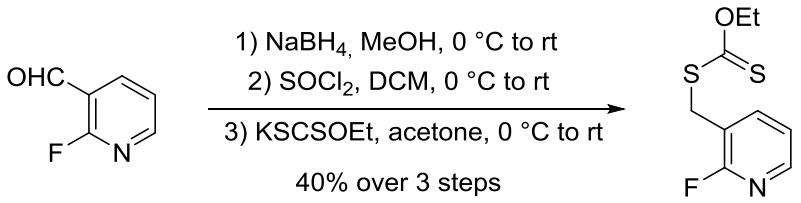
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{11}$), 163.3 (C_1), 156.6 (C_3), 142.0 (C_5), 134.2 (2CH), 133.1 (C_4), 132.0 ($2C_{12}$), 123.5 (2CH), 106.2 (C_2), 53.7 (C_6), 44.0 (C_9), 41.2 (C_{10}), 30.7 (C_8), 27.6 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 3014, 2948, 2859, 1772, 1714, 1620, 1570, 1480, 1435, 1396, 1382, 1362, 1323, 1189, 1119, 1031.

HRMS (EI+) calculated for $C_{18}H_{16}N_2O_3$: 308.1161; Found: 308.1163.

mp: 129-130 ℃

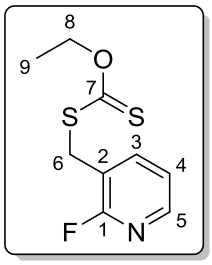
O-Ethyl *S*-((2-fluoropyridin-3-yl)methyl) carbonodithioate (II-62b)



Into solution of 2-fluoronicotinaldehyde (2.50 g, 20.0 mmol, 1.0 equiv) in MeOH (100 mL) was added at 0 ℃ $NaBH_4$ (1.51 g, 40.0 mmol, 2.0 equiv). The mixture was allowed to warm up slowly to room temperature and stirred overnight. Sat. aqueous NH_4Cl was then added and the mixture was extracted with EtOAc for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (2-fluoropyridin-3-yl)methanol (1.44 g, 11.3 mmol), which was directly used in the next step.

(2-Fluoropyridin-3-yl)methanol was dissolved in 34 mL dichloromethane and the solution was then cooled down to 0 ℃. Thionyl chloride (2.70 g, 1.6 mL, 22.7 mmol, 2.0 equiv) was then added dropwise into the solution above and the mixture was allowed to warm up to room temperature and stirred for 4 h. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and then neutralized with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 3-(chloromethyl)-2-fluoropyridine (1.57 g, 10.8 mmol), which was directly used in the next step.

Potassium *O*-ethylxanthate (1.81 g, 11.3 mmol, 1.05 equiv) was added portionwise to a solution of 3-(chloromethyl)-2-fluoropyridine in acetone (22 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/diethyl ether = 4:1) afforded product **II-62b** as a light yellow oil (1.85 g, 8.0 mmol, 40% yield over 3 steps).



Chemical Formula: $C_9H_{10}FNOS_2$
Molecular Weight: 231,30

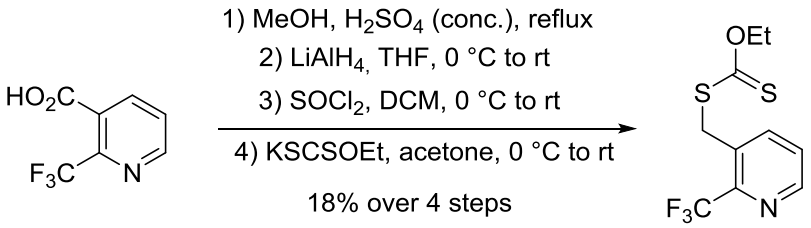
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.12 (dd, J = 5.0, 1.5 Hz, 1H, H_5), 7.87 (ddd, J = 9.5, 7.3, 2.0 Hz, 1H, H_3), 7.15 (ddd, J = 7.4, 4.9, 1.7 Hz, 1H, H_4), 4.64 (q, J = 7.1 Hz, 2H, H_8), 4.36 (s, 2H, H_6), 1.40 (t, J = 7.1 Hz, 3H, H_9).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.0 (C_7), 161.6 (d, J = 238.1 Hz, C_1), 146.8 (d, J = 14.6 Hz, C_5), 141.3 (d, J = 4.6 Hz, C_3), 121.6 (d, J = 4.4 Hz, C_4), 119.0 (d, J = 29.4 Hz, C_2), 70.7 (C_8), 33.0 (d, J = 2.7 Hz, C_6), 13.9 (C_9).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 1606, 1579, 1443, 1365, 1293, 1256, 1225, 1189, 1149, 1112, 1049.

HRMS (EI+) calculated for $C_9H_{10}FNOS_2$: 231.0188; Found: 231.0183.

_O_-Ethyl _S_-((2-(trifluoromethyl)pyridin-3-yl)methyl) carbonodithioate (II-62c)



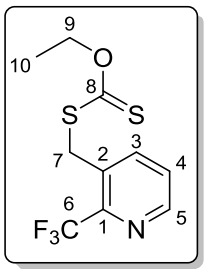
To a solution of 6-(trifluoromethyl)nicotinic acid (3.82 g, 20 mmol) in 120 mL of methanol was added 5 mL of concentrated H_2SO_4 and the mixture was refluxed for 8 h. Most of the solvent was removed under reduced pressure and the residue was then neutralized with sat. aqueous $NaHCO_3$.The mixture was extracted with ethyl acetate for three times The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give methyl 2-(trifluoromethyl)nicotinate as an orange oil (2.93 g, 14.3 mmol), which was used without further purification.

Into a suspension of $LiAlH_4$ (650 mg, 17.1 mmol, 1.2 equiv) in dry THF (30 mL) at 0 ℃ was added dropwise a solution of methyl 2-(trifluoromethyl)nicotinate in dry THF (6 mL). The mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The reaction mixture was quenched with sat. aqueous Na_2SO_4 at 0 ℃. The mixture was filtered over a pad of Celite, and the solid washed with ethyl acetate. The organic layer of filtrate was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (2-(trifluoromethyl)pyridin-3-yl)methanol as a brown oil (1.60 g, 13.7 mmol), which was used without further purification.

(2-(Trifluoromethyl)pyridin-3-yl)methanol was dissolved in 41 mL dichloromethane and the solution was then cooled down to 0 ℃. Thionyl chloride (3.25 g, 2.0 mL, 27.3 mmol, 2.0 equiv) was then added dropwise into the solution above and the mixture was allowed to warm up to room temperature and stirred overnight. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and then neutralized with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced

pressure to give 3-(chloromethyl)-2-(trifluoromethyl)pyridine as a light brown oil (1.37 g, 7.00 mmol), which was used without further purification.

Potassium *O*-ethylxanthate (1.18 g, 7.36 mmol, 1.05 equiv) was added portionwise to a solution of 3-(chloromethyl)-2-methoxypyridine in acetone (14 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) afforded product **II-62c** as a light orange oil (998 mg, 3.55 mmol, 18% yield over 4 steps).



Chemical Formula: $C_{10}H_{10}F_3NOS_2$
Molecular Weight: 281,31

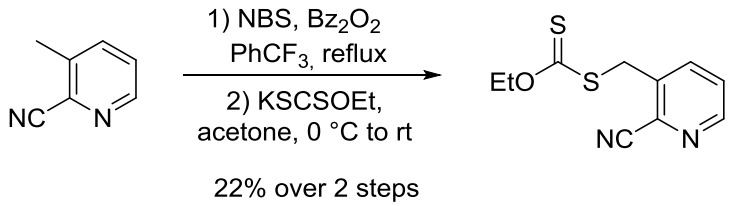
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.61 (dd, J = 4.7, 1.5 Hz, 1H, H_5), 8.03 (ddd, J = 7.9, 1.6, 0.7 Hz, 1H, H_3), 7.47 (dd, J = 7.9, 4.7 Hz, 1H, H_4), 4.67 (q, J = 7.1 Hz, 2H, H_7), 4.61 (q, J = 1.4 Hz, 2H, H_7), 1.41 (t, J = 7.1 Hz, 3H, H_8).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 213.0 (C_8), 148.0 (C_5), 145.8 (q, J = 32.9 Hz, C_1), 139.6 (C_3), 131.6 (C_2), 126.6 (C_4), 122.1 (q, J = 274.0 Hz, CF_3), 70.9 (C_9), 35.4 (q, J = 2.5 Hz, C_7), 13.9 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2988, 1452, 1326, 1226, 1184, 1135, 1114, 1073, 1048.

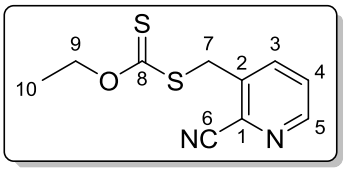
HRMS (EI+) calculated for $C_{10}H_{10}F_3NOS_2$: 281.0156; Found: 281.0151.

S-((2-Cyanopyridin-3-yl)methyl) *O*-ethyl carbonodithioate (II-62d)



3-Methylpicolinonitrile (5.00 g, 42.4 mmol, 1.0 equiv), NBS (11.3 g, 63.6 mmol, 1.5 equiv) and Bz_2O_2 (2.06 g, 8.5 mmol, 0.2 equiv) in $PhCF_3$ (127 mL) was refluxed under N_2 for 6 h. The suspension was cooled down to room temperature and the solid was removed by filtration and to the filtrate was added dichloromethane. Sat. aqueous K_2CO_3 was added and the organic phase was separated. The aqueous phase was extracted by dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9:1) to give 3-(bromomethyl)picolinonitrile (2.33 g, 11.8 mmol, 28% yield).

Potassium *O*-ethylxanthate (2.83 g, 17.7 mmol, 1.5 equiv) was added portionwise to a solution of 3-(bromomethyl)picolinonitrile in acetone (24 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9:1) to give the desired product **II-62d** as a white solid (2.25 g, 9.4 mmol, 80% yield).



Chemical Formula: $C_{10}H_{10}N_2OS_2$
Molecular Weight: 238,32

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.60 (dd, J = 4.7, 1.6 Hz, 1H, H_5), 7.96 (dd, J = 8.1, 1.5 Hz, 1H, H_3), 7.48 (dd, J = 8.1, 4.7 Hz, 1H, H_4), 4.64 (q, J = 7.1 Hz, 2H, H_9), 4.55 (s, 2H, H_7), 1.40 (t, J = 7.1 Hz, 3H, H_{10}).

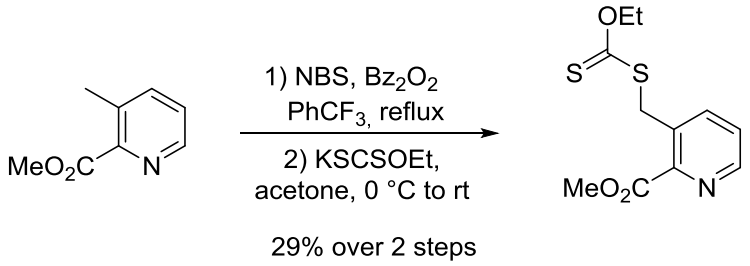
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.9 (C_8), 149.8 (C_5), 137.8 (C_3), 134.0 (C_1), 126.8 (C_4), 115.9 (C_6), 71.0 (C_9), 36.1 (C_7), 13.8 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 1567, 1430, 1229, 1113, 1048.

HRMS (EI+) calculated for $C_{10}H_{10}N_2OS_2$: 238.0235; Found: 238.0234.

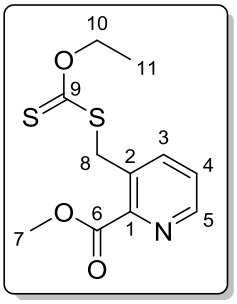
mp : 46-47 ℃

Methyl 3-(((ethoxycarbonothioyl)thio)methyl)picolinate (II-62e)



Methyl 3-methylpicolinate (3.02 g, 20.0 mmol, 1.0 equiv), NBS (4.27 g, 24.0 mmol, 1.2 equiv) and Bz_2O_2 (969 mg, 4.0 mmol, 0.2 equiv) in $PhCF_3$ (60 mL) was refluxed under N_2 for 2 h. The suspension was cooled down to room temperature and the solid was removed by filtration and to the filtrate was added dichloromethane. Sat. aqueous K_2CO_3 was added and the organic phase was separated. The aqueous phase was extracted by dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 2:1 to 1:1) to give a mixture of the starting compound (1.5 mmol estimated by ^{1}H NMR of the mixture, 224 mg) and methyl 3-(bromomethyl)picolinate (7.7 mmol estimated by ^{1}H NMR of the mixture, 1.77 g).

Potassium *O*-ethylxanthate (1.84 g, 11.5 mmol, 1.5 equiv) was added portionwise to a solution of the mixture containing methyl 3-(bromomethyl)picolinate in acetone (15 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization of the residue from ethyl acetate/pentane afforded the desired product **II-62e** as a white solid (1.55 g, 5.7 mmol, 29% yield over two steps).



Chemical Formula: $C_{11}H_{13}NO_3S_2$
Molecular Weight: 271,35

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.61 (dd, J = 4.7, 1.6 Hz, 1H, H_5), 7.97 (dd, J = 7.9, 1.6 Hz, 1H, H_3), 7.40 (dd, J = 7.9, 4.6 Hz, 1H, H_4), 4.75 (s, 2H, H_8), 4.60 (q, J = 7.1 Hz, 2H, H_{10}), 3.99 (s, 3H, H_7), 1.37 (t, J = 7.1 Hz, 3H, H_{11}).

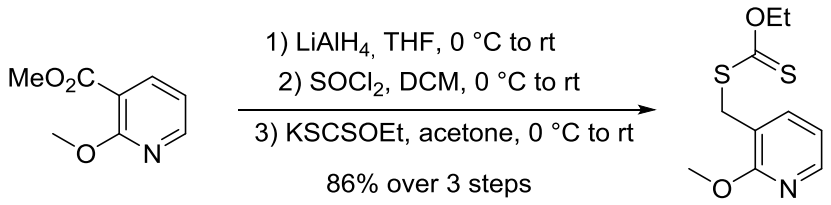
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 214.1 (C_9), 166.2 (C_6), 148.5 (C_5), 146.4 (C_1), 139.7 (C_3), 135.4 (C_2), 126.3 (C_4), 70.4 (C_{10}), 53.1 (C_7), 37.4 (C_8), 13.9 (C_{11}).

IR (ν, cm^{-1}, $CDCl_3$) 2991, 2955, 1724, 1569, 1449, 1431, 1364, 1307, 1220, 1139, 1113, 1091, 1050.

HRMS (EI+) calculated for $C_{11}H_{13}NO_3S_2$: 271.0337; Found: 271.0338.

mp: 83-84 ℃

_O_-Ethyl _S_-((2-methoxypyridin-3-yl)methyl) carbonodithioate (II-62f)

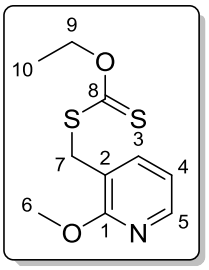


Into a suspension of $LiAlH_4$ (1.22 g, 32.1 mmol, 1.2 equiv) in dry THF (20 mL) at 0 ℃ was added dropwise a solution of methyl 2-methoxynicotinate (4.42 g, 26.5 mmol, 1.0 equiv) in dry THF (10 mL). The mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The reaction mixture was quenched with sat. aqueous Na_2SO_4 at 0 ℃. The mixture was filtered over a pad of Celite, and the solid washed with ethyl acetate. The organic layer of filtrate was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (2-methoxypyridin-3-yl)methanol as a white solid (3.56 g, 25.6 mmol), which was used without further purification.

(2-Methoxypyridin-3-yl)methanol was dissolved in 75 mL dichloromethane and the solution was then cooled down to 0 ℃. Thionyl chloride (6.08 g, 3.7 mL, 51.1 mmol, 2.0 equiv) was then added dropwise into the solution above and the mixture was allowed to warm up to room temperature and stirred for 2.5 h. The mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and then neutralized with sat. aqueous $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 3-(chloromethyl)-2-methoxypyridine as a light brown oil (3.84 g, 24.4 mmol), which was used without further purification.

Potassium _O_-ethylxanthate (4.10 g, 25.6 mmol, 1.05 equiv) was added portionwise to a solution of 3-(chloromethyl)-2-methoxypyridine in acetone (50 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic

extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) afforded product **II-62f** as a light yellow oil (5.53 g, 22.7 mmol, 86% yield over 3 steps).



Chemical Formula: $C_{10}H_{13}NO_2S_2$
Molecular Weight: 243,34

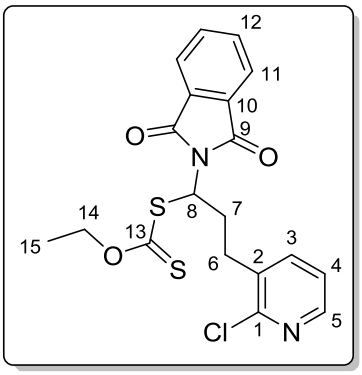
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.08 (dd, J = 5.0, 1.9 Hz, 1H, H_5), 7.68 – 7.62 (m, 1H, H_3), 6.83 (dd, J = 7.2, 5.0 Hz, 1H, H_4), 4.64 (q, J = 7.1 Hz, 2H, H_9), 4.32 (s, 2H, H_7), 3.97 (s, 3H, H_6), 1.41 (t, J = 7.1 Hz, 3H, H_{10}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 214.5 (C_8), 162.0 (C_1), 146.2 (C_5), 138.7 (C_3), 119.0 (C_2), 116.7 (C_4), 70.2 (C_9), 53.7 (C_6), 34.8 (C_7), 13.9 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 2953, 1588, 1468, 1453, 1414, 1312, 1261, 1221, 1148, 1112, 1050, 1023.

HRMS (EI+) calculated for $C_{10}H_{13}NO_2S_2$: 243.0388; Found: 243.0379.

_S_-(3-(2-Chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl) _O_-ethyl carbonodithioate (II-63a)



Chemical Formula: $C_{19}H_{17}ClN_2O_3S_2$
Molecular Weight: 420,93

According to the general procedure A, the reaction was carried out with xanthate **II-62a** (991 mg, 4.00 mmol) and *N*-vinylphthalimide (173 mg, 1.00 mmol) in ethyl acetate (4.0 mL), and needed 14 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 9:1 to 3:1) followed by further purification (toluene/ethyl acetate = 5:1) afforded product **II-63a** as a light yellow oil (296 mg, 0.70 mmol, 70% yield).

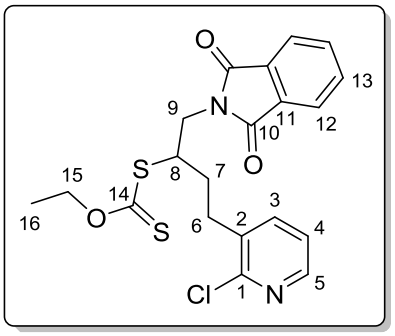
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 (dd, J = 4.7, 1.9 Hz, 1H, H_5), 7.86 (dd, J = 5.4, 3.1 Hz, 2H), 7.80 – 7.72 (m, 2H), 7.56 (dd, J = 7.5, 1.9 Hz, 1H, H_3), 7.15 (dd, J = 7.5, 4.8 Hz, 1H, H_4), 6.28 (dd, J = 9.2, 6.6 Hz, 1H, H_8), 4.61 (q, J = 7.2 Hz, 2H, H_{14}), 2.91 – 2.74 (m, 2H, H_6), 2.65 (dtd, J = 13.8, 9.3, 5.8 Hz, 1H, H_{7a}), 2.48 (ddt, J = 13.9, 9.5, 6.5 Hz, 1H, H_{7b}), 1.38 (t, J = 7.1 Hz, 3H, H_{15}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{13}), 166.9 ($2C_9$), 151.4 (C_1), 147.9 (C_5), 139.1 (C_3), 134.6 (2CH), 134.2 (C_2), 131.6 ($2C_{10}$), 123.8 (2CH), 122.8 (C_4), 70.7 (C_{14}), 57.2 (C_8), 32.7 (C_7), 30.5 (C_6), 13.8 (C_{15}).

IR (v, cm^{-1}, $CDCl_3$) 2986, 2939, 1780, 1721, 1566, 1470, 1443, 1411, 1380, 1364, 1334, 1293, 1233, 1112, 1076, 1049.

HRMS (EI+) calculated for $C_{19}H_{17}ClN_2O_3S_2$: 420.0369, M-Xa: $C_{16}H_{12}ClN_2O_2$: 299.0587; Found: 299.0578.

_S_-(4-(2-Chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-63b)



Chemical Formula: $C_{20}H_{19}ClN_2O_3S_2$
Molecular Weight: 434,95

According to the general procedure B, the reaction was carried out with xanthate **II-62a** (372 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 12 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 7:3) afforded product **II-63b** as a light yellow oil (360 mg, 0.83 mmol, 55% yield).

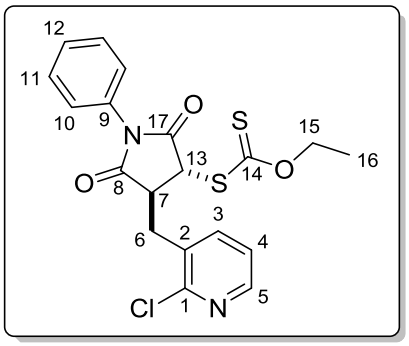
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (dd, J = 4.7, 1.9 Hz, 1H, H_5), 7.85 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.58 (dd, J = 7.5, 1.9 Hz, 1H, H_3), 7.17 (dd, J = 7.5, 4.8 Hz, 1H, H_4), 4.66 – 4.53 (m, 2H, H_{15}), 4.21 – 4.12 (m, 1H, H_8), 4.07 – 3.95 (m, 2H, H_9), 3.02 (ddd, J = 13.9, 10.4, 5.3 Hz, 1H, H_{6a}), 2.88 (ddd, J = 13.8, 10.4, 5.9 Hz, 1H, H_{6b}), 2.10 (dddd, J = 14.3, 10.7, 5.9, 5.0 Hz, 1H, H_{7a}), 1.96 (dddd, J = 14.1, 10.4, 8.5, 5.3 Hz, 1H, H_{7b}), 1.40 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.4 (C_{14}), 168.2 ($2C_{10}$), 151.4 (C_1), 147.8 (C_5), 139.2 (C_3), 135.2 (C_2), 134.3 (2CH), 131.9 ($2C_{11}$), 123.6 (2CH), 122.8 (C_4), 70.5 (C_{15}), 49.1 (C_8), 40.9 (C_9), 31.2 (C_7), 30.8 (C_6), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2938, 1774, 1718, 1566, 1431, 1411, 1395, 1364, 1227, 1111, 1050.

HRMS (EI+) calculated for $C_{20}H_{19}ClN_2O_3S_2$: 434.0526, M-Xa: $C_{17}H_{14}ClN_2O_2$: 313.0744; Found: 313.0733.

_S_-(4-((2-Chloropyridin-3-yl)methyl)-2,5-dioxo-1-phenylpyrrolidin-3-yl) _O_-ethyl carbonodithioate (II-63c)



Chemical Formula: $C_{19}H_{17}ClN_2O_3S_2$
Molecular Weight: 420,93

According to the general procedure A, the reaction was carried out with xanthate **II-62a** (743 mg, 3.00 mmol) and *N*-phenylmaleimide (260 mg, 1.50 mmol) in 1,2-dichloroethane (3.0 mL), and needed 2 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 7:3) afforded product **II-63c** as a light yellow solid (513 mg, 1.22 mmol, 81% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.35 (dd, J = 4.8, 1.9 Hz, 1H, H_5), 7.71 (dd, J = 7.6, 2.0 Hz, 1H, H_3), 7.52 – 7.44 (m, 2H), 7.44 – 7.38 (m, 1H, H_{12}), 7.34 – 7.28 (m, 2H), 7.22 (dd, J = 7.6, 4.8 Hz, 1H, H_4), 4.69 – 4.55 (m, 2H, H_{15}), 4.17 (d, J = 7.1 Hz, 1H, H_{13}), 3.87 (q, J = 7.0 Hz, 1H, H_7), 3.56 (dd, J = 14.3, 6.3 Hz, 1H, H_{6a}), 3.29 (dd, J = 14.3, 7.3 Hz, 1H, H_{6b}), 1.38 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 209.9 (C_{14}), 175.1 (C_8 or C_{17}), 171.4 (C_8 or C_{17}), 151.6 (C), 149.0 (CH), 140.5 (CH), 131.8 (C), 131.5 (C), 129.4 (2CH), 129.1 (CH), 126.3 (2CH), 123.0 (CH), 71.2 (C_{15}), 50.0 (C_{13}), 45.9 (C_7), 32.7 (C_6), 13.8 (C_{16}).

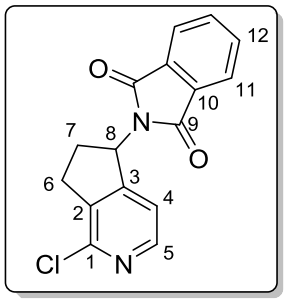
IR (ν, cm^{-1}, $CDCl_3$) 2987, 1721, 1584, 1566, 1500, 1413, 1380, 1238, 1185, 1112, 1076, 1050.

HRMS (EI+) calculated for $C_{19}H_{17}ClN_2O_3S_2$: 420.0369, M-Xa: $C_{16}H_{12}ClN_2O_2$: 299.0587; Found: 299.0588.

mp : 92-94 ℃

2-(1-Chloro-6,7-dihydro-5H-cyclopenta[c]pyridin-5-yl)isoindoline-1,3-dione (II-64a)

According to the general procedure C, the reaction was carried out with xanthate **II-63a** (265 mg, 0.66 mmol) and TFA (90 mg, 60 μL, 0.79 mmol) in 6.6 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 2:5) gave product **II-64a** as a white solid (155 mg, 0.52 mmol, 79% yield).

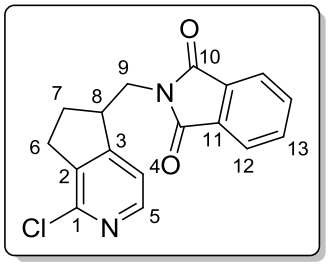


Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,73

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (dt, J = 5.0, 0.9 Hz, 1H, H_5), 7.88 – 7.83 (m, 2H), 7.78 – 7.73 (m, 2H), 6.99 (dd, J = 5.0, 1.0 Hz, 1H, H_4), 5.90 – 5.86 (m, 1H, H_8), 3.37 (ddd, J = 16.8, 9.4, 4.0 Hz, 1H, H_{6a}), 3.04 (dt, J = 16.5, 8.1 Hz, 1H, H_{6b}), 2.61 (ddt, J = 13.8, 9.1, 4.4 Hz, 1H, , H_{7a}), 2.51 (ddt, J = 13.3, 9.4, 7.6 Hz, 1H, H_{7b}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.6 ($2C_9$), 152.7 (C_3), 148.6 (C_1), 148.2 (C_5), 138.3 (C_2), 134.5 (2CH), 131.8 ($2C_{10}$), 123.7 (2CH), 117.8 (C_4), 54.7 (C_8), 29.9 (C_6), 29.0 (C_7).
IR (ν, cm^{-1}, $CDCl_3$) 1773, 1717, 1601, 1564, 1404, 1387, 1367, 1106.
HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0502.
mp: 139-140 ℃

2-((1-Chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-64b)

According to the general procedure C, the reaction was carried out with xanthate **II-63b** (335 mg, 0.77 mmol) and TFA (105 mg, 70 μL, 0.92 mmol) in 7.7 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:5 to 1:3) gave **II-64b** (89 mg, 0.28 mmol, 37% yield) as a white solid product and **II-65** (17 mg, 0.03 mmol, 4% yield) as a white solid



Chemical Formula: $C_{17}H_{13}ClN_2O_2$
Molecular Weight: 312,75

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (dd, J = 5.0, 0.9 Hz, 1H, H_5), 7.87 (dd, J = 5.5, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.15 (dd, J = 4.9, 0.8 Hz, 1H, H_4), 3.94 (dd, J = 13.3, 5.5 Hz, 1H, H_{9a}), 3.83 (dd, J = 13.3, 8.9 Hz, 1H, H_{9b}), 3.76 (tt, J = 8.7, 5.9 Hz, 1H, H_8), 3.15 – 3.02 (m, 1H, H_{6a}), 2.97 – 2.86 (m, 1H, H_{6b}), 2.32 – 2.19 (m, 1H, H_{7a}), 1.99 (ddt, J = 13.1, 8.8, 6.1 Hz, 1H, H_{7b}).

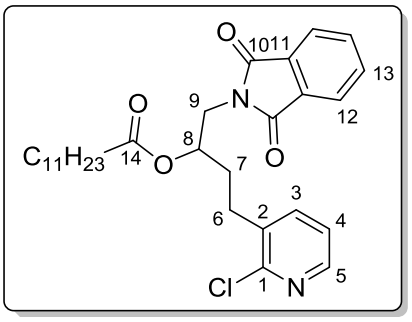
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{10}$), 156.0 (C_3), 148.3 (C_1), 148.1 (C_5), 139.0 (C_2), 134.4 (2CH), 131.9 ($2C_{11}$), 123.6 (2CH), 118.8 (C_4), 45.3 (C_8), 41.2 (C_9), 29.9 (C_6), 28.8 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 2939, 1773, 1716, 1591, 1560, 1435, 1407, 1396, 1362, 1190, 1150, 1102, 1030.

HRMS (EI+) calculated for $C_{17}H_{13}ClN_2O_2$: 312.0666; Found: 312.0674.

mp: 153-154 ℃

4-(2-Chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)butan-2-yl dodecanoate (II-65)



Chemical Formula: $C_{29}H_{37}ClN_2O_4$
Molecular Weight: 513,07

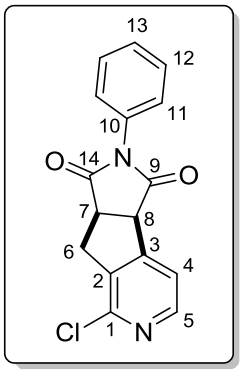
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (dd, J = 4.8, 2.0 Hz, 1H, H_5), 7.89 – 7.82 (m, 2H), 7.76 – 7.70 (m, 2H), 7.57 (dd, J = 7.5, 1.9 Hz, 1H, H_3), 7.17 (dd, J = 7.5, 4.7 Hz, 1H, H_4), 4.10 (dtd, J = 9.0, 7.1, 4.7 Hz, 1H, H_8), 4.02 – 3.90 (m, 2H, H_9), 3.04 – 2.94 (m, 1H), 2.90 – 2.76 (m, 3H), 2.08 (dddd, J = 14.2, 10.6, 5.8, 4.6 Hz, 1H), 1.92 (dddd, J = 14.2, 10.6, 9.0, 5.2 Hz, 1H), 1.50 – 1.38 (m, 2H), 1.28 – 1.17 (m, 16H), 0.92 – 0.80 (m, 3H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 188.6 (C_{14}), 168.2 ($2C_{10}$), 151.4 (C_1), 147.8 (C_5), 139.2 (C_3), 135.2 (C_2), 134.2 (2CH), 132.0 ($2C_{11}$), 123.6 (2CH), 122.8 (C_4), 44.8 (C_8), 41.7 (C_9), 32.1, 31.6, 30.9, 30.8, 29.74, 29.72, 29.6, 29.5, 29.2, 28.8, 22.8, 14.3 (CH_3).

IR (v, cm^{-1}, $CDCl_3$) 2928, 2856, 1774, 1718, 1643, 1469, 1431, 1411, 1395, 1365, 1109, 1080.

HRMS (EI+) calculated for $C_{29}H_{37}ClN_2O_4$: 512.2442, M-$C_{11}H_{23}COO$: $C_{17}H_{14}ClN_2O_2$, 313.0744; Found: 313.0749.

7-Chloro-2-phenyl-8,8a-dihydropyrrolo[3',4':3,4]cyclopenta[1,2-*c*]pyridine-1,3(2*H*,3a*H*)-dione (II-64c)



Chemical Formula: $C_{16}H_{11}ClN_2O_2$
Molecular Weight: 298,73

According to the general procedure C, the reaction was carried out with xanthate **II-63c** (211 mg, 0.50 mmol) and TFA (68 mg, 46 μL, 0.60 mmol) in 5.0 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 2:3 to 1:1) gave product **II-64c** as a white solid (40 mg, 0.13 mmol, 27% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.35 (d, J = 5.1 Hz, 1H, H_5), 7.52 (dd, J = 5.0, 1.0 Hz, 1H, H_4), 7.48 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H, H_{13}), 7.25 – 7.20 (m, 2H), 4.57 (dq, J = 8.4, 1.0 Hz, 1H, H_8), 3.87 (td, J = 8.5, 5.0 Hz, 1H, H_7), 3.60 – 3.54 (m, 2H, H_6).

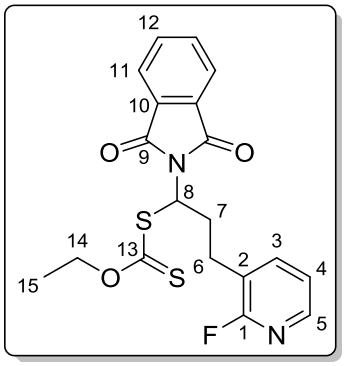
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 177.6 (C_{14}), 174.2 (C_9), 149.2(C_5), 149.1 (C), 148.6 (C), 136.6 (C_3), 131.5 (C_{10}), 129.4 (2CH), 129.1 (C_{13}), 126.4 (2CH), 119.6 (C_4), 52.6 (C_8), 42.7 (C_7), 34.2 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 3064, 2933, 1780, 1718, 1591, 1563, 1501, 1456, 1442, 1405, 1379, 1298, 1198, 1185, 1144, 974.

HRMS (EI+) calculated for $C_{16}H_{11}ClN_2O_2$: 298.0509; Found: 298.0512.

mp: 162-163 ℃

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(2-fluoropyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-66a)



Chemical Formula: $C_{19}H_{17}FN_2O_3S_2$
Molecular Weight: 404,47

According to the general procedure A, the reaction was carried out with xanthate **II-62b** (1.39 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and took 16 h to go to completion. Flash chromatography on silica gel (gradient of toluene/ethyl acetate = 9:1 to 5:1) afforded product **II-66a** as a white powder (238 mg, 0.59 mmol, 39% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.03 (dt, J = 4.9, 1.5 Hz, 1H, H_5), 7.86 (dd, J = 5.4, 3.1 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.61 (ddd, J = 9.6, 7.3, 1.9 Hz, 1H, H_3), 7.09 (ddd, J = 7.1, 4.9, 1.8 Hz, 1H, H_4), 6.27 (dd, J = 9.1, 6.6 Hz, 1H, H_8), 4.61 (q, J = 7.1 Hz, 2H, H_{14}), 2.76 (dq, J = 8.5, 6.5, 5.5 Hz, 2H, H_6), 2.70 – 2.59 (m, 1H, H_{7a}), 2.47 (ddt, J = 13.7, 8.9, 6.7 Hz, 1H, H_{7b}), 1.38 (t, J = 7.1 Hz, 3H, H_{15}).

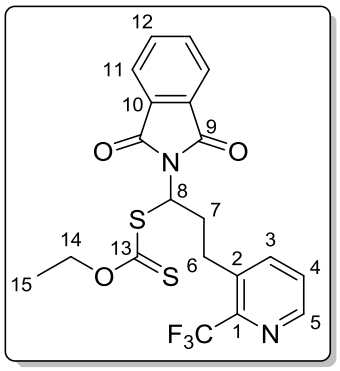
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{13}), 166.9 ($2C_9$), 162.0 (d, J = 237.3 Hz, C_1), 145.8 (d, J = 14.5 Hz, C_5), 141.0 (d, J = 5.6 Hz, C_3), 134.6 (2CH), 131.6 ($2C_{10}$), 123.8 (2CH), 121.8 (d, J = 30.5 Hz, C_2), 121.6 (d, J = 4.3 Hz, C_4), 70.7 (C_{14}), 57.2 (C_8), 32.8 (C_7), 26.3 (d, J = 2.0 Hz, C_6), 13.8 (C_{15}).

IR (ν, cm^{-1}, $CDCl_3$) 2985, 2937, 1781, 1721, 1608, 1580, 1470, 1445, 1380, 1364, 1333, 1232, 1188, 1112, 1085, 1048.

HRMS (EI+) calculated for $C_{19}H_{17}FN_2O_3S_2$: 404.0665, M-Xa: $C_{16}H_{12}FN_2O_2$: 283.0883; Found: 283.0871.

mp: 106-107 ℃

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-66b)



Chemical Formula: $C_{20}H_{17}F_3N_2O_3S_2$
Molecular Weight: 454,48

According to the general procedure A, the reaction was carried out with xanthate **II-62c** (975 mg, 3.47 mmol) and *N*-vinylphthalimide (150 mg, 0.87 mmol) in ethyl acetate (3.5 mL), and needed 15 h to go to completion. Flash chromatography on silica gel (gradient of toluene/ethyl acetate = 8:1 to 6:1) afforded product **II-66b** as a light yellow oil (243 mg, 0.53 mmol, 61% yield).

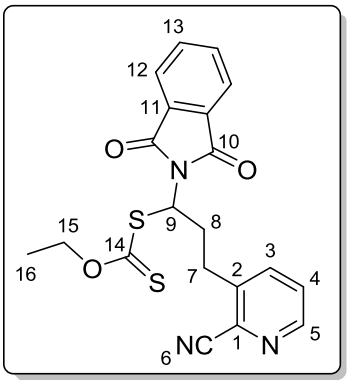
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.55 (dd, J = 4.7, 1.5 Hz, 1H, H_5), 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.77 (dd, J = 5.5, 3.0 Hz, 2H), 7.73 (dt, J = 8.4, 1.3 Hz, 1H, H_3), 7.43 (dd, J = 7.8, 4.7 Hz, 1H, H_4), 6.34 (dd, J = 9.1, 6.7 Hz, 1H, H_8), 4.64 (q, J = 7.1 Hz, 2H, H_{14}), 3.01 – 2.90 (m, 1H, H_{6a}), 2.90 – 2.79 (m, 1H, H_{6b}), 2.61 (dddd, J = 14.3, 10.7, 9.1, 5.2 Hz, 1H, H_{7a}), 2.47 (ddt, J = 14.0, 10.8, 6.2 Hz, 1H, H_{7b}), 1.40 (t, J = 7.1 Hz, 3H, H_{15}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.8 (C_{13}), 167.0 ($2C_9$), 147.2 (C_5), 145.8 (q, J = 32.5 Hz, C_1), 139.7 (C_3), 134.8 (C_2), 134.7 (2CH), 131.6 ($2C_{10}$), 126.6 (C_4), 123.9 (2CH), 122.3 (q, J = 273.9 Hz, CF_3), 70.8 (C_{14}), 57.3 (C_8), 34.8 (C_7), 28.7 (q, J = 2.2 Hz, C_6), 13.8 (C_{15}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 1781, 1721, 1470, 1457, 1380, 1364, 1328, 1292, 1234, 1183, 1134, 1075, 1051.

HRMS (EI+) calculated for $C_{20}H_{17}F_3N_2O_3S_2$: 454.0633, M-Xa: $C_{17}H_{12}F_3N_2O_2$: 333.0851; Found: 333.0852.

_S_-(3-(2-Cyanopyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl) _O_-ethylcarbonodithioate (II-66c)



Chemical Formula: $C_{20}H_{17}N_3O_3S_2$
Molecular Weight: 411,49

According to the general procedure A, the reaction was carried out with xanthate **II-62d** (1.42 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and needed 9 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 3:2) afforded product **II-66c** as an orange oil (535 mg, 1.30 mmol, 87% yield).

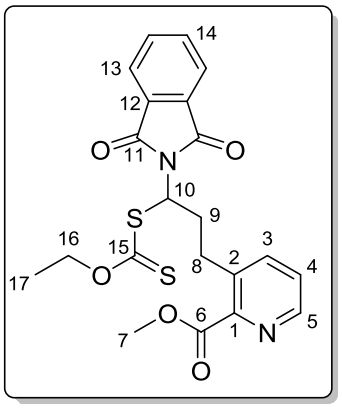
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.55 (dd, J = 4.7, 1.6 Hz, 1H, H_5), 7.87 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.4, 3.1 Hz, 2H), 7.73 (dd, J = 8.0, 1.6 Hz, 1H, H_3), 7.45 (dd, J = 8.0, 4.7 Hz, 1H, H_4), 6.27 (dd, J = 9.3, 6.3 Hz, 1H, H_9), 4.62 (q, J = 7.1 Hz, 2H, H_{15}), 3.06 – 2.89 (m, 2H, H_7), 2.74 (dtd, J = 14.3, 9.1, 6.1 Hz, 1H, H_{8a}), 2.61 – 2.48 (m, 1H, H_{8b}), 1.39 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 210.7 (C_{14}), 166.9 ($2C_{10}$), 149.2 (C_5), 140.4 (C_2), 137.5 (C_3), 134.7 (2CH), 134.0 (C_1), 131.6 ($2C_{11}$), 126.8 (C_4), 123.9 (2CH), 116.0 (C_6), 70.8 (C_{15}), 56.9 (C_9), 33.8 (C_8), 29.8 (C_7), 13.8 (C_{16}).

IR (v, cm^{-1}, $CDCl_3$) 2985, 2939, 1781, 1721, 1612, 1568, 1470, 1430, 1380, 1363, 1333, 1293, 1230, 1150, 1112, 1084, 1049, 1022, 1003.

HRMS (EI+) calculated for $C_{20}H_{17}N_3O_3S_2$: 411.0711, M-Xa: $C_{17}H_{12}N_3O_2$: 290.0930; Found: 290.0932.

Methyl 3-(3-(1,3-dioxoisoindolin-2-yl)-3-((ethoxycarbonothioyl)thio)propyl) picolinate (II-66d)



Chemical Formula: $C_{21}H_{20}N_2O_5S_2$
Molecular Weight: 444,52

According to the general procedure A, the reaction was carried out with xanthate **II-62e** (1.08 g, 4.00 mmol) and *N*-vinylphthalimide (173 mg, 1.00 mmol) in ethyl acetate (4.0 mL), and needed 12 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 3:2 to 2:3) afforded product **II-66d** as a colorless oil (341 mg, 0.77 mmol, 77% yield).

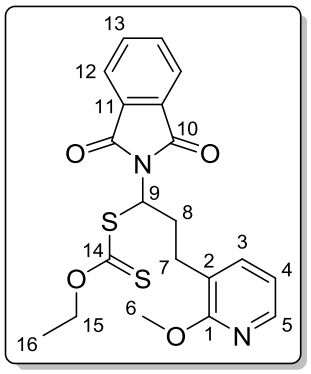
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.54 (dd, J = 4.6, 1.7 Hz, 1H, H_5), 7.87 (dd, J = 5.5, 3.1 Hz, 2H), 7.78 – 7.72 (m, 2H), 7.64 (dd, J = 7.8, 1.6 Hz, 1H, H_3), 7.35 (dd, J = 7.8, 4.6 Hz, 1H, H_4), 6.31 (dd, J = 9.5, 6.2 Hz, 1H, H_{10}), 4.62 (q, J = 7.1 Hz, 2H, H_{16}), 3.90 (s, 3H, H_7), 3.05 (ddd, J = 9.2, 6.3, 3.0 Hz, 2H, H_8), 2.70 – 2.57 (m, 1H, H_{9a}), 2.45 (ddt, J = 13.9, 9.2, 6.5 Hz, 1H, H_{9b}), 1.39 (t, J = 7.1 Hz, 3H, H_{17}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.1 (C_{15}), 167.0 ($2C_{11}$), 166.2 (C_6), 147.7 (C_5), 147.0 (C_1), 139.5 (C_3), 137.7 (C_2), 134.5 (2CH), 131.8 ($2C_{12}$), 126.3 (C_4), 123.7 (C_4), 70.6 (C_{16}), 57.5 (C_{10}), 52.9 (C_7), 34.7 (C_9), 30.5 (C_8), 13.9 (C_{17}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2954, 1781, 1721, 1453, 1430, 1380, 1364, 1333, 1305, 1232, 1139, 1108, 1085, 1049.

HRMS (EI+) calculated for $C_{21}H_{20}N_2O_5S_2$: 444.0814, M-Xa: $C_{18}H_{15}N_2O_4$: 323.1032; Found: 323.1019.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(2-methoxypyridin-3-yl)propyl) _O_-ethyl carbonodithioate (II-66e)



Chemical Formula: $C_{20}H_{20}N_2O_4S_2$
Molecular Weight: 416,51

According to the general procedure A, the reaction was carried out with xanthate **II-62f** (1.46 g, 6.00 mmol) and *N*-vinylphthalimide (260 mg, 1.50 mmol) in ethyl acetate (6.0 mL), and no evolvement for the reaction after 21 h. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) afforded product **II-66e** as a light yellow oil (358 mg, 0.85 mmol, 57% yield).

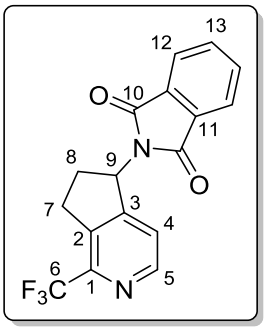
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.97 (dd, J = 5.0, 1.9 Hz, 1H, H_5), 7.86 (dd, J = 5.5, 3.1 Hz, 2H), 7.80 – 7.73 (m, 2H), 7.37 (dd, J = 7.2, 2.0 Hz, 1H, H_3), 6.76 (dd, J = 7.2, 5.0 Hz, 1H, H_4), 6.29 – 6.21 (m, 1H, H_9), 4.62 (q, J = 7.1 Hz, 2H, H_{15}), 3.89 (s, 3H, H_6), 2.78 – 2.59 (m, 3H, H_7 and H_{8a}), 2.49 – 2.34 (m, 1H, H_{8b}), 1.39 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.1 (C_{14}), 166.9 ($2C_{10}$), 162.1 (C_1), 144.9 (C_5), 138.1 (C_3), 134.5 (2CH), 131.7 ($2C_{11}$), 123.7 (2CH), 122.5 (C_2), 116.7 (C_4), 70.5 (C_{15}), 57.5 (C_9), 53.4 (C_6), 32.2 (C_8), 27.5 (C_7), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2984, 2952, 2857, 1780, 1720, 1594, 1468, 1453, 1413, 1380, 1363, 1333, 1230, 1112, 1048, 1025.

HRMS (EI+) calculated for $C_{20}H_{20}N_2O_4S_2$: 416.0864, M-Xa: $C_{17}H_{15}N_2O_3$: 295.1083; Found: 295.1073.

2-(1-(Trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)isoindoline-1,3-dione (II-67b)



Chemical Formula: $C_{17}H_{11}F_3N_2O_2$
Molecular Weight: 332,28

According to the general procedure C, the reaction was carried out with xanthate **II-66b** (223 mg, 0.49 mmol) and TFA (67 mg, 45 μL, 0.59 mmol) in 4.9 mL 1,2-dichloroethane and needed 9 h to go to completion. Flash chromatography on silica gel (ethyl acetate/toluene = 1:20) gave product **II-67b** as a white powder (58 mg, 0.17 mol, 36% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.50 (d, J = 4.9 Hz, 1H, H_5), 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 7.23 (d, J = 4.8 Hz, 1H, H_4), 5.87 (ddd, J = 8.9, 7.7, 1.0 Hz, 1H, H_9), 3.56 (dddd, J = 17.0, 9.0, 3.9, 1.9 Hz, 1H, H_{8a}), 3.20 (dt, J = 16.9, 8.3 Hz, 1H, H_{8b}), 2.68 – 2.48 (m, 2H, H_7).

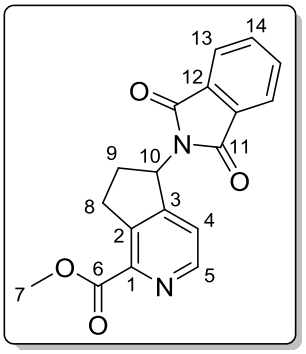
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.6 ($2C_{10}$), 153.1 (C_3), 147.8 (C_5), 144.5 (q, J = 34.5 Hz, C_1), 137.6 (q, J = 0.9 Hz, C_2), 134.6 (2CH), 131.8 ($2C_{11}$), 123.7 (2CH), 121.8 (q, J = 273.1 Hz, C_6), 121.6 (C_4), 53.8 (C_9), 29.5 (C_8), 29.2 (q, J = 1.8 Hz, C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2957, 1773, 1718, 1603, 1469, 1440, 1388, 1369, 1335, 1309, 1179, 1140, 1127, 1107, 1089, 1069, 1018.

HRMS (EI+) calculated for $C_{17}H_{11}F_3N_2O_2$: 332.0773; Found: 332.0764.

mp: 130-131 ℃

Methyl 5-(1,3-dioxoisoindolin-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-1-carboxylate (II-67d)



Chemical Formula: $C_{18}H_{14}N_2O_4$
Molecular Weight: 322,32

According to the general procedure C, the reaction was carried out with xanthate **II-66d** (321 mg, 0.72 mmol) and TFA (99 mg, 66 μL, 0.87 mmol) in 7.2 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:1 to 7:3) gave product **II-67d** as a white solid (173 mg, 0.54 mmol, 75% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.55 (d, J = 4.8 Hz, 1H, H_5), 7.88 – 7.82 (m, 2H), 7.78 – 7.72 (m, 2H), 7.22 (dd, J = 4.8, 1.1 Hz, 1H, H_4), 5.87 (ddd, J = 9.1, 7.9, 1.2 Hz, 1H, H_{10}), 4.01 (s, 3H, H_7), 3.84 – 3.73 (m, 1H, H_{9a}), 3.42 – 3.30 (m, 1H, H_{9b}), 2.65 – 2.46 (m, 2H, H_8).

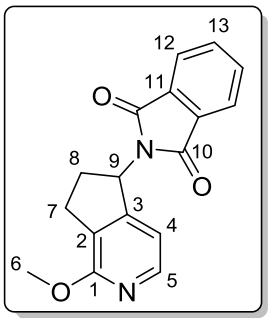
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.7 ($2C_{11}$), 165.9 (C_6), 152.7 (C_3), 148.0 (C_5), 144.1 (C_1), 142.6 (C_2), 134.5 (2CH), 131.9 ($2C_{12}$), 123.7 (2CH), 121.9 (C_4), 53.9 (C_{10}), 52.8 (C_7), 31.2 (C_9), 29.6 (C_8).

IR (v, cm^{-1}, $CDCl_3$) 2954, 1772, 1718, 1600, 1446, 1422, 1388, 1368, 1318, 1290, 1233, 1198, 1149, 1106, 1071, 997.

HRMS (EI+) calculated for $C_{18}H_{14}N_2O_4$: 322.0954; Found: 322.0967.

mp: decomposed at 191 ℃

2-(1-Methoxy-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)isoindoline-1,3-dione (II-67e)



Chemical Formula: $C_{17}H_{14}N_2O_3$
Molecular Weight: 294,31

According to the general procedure C, the reaction was carried out with xanthate **II-66e** (352 mg, 0.85 mmol) and TFA (116 mg, 78 μL, 1.01 mmol) in 8.5 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 3:7) gave product **II-67e** as a white solid (110 mg, 0.37 mmol, 44% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.98 (dt, J = 5.3, 0.9 Hz, 1H, H_5), 7.86 – 7.81 (m, 2H), 7.76 – 7.70 (m, 2H), 6.66 (dd, J = 5.2, 0.7 Hz, 1H, H_4), 5.82 (ddd, J = 9.2, 7.2, 0.9 Hz, 1H, H_9), 3.99 (s, 3H, H_6), 3.30 – 3.19 (m, 1H, H_{8a}), 2.94 – 2.84 (m, 1H, H_{8b}), 2.57 (dtd, J = 13.1, 9.1, 4.1 Hz, 1H, H_{7a}), 2.46 (ddt, J = 13.3, 9.4, 7.1 Hz, 1H, H_{7b}).

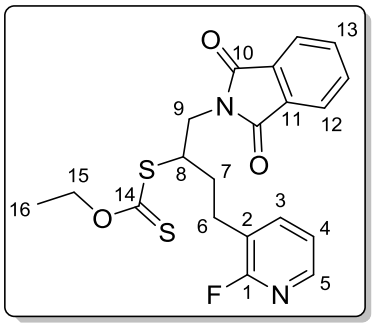
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.8 ($2C_{10}$), 161.2 (C_1), 151.9 (C_3), 145.5 (C_5), 134.3 (2CH), 132.0 ($2C_{11}$), 125.8 (C_2), 123.5 (2CH), 112.3 (C_4), 54.7 (C_9), 53.5 (C_6), 29.5 (C_8), 27.6 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 2983, 2952, 1771, 1716, 1602, 1589, 1469, 1460, 1406, 1388, 1367, 1330, 1175, 1105, 1087, 1066, 1019.

HRMS (EI+) calculated for $C_{17}H_{14}N_2O_3$: 294.1004; Found: 294.1008.

mp: 252-253 ℃

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(2-fluoropyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-70a)



Chemical Formula: $C_{20}H_{19}FN_2O_3S_2$
Molecular Weight: 418,50

According to the general procedure B, the reaction was carried out with xanthate **II-62b** (347 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 13 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 7:3) afforded product **II-70a** as a light yellow oil (306 mg, 0.73 mmol, 49% yield).

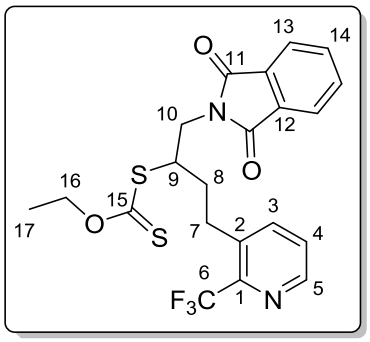
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.06 (ddd, J = 4.9, 1.9, 1.2 Hz, 1H, H_5), 7.90 – 7.82 (m, 2H), 7.77 – 7.70 (m, 2H), 7.68 – 7.60 (m, 1H, H_3), 7.11 (ddd, J = 7.1, 4.9, 1.8 Hz, 1H, H_4), 4.65 – 4.51 (m, 2H, H_{15}), 4.15 (dtd, J = 8.7, 7.2, 5.1 Hz, 1H, H_8), 4.06 – 3.94 (m, 2H, H_9), 2.93 (ddd, J = 15.1, 10.1, 5.4 Hz, 1H, H_{6a}), 2.80 (ddd, J = 14.0, 10.2, 6.1 Hz, 1H, H_{6b}), 2.08 (dddd, J = 14.2, 10.1, 6.1, 5.1 Hz, 1H, H_{7a}), 1.95 (dddd, J = 14.2, 10.2, 8.7, 5.4 Hz, 1H, H_{7b}), 1.40 (t, J = 7.1 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.3 (C_{14}), 168.2 ($2C_{10}$), 162.1 (d, J = 237.1 Hz, C_1), 145.7 (d, J = 14.7 Hz, C_5), 141.2 (d, J = 5.7 Hz, C_3), 134.3 (2CH), 131.9 ($2C_{11}$), 123.6 (2CH), 122.7 (d, J = 30.6 Hz, C_2), 121.6 (d, J = 4.1 Hz, C_4), 70.5 (C_{15}), 49.0 (C_8), 40.9 (C_9), 31.6 (C_7), 26.6 (d, J = 2.0 Hz, C_6), 13.8 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2985, 2938, 1774, 1718, 1607, 1580, 1469, 1445, 1394, 1364, 1226, 1113, 1050.

HRMS (EI+) calculated for $C_{20}H_{19}FN_2O_3S_2$: 418.0821, M-Xa: $C_{17}H_{14}FN_2O_2$: 297.1039; Found: 297.1044.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(2-(trifluoromethyl)pyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-70b)



Chemical Formula: $C_{21}H_{19}F_3N_2O_3S_2$
Molecular Weight: 468,51

According to the general procedure B, the reaction was carried out with xanthate **II-62c** (392 mg, 1.39 mmol) and *N*-allylphthalimide (782 mg, 4.18 mmol) in 1,2-dichloroethane (1.4 mL), and needed 10 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 9:1 to 3:1) afforded product **II-70b** as a light yellow oil (369 mg, 0.79 mmol, 57% yield).

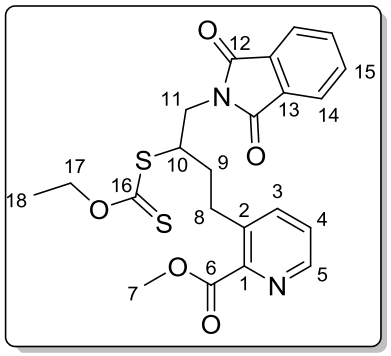
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.59 – 8.51 (m, 1H, H_5), 7.90 – 7.81 (m, 2H), 7.79 – 7.69 (m, 3H), 7.42 (dd, J = 7.9, 4.7 Hz, 1H, H_4), 4.67 – 4.54 (m, 2H, H_{16}), 4.21 (qd, J = 7.4, 5.1 Hz, 1H, H_9), 4.07 – 3.94 (m, 2H, H_{10}), 3.09 (td, J = 12.6, 11.5, 5.2 Hz, 1H, H_{7a}), 2.96 (td, J = 13.9, 12.9, 5.6 Hz, 1H, H_{7b}), 2.06 (ddt, J = 14.2, 11.0, 5.4 Hz, 1H, H_{8a}), 1.95 (dddd, J = 14.0, 11.1, 8.4, 5.2 Hz, 1H, H_{8b}), 1.41 (t, J = 7.1 Hz, 3H, H_{17}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.3 (C_{15}), 168.3 ($2C_{11}$), 147.1 (C_5), 145.8 (q, J = 32.5 Hz, C_1), 139.9 (C_3), 135.8 (C_2), 134.4 (2CH), 131.9 ($2C_{12}$), 126.6 (C_4), 123.6 (2CH), 122.4 (q, J = 273.9 Hz, C_6), 70.5 (C_{16}), 49.2 (C_9), 40.8 (C_{10}), 33.6 (C_8), 29.0 (q, J = 2.0 Hz, C_7), 13.8 (C_{17}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 2939, 1774, 1718, 1469, 1456, 1431, 1395, 1364, 1328, 1230, 1182, 1135, 1112, 1076, 1050, 1001.

HRMS (EI+) calculated for $C_{21}H_{19}F_3N_2O_3S_2$: 468.0789, M-Xa: $C_{18}H_{14}F_3N_2O_2$: 347.1007; Found: 347.0998.

Methyl 3-(4-(1,3-dioxoisoindolin-2-yl)-3-((ethoxycarbonothioyl)thio)butyl)-picolinate (II-70c)



Chemical Formula: $C_{22}H_{22}N_2O_5S_2$
Molecular Weight: 458,55

According to the general procedure B, the reaction was carried out with xanthate **II-62e** (407 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 8 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:1 to 1:3) afforded product **II-70c** as a white powder (441 mg, 0.96 mmol, 64% yield).

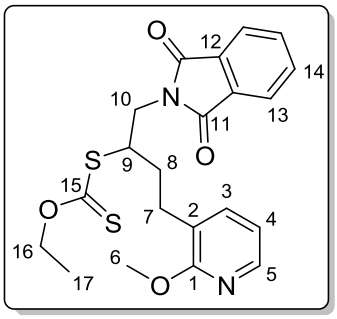
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.56 (dd, J = 4.6, 1.7 Hz, 1H, H_5), 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.66 (dd, J = 7.9, 1.7 Hz, 1H, H_3), 7.37 (dd, J = 7.8, 4.6 Hz, 1H, H_4), 4.66 – 4.52 (m, 2H, H_{17}), 4.25 – 4.15 (m, 1H, H_{10}), 4.05 – 3.99 (m, 2H, H_{11}), 3.89 (s, 3H, H_7), 3.14 (dddd, J = 29.7, 13.0, 10.5, 5.5 Hz, 2H, H_8), 2.10 (ddt, J = 14.1, 10.7, 5.5 Hz, 1H, H_{9a}), 2.04 – 1.91 (m, 1H, H_{9b}), 1.40 (t, J = 7.1 Hz, 3H, H_{18}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.6 (C_{16}), 168.3 ($2C_{12}$), 166.3 (C_6), 147.6 (C_5), 147.0 (C_1), 139.6 (C_3), 138.6 (C_2), 134.2 (2CH), 132.0 ($2C_{13}$), 126.4 (C_4), 123.6 (2CH), 70.4 (C_{17}), 52.8 (C_7), 49.3 (C_{10}), 40.9 (C_{11}), 33.3 (C_9), 30.8 (C_8), 13.8 (C_{18}).

IR (ν, cm^{-1}, $CDCl_3$) 2987, 2954, 1774, 1718, 1469, 1453, 1445, 1430, 1395, 1364, 1305, 1228, 1139, 1112, 1093, 1050.

HRMS (EI+) calculated for $C_{22}H_{22}N_2O_5S_2$: 458.0970; Found: 458.0963.

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-4-(2-methoxypyridin-3-yl)butan-2-yl) _O_-ethyl carbonodithioate (II-70d)



Chemical Formula: $C_{21}H_{22}N_2O_4S_2$
Molecular Weight: 430,54

According to the general procedure B, the reaction was carried out with xanthate **II-62f** (365 mg, 1.50 mmol) and *N*-allylphthalimide (842 mg, 4.50 mmol) in 1,2-dichloroethane (1.5 mL), and needed 18 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:1 to 2:1) afforded product **II-70d** as a light yellow oil (250 mg, 0.58 mmol, 39% yield).

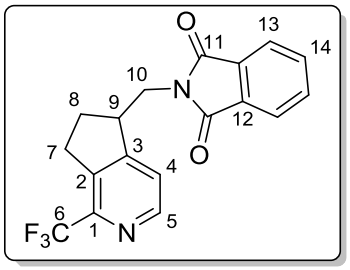
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.01 (dd, J = 5.1, 1.9 Hz, 1H, H_5), 7.85 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.38 (dd, J = 7.1, 1.9 Hz, 1H, H_3), 6.79 (dd, J = 7.2, 5.0 Hz, 1H, H_4), 4.65 – 4.50 (m, 2H, H_{16}), 4.18 – 4.09 (m, 1H, H_9), 3.99 (dd, J = 7.3, 2.0 Hz, 2H, H_{10}), 3.85 (s, 3H, H_6), 2.85 (ddd, J = 14.7, 9.9, 5.3 Hz, 1H, H_{7a}), 2.69 (ddd, J = 13.7, 9.9, 6.2 Hz, 1H, H_{7b}), 2.10 – 1.99 (m, 1H, H_{8a}), 1.96 – 1.83 (m, 1H, H_{8b}), 1.40 (t, J = 7.1 Hz, 3H, H_{17}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.7 (C_{15}), 168.2 ($2C_{11}$), 162.2 (C_1), 144.8 (C_5), 138.2 (C_3), 134.3 (2CH), 132.0 ($2C_{12}$), 123.6 (2CH), 123.5 (C_2), 116.9 (C_4), 70.3 (C_{16}), 53.3 (C_6), 49.0 (C_9), 41.2 (C_{10}), 30.9 (C_8), 27.8 (C_7), 13.8 (C_{17}).

IR (ν, cm^{-1}, $CDCl_3$) 2951, 1774, 1718, 1594, 1468, 1412, 1394, 1223, 1114, 1049.

HRMS (EI+) calculated for $C_{21}H_{22}N_2O_4S_2$: 430.1021, M-Xa: $C_{18}H_{17}N_2O_3$: 309.1239; Found: 309.1239.

2-((1-(Trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-71b)



Chemical Formula: $C_{18}H_{13}F_3N_2O_2$
Molecular Weight: 346,31

According to the general procedure C, the reaction was carried out with xanthate **II-70b** (350 mg, 0.75 mmol) and TFA (102 mg, 69 μL, 0.90 mmol) in 7.5 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 3:7) gave product **II-71b** as a white powder (187 mg, 0.54 mol, 72% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.50 (d, J = 4.9 Hz, 1H, H_5), 7.87 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.42 (d, J = 4.9 Hz, 1H, H_4), 3.96 (dd, J = 13.6, 5.6 Hz, 1H, H_{10a}), 3.85 (dd, J = 13.6, 8.9 Hz, 1H, H_{10b}), 3.78 – 3.68 (m, 1H, H_9), 3.25 (dddd, J = 16.7, 8.3, 6.3, 1.8 Hz, 1H, H_{7a}), 3.15 – 3.01 (m, 1H, H_{7b}), 2.28 (dtd, J = 13.1, 8.4, 6.1 Hz, 1H, H_{8a}), 2.01 (ddt, J = 12.9, 8.6, 6.3 Hz, 1H, H_{8b}).

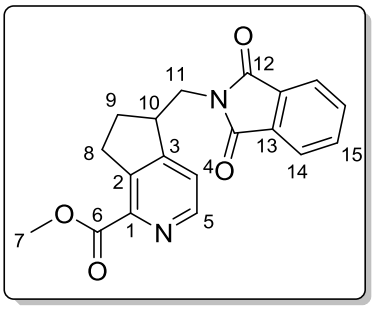
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{11}$), 156.2 (C_3), 147.6 (C_5), 144.2 (q, J = 34.4 Hz, C_1), 138.4 (C_2), 134.4 (2CH), 131.9 ($2C_{12}$), 123.6 (2CH), 122.5 (C_4), 122.2 (q, J = 273.1 Hz, C_6), 44.2 (C_9), 41.0 (C_{10}), 29.5 (C_8), 29.0 (q, J = 1.6 Hz, C_7).

IR (ν, cm^{-1}, $CDCl_3$) 3065, 2971, 2939, 1773, 1716, 1601, 1469, 1436, 1396, 1362, 1336, 1295, 1233, 1178, 1139, 1072, 1089.

HRMS (EI+) calculated for $C_{18}H_{13}F_3N_2O_2$: 346.0929; Found: 346.0939

mp: 147-148 ℃

Methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)-6,7-dihydro-5*H*-cyclopenta[*c*]-pyridine-1-carboxylate (II-71c)



Chemical Formula: $C_{19}H_{16}N_2O_4$
Molecular Weight: 336,35

According to the general procedure C, the reaction was carried out with xanthate **II-70c** (367 mg, 0.80 mmol) and TFA (109 mg, 73 μL, 0.96 mmol) in 8.0 mL 1,2-dichloroethane and needed 8 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:1 to 3:1) gave product **II-71c** as a white powder (110 mg, 0.33 mol, 41% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.54 (dd, J = 4.8, 0.8 Hz, 1H, H_5), 7.87 (dd, J = 5.4, 3.1 Hz, 2H), 7.79 – 7.72 (m, 2H), 7.39 (dd, J = 4.8, 1.0 Hz, 1H, H_4), 3.96 (dd, J = 13.5, 8.9 Hz, 1H, H_{11a}), 3.98 (s, 3H, H_7), 3.84 (dd, J = 13.5, 8.9 Hz, 1H, H_{11b}), 3.78 – 3.68 (m, 1H, H_{10}), 3.46 (ddd, J = 18.0, 8.7, 6.1 Hz, 1H, H_{8a}), 3.27 (ddd, J = 18.0, 8.8, 6.3 Hz, 1H, H_{8b}), 2.25 (dddd, J = 13.1, 8.7, 8.1, 6.1 Hz, 1H, H_{9a}), 1.98 (ddt, J = 13.1, 8.6, 6.2 Hz, 1H, H_{9b}).

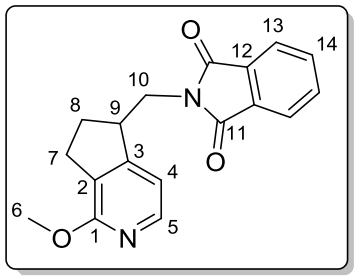
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.5 ($2C_{12}$), 166.1 (C_6), 155.8 (C_3), 147.8 (C_5), 143.8 (C), 143.5 (C), 134.3 (2CH), 131.9 ($2C_{13}$), 123.6 (2CH), 122.8 (C_4), 52.7 (C_7), 44.1 (C_{10}), 41.2 (C_{11}), 31.0 (C_8), 29.5 (C_9).

IR (v, cm^{-1}, $CDCl_3$) 2954, 1773, 1717, 1596, 1445, 1396, 1361, 1310, 1231, 1202, 1148, 1102, 1073, 1032.

HRMS (EI+) calculated for $C_{19}H_{16}N_2O_4$: 336.1110; Found: 336.1104.

mp: 174-175 ℃

2-((1-Methoxy-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)methyl)isoindoline-1,3-dione (II-71d)



Chemical Formula: $C_{18}H_{16}N_2O_3$
Molecular Weight: 308,34

According to the general procedure C, the reaction was carried out with xanthate **II-70d** (234 mg, 0.54 mmol) and TFA (74 mg, 50 μL, 0.65 mmol) in 5.4 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:10 to 1:3) gave product **II-71d** as a white powder (22 mg, 0.07 mol, 13% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.98 (dt, J = 5.2, 0.9 Hz, 1H, H_5), 7.90 – 7.84 (m, 2H), 7.78 – 7.71 (m, 2H), 6.82 (dd, J = 5.2, 0.7 Hz, 1H, H_4), 3.96 (s, 3H, H_6), 3.95 – 3.90 (m, 1H, H_{10a}), 3.78 (dd, J = 13.4, 9.2 Hz, 1H, H_{10b}), 3.72 – 3.63 (m, 1H, H_9), 2.99 – 2.89 (m, 1H, H_{7a}), 2.82 – 2.72 (m, 1H, H_{7b}), 2.20 (dddd, J = 13.0, 8.8, 8.0, 6.0 Hz, 1H, H_{8a}), 1.94 (ddt, J = 13.0, 8.7, 5.7 Hz, 1H, H_{8b}).

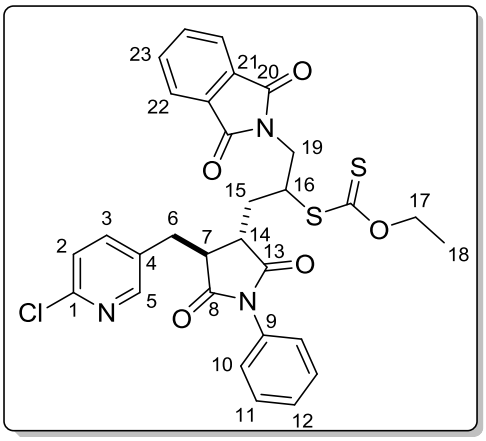
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 168.6 ($2C_{11}$), 161.1 (C_1), 155.4 (C_3), 145.3 (C_5), 134.3 (2CH), 132.1 ($2C_{12}$), 125.9 (C_2), 123.5 (2CH), 113.4 (C_4), 53.3 (C_6), 44.7 (C_9), 41.6 (C_{10}), 29.3 (C_8), 27.3 (C_7).

IR (v, cm^{-1}, $CDCl_3$) 2950, 1772, 1715, 1603, 1578, 1468, 1435, 1407, 1396, 1361, 1338, 1089, 1030.

HRMS (EI+) calculated for $C_{18}H_{16}N_2O_3$: 308.1161; Found: 308.1164.

mp: 150-152 ℃

_S_-(1-(4-((6-Chloropyridin-3-yl)methyl)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-(1,3-dioxoisoindolin-2-yl)propan-2-yl) _O_-ethyl carbonodithioate (II-73)



Chemical Formula: $C_{30}H_{26}ClN_3O_5S_2$
Molecular Weight: 608,12

According to the general procedure B, the reaction was carried out with xanthate **II-44b** (252 mg, 0.60 mmol) and *N*-allylphthalimide (337 mg, 1.80 mmol) in 1,2-dichloroethane (1.5 mL), and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:2 to 2:3) afforded product **II-73** as 1:1 diasteroisomer (278 mg, 0.46 mmol, 76% yield). Analytical samples could be obtained by flash chromatography on silica gel (gradient of dichloromethane/diethyl ether = 20:1 to 15:1).

Diastereoisomer 1:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.29 (dd, J = 2.5, 0.7 Hz, 1H, H_5), 7.87 (dd, J = 5.5, 3.1 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.57 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.48 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H, H_{12}), 7.30 – 7.25 (m, 1H, H_2), 7.16 – 7.12 (m, 2H), 4.65 (q, J = 7.1 Hz, 2H, H_{17}), 4.32 (dq, J = 11.1, 6.1 Hz, 1H, H_{16}), 4.07 (dd, J = 6.5, 3.1 Hz, 2H, H_{19}), 3.35 (dd, J = 13.8, 4.5 Hz, 1H, H_{6a}), 3.13 – 2.98 (m, 3H, H_{6b}, H_7 and H_{14}), 2.32 (ddd, J = 15.0, 10.6, 4.7 Hz, 1H, H_{15a}), 2.13 – 2.02 (m, 1H, H_{15b}), 1.43 (t, J = 7.1 Hz, 3H, H_{18}).

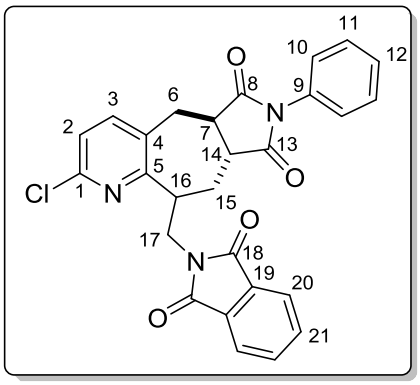
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.8 (C=S), 176.8 (C_8 or C_{13}), 176.7 (C_8 or C_{13}), 168.4 ($2C_{20}$), 150.9 (C_1 and C_5), 140.2 (C_3), 134.5 (2CH), 131.9 (C), 131.5 (C), 131.1 (C), 129.4 (C), 129.0 (C_{12}), 126.4 (2CH), 124.4(C_2), 123.8 (2CH), 71.1 (C_{17}), 47.7 (C_{16}), 46.7 (CH), 41.62 (C_{19}), 41.60 (CH), 32.8 (C_{15}), 32.3 (C_{16}), 13.9 (C_{18}).

mp: 77-79 ℃

Diastereoisomer 2:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.42 (d, J = 2.5 Hz, 1H, H_5), 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 7.69 (dd, J = 8.2, 2.5 Hz, 1H, H_3), 7.48 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H, H_{12}), 7.31 (d, J = 8.1 Hz, 1H, H_2), 7.21 – 7.15 (m, 2H), 4.61 (q, J = 7.1 Hz, 2H, H_{17}), 4.41 (tt, J = 8.0, 6.3 Hz, 1H, H_{16}), 4.12 – 3.92 (m, 2H, H_{19}), 3.43 – 3.21 (m, 3H), 2.92 (q, J = 6.5 Hz, 1H), 2.28 (dt, J = 14.7, 6.7 Hz, 1H, H_{15a}), 2.07 (ddd, J = 14.9, 8.5, 6.7 Hz, 1H, H_{15b}), 1.41 (t, J = 7.1 Hz, 3H, H_{18}).
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.0 (C=S), 176.7 (C_8 or C_{13}), 176.6 (C_8 or C_{13}), 168.2 ($2C_{20}$), 150.8 (C_1), 150.7 (C_5), 140.2 (C_3), 134.5 (2CH), 131.9 (C), 131.6 (C), 131.5 (C), 129.3 (2CH), 129.0 (C_{12}), 126.4 (2CH), 124.6 (C_2), 123.8 (2CH), 70.9 (C_{17}), 48.2 (C_{16}), 46.7 (CH), 42.2 (CH), 40.5 (C_{19}), 33.9 (C_{15}), 32.1 (C_6), 13.8 (C_{18}).
mp: 92-94 ℃

2-Chloro-10-((1,3-dioxoisoindolin-2-yl)methyl)-7-phenyl-5a,8a,9,10-tetrahydropyrrolo[3',4':4,5]cyclohepta[1,2-*b*]pyridine-6,8(5H,7H)-dione (II-74)



Chemical Formula: $C_{27}H_{20}ClN_3O_4$
Molecular Weight: 485,92

According to the general procedure C, the reaction was carried out with xanthate **II-73** (254 mg, 0.42 mmol) and TFA (57 mg, 38 μL, 0.50 mmol) in 4.2 mL 1,2-dichloroethane and needed 6 h to go to completion. Flash chromatography on silica gel (14-40 μm, gradient of ethyl acetate/toluene = 1:10 to 1:7) gave the 1st diastereoisomer as a white solid (50 mg, 0.10 mmol), and 2nd diastereoisomer as white solid (30 mg, 0.06 mmol) and a mixture of the two diastereoisomers (42 mg, 0.09 mmol) in a global yield of 60% (dr = 1.4:1).

1st diastereoisomer:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.95 – 7.83 (m, 2H), 7.79 – 7.70 (m, 2H), 7.54 (d, J = 7.9 Hz, 1H, H_3), 7.43 (dd, J = 8.4, 6.7 Hz, 2H, H_{11}), 7.39 – 7.32 (m, 1H, H_{12}), 7.25 – 7.20 (m, 2H, H_{10}), 7.17 (d, J = 7.9 Hz, 1H, H_2), 4.37 (qd, J = 14.3, 7.6 Hz, 2H, H_{17}), 3.62 – 3.43 (m, 2H), 2.99 (td, J = 11.2, 3.0 Hz, 2H), 2.61 – 2.45 (m, 2H, H and H_{15a}), 1.66 – 1.48 (m, 1H, H_{15b}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 174.8 (C=O), 174.5 (C=O), 168.9 ($2C_{18}$), 160.7 (C_5), 148.7 (C_1), 140.2 (C_3), 134.24 ($2C_{20}$ or $2C_{21}$), 134.16 (C), 132.2 (C), 131.8 (C), 129.3 ($2C_{11}$), 128.6 (C_{12}), 126.2 ($2C_{10}$), 123.6 ($2C_{20}$ or $2C_{21}$), 122.5 (C_2), 51.9 (CH), 47.4 (CH), 43.2 (CH), 41.2 (C_{17}), 32.2 (CH_2), 27.4 (CH_2).

IR (ν, cm^{-1}, $CDCl_3$) 2954, 1773, 1719, 1600, 1580, 1559, 1501, 1433, 1399, 1367, 1198, 1173, 1146, 1113, 1029.

HRMS (EI+) calculated for $C_{27}H_{20}ClN_3O_4$: 485.1142; Found: 485.1142.

mp: 276-277 ℃

2nd diastereoisomer:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.83 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H, H_3), 7.48 – 7.42 (m, 2H, H_{11}), 7.40 – 7.34 (m, 1H, H_{12}), 7.29 – 7.25 (m, 2H, H_{10}), 7.15 (d, J = 8.0 Hz, 1H, H_2), 4.17 (td, J = 14.8, 13.8, 8.1 Hz, 2H, H_{17}), 3.94 – 3.81 (m, 1H), 3.57 (dd, J = 16.3, 6.1 Hz, 1H), 3.29 (dd, J = 16.3, 9.0 Hz, 1H), 3.13 – 2.86 (m, 2H), 2.47 – 2.41 (m, 1H), 2.03 (ddd, J = 13.9, 12.0, 4.9 Hz, 1H).

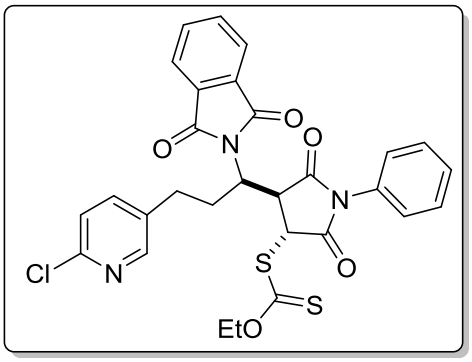
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 175.8 (C=O), 175.7 (C=O), 168.3 ($2C_{18}$), 158.8 (C_5), 149.0 (C_1), 141.4 (C_3), 134.2 (2CH), 132.5 (C), 132.0 (C), 131.8 (C), 129.3 ($2C_{11}$), 128.7 (C_{12}), 126.3 ($2C_{10}$), 126.2 (C), 123.5 (2CH), 122.9 (C_2), 44.7 (CH), 44.5 (CH), 43.6 (CH), 39.5 (C_{17}), 30.7 (CH_2), 27.5 (CH_2).

IR (v, cm^{-1}, $CDCl_3$) 2939, 1773, 1718, 1599, 1578, 1559, 1501, 1435, 1397, 1376, 1177, 1151, 1115, 1030, 1014.

HRMS (EI+) calculated for $C_{27}H_{20}ClN_3O_4$: 485.1142; Found: 485.1142.

mp: 215-216 ℃

_S_-(-4-(3-(6-chloropyridin-3-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl)-2,5-dioxo-1-phenylpyrrolidin-3-yl) _O_-ethyl carbonodithioate (II-75)



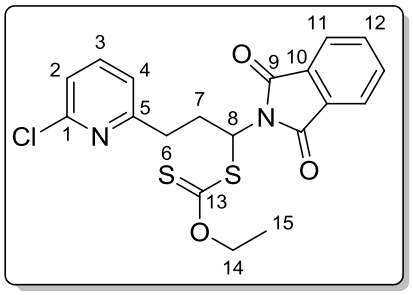
Chemical Formula: $C_{29}H_{24}ClN_3O_5S_2$
Molecular Weight: 594,10

According to the general procedure A, the reaction was carried out with xanthate **II-44f** (604 mg, 1.50 mmol) and *N*-phenylmaleimide (173 mg, 1.00 mmol) in 1,2-dichloroethane (3.0 mL), and needed 1 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:2 to 2:3) afforded product **II-75** as 1.4:1 diasteroisomer (341 mg, 0.57 mmol, 57% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.15 (dd, J = 2.6, 0.7 Hz, 1H), 8.12 (dd, J = 2.6, 0.7 Hz, 1.5 H), 7.87 – 7.81 (m, 5H), 7.80 – 7.72 (m, 5H), 7.50 – 7.33 (m, 10H), 7.27 (ddd, J = 6.6, 3.2, 1.6 Hz, 5H), 7.17 (dd, J = 8.2, 0.7 Hz, 1H), 7.13 (dd, J = 8.1, 0.7 Hz, 1.5 H), 4.82 – 4.57 (m, 5H), 4.49 – 4.36 (m, 5H), 4.37 (d, J = 6.2 Hz, 1H), 4.17 (dd, J = 10.2, 6.8 Hz, 1.5 H), 4.02 (dd, J = 9.3, 6.2 Hz, 1H), 2.92 – 2.74 (m, 4H), 2.70 – 2.54 (m, 5H), 2.20 – 2.10 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 4.5H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 209.8, 209.2, 173.3, 173.2, 171.3, 171.1, 168.6, 168.5, 149.7, 149.6, 149.5, 138.9, 138.8, 134.8, 134.60, 134.56, 134.5, 131.61, 131.59, 131.6, 131.1, 129.4, 129.3, 129.10, 129.06, 126.32, 126.30, 124.2, 124.1, 123.89, 71.6, 71.2, 51.7, 51.1, 49.6, 49.4, 47.6, 47.1, 30.8, 30.6, 29.2, 29.1, 13.8, 13.7.

_S_-(3-(6-Chloropyridin-2-yl)-1-(1,3-dioxoisoindolin-2-yl)propyl) _O_-ethyl carbonodithioate (II-83)



Chemical Formula: $C_{19}H_{17}ClN_2O_3S_2$
Molecular Weight: 420,93

According to the general procedure A, the reaction was carried out with xanthate **II-82** (1.98 g, 8.00 mmol) and *N*-vinylphthalimide (346 mg, 2.00 mmol) in ethyl acetate (8.0 mL), and needed 12 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 15:1 to 4:1) afforded product **II-83** as a light yellow oil (569 mg, 1.35 mmol, 68% yield).

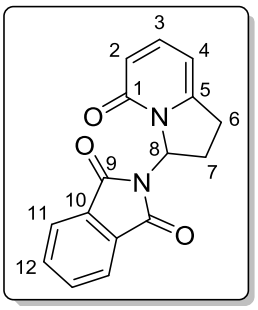
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.87 – 7.80 (m, 2H), 7.77 – 7.69 (m, 2H), 7.49 (t, J = 7.7 Hz, 1H, H_3), 7.10 – 7.02 (m, 2H, H_4 and H_2), 6.31 (dd, J = 9.1, 6.6 Hz, 1H, H_8), 4.61 (q, J = 7.1 Hz, 2H, H_{14}), 2.98 – 2.83 (m, 2H, H_6), 2.83 – 2.72 (m, 1H, H_{7a}), 2.66 – 2.53 (m, 1H, H_{7b}), 1.38 (t, J = 7.1 Hz, 3H, H_{15}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 211.0 (C_{13}), 166.8 (C_9), 160.7 (C), 151.1 (C), 139.1 (C_3), 134.5 (CH), 131.7 (C), 123.7 (2CH), 122.0 (CH), 121.5 (CH), 70.6 (C_{14}), 57.3 (C_8), 35.0 (C_6), 32.6 (C_7), 13.9 (C_{15}).

IR (v, cm^{-1}, $CDCl_3$) 2985, 2930, 1780, 1720, 1586, 1562, 1441, 1380, 1363, 1333, 1231, 1154, 1139, 1111, 1049.

HRMS (EI+) calculated for $C_{19}H_{17}ClN_2O_3S_2$: 420.0369, M-Xa: $C_{16}H_{12}ClN_2O_2$: 299.0587; Found: 299.0592.

2-(5-Oxo-1,2,3,5-tetrahydroindolizin-3-yl)isoindoline-1,3-dione (II-85)



Chemical Formula: $C_{16}H_{12}N_2O_3$
Molecular Weight: 280,28

According to the general procedure, the reaction was carried out with xanthate **II-83** (282 mg, 0.70 mmol) and TFA (96 mg, 64 μL, 0.84 mmol) in 7.0 mL 1,2-dichloroethane and needed 7 h to go to completion. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:1) gave the desired product **II-85** as a white solid (160 mg, 0.57 mmol, 82% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.82 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.33 (dd, J = 9.1, 6.8 Hz, 1H, H_3), 6.75 (dd, J = 9.5, 2.5 Hz, 1H, H_8), 6.27 (dq, J = 9.1, 1.0 Hz, 1H, H_2), 6.14 (dq, J = 6.8, 1.3 Hz, 1H, H_4), 3.72 (dddt, J = 17.1, 10.0, 8.7, 1.3 Hz, 1H, H_{7a}), 3.12 (dddt, J = 17.2, 10.2, 2.9, 0.9 Hz, 1H, H_{7b}), 2.70 (dddd, J = 14.1, 10.2, 9.5, 8.7 Hz, 1H, H_{6a}), 2.35 (ddt, J = 14.0, 9.9, 2.7 Hz, 1H, H_{6b}).

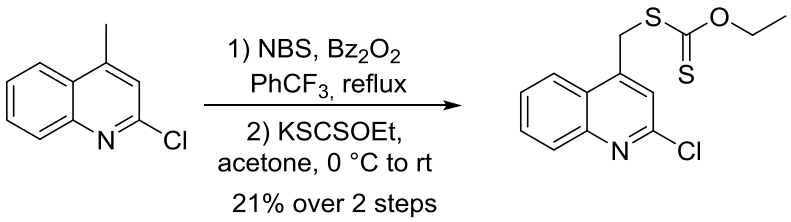
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 167.0 (C_9), 151.6 (C_5), 141.4 (C_3), 134.4 (CH), 131.7 (C_{10}), 123.8 (CH), 117.7 (C_2), 101.0 (C_4), 65.4 (C_8), 30.5 (C_7), 26.8 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 2958, 1778, 1723, 1665, 1590, 1547, 1470, 1435, 1424, 1400, 1367, 1355, 1297, 1178, 1297, 1158, 1149, 1111, 1089, 1030, 1017.

HRMS (EI+) calculated for $C_{16}H_{12}N_2O_3$: 280.0848; Found: 280.0835.

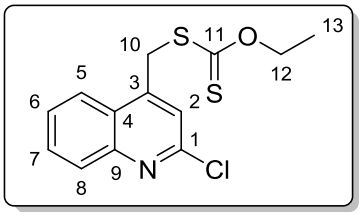
mp: 203-204 ℃

S-((2-Chloroquinolin-4-yl)methyl) *O*-ethyl carbonodithioate (II-95)



2-Chloro-4-methylquinoline (3.48 g, 19.6 mmol, 1.0 equiv), NBS (6.99 g, 39.3 mmol, 2.0 equiv) and Bz_2O_2 (0.46 g, 1.96 mmol, 0.1 equiv) in $PhCF_3$ (59 mL) was refluxed under N_2 for 4 h. The suspension was cooled down to room temperature and the solid was removed by filtration and to the filtrate was added dichloromethane. Sat. aqueous K_2CO_3 was added and the organic phase was separated. The aqueous phase was extracted by dichloromethane twice. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethy acetate = 10:1 to 8:1) to give 4-(bromomethyl)-2-chloroquinoline (1.08 g, 4.2 mmol).

Potassium *O*-ethylxanthate (0.74 g, 4.6 mmol, 1.1 equiv) was added portionwise to a solution of 4-(bromomethyl)-2-chloroquinoline (1.08 g, 4.2 mmol) in acetone (8.4 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 1 h. Water was then added and extracted with dichloromethane for 3 times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 4:1) to give the desired product **II-95** as a white solid (1.27 g, 4.2 mmol, 21% yield over 2 steps).



Chemical Formula: $C_{13}H_{12}ClNOS_2$
Molecular Weight: 297,82

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.05 (dd, J = 8.3, 1.2 Hz, 1H), 7.98 (dd, J = 8.6, 1.4 Hz, 1H), 7.76 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.61 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.49 (s, 1H, H_2), 4.76 (s, 2H, H_{10}), 4.68 (q, J = 7.1 Hz, 2H, H_{12}), 1.43 (t, J = 7.2 Hz, 3H, H_{13}).

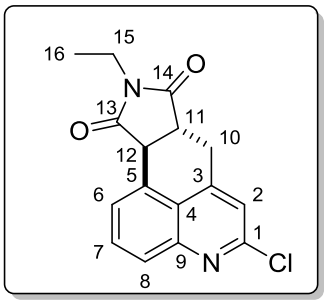
^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.4 (C_{11}), 150.5 (C), 148.3 (C), 144.9 (C), 130.8 (CH), 129.7 (CH), 127.5 (CH), 125.7 (C), 123.5 (CH), 122.8 (C_2), 71.0 (C_{12}), 36.5 (C_{10}), 13.9 (C_{13}).

IR (v, cm^{-1}, $CDCl_3$) 3074, 2987, 2940, 1587, 1561, 1511, 1414, 1301, 1244, 1229, 1220, 1151, 1105, 1049.

HRMS (EI+) calculated for $C_{13}H_{12}ClNOS_2$: 297.0049, M-Xa: $C_{10}H_7ClN$; 176.0267; Found: 176.0267.

mp: 53-55 ℃

5-Chloro-9-ethyl-7a,10a-dihydroisoindolo[6,5,4-*de*]quinoline-8,10(7*H*,9*H*)-dione (II-97)



Chemical Formula: $C_{16}H_{13}ClN_2O_2$
Molecular Weight: 300,74

According to the general procedure A, the reaction was carried out with xanthate **II-95** (617 mg, 2.07 mmol, 2.0 equiv) and *N*-ethylmaleimide (130 mg, 1.04 mmol, 1.0 equiv) in 1,2-dichloroethane (2.0 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 6:1 to 2:1) afforded product **II-97** as a white solid (52 mg, 0.17 mmol, 17% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.98 – 7.93 (m, 2H), 7.78 (dd, J = 8.4, 7.5 Hz, 1H), 7.28 (d, J = 1.3 Hz, 1H, H_2), 4.42 (dt, J = 7.8, 1.0 Hz, 1H, H_{12}), 3.59 – 3.52 (m, 2H, H_{11} and H_{10a}), 3.48 (qd, J = 6.5, 1.8 Hz, 2H, H_{15}), 3.30 (ddd, J = 18.1, 8.4, 1.4 Hz, 1H, H_{10b}), 1.07 (t, J = 7.2 Hz, 3H, H_{16}).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 177.5 (C=O), 176.2 (C=O), 150 9 (C), 147.5 (C), 143.4 (C), 130.9 (CH), 128.4 (CH), 127.1 (CH), 126.9 (C), 122.8 (C), 120.9 (C_2), 42.9 (C_{12}), 38.3 (C_{11}), 34.4 (C_{15}), 26.0 (C_{10}), 13.0 (C_{16}).

IR (ν, cm^{-1}, $CDCl_3$) 2984, 2942, 1780, 1710, 1596, 1566, 1507, 1444, 1426, 1403, 1380, 1352, 1226, 1143, 1100.

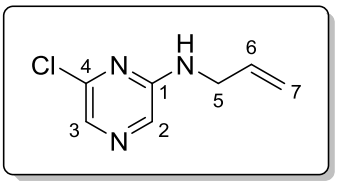
HRMS (EI+) calculated for $C_{16}H_{13}ClN_2O_2$: 300.0666; Found: 300.0674.

Chapter 3: Xanthate-Based Radical Alkylation of Pyrazines

General procedure

A magnetically stirred solution of xanthate (2.0 equiv) and pyrazine (1.0 equiv) in 1, 2-dichloroethane (1.0 mmol/mL of xanthate) was refluxed for 15 min under a flow of nitrogen. 20 mol % of DLP was then added every hour until total consumption of one substrate. The reaction mixture was then cooled to room temperature and the solvent was then evaporated under reduced pressure. Unless otherwise specified, the crude product was directly purified by flash chromatography on silica gel.

N-Allyl-6-chloropyrazin-2-amine (III-13)



In a sealed tube, 2,6-dichloropyrazine (2.0 g, 13.4 mmol, 1 equiv) was heated with allylamine (2.30 g, 3.0 mL, 40.2 mmol, 3 equiv) at 100 ℃ for 48 h. The solution was then cooled to room temperature. Solvent and excess of allylamine were then removed under reduced pressure. The residue was then redissolved in dichloromethane and washed three times with water. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was further purified by flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:4 to 1:2). The product **III-13** was obtained as light yellow solid (2.1g, 12.4 mmol, 92% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.82 (s, 1H), 7.76 (s, 1H), 5.93 (ddt, J = 17.1, 10.6, 5.4 Hz, 1H, H_6), 5.25 (dddd, J = 24.1, 10.3, 2.8, 1.4 Hz, 2H, H_7), 4.84 (s, 1H, *N*H), 4.00 (tt, J = 5.8, 1.6 Hz, 2H, H_5).

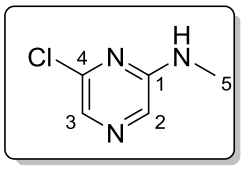
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 154.0 (C), 147.1 (C), 133.8 (CH), 131.4 (CH), 129.0 (CH), 117.3 (C_7), 44.2 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3440, 1575, 1534, 1498, 1421, 1170.

HRMS (EI+) calculated for $C_7H_8ClN_3$: 169.0407; Found: not found.

mp: 52-53 ℃

6-Chloro-*N*-methylpyrazin-2-amine (III-18a)



Chemical Formula: $C_5H_6ClN_3$
Molecular Weight: 143,57

In a sealed tube, 2,6-dichloropyrazine (3.3 g, 22.1 mmol, 1 equiv) was heated with ethanolic methylamine (33% w/w; 10.3 g, 110.5 mmol, 5 equiv) at 80 °C for 0.5 h. Solvent and excess of methylamine were then removed under reduced pressure. The residue was then dissolved in dichloromethane and washed three times with water. The organic phase was then evaporated under reduced pressure. The pure product **III-18a** was obtained by recrystallization from DCM/petroleum ether as a white solid (2.8 g, 19.5 mmol, 88% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.79 (s, 1H), 7.76 (s, 1H), 4.88 (br, 1H, *N*H), 2.99 (d, J = 5.2 Hz, 3H, H_5).

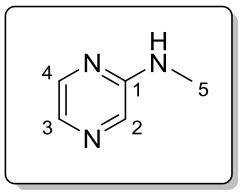
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 154.9 (C), 147.1 (C), 130.8 (CH), 128.8 (CH), 28.6 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3460, 2948, 2906, 1585, 1536, 1508, 1450, 1413, 1380, 1321, 1195, 1128, 996.

HRMS (EI+) calculated for $C_5H_6ClN_3$: 143.0250; Found: 143.0241.

mp : 100-101 °C

N-Methylpyrazin-2-amine (III-18c)



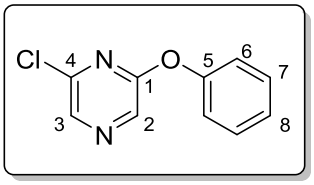
Chemical Formula: $C_5H_7N_3$
Molecular Weight: 109,13

In a sealed tube, 2-chloropyrazine (1.0 g, 8.7 mmol, 1 equiv) was heated with ethanolic methylamine (33% w/w; 4.0 g, 43.6 mmol, 5 equiv) at 95 °C for 1 h. Solvent and excess of methylamine were then removed under reduced pressure. The residue was then dissolved in dichloromethane and washed three times with water. The organic phase was then evaporated under reduced pressure and the crude product was further purified by flash chromatography on silica gel (EtOAc/Et_2O= 1:6 to 1:4). The product **III-18c** was obtained as a colorless oil (0.73 g, 6.7 mmol, 77% yield), which solidified as a light brown solid. The spectra is in agreement with the literature report.[128]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.99 (dd, J = 2.7, 1.5 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.80 (d, J = 2.8 Hz, 1H), 4.63 (br, 1H, *N*H), 2.97 (d, J = 5.2 Hz, 3H, H_5).

[128] (a) Li, F.; Xie, J.; Shan, H.; Sun C.; Chen, L. *RSC Advances* **2012**, *2*, 8645. (b) Cheeseman, G. W. H. *J. Chemical Society* **1960**, 242.

2-Chloro-6-phenoxypyrazine (III-18e)



Chemical Formula: $C_{10}H_7ClN_2O$
Molecular Weight: 206,63

2, 6-dichloropyrazine (5.0 g, 33.6 mmol, 1 equiv) and potassium carbonate (5.1 g, 37.0 mmol, 1.1 equiv) were dissolved in 30 mL DMF and stirred for 15 min at rt. A solution of phenol (3.1 g, 33.6 mmol, 1 equiv) in 40 mL DMF was added dropwise to the reaction mixture above. The reaction was monitored by TLC and it took 5 h for the reaction to go to completion. The reaction mixture was then poured into 250 mL ice-water and extracted with EtOAc for three times. The combined organic layer was then washed with water and brine, dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the crude product was further purified by flash chromatography on silica gel (EtOAc/petroleum ether = 1:20) to give the desired product **III-18e** as a white solid (5.2 g, 25.0 mmol, 74% yield).

^{1}H NMR (δ, ppm) (400 MHz, CD_2Cl_2) 8.30 (s, 1H), 8.29 (s, 1H), 7.49 – 7.43 (m, 2H), 7.30 (t, J = 7.4 Hz, 1H), 7.18 (dd, J = 5.2, 3.5 Hz, 2H).

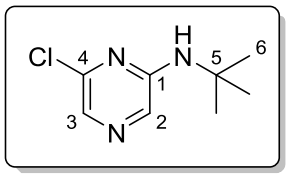
^{13}C NMR (δ, ppm) (101 MHz, CD_2Cl_2) 159.5 (C), 153.4 (C), 146.2 (C), 138.2 (CH), 133.7 (CH), 130.5 (2CH), 126.4 (C_8), 121.8 (2CH).

IR (ν, cm^{-1}, $CDCl_3$) 1600, 1566, 1527, 1490, 1400, 1301, 1169, 1004.

HRMS (EI+) calculated for $C_{10}H_7ClN_2O$: 206.0247; Found: 206.0243.

mp: 43-44 ℃

N-(*tert*-Butyl)-6-chloropyrazin-2-amine (III-18h)



Chemical Formula: $C_8H_{12}ClN_3$
Molecular Weight: 185,66

In a sealed tube, 2,6-dichloropyrazine (1.50 g, 10.1 mmol, 1 equiv), *tert*-butylamine (3.68 g, 50.3 mmol, 5 equiv) and *N*, *N*-diisopropylethylamine (1.96 g, 15.1 mmol, 1.5 equiv) in 5 mL EtOH were heated at 120 ℃ for 20 h. Solvent was then removed under reduced pressure. The residue was then dissolved in dichloromethane and washed three times with water and once with brine. The organic phase was then evaporated under reduced pressure and the crude product was further purified by flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:6 to 1:2). The product **III-18h** was obtained as a light grey solid (968 mg, 5.2 mmol, 52% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.73 (s, 1H), 7.71 (s, 1H), 4.68 (br, 1H), 1.44 (s, 9H, H_6).

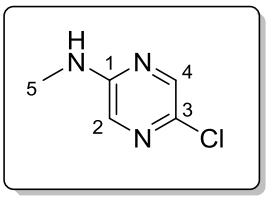
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 153.8 (C), 146.7 (C), 130.4 (CH), 130.0 (CH), 51.9 (C_5), 29.0 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3436, 2980, 2969, 1576, 1533, 1497, 1456, 1428, 1366, 1329, 1218, 1163, 1144, 999.

HRMS (EI+) calculated for $C_8H_{12}ClN_3$: 185.0720; Found: 185.0714.

mp: 113-114 ℃

5-Chloro-*N*-methylpyrazin-2-amine (III-18o)



Chemical Formula: $C_5H_6ClN_3$
Molecular Weight: 143,57

A solution of 3-amino-6-chloropyridine[129](146 mg, 1.13 mmol, 1 equiv) in dry THF (2.8 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 50 mg, 1.24 mmol, 1.1 equiv) in THF (7.6 mL). The suspension was stirred at room temperature for 3 hours, iodomethane (176 mg, 77 μL, 1.24 mmol, 1.1 equiv) was added and the reaction was heated to 40 ℃ for 9 hours. After cooling to room temperature, the solvent was removed. Water was added and it was extracted twice with dichloromethane. The organic layer was gathered and was dried over anhydrous Na_2SO_4, concentrated to give the crude product. Purification by flash chromatography on silica gel (Et_2O/petroleum ether = 1:2 to 1:1) afforded the desired product **III-18o** as a yellow solid (62 mg, 0.43 mmol, 38% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.01 (d, J = 1.3 Hz, 1H), 7.65 (d, J = 1.4 Hz, 1H), 4.70 (br, 1H, *N*H), 2.96 (d, J = 5.2 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 154.1 (C_1), 141.4 (C_3), 136.1 (CH), 129.7 (CH), 28.8 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3460, 2945, 1587, 1537, 1501, 1419, 1370, 1283, 1199, 1137, 1010.

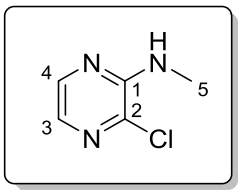
HRMS (EI+) calculated for $C_5H_6ClN_3$: 143.0250; Found: 143.0255.

mp: 108-111 ℃.

---

[129] Cai, L.; Cuevas, J.; Temme, S.; Herman, M.; Dagostin, C.; Widdowson, D.; Innis, R.; Pike, V. *J. Med. Chem.* **2007**, *50*, 4746.

3-Chloro-*N*-methylpyrazin-2-amine (III-18q)



Chemical Formula: $C_5H_6ClN_3$
Molecular Weight: 143,57

In a sealed tube, 2,3-dichloropyrazine (525 mg, 3.53 mmol, 1 equiv) was heated with ethanolic methylamine (33% w/w; 1.64 g, 17.63 mmol, 5 equiv) at 80 ℃ for 1 h. Solvent and excess of methylamine were then removed under reduced pressure. The residue was then dissolved in dichloromethane and washed three times with water. The organic phase was then evaporated under reduced pressure and the crude product was further purified by flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:6 to 1:5). The product **III-18q** was obtained as a colorless oil (472 mg, 3.29 mmol, 93% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (d, J = 2.7 Hz, 1H, H_4), 7.56 (d, J = 2.7 Hz, 1H, H_3), 5.23 (br, 1H, *N*H), 3.04 (d, J = 5.0 Hz, 3H, H_5).

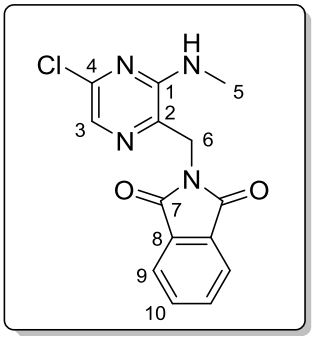
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 151.9 (C_1), 140.8 (C_4), 135.0 (C_2), 130.5 (C_3), 28.3 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3457, 2951, 2905, 1588, 1531, 1508, 1418, 1362, 1321, 1238, 1187, 1110, 1128, 1048.

HRMS (EI+) calculated for $C_5H_6ClN_3$: 143.0250; Found: 143.0259.

2-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19a)

According to the general procedure, the reaction was carried out with xanthate **III-14** (155 mg, 0.55 mmol) and **III-18a** (40 mg, 0.28 mmol) in 0.6 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1/2 to 0/1) afforded the desired single addition product **III-19a** as a white solid (62 mg, 0.20 mmol, 73% yield) and the double addition product **III-20a** as a white solid (7 mg, 0.01 mmol, 5% yield).



Chemical Formula: $C_{14}H_{11}ClN_4O_2$
Molecular Weight: 302,72

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.92 – 7.84 (m, 2H, H_{Ar}), 7.77 – 7.73 (m, 2H, H_{Ar}), 7.71 (s, 1H, H_3), 6.04 (br, 1H, *N*H), 4.84 (s, 2H, H_6), 3.01 (d, J = 4.7 Hz, 3H, H_5).

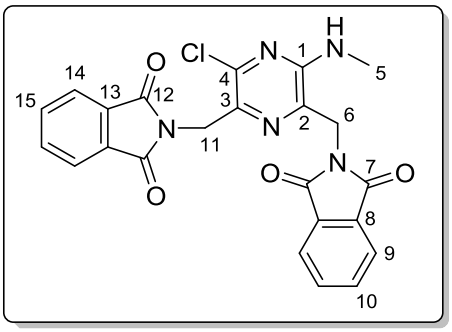
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.7 (C=O), 153.2 (C_1), 147.1 (C_4), 134.6 (CH), 133.8 (C_2), 132.0 (C_8), 129.2 (C_3), 123.9 (CH), 39.9 (C_6), 28.6 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3384, 2942, 1771, 1714, 1582, 1511, 1429, 1392, 1382, 1329, 1235, 1106, 1084.

HRMS (EI+) calculated for $C_{14}H_{11}ClN_4O_2$: 302.0571; Found: 302.0575.

mp: 175-176 ℃

2,2'-((3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20a)



Chemical Formula: $C_{23}H_{16}ClN_5O_4$
Molecular Weight: 461,86

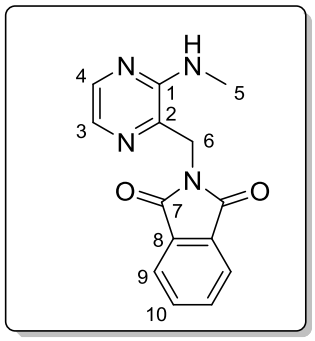
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 – 7.85 (m, 3H), 7.85 – 7.78 (m, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.70 (s, 1H), 5.91 (br, J = 4.4 Hz, 1H, *N*H), 4.97 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 2.99 (d, J = 4.7 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.3, 168.2, 167.9, 153.1, 143.7, 134.6, 134.5, 133.66, 132.0, 131.5, 129.2, 124.3, 123.8, 123.7, 41.3, 39.9, 28.5.

IR (ν, cm^{-1}, $CDCl_3$) 3386, 1775, 1719, 1582, 1512, 1394, 1392, 1235, 1105, 1086.

HRMS (EI+) calculated for $C_{23}H_{16}ClN_5O_4$: 461.0891; Found: 461.0902.

2-((3-(Methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19c)



Chemical Formula: $C_{14}H_{12}N_4O_2$
Molecular Weight: 268,28

Following the general procedure, the reaction was carried out with xanthate **III-14** (566 mg, 2.01 mmol) and **III-18c** (110 mg, 1.01 mmol) in 2.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 0:1) afforded the desired product **III-19c** as a light yellow solid (181 mg, 0.67 mmol, 67% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.98 (d, J = 2.7 Hz, 1H), 7.87 (dd, J = 5.4, 3.0 Hz, 2H), 7.74 (ddd, J = 7.3, 4.7, 2.8 Hz, 3H), 5.68 (br, 1H, *N*H), 4.85 (s, 2H, H_6), 3.00 (d, J = 4.7 Hz, 3H, H_5).

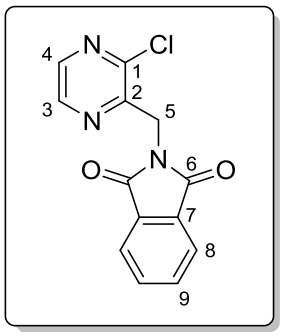
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.7 ($2C_7$), 153.6 (C), 142.0 (CH), 136.2 (C), 134.4 (2CH), 132.2 ($2C_8$), 131.5 (CH), 123.8 (2CH), 40.4 (C_6), 28.4 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3398, 2930, 1772, 1714, 1587, 1523, 1422, 1392, 1334, 1205, 1084.

HRMS (EI+) calculated for $C_{14}H_{12}N_4O_2$: 268.0960; Found: 268.0959.

mp: 168-169 ℃

2-((3-Chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19d)



Chemical Formula: $C_{13}H_8ClN_3O_2$
Molecular Weight: 273,68

Following the general procedure, the reaction was carried out with xanthate **III-14** (258 mg, 0.92 mmol) and 2-chloropyrazine **III-18d** (52 mg, 0.46 mmol) in 0.9 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAC = 10:1 to 4:1) afforded the desired product **III-19d** as a white solid (44 mg, 0.16 mmol, 35% yield), and 15 mg 2-chloropyrazine (0.13 mmol) was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (d, J = 2.5 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 7.91 (dd, J = 5.4, 3.1 Hz, 2H), 7.77 (dd, J = 5.4, 3.1 Hz, 2H), 5.14 (s, 2H, H_5).

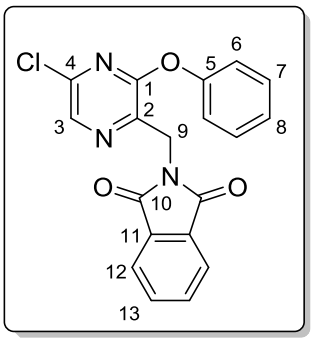
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.1 ($2C_6$), 149.0 (C), 147.7 (C), 142.8 (C_3 or C_4), 142.2(C_3 or C_4), 134.3 ($2C_8$ or $2C_9$), 132.5($2C_7$), 123.8 ($2C_8$ or $2C_9$), 40.1(C_5).

IR (v, cm^{-1}, $CDCl_3$) 2930, 1775, 1720, 1602, 1421, 1395, 1331, 1192, 1153, 1115, 1083, 1063.

HRMS (EI+) calculated for $C_{13}H_8ClN_3O_2$: 273.0305; Found: 273.0309.

mp: 137-140 ℃

2-((5-Chloro-3-phenoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19e)



Chemical Formula: $C_{19}H_{12}ClN_3O_3$
Molecular Weight: 365,77

Following the general procedure, the reaction was carried out with xanthate **III-14** (287 mg, 1.02 mmol) and pyrazine **III-18e** (105 mg, 0.51 mmol) in 1.0 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 1:1) afforded the desired product **III-19e** as a white solid (130 mg, 0.36 mmol, 70% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.06 (s, 1H, H_3), 7.92 (dd, J = 5.4, 3.1 Hz, 2H, H_{12} or H_{13}), 7.79 – 7.75 (m, 2H, H_{12} or H_{13}), 7.47 – 7.41 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H, H_8), 7.24 – 7.19 (m, 2H), 5.17 (s, 2H, H_9).

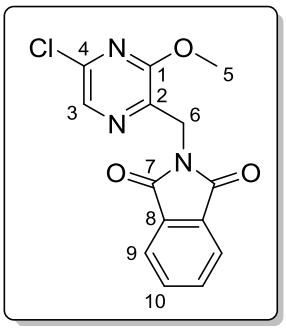
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.2 ($2C_{10}$), 155.9 (C), 152.4 (C), 144.4 (C), 138.5 (C), 136.7 (C_3), 134.2 (2CH), 132.4 (2C), 129.9 (2CH), 125.9 (C_8), 123.7 (2CH), 121.4 (2CH), 38.0 (C_9).

IR (ν, cm^{-1}, $CDCl_3$) 2929, 1775, 1719, 1601, 1542, 1490, 1419, 1396, 1384, 1219, 1175, 1114.

HRMS (EI+) calculated for $C_{19}H_{12}ClN_3O_3$: 365.0567; Found: 365.0576.

mp: 170-173 ℃

2-((5-Chloro-3-methoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19f)



Chemical Formula: $C_{14}H_{10}ClN_3O_3$
Molecular Weight: 303,70

Following the general procedure, the reaction was carried out with xanthate **III-14** (342 mg, 1.22 mmol) and pyrazine **III-18f** (88 mg, 0.61 mmol) in 1.2 mL DCE and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of toluene/dichloromethane = 4:1 to 2:1) afforded the desired product **III-19f** as a white solid (119 mg, 0.39 mmol, 64% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.93 (s, 1H, H_3), 7.89 (dd, J = 5.5, 3.0 Hz, 2H), 7.75 (dd, J = 5.4, 3.1 Hz, 2H), 4.97 (s, 2H, H_6), 4.06 (s, 3H, H_5).

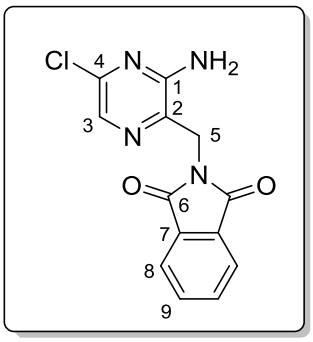
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.2 (2C=O), 156.8 (C), 144.3 (C), 138.2 (C), 134.4 (C_3), 134.2 (2CH), 132.4 ($2C_8$), 123.7 (2CH), 54.8 (C_5), 37.9 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3422, 3360, 2944, 1686, 1580, 1541, 1508, 1447, 1376, 1328, 1278, 1259, 1214, 1177, 1124.

HRMS (EI+) calculated for $C_{14}H_{10}ClN_3O_3$: 303.0411; Found: 303.0405.

mp: 185-186 ℃

2-((3-Amino-5-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19g)



Chemical Formula: $C_{13}H_9ClN_4O_2$
Molecular Weight: 288,69

Following the general procedure, the reaction was carried out with xanthate **III-14** (434 mg, 1.54 mmol) and pyrazine **III-18g** (100 mg, 0.78 mmol) in 1.5 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:3 to 0:1) afforded the desired compound **III-19g** as a white solid (114 mg, 0.39 mmol, 51% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.89 (dd, J = 5.5, 3.0 Hz, 2H), 7.87 (s, 1H, H_3), 7.75 (dd, J = 5.5, 3.0 Hz, 2H), 5.45 (s, 2H, NH_2), 4.89 (s, 2H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.6 ($2C_6$), 152.8 (C), 146.7 (C), 134.6 (2CH), 133.4 (C), 132.1 (CH), 132.0 (2C), 123.9 (2CH), 39.9 (C_5).

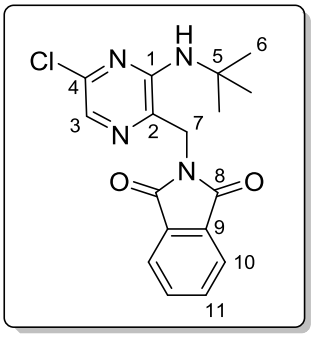
IR (ν, cm^{-1}, $CDCl_3$) 3481, 3363, 1771, 1714, 1624, 1536, 1439, 1423, 1392, 1327, 1234, 1208, 1083.

HRMS (EI+) calculated for $C_{13}H_9ClN_4O_2$: 288.0414; Found: 288.0412.

mp: 220-221 ℃

2-((3-(*tert*-Butylamino)-5-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19h)

Following the general procedure, the reaction was carried out with xanthate **III-14** (579 mg, 2.06 mmol) and pyrazine **III-18h** (191 mg, 1.03 mmol) in 2.1 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:1 to 1:2) afforded the single addition product **III-19h** as a white solid (234 mg, 0.68 mmol, 66% yield) and the double addition product **III-20h** as a white solid (128 mg, 0.25 mmol, 25% yield).



Chemical Formula: $C_{17}H_{17}ClN_4O_2$
Molecular Weight: 344,80

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.89 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (s, 1H, H_3), 5.74 (br, 1H, *N*H), 4.80 (s, 2H, H_7), 1.48 (s, 9H, H_6).

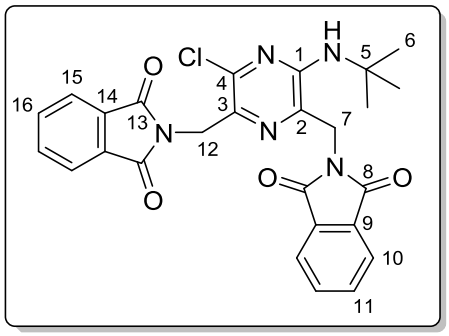
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.6 ($2C_8$), 152.0 (C_1), 146.1 (C_4), 134.5 (2CH), 133.7 (C_2), 132.0 ($2C_9$), 128.7 (C_3), 123.8 (2CH), 52.6 (C_5), 40.0 (C_7), 28.7 ($3C_6$).

IR (ν, cm^{-1}, $CDCl_3$) 3374, 2968, 1772, 1714, 1575, 1545, 1457, 1429, 1392, 1366, 1328, 1256, 1233, 1213, 1117, 1079, 987.

HRMS (EI+) calculated for $C_{17}H_{17}ClN_4O_2$: 344.1040; Found: 344.1042.

mp: 158-159 ℃

2,2'-((3-(*tert*-Butylamino)-5-chloropyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20h)



Chemical Formula: $C_{26}H_{22}ClN_5O_4$
Molecular Weight: 503,94

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 7.69 (q, J = 3.1, 2.4 Hz, 2H), 7.66 (m, 4H), 5.25 (s, 1H, *N*H), 4.89 (s, 2H, CH_2), 4.57 (s, 2H, CH_2), 1.46 (s, 9H, H_6).

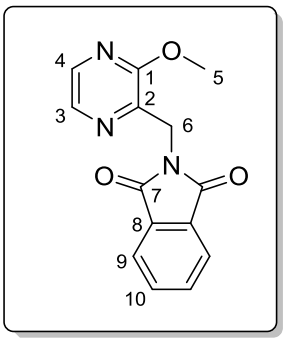
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.2, 167.9, 150.9, 143.2, 134.1, 133.8, 133.2, 132.40, 131.9, 131.5, 123.5, 123.3, 52.6 (C_5), 39.2 (CH_2), 39.1 (CH_2), 28.8 ($3C_6$).

IR (ν, cm^{-1}, $CDCl_3$) 3373, 2968, 1775, 1718, 1576, 1503, 1469, 1456, 1428, 1396, 1365, 1322, 1213, 1187, 1112, 1087, 1036.

HRMS (EI+) calculated for $C_{26}H_{22}ClN_5O_4$: 503.1360; Found: 503.1355.

mp: 242-244 ℃

2-((3-Methoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19i)



Chemical Formula: $C_{14}H_{11}N_3O_3$
Molecular Weight: 269,26

Following the general procedure, the reaction was carried out with xanthate **III-14** (331 mg, 1.18 mmol) and pyrazine **III-18i** (65 mg, 0.59 mmol) in 1.2 mL DCE and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 2:1) afforded the desired product **III-19i** as a white solid (96 mg, 0.36 mmol, 61% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (d, J = 2.7 Hz, 1H), 7.92 (d, J = 2.8 Hz, 1H), 7.90 (dd, J = 5.4, 3.1 Hz, 2H), 7.74 (dd, J = 5.4, 3.1 Hz, 2H), 5.01 (s, 2H, H_6), 4.03 (s, 3H, H_5).

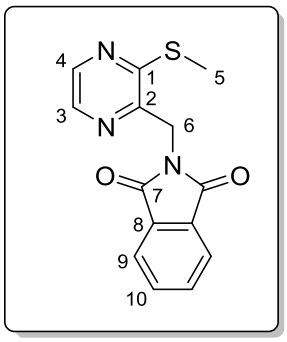
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 ($2C_7$), 157.9 (C), 140.4 (C), 139.5 (CH), 135.8 (CH), 134.1 (2CH), 132.5 ($2C_8$), 123.6 (2CH), 53.8 (C_5), 38.4 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 2952, 1774, 1718, 1602, 1548, 1462, 1424, 1395, 1360, 1172, 1144, 1011.

HRMS (EI+) calculated for $C_{14}H_{11}N_3O_3$: 269.0800; Found: 269.0796.

mp: 158-160 ℃

2-((3-(Methylthio)pyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19j)



Chemical Formula: $C_{14}H_{11}N_3O_2S$
Molecular Weight: 285,32

Following the general procedure, the reaction was carried out with xanthate **III-14** (332 mg, 1.18 mmol) and pyrazine **III-18j** (74 mg, 0.59 mmol) in 1.2 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 2:1) afforded the desired product **III-19j** as a white solid (67 mg, 0.23 mmol, 40% yield) and 4 mg (0.05 mmol) pyrazine **III-18j** was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (d, J = 2.7 Hz, 1H), 8.01 (d, J = 2.6 Hz, 1H), 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 4.94 (s, 2H, H_6), 2.62 (s, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.2 ($2C_7$), 154.8 (C), 147.3 (C), 142.4 (CH), 138.1 (CH), 134.1 (2CH), 132.5 ($2C_8$), 123.6 (2CH), 39.4 (C_6), 12.7 (C_5).

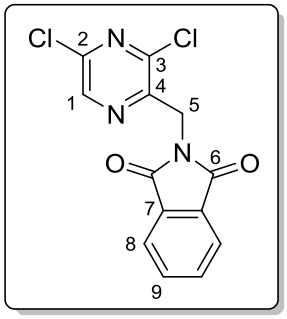
IR (ν, cm^{-1}, $CDCl_3$) 3055, 2932, 1775, 1718, 1520, 1470, 1422, 1396, 1324, 1192, 1154, 1114, 1088, 1066.

HRMS (EI+) calculated for $C_{14}H_{11}N_3O_2S$: 285.0572; Found: 285.0579.

mp: 172-173 ℃

2-((3,5-Dichloropyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19k)

Following the general procedure, the reaction was carried out with xanthate **III-14** (281 mg, 1.00 mmol, 2.0 equiv), pyrazine **III-18k** (74 mg, 0.50 mmol, 1.0 equiv) and TFA (68 mg, 48 μL, 0.6 mmol, 1.2 equiv) in 1.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/dichloromethane = 1:1 to 2:3, then ethyl acetate/petroleum ether = 1:1) afforded product **III-19k** (78 mg, 0.25 mmol, 51% yield) as a white solid and product **III-20k** (36 mg, 0.08 mmol, 15% yield) as a white solid.



Chemical Formula: $C_{13}H_7Cl_2N_3O_2$
Molecular Weight: 308,12

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (s, 1H, H_1), 7.91 (dd, J = 5.5, 3.1 Hz, 2H), 7.77 (dd, J = 5.5, 3.1 Hz, 2H), 5.10 (s, 2H, H_5).

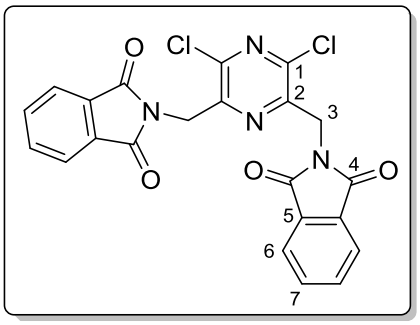
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.9 (C_6), 146.9 (C), 146.5 (C), 145.6 (C), 141.9 (C_1), 134.4 (CH), 132.2 (C_7), 123.8 (CH), 39.5 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 1776, 1722, 1520, 1470, 1424, 1415, 1395, 1322, 1290, 1258, 1195, 1174, 1156, 1116, 1072.

HRMS (EI+) calculated for $C_{13}H_7Cl_2N_3O_2$: 306.9915; Found: 306.9906.

mp: 175-176 ℃

2,2'-((3,5-Dichloropyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20k)



Chemical Formula: $C_{22}H_{12}Cl_2N_4O_4$
Molecular Weight: 467,26

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.62 – 7.57 (m, 4H), 7.53 – 7.48 (m, 4H), 4.96 (s, 4H, H_3).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.2 (C_4), 146.5 (C), 144.1 (C), 134.0 (CH), 131.7 (C), 123.4 (CH), 39.1 (C_3).

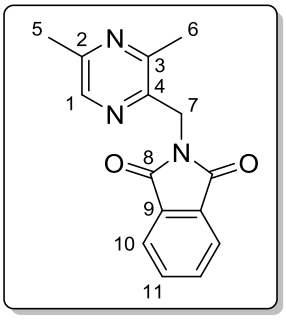
IR (ν, cm^{-1}, $CDCl_3$) 1777, 1726, 1602, 1470, 1422, 1404, 1381, 1310, 1194, 1163, 1104.

HRMS (EI+) calculated for $C_{22}H_{12}Cl_2N_4O_4$: 466.0236; Found: 466.0241.

mp: 303-304 ℃

2-((3,5-Dimethylpyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19l)

Following the general procedure, the reaction was carried out with xanthate **III-14** (563 mg, 2.00 mmol, 2.0 equiv), pyrazine **III-18l** (108 mg, 1.00 mmol, 1.0 equiv) and TFA (137 mg, 92 μL, 1.20 mmol, 1.2 equiv) in 1.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 1:1 to 2:3, then ethyl acetate/petroleum ether = 1:1 to 2:1) afforded product **III-19l** (120 mg, 0.45 mmol, 45% yield) as a white solid and double-addition product **III-20l** (26 mg, 0.08 mmol, 6% yield) as a white solid.



Chemical Formula: $C_{15}H_{13}N_3O_2$
Molecular Weight: 267,29

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.08 (s, 1H, H_1), 7.91 – 7.84 (m, 2H), 7.76 – 7.70 (m, 2H), 4.97 (s, 2H, H_7), 2.63 (s, 3H, H_6), 2.45 (s, 3H, H_5).

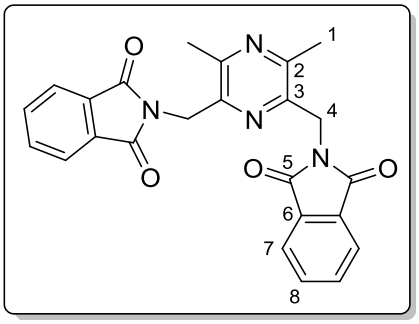
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 (C_8), 151.6 (C_2), 150.1 (C_3), 145.1 (C_4), 141.2 (C_1), 134.1 (CH), 132.4 (C_9), 123.6 (CH), 39.8 (C_7), 21.2 (C_5 and C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3052, 2928, 1774, 1716, 1469, 1420, 1396, 1345, 1324, 1276, 1194, 1175, 1133, 1111, 1089.

HRMS (EI+) calculated for $C_{15}H_{13}N_3O_2$: 267.1008; Found: 267.1000.

mp: 137-138 ℃

2,2'-((3,5-Dimethylpyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20l)



Chemical Formula: $C_{24}H_{18}N_4O_4$
Molecular Weight: 426,43

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.64 – 7.58 (m, 4H), 7.56 – 7.49 (m, 4H), 4.81 (s, 4H, H_4), 2.59 (s, 6H, H_1).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.7 (C_5), 148.7 (C_2), 144.7 (C_3), 133.7 (CH), 132.0 (C_6), 123.2 (CH), 39.4 (C_4), 20.6 (C_1).

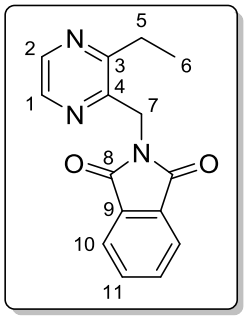
IR (ν, cm^{-1}, $CDCl_3$) 1775, 1721, 1469, 1428, 1397, 1343, 1323, 1198, 1178, 1112.

HRMS (EI+) calculated for $C_{24}H_{18}N_4O_4$: 426.1328; Found: 426.1324.

mp: 282-283 ℃

2-((3-Ethylpyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19m)

Following the general procedure, the reaction was carried out with xanthate **III-14** (563 mg, 2.00 mmol, 2.0 equiv), pyrazine **III-18m** (108 mg, 1.00 mmol, 1.0 equiv) and TFA (137 mg, 92 μL, 1.20 mmol, 1.2 equiv) in 1.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:2 to 1:2) afforded product **III-19m** (43 mg, 0.16 mmol, 16% yield) as a white solid and 1:1 mixture of products **III-20ma** and **III-20mb** (48 mg, 0.11 mmol, 11% yield) as a white solid.



Chemical Formula: $C_{15}H_{13}N_3O_2$
Molecular Weight: 267,29

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.37 (d, J = 2.6 Hz, 1H, H_2), 8.21 (d, J = 2.5 Hz, 1H, H_1), 7.93 – 7.87 (m, 2H), 7.79 – 7.72 (m, 2H), 5.04 (s, 2H, H_7), 2.97 (q, J = 7.5 Hz, 2H, H_5), 1.40 (t, J = 7.5 Hz, 3H, H_6).

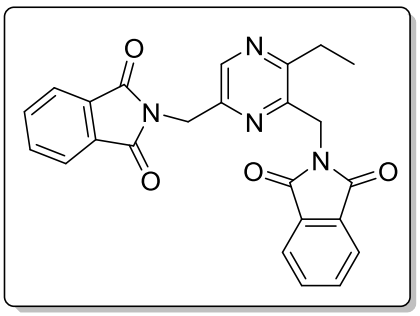
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 (C_8), 155.8 (C_3), 148.0 (C_4), 142.8 (C_2), 141.5 (C_1), 134.2 (CH), 132.5 (C_9), 123.6 (CH), 39.7 (C_7), 27.3 (C_5), 12.1 (C_6).

IR (v, cm^{-1}, $CDCl_3$) 3056, 2978, 2939, 2879, 1774, 1718, 1602, 1469, 1426, 1410, 1395, 1351, 1325, 1193, 1161, 1112, 1089.

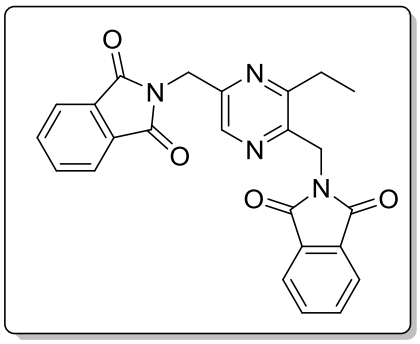
HRMS (EI+) calculated for $C_{15}H_{13}N_3O_2$: 267.1008; Found: 267.1019.

mp: 142-143 ℃

2,2'-((3-Ethylpyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20ma) and 2,2'-((3-Ethylpyrazine-2,5-diyl)bis(methylene))bis (isoindoline-1,3-dione) (III-20mb)



Chemical Formula: $C_{24}H_{18}N_4O_4$
Molecular Weight: 426,43



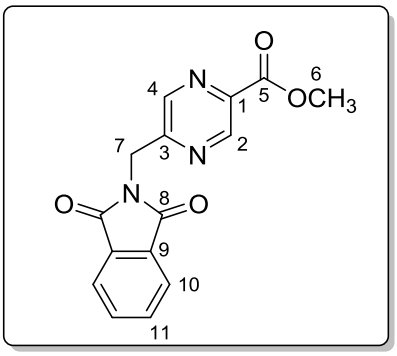
Chemical Formula: $C_{24}H_{18}N_4O_4$
Molecular Weight: 426,43

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.20 (s, 1H), 8.15 (s, 1H), 7.88 (dddd, J = 12.7, 4.5, 3.7, 2.3 Hz, 8H), 7.74 (qd, J = 5.4, 3.0 Hz, 8H), 5.20 (s, 2H), 5.14 (s, 2H), 4.98 (d, J = 1.9 Hz, 4H), 2.87 (q, J = 7.5 Hz, 2H), 2.60 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.34, 168.31, 168.2, 168.0, 156.8, 154.9, 148.6, 146.7, 146.4, 144.7, 142.0, 139.4, 134.23, 134.16, 134.13, 134.11, 132.5, 132.44, 132.40, 132.2, 123.7, 123.60, 123.58, 40.6, 39.7, 39.4, 39.3, 28.0, 26.9, 12.6, 11.7.

HRMS (EI+) calculated for $C_{24}H_{18}N_4O_4$: 426.1328; Found: 426.1338.

Methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)pyrazine-2-carboxylate (III-19n)



Chemical Formula: $C_{15}H_{11}N_3O_4$
Molecular Weight: 297,27

Following the general procedure, the reaction was carried out with xanthate **III-14** (416 mg, 1.48 mmol) and pyrazine **III-18n** (102 mg, 0.74 mmol) in 1.5 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3/1 to 1/2) afforded the desired product **III-19n** as a white solid (84 mg, 0.28 mmol, 38% yield), and 36 mg pyrazine (0.26 mmol) was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 9.17 (d, J = 1.4 Hz, 1H, H_2), 8.75 (d, J = 1.4 Hz, 1H, H_4), 7.90 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 5.12 (s, 2H, H_7), 4.01 (s, 3H, H_6).

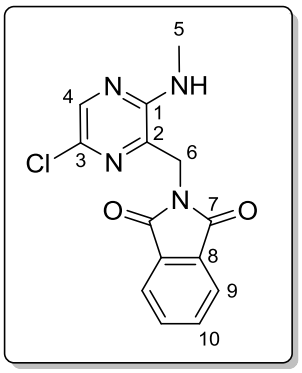
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.9 (2C=O), 164.4 (C_5), 154.4 (C_3), 145.7 (C_2), 143.1 (C_4), 142.3 (C_1), 134.4 (2CH), 132.2 ($2C_9$), 123.8 (2CH), 53.2 (C_6), 40.8 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2929, 1776, 1721, 1602, 1423, 1395, 1316, 1273, 1135, 1032.

HRMS (EI+) calculated for $C_{15}H_{11}N_3O_4$: 297.0750; Found: 297.0759.

mp: 167-170 ℃

2-((6-Chloro-3-(methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19o)



Chemical Formula: $C_{14}H_{11}ClN_4O_2$
Molecular Weight: 302,72

Following the general procedure, the reaction was carried out with xanthate **III-14** (231 mg, 0.82 mmol) and pyrazine **III-18o** (59 mg, 0.41 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:2 to 1:3) afforded the desired product **III-19o** as a light yellow solid (36 mg, 0.12 mmol, 29% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.00 (s, 1H, H_4), 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.75 (dd, J = 5.4, 3.1 Hz, 2H), 5.74 (br, 1H, *N*H), 4.83 (s, 2H, H_6), 2.99 (d, J = 4.7 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5 (C_7), 152.3 (C_1), 141.2 (C_4), 134.9 (C), 134.5 (2CH), 134.4 (C), 132.0 ($2C_8$), 123.9 (C), 40.0 (C_6), 28.8 (C_5).

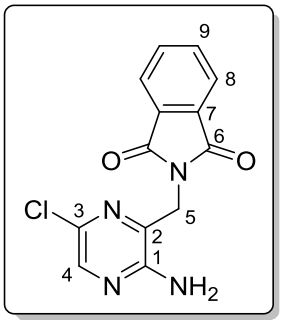
IR (ν, cm^{-1}, $CDCl_3$) 3392, 2944, 1773, 1714, 1582, 1511, 1427, 1389, 1370, 1327, 1210, 1083.

HRMS (EI+) calculated for $C_{14}H_{11}ClN_4O_2$: 302.0571; Found: 302.0559.

mp: 185-186 ℃

2-((3-Amino-6-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19p)

Following the general procedure, the reaction was carried out with xanthate **III-14** (563 mg, 2.00 mmol) and pyrazine **III-18p** (130 mg, 1.00 mmol) in 2.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:4 to 1:0) afforded product **III-19p** as a white solid (112 mg, 0.39 mmol, 39% yield) and the double addition product **III-20p** as a white solid (112 mg, 0.25 mmol, 25% yield).



Chemical Formula: $C_{13}H_9ClN_4O_2$
Molecular Weight: 288,69

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (s, 1H, H_4), 7.88 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.0 Hz, 2H), 5.25 (s, 2H, NH_2), 4.86 (s, 2H, H_5).

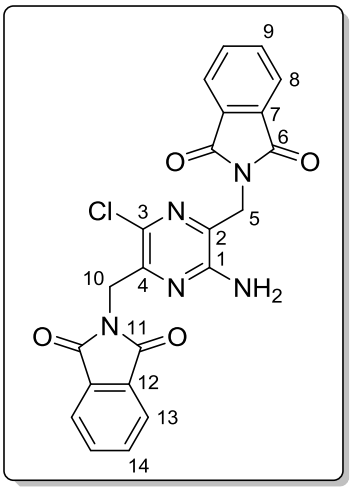
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5 (C_6), 151.9 (C_1), 141.7 (C_4), 136.6 (C_3), 134.6 (2CH and C_2), 131.9 ($2C_7$), 123.9 (2CH), 40.1 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3485, 3372, 1774, 1715, 1623, 1448, 1428, 1399, 1387, 1352, 1325, 1201, 1171, 1079.

HRMS (EI+) calculated for $C_{13}H_9ClN_4O_2$: 288.0414; Found: 288.0426.

mp: 199-200 ℃

2,2'-((3-Amino-6-chloropyrazine-2,5-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20p)



Chemical Formula: $C_{22}H_{14}ClN_5O_4$
Molecular Weight: 447,83

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.89-7.85 (m, 4H), 7.77-7.73 (m, 4H), 5.12 (s, 2H, NH_2), 4.94 (s, 2H, H_5 or H_{10}), 4.82 (s, 2H, H_5 or H_{10}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 ($2C_6$ or $2C_{11}$), 168.1 ($2C_6$ or $2C_{11}$), 151.7 (C_1), 145.7 (C_3), 134.5 (2CH), 134.2 (2CH), 133.7 (C), 133.3 (C), 132.4 (2C), 131.9 (2C), 123.8 (2CH), 123.6 (2CH), 39.7 (C_5 or C_{10}), 39.6 (C_5 or C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 3484, 3368, 1775, 1718, 1622, 1470, 1418, 1392, 1321, 1213, 1193, 1115, 1087.

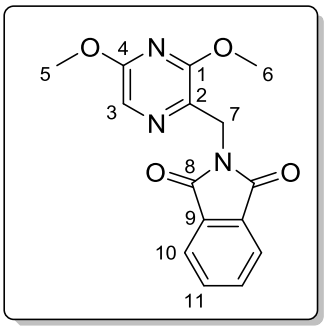
HRMS (EI+) calculated for $C_{22}H_{14}ClN_5O_4$: 447.0734; Found: 447.0736.

mp: 256-258 ℃

2-((3,5-Dimethoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (III-19r)

Entry 1: A magnetically stirred solution of xanthate **III-14** (281 mg, 1.00 mmol, 1.0 equiv) and pyrazine **III-18r** (283 mg, 2.00 mmol, 2.0 equiv) in 1 mL DCE was refluxed for 15 min under a flow of nitrogen. 20 mol % of DLP was then added every hour until the total consumption of one substrate. After 6 h, the reaction mixture was cooled to room temperature and the solvent was then evaporated. The crude product was purified by flash chromatography on silica gel (toluene/EtOAc = 5:1) to give the single addition product **III-19r** as a white solid (166 mg, 0.55 mmol, 55% yield) and double addition product **III-20r** as a white solid (42 mg, 0.09 mmol, 9% yield).

Entry 2: A magnetically stirred solution of xanthate **III-14** (452 mg, 1.61 mmol, 3.0 equiv) and pyrazine **III-18r** (75 mg, 0.54 mmol, 1.0 equiv) in 1 mL DCE was refluxed for 15 min under a flow of nitrogen. 20 mol % of DLP was then added every hour until the total consumption of one substrate. After 6 h, the reaction mixture was cooled to room temperature and the solvent was then evaporated. The crude product was purified by flash chromatography on silica gel (toluene/EtOAc = 5:1) to give the single addition product **III-19r** as a white solid (41 mg, 0.17 mmol, 25% yield) and double addition product **III-20r** as a white solid (123 mg, 0.27 mmol, 50% yield).



Chemical Formula: $C_{15}H_{13}N_3O_4$
Molecular Weight: 299,29

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.87 (dd, J = 5.4, 3.0 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.60 (s, 1H, H_3), 4.94 (s, 2H, H_7), 4.00 (s, 3H), 3.91 (s, 3H).

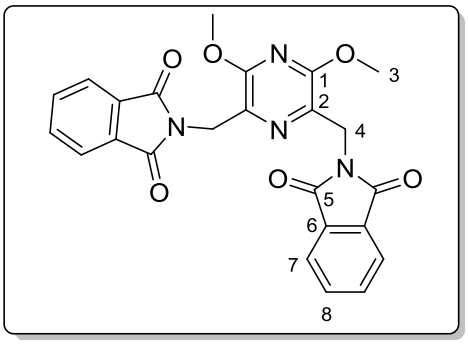
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 ($2C_8$), 158.7 (C), 155.9 (C), 134.0 (2CH), 132.6 (C), 129.5 (C), 123.5 (2CH), 123.2 (C_3), 53.9 (CH_3), 53.7 (CH_3), 37.8 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 2849, 1774, 1717, 1584, 1547, 1485, 1456, 1423, 1398, 1380, 1365, 1313, 1176, 1112, 1047, 1013.

HRMS (EI+) calculated for $C_{15}H_{13}N_3O_4$: 299.0906; Found: 299.0906.

mp: 197-198 ℃

2,2'-((3,5-Dimethoxypyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-20r)



Chemical Formula: $C_{24}H_{18}N_4O_6$
Molecular Weight: 458,43

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.58 (dt, J = 7.1, 3.5 Hz, 4H), 7.55 – 7.48 (m, 4H), 4.78 (s, 4H, H_4), 3.99 (s, 6H, H_3).

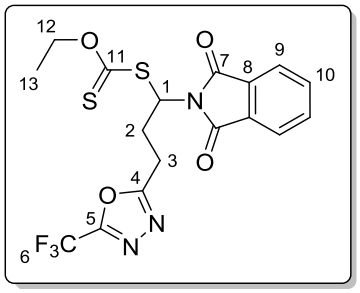
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.8 ($4C_5$), 155.2 (2C), 133.6 (4CH), 132.1 ($4C_6$), 128.0 (2C), 123.1 (4CH), 53.9 ($2C_3$), 37.2 ($2C_4$).

IR (ν, cm^{-1}, $CDCl_3$) 2988, 2946, 1775, 1721, 1479, 1455, 1430, 1419, 1396, 1353, 1199, 1184, 1112, 1014.

HRMS (EI+) calculated for $C_{24}H_{18}N_4O_6$: 458.1226; Found: 458.1235.

mp: 318-319 ℃

_S_-(1-(1,3-Dioxoisoindolin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl) _O_-ethyl carbonodithioate (III-21b)



Chemical Formula: $C_{17}H_{14}F_3N_3O_4S_2$
Molecular Weight: 445,43

A magnetically stirred solution of the *N*-vinylphthalimide (173 mg, 1.00 mmol, 1.0 equiv) and xanthate **III-38**[94] (408 mg, 1.50 mmol, 1.5 equiv) in ethyl acetate (2 mL) was refluxed for 15 min under a flow of nitrogen. DLP (10 mol %) was then added to the refluxing solution and the olefin was totally consumed in 90 min. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (Et_2O/petroleum ether = 1:2) to give the desired compound **III-21b** as a white solid (419 mg, 0.94 mmol, 94% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.89 – 7.84 (m, 2H), 7.79 – 7.74 (m, 2H), 6.42 (dd, J = 8.4, 7.4 Hz, 1H, , H_1), 4.64 (q, J = 7.1 Hz, 2H, H_{12}), 3.20 – 3.04 (m, 2H), 2.88 – 2.72 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H, H_{13}).

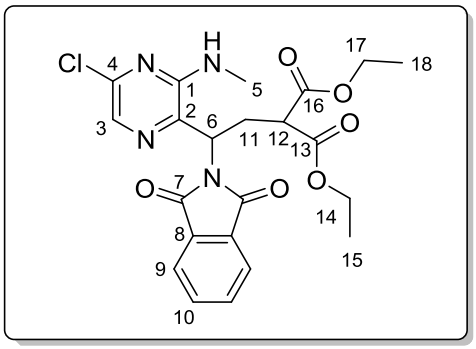
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 210.5 (C_{11}), 167.5 (C), 166.8 (C), 155.6 (q, J = 44.2 Hz, C_5), 134.8 (2CH), 131.6 (C_8), 124.0 (2CH), 116.3 (q, J = 270.0 Hz, CF_3), 71.0 (C_{12}), 56.8 (C_1), 30.0 (CH_2), 23.0 (CH_2), 13.8 (C_{13}).

IR (ν, cm^{-1}, $CDCl_3$) 2986, 2940, 1781, 1722, 1591, 1566, 1380, 1366, 1216, 1176, 1133, 1050.

HRMS (EI+) calculated for $C_{17}H_{14}F_3N_3O_4S_2$: 445.0378, M-Xa: $C_{14}H_9F_3N_3O_3$: 324.0596; Found: 324.0592.

mp: 82-84 ℃

Diethyl 2-(2-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-(1,3-dioxoisoindolin-2-yl) ethyl) malonate (III-22a)



Chemical Formula: $C_{22}H_{23}ClN_4O_6$
Molecular Weight: 474,90

Following the general procedure, the reaction was carried out with xanthate **III-21a** (660 mg, 1.46 mmol) and pyrazine **III-18a** (105 mg, 0.73 mmol) in 1.5 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 2:3) afforded the desired product **III-22a** as a colorless oil (226 mg, 0.48 mmol, 65% yield).

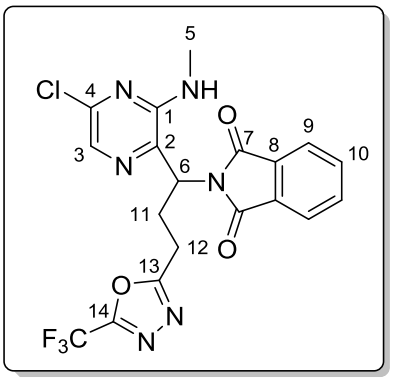
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 7.69 (s, 1H, H_3), 5.87 (br, 1H, *N*H), 5.36 (dd, J = 10.0, 4.7 Hz, 1H, H_6), 4.27 – 4.11 (m, 4H, H_{14} and H_{17}), 3.42 (dd, J = 9.4, 5.3 Hz, 1H, H_{12}), 3.26 (ddd, J = 15.1, 10.0, 5.3 Hz, 1H, H_{11a}), 2.99 (d, J = 4.7 Hz, 3H, H_5), 2.91 (ddd, J = 14.4, 9.4, 4.7 Hz, 1H, , H_{11b}), 1.26 (t, J = 7.2 Hz, 3H, H_{15} or H_{18}), 1.23 (t, J = 7.2 Hz, 3H, H_{15} or H_{18}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.4 (C=O), 168.7 (C=O), 168.6 (2C=O), 152.2 (C), 146.7 (C), 134.8 (C), 134.5 (2CH), 131.7 ($2C_8$), 128.5 (C_3), 123.8 (2CH), 62.2 (C_{14} or C_{17}), 62.0 (C_{14} or C_{17}), 49.4 (C_6 or C_{12}), 49.2 (C_6 or C_{12}), 28.6 (C_5), 27.1 (C_{11}), 14.1 (C_{15} and C_{18}).

IR (ν, cm^{-1}, $CDCl_3$) 3396, 2985, 2941, 1773, 1717, 1579, 1511, 1470, 1446, 1379, 1331, 1279, 1217, 1192, 1116, 1099, 1030.

HRMS (EI+) calculated for $C_{22}H_{23}ClN_4O_6$: 474.1306; Found: 474.1305.

2-(1-(5-Chloro-3-(methylamino)pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl)isoindoline-1,3-dione (III-22b)



Chemical Formula: $C_{19}H_{14}ClF_3N_6O_3$
Molecular Weight: 466,81

Following the general procedure, the reaction was carried out with xanthate **III-21b** (359 mg, 0.81 mmol) and pyrazine **III-18a** (58 mg, 0.40 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 1:1) afforded the desired product **III-22b** as a white solid (145 mg, 0.31 mmol, 78% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.6, 2.9 Hz, 2H), 7.76 (s, 1H, H_3), 5.73 (br, 1H, *N*H), 5.43 (t, J = 7.2 Hz, 1H, H_6), 3.17 – 3.10 (m, 2H, H_{11} or H_{12}), 3.10 – 3.04 (m, 2H, H_{11} or H_{12}), 2.97 (d, J = 4.7 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.6 ($2C_7$), 168.4 (C), 155.7 (q, J = 44.2 Hz, C_{14}), 152.5 (C), 147.1 (C), 134.8 (2CH), 134.0 (C), 131.5 (C), 128.8 (C_3), 123.9 (2CH), 116.3 (q, J = 269.9 Hz, CF_3), 49.8 (C_6), 28.6 (C_5), 24.8 (C_{11} or C_{12}), 22.8 (C_{11} or C_{12}).

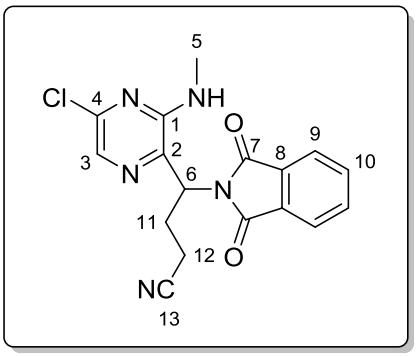
IR (ν, cm^{-1}, $CDCl_3$) 3417, 2943, 1775, 1714, 1581, 1510, 1407, 1380, 1215, 1177, 1132.

HRMS (EI+) calculated for $C_{19}H_{14}ClF_3N_6O_3$: 466.0768; Found: 466.0771.

mp: 54-55 ℃

4-(5-Chloro-3-(methylamino)pyrazin-2-yl)-4-(1,3-dioxoisoindolin-2-yl)butanenitrile (III-22c)

Following the general procedure, the reaction was carried out with xanthate **III-21c** (362 mg, 1.08 mmol) and pyrazine **III-18a** (78 mg, 0.54 mmol) in 1.1 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 0:1) afforded the single addition product **III-22c** (141 mg, 0.40 mmol, 73% yield) as a white solid and the double addition product **III-23c** (81 mg, 0.14 mmol, 26% yield) as a mixture of diastereoisomers (*dr* = 1:1) as colorless oil.



Chemical Formula: $C_{17}H_{14}ClN_5O_2$
Molecular Weight: 355,78

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.88 – 7.82 (m, 2H), 7.80 (s, 1H, H_3), 7.77 (td, *J* = 5.2, 2.0 Hz, 2H), 5.49 (br, 1H, *N*H), 5.34 (t, *J* = 7.5 Hz, 1H, H_6), 3.04 (tt, *J* = 10.8, 5.4 Hz, 1H, H_{11a}), 2.94 (d, *J* = 4.7 Hz, 3H, H_5), 2.82 (td, *J* = 14.4, 7.7 Hz, 1H, H_{11b}), 2.57 – 2.41 (m, 2H, H_{12}).

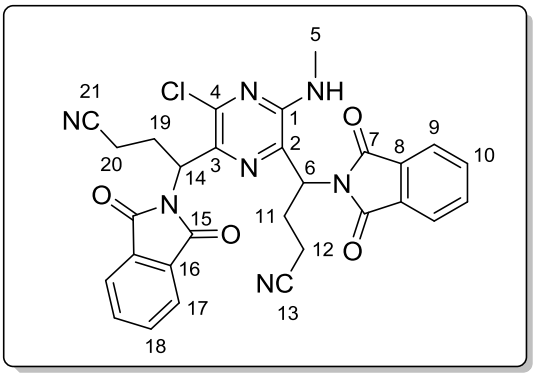
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5 ($2C_7$), 152.7 (C), 147.3 (C), 134.8 (2CH), 133.3 (C), 131.4 ($2C_8$), 128.9 (C_3), 124.0 (2CH), 118.6 (C_{13}), 49.2 (C_6), 28.7 (C_5), 25.1 (C_{12}), 15.0 (C_{11}).

IR (ν, cm^{-1}, $CDCl_3$) 3418, 2944, 1779, 1765, 1713, 1576, 1508, 1448, 1383, 1380, 1351, 1331, 1270, 1191, 1100.

HRMS (EI+) calculated for $C_{17}H_{14}ClN_5O_2$: 355.0836; Found: 355.0839.

mp: 146-147 ℃

4,4'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(4-(1,3-dioxoisoindolin-2-yl) butanenitrile) (III-23c)



Chemical Formula: $C_{29}H_{22}ClN_7O_4$
Molecular Weight: 567,99

(80 mg, 0.14 mmol, 26% yield)

1st diastereoisomer:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (td, *J* = 5.3, 2.0 Hz, 2H), 7.75 – 7.71 (m, 2H), 5.67 – 5.57 (m, 2H, *N*H and H_6 or H_{14}), 5.39 (dd, *J* = 9.1, 6.0 Hz, 1H, H_6 or H_{14}), 3.48 – 3.37 (m, 1H), 3.07 (dtd, *J* = 14.1, 8.5, 5.5 Hz, 1H), 2.92 (d, *J* = 4.7 Hz, 3H, H_5), 2.83 (ddd, *J* = 16.8, 8.4, 5.5 Hz, 1H), 2.73 (ddd, *J* = 7.7, 6.3, 3.3 Hz, 2H), 2.67 – 2.42 (m, 3H).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.4 (2C), 167.6 (2C), 152.4 (C), 146.5 (C), 134.9 (2CH), 134.4 (2CH), 131.8 (C), 131.7 (2C), 131.4 (C), 131.4 (2C), 124.0 (2CH), 123.6 (2CH), 119.3 (CN), 119.0 (CN), 50.3 (CH), 48.6 (CH), 28.8 (C_5), 26.8 (CH_2), 25.3 (CH_2), 14.7 (CH_2), 14.6 (CH_2).

2nd diastereoisomer:

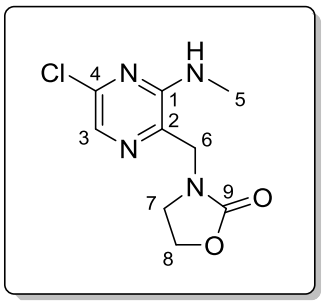
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.76 – 7.68 (m, 4H), 5.67 (dd, *J* = 9.3, 4.9 Hz, 1H), 5.54 (q, *J* = 4.6 Hz, 1H), 5.31 (t, *J* = 7.5 Hz, 1H), 2.92 (d, *J* = 4.7 Hz, 3H), 2.84 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.75 – 2.64 (m, 3H), 2.57 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.51 – 2.42 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 1H).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5 (2C), 168.2 (2C), 152.2 (C), 145.2 (C), 134.7 (2CH), 134.3 (2CH), 133.4 (C), 132.5 (C), 132.0 (2C), 131.4 (2C), 124.0 (2CH),

123.6 (2CH), 119.0 (CN), 118.6 (CN), 51.5 (CH), 49.1 (CH), 31.0 (s), 28.8 (CH_2), 26.5 (CH_2), 24.9 (CH_2), 15.0 (CH_2).

IR (*v*, cm^{-1}, $CDCl_3$) 3414, 2943, 1779, 1766, 1715, 1579, 1511, 1470, 1384, 1364, 1331, 1217, 1176, 1111, 1087.

HRMS (EI+) calculated for $C_{29}H_{22}ClN_7O_4$: 567.1422; Found: 567.1438.

3-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)oxazolidin-2-one (III-22e)



Chemical Formula: $C_9H_{11}ClN_4O_2$
Molecular Weight: 242,66

Following the general procedure, the reaction was carried out with xanthate **III-21e** (308 mg, 1.39 mmol) and pyrazine **III-18a** (100 mg, 0.70 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to EtOAc/petroleum ether = 2:1) afforded the desired product **III-22e** as a white solid (79 mg, 0.33 mmol, 47% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.62 (s, 1H, H_3), 6.40 (br, 1H, *N*H), 4.41 (s, 2H, H_6), 4.40 – 4.36 (m, 2H, H_8), 3.61 – 3.57 (m, 2H, H_7), 2.97 (d, J = 4.7 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 159.8 (C_9), 153.8 (C), 147.6 (C), 134.0 (C), 128.1 (C_3), 62.6 (C_8), 47.1 (C_6), 44.7 (C_7), 28.4 (C_5).

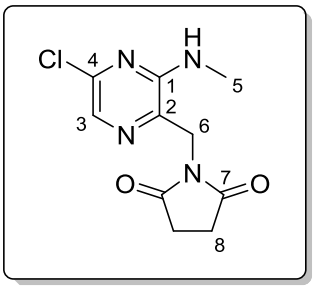
IR (ν, cm^{-1}, $CDCl_3$) 3361, 2941, 1732, 1585, 1512, 1444, 1383, 1272, 1237, 1103, 1088, 1037.

HRMS (EI+) calculated for $C_9H_{11}ClN_4O_2$: 242.0571; Found: 242.0580.

mp: 167-169 ℃

1-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)pyrrolidine-2,5-dione (III-22f)

Following the general procedure, the reaction was carried out with xanthate **III-21f** (284 mg, 1.22 mmol) and pyrazine **III-18a** (87 mg, 0.61 mmol) in 1.2 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:2 to 0:1) afforded the desired product **III-22f** as a white solid (81 mg, 0.32 mmol, 52% yield) and the double addition product **III-23f** as a white solid (64 mg, 0.17 mmol, 28% yield).



Chemical Formula: $C_{10}H_{11}ClN_4O_2$
Molecular Weight: 254,67

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.69 (s, 1H, H_3), 6.00 (s, 1H, *N*H), 4.65 (s, 2H, H_6), 2.97 (d, J = 4.7 Hz, 3H, H_5), 2.79 (s, 4H, H_8).

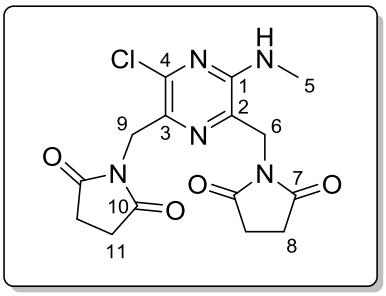
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 177.6 ($2C_7$), 153.2 (C), 147.0 (C), 133.1 (C), 129.1 (C_3), 40.6 (C_6), 28.4 (C_5), 28.3 ($2C_8$).

IR (ν, cm^{-1}, $CDCl_3$) 3376, 2944, 1779, 1704, 1583, 1543, 1511, 1430, 1397, 1383, 1337, 1266, 1236, 1217, 1175, 1154, 1102.

HRMS (EI+) calculated for $C_{10}H_{11}ClN_4O_2$: 254.0571; Found: 254.0578.

mp: 139-140 ℃

1,1'-((3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(methylene))bis(pyrrolidine -2,5-dione) (III-23f)



Chemical Formula: $C_{15}H_{16}ClN_5O_4$
Molecular Weight: 365,77

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 5.95 (br, 1H, *N*H), 4.75 (s, 2H), 4.52 (s, 2H), 2.96 (d, J = 4.7 Hz, 3H, H_5), 2.87 (s, 4H), 2.74 (s, 4H).

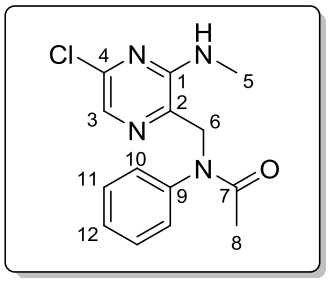
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 177.8 (2C=O), 177.5 (2C=O), 152.8 (C), 144.6 (C), 132.9 (C), 131.4 (C), 40.0 (CH_2), 39.4 (CH_2), 28.7 (CH_3), 28.6 ($2CH_2$), 28.4 ($2CH_2$).

IR (ν, cm^{-1}, $CDCl_3$) 3376, 2944, 1778, 1705, 1586, 1514, 1428, 1401, 1359, 1329, 1294, 1233, 1173, 1153, 1018.

HRMS (EI+) calculated for $C_{15}H_{16}ClN_5O_4$: 365.0891; Found: 365.0887.

mp: 111-114 ℃

N-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)-*N*-phenylacetamide (III-22g)



Chemical Formula: $C_{14}H_{15}ClN_4O$
Molecular Weight: 290,75

Following the general procedure, the reaction was carried out with xanthate **III-21g** (345 mg, 1.28 mmol) and pyrazine **III-18a** (92 mg, 0.64 mmol) in 1.3 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 1:2) afforded the desired product **III-22g** as a white solid (125 mg, 0.43 mmol, 67% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.43 (s, 1H, H_3), 7.40 – 7.33 (m, 3H), 7.13 (br, 1H, *N*H), 6.95 – 6.93 (m, 2H), 4.91 (s, 2H, H_6), 3.01 (d, J = 4.7 Hz, 3H, H_5), 1.88 (s, 3H, H_8).

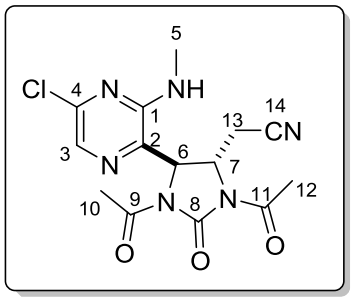
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 172.5 (C_7), 153.8 (C), 147.1 (C), 141.5 (C), 135.0 (C), 130.1 (CH), 128.8 (CH), 128.1 (CH), 127.7 (CH), 51.6 (C_6), 28.4 (C_5), 22.7 (C_8).

IR (ν, cm^{-1}, $CDCl_3$) 3320, 3126, 2944, 1637, 1596, 1516, 1495, 1440, 1385, 1299, 1239, 1198, 1104, 1013.

HRMS (EI+) calculated for $C_{14}H_{15}ClN_4O$: 290.0934; Found: 290.0930.

mp: 133-135 ℃

2-(1,3-Diacetyl-5-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl) acetonitrile (III-22h)



Chemical Formula: $C_{14}H_{15}ClN_6O_3$
Molecular Weight: 350,76

Following the general procedure, the reaction was carried out with xanthate **III-21h** (272 mg, 0.83 mmol) and pyrazine **III-18a** (59 mg, 0.41 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to1:3) afforded the desired product **III-22h** as a light brown oil (99 mg, 0.28 mmol, 69% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.68 (s, 1H, H_3), 6.15 (br, 1H, *N*H), 5.12 (d, J = 1.3 Hz, 1H, H_6), 4.69 (ddd, J = 6.3, 3.3, 1.3 Hz, 1H, H_7), 3.01 (dd, J = 17.1, 3.4 Hz, 1H, H_{13a}), 2.98 (d, J = 4.8 Hz, 3H, H_5), 2.84 (dd, J = 17.1, 3.4 Hz, 1H, H_{13b}), 2.60 (s, 3H), 2.55 (s, 3H).

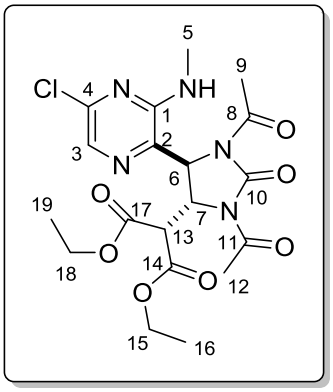
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 171.9 (C), 170.6 (C), 152.9 (C), 150.7 (C), 147.7 (C), 134.9 (C), 130.0 (C_3), 116.0 (CN), 54.1 (C_6), 53.0 (C_7), 28.6 (C_5), 24.4 (CH_3), 24.0 (CH_3), 22.2 (C_{13}).

IR (ν, cm^{-1}, $CDCl_3$) 3362, 2938, 1769, 1705, 1577, 1537, 1507, 1370, 1265, 1245, 1212, 1160, 1120, 1093, 984.

HRMS (EI+) calculated for $C_{14}H_{15}ClN_6O_3$: 350.0894; Found: 350.0901.

Diethyl 2-(1,3-diacetyl-5-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-oxoimidazo-lidin-4-yl)malonate (III-22i)

Following the general procedure, the reaction was carried out with xanthate **III-21i** (457 mg, 1.02 mmol) and pyrazine **III-18a** (73 mg, 0.51 mmol) in 1.0 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 1:2) afforded the desired product **III-22i** as a white solid (202 mg, 0.43 mmol, 84% yield) and the double addition product **III-23i** as colorless oil (56 mg, 0.07 mmol, 14% yield, *dr* = 1.0:1.1).



Chemical Formula: $C_{19}H_{24}ClN_5O_7$
Molecular Weight: 469,88

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.60 (s, 1H, H_3), 6.73 (br, 1H, *N*H), 5.46 (s, 1H, H_6), 4.65 (dd, *J* = 4.2, 0.6 Hz, 1H, H_7), 4.30 – 4.13 (m, 4H, H_{15} and H_{18}), 4.11 (d, *J* = 4.2 Hz, 1H, H_{13}), 3.03 (d, *J* = 4.7 Hz, 3H, H_5), 2.55 (s, 3H), 2.50 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

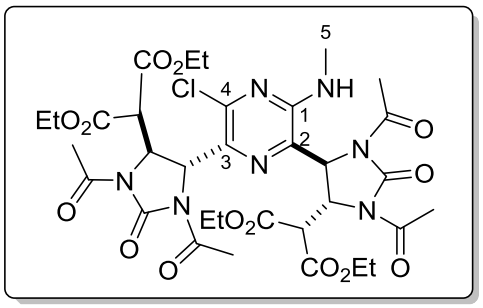
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.8 (C), 170.4 (C), 168.1 (C), 166.7 (C), 152.4 (C), 151.7 (C), 147.1 (C), 134.9 (C), 128.8 (C_3), 62.9 (CH_2), 62.8 (CH_2), 54.5 (C_7), 52.7 (C_6), 51.3 (C_{13}), 28.4 (C_5), 24.3 (CH_3), 24.0 (CH_3), 14.0 (CH_3), 14.0 (CH_3).

IR (ν, cm^{-1}, $CDCl_3$) 3384, 2987, 2942, 1769, 1741, 1724, 1703, 1586, 1514, 1372, 1331, 1262, 1211, 1161, 1117, 1034.

HRMS (EI+) calculated for $C_{19}H_{24}ClN_5O_7$: 469.1364; Found: 469.1358.

mp: 152-153 ℃

III-23i



Chemical Formula: $C_{33}H_{42}ClN_7O_{14}$
Molecular Weight: 796,18

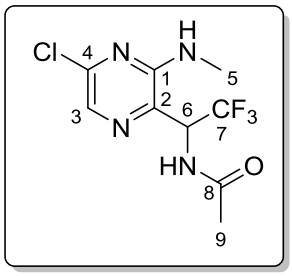
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.18 (br, 1H, 2nd dia), 6.87 (br, 1H, 1st dia), 5.77 (d, J = 2.2 Hz, 1H, 2nd dia), 5.70 (d, J = 2.2 Hz, 1H, 1st dia), 5.41 (s, 1H, 1st dia), 5.37 (s, 1H, 2nd dia), 4.57 (dd, J = 4.0, 2.3 Hz, 1H, 1st dia), 4.51 (d, J = 4.1 Hz, 1H, 2nd dia), 4.50 (dd, J = 4.0, 2.3 Hz, 1H, 2nd dia), 4.04 (d, J = 4.1 Hz, 2H), 4.39 (d, J = 4.2 Hz, 1H, 1st dia), 4.34 – 4.06 (m, 32H, 1st and 2nd dia), 4.04 (d, J = 4.1 Hz, 2H, 2nd dia), 4.01 (d, J = 4.1 Hz, 1H, 1st dia), 3.03 (d, J = 4.4Hz, 3H, 1st dia), 3.00 (d, J = 4.4Hz, 3H, 2nd dia), 2.65 (s, 6H, 1st and 2nd dia), 2.55 (s, 3H, 1st dia), 2.45 (s, 6H, 2nd dia), 2.36 (s, 3H, 2nd dia), 2.35 (s, 3H, 1st dia), 2.33 (s, 3H, 1st dia), 1.30 – 1.20 (m, 24H, 1st and 2nd dia).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 171.3, 171.1, 170.7, 169.6, 169.5, 169.4, 169.4, 168.7, 168.4, 166.6, 166.6, 166.4, 166.2, 152.0, 151.9, 151.6, 151.5, 151.4, 146.0, 145.8, 135.3, 134.9, 134.7, 134.0, 63.1, 63.0, 62.9, 62.8, 62.4, 62.4, 62.2, 62.2, 55.8, 55.5, 54.2, 53.5, 53.2, 53.0, 52.0, 50.7, 50.6, 28.5, 28.4, 24.8, 24.8, 24.2, 24.2, 24.0, 24.0, 23.6, 23.4, 14.1, 14.0, 14.0, 13.9, 13.9.

IR (ν, cm^{-1}, $CDCl_3$) 3378, 2986, 2924, 1770, 1744, 1725, 1702, 1589, 1524, 1368, 1332, 1265, 1204, 1164, 1117, 1036.

HRMS (EI+) calculated for $C_{33}H_{42}ClN_7O_{14}$: 795.2478; Found: 795.2434.

_N_-(1-(5-chloro-3-(methylamino)pyrazin-2-yl)-2,2,2-trifluoroethyl)acetamide (III-22j)



Chemical Formula: $C_9H_{10}ClF_3N_4O$
Molecular Weight: 282,65

Following the general procedure, the reaction was carried out with xanthate **III-21j** (522 mg, 2.00 mmol) and pyrazine (143 mg, 1.00 mmol) in 2.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:1 to 1:1) afforded the desired product **III-22j** as a white solid (208 mg, 0.74 mmol, 74% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.74 (s, 1H, H_3), 6.97 (br, 1H, *N*H), 6.08 (br, 1H, *N*H), 6.01 – 5.92 (m, 1H, H_6), 2.99 (d, J = 4.7 Hz, 3H, H_5), 2.14 (s, 3H, H_9).

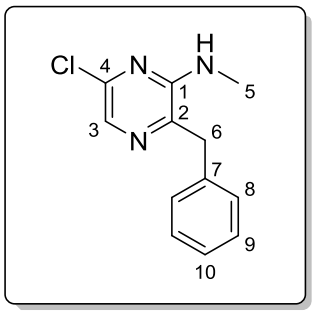
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.5 (C_8), 153.1 (C), 148.1 (C), 130.1 (C), 128.5 (C_3), 124.2 (q, J = 282.1 Hz, CF_3), 49.1 (q, J = 31.8 Hz, C_6), 28.5 (C_5), 23.3 (C_9).

IR (ν, cm^{-1}, $CDCl_3$) 3422, 3360, 2944, 1686, 1580, 1541, 1508, 1447, 1376, 1328, 1278, 1259, 1214, 1177, 1124.

HRMS (EI+) calculated for $C_9H_{10}ClF_3N_4O$: 282.0495; Found: 282.0490.

mp: 201-202 ℃

3-Benzyl-6-chloro-*N*-methylpyrazin-2-amine (III-22k)



Chemical Formula: $C_{12}H_{12}ClN_3$
Molecular Weight: 233,70

Following the general procedure, the reaction was carried out with xanthate **III-21k** (226 mg, 1.06 mmol) and pyrazine **III-18a** (76 mg, 0.53 mmol) in 1.1 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 8:1 to 1:1) afforded the desired product **III-22k** as a light brown solid (59 mg, 0.25 mmol, 48% yield), and 25 mg **III-18a** (0.17 mmol) was recovered.

^{1}H NMR (δ, ppm) (400 MHz, CD_2Cl_2) 7.73 (s, 1H, H_3), 7.31 (t, J = 7.2 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H, H_{10}), 7.17 (d, J = 7.2 Hz, 2H), 4.52 (br, 1H, *N*H), 4.00 (s, 2H, H_6), 2.87 (d, J = 4.8 Hz, 3H, H_5).

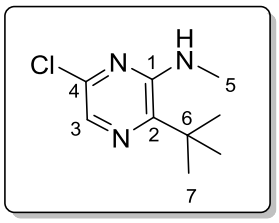
^{13}C NMR (δ, ppm) (101 MHz, CD_2Cl_2) 153.6 (C), 145.8 (C), 140.3 (C), 137.0 (C), 129.5 (2CH), 129.4 (CH), 129.1 (2CH), 127.6 (CH), 40.2 (C_6), 28.7 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3456, 3067, 3030, 2944, 1573, 1539, 1509, 1441, 1373, 1299, 1267, 1234, 1188, 1148, 1100.

HRMS (EI+) calculated for $C_{12}H_{12}ClN_3$: 233.0720; Found: 233.0710.

mp: 135-137 ℃

3-(*tert*-Butyl)-6-chloro-*N*-methylpyrazin-2-amine (III-22l)



Chemical Formula: $C_9H_{14}ClN_3$
Molecular Weight: 199,68

Following the general procedure, the reaction was carried out with xanthate **III-21l** (249 mg, 1.40 mmol) and pyrazine (100 mg, 0.70 mmol) in 1.4 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 6:1 to 2:1) afforded the desired product **III-22l** as an orange oil (51 mg, 0.26 mmol, 36% yield).

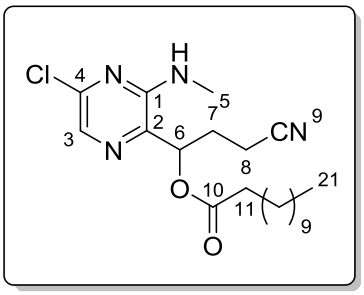
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.70 (s, 1H, H_3), 4.73 (br, 1H, *N*H), 3.03 (d, J = 4.8 Hz, 3H, H_5), 1.37 (s, 9H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 152.2 (C), 146.2 (C), 144.2 (C), 128.0 (C_3), 36.5 (C_6), 28.8 (C_5), 28.4 ($3C_7$).

IR (ν, cm^{-1}, $CDCl_3$) 3509, 2972, 2871, 1561, 1533, 1505, 1476, 1437, 1405, 1358, 1261, 1194, 1125, 1017.

HRMS (EI+) calculated for $C_9H_{14}ClN_3$: 199.0876; Found: 199.0883.

1-(5-Chloro-3-(methylamino)pyrazin-2-yl)-3-cyanopropyl dodecanoate (III-25)



Chemical Formula: $C_{21}H_{33}ClN_4O_2$
Molecular Weight: 408.97

Following the general procedure, the reaction was carried out with xanthate **III-21n** (356 mg, 1.44 mmol) and pyrazine **III-18a** (103 mg, 0.72 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 4:1) afforded the title compound **III-25** as a light brown oil (92 mg, 0.22 mmol, 31% yield).

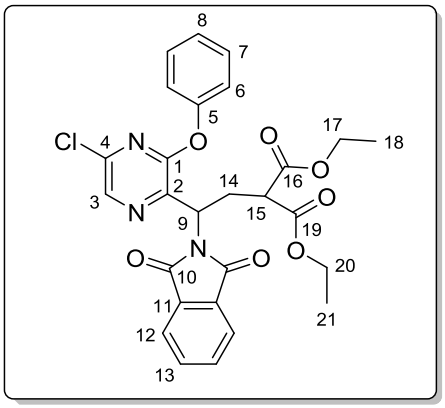
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.73 (s, 1H, H_3), 5.86 (m, 2H, *N*H and H_6), 2.98 (d, J = 4.7 Hz, 3H, H_5), 2.48 (m, 3H), 2.38 (m, 3H), 1.65 – 1.56 (m, 2H, H_{12}), 1.24 (s, 16H, H_{13}-H_{20}), 0.87 (t, J = 6.8 Hz, 3H, H_{21}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 174.7 (C_{10}), 153.3 (C), 147.6 (C), 134.6 (C), 129.2 (C_3), 118.8 (C_9), 69.7 (C_6), 34.2, 32.0, 29.7, 29.7, 29.5, 29.4, 29.3, 29.1, 28.5, 27.8, 24.9 (C_{12}), 22.8, 14.2, 14.0 (C_{21}).

IR (ν, cm^{-1}, $CDCl_3$) 3391, 2928, 2856, 1721, 1578, 1540, 1508, 1446, 1379, 1261, 1222, 1187, 1155, 1103, 1029.

HRMS (EI+) calculated for $C_{21}H_{33}ClN_4O_2$: 408.2292; Found: 408.2284.

Diethyl 2-(2-(5-chloro-3-phenoxypyrazin-2-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl) malonate (III-27a)



Chemical Formula: $C_{27}H_{24}ClN_3O_7$
Molecular Weight: 537,95

Following the general procedure, the reaction was carried out with xanthate **III-21a** (366 mg, 0.81 mmol) and pyrazine **III-18a** (83 mg, 0.40 mmol) in 0.8 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 5:1 to 1:1) afforded the desired product **III-27a** as a colorless oil (151 mg, 0.28 mmol, 70% yield).

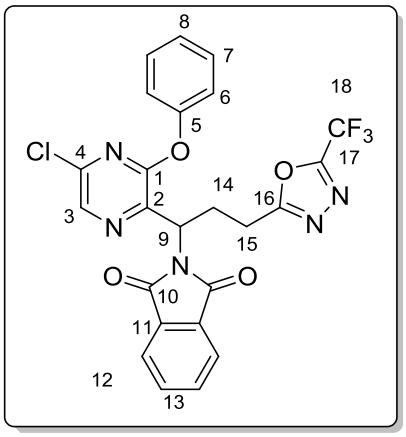
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (s, 1H, H_3), 7.84 – 7.79 (m, 2H), 7.73 (td, J = 5.2, 2.1 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.18 – 7.12 (m, 1H, H_8), 6.97 – 6.92 (m, 2H), 5.82 (dd, J = 9.9, 5.3 Hz, 1H, H_9), 4.27 – 4.18 (m, 2H, H_{17} or H_{20}), 4.16 – 4.06 (m, 2H, H_{17} or H_{20}), 3.55 (dd, J = 8.7, 6.3 Hz, 1H, H_{15}), 3.19 (ddd, J = 14.2, 8.7, 5.4 Hz, 1H, H_{14a}), 3.09 (ddd, J = 14.5, 10.0, 6.3 Hz, 1H, H_{14b}), 1.26 (t, J = 7.1 Hz, 3H, H_{18} or H_{21}), 1.21 (t, J = 7.1 Hz, 3H, H_{18} or H_{21}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.9 (C_{16} or C_{19}), 168.7 (C_{16} or C_{19}), 167.9 ($2C_{10}$), 155.6 (C), 152.5 (C), 145.0 (C), 140.5 (C), 136.7 (C_3), 134.3 (2CH), 131.9 ($2C_{11}$), 129.7 (2CH), 125.6 (C_8), 123.6 (2CH), 120.9 (2CH), 61.9 (C_{17} and C_{20}), 49.5 (C_9 or C_{15}), 49.2 (C_9 or C_{15}), 28.7 (C_{14}), 14.2 (C_{18} or C_{21}), 14.1 (C_{18} or C_{21}).

IR (ν, cm^{-1}, $CDCl_3$) 2985, 1719, 1601, 1539, 1490, 1424, 1380, 1217, 1174, 1162, 1024.

HRMS (EI+) calculated for $C_{27}H_{24}ClN_3O_7$: 537.1303; Found: 537.1308.

2-(1-(5-Chloro-3-phenoxypyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl)isoindoline-1,3-dione (III-27b)



Chemical Formula: $C_{24}H_{15}ClF_3N_5O_4$
Molecular Weight: 529,86

Following the general procedure, the reaction was carried out with xanthate **III-21b** (359 mg, 0.81 mmol) and pyrazine **III-18e** (83 mg, 0.40 mmol) in 0.8 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 8:1 to 1:1) afforded the title compound **III-27b** as a colorless oil (110 mg, 0.21 mmol, 52% yield), and 6 mg pyrazine **III-18e** (0.03 mmol) was recovered.

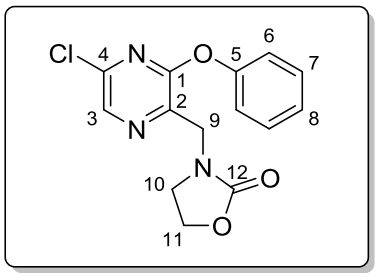
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (s, 1H, H_3), 7.85 – 7.79 (m, 2H), 7.74 (td, J = 5.2, 2.0 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.19 – 7.12 (m, 1H, H_8), 6.97 – 6.89 (m, 2H), 5.83 (dd, J = 9.1, 5.6 Hz, 1H, H_9), 3.24 – 3.17 (m, 2H, H_{15}), 3.17 – 3.09 (m, 1H, H_{14a}), 3.08 – 3.00 (m, 1H, H_{14b}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.3 (2C=O), 168.0 (C), 155.7 (C), 155.5 (q, J = 44.0 Hz, C_{17}), 152.3 (C), 145.2 (C), 139.9 (C), 136.7 (C_3), 134.5 (2CH), 131.6 (C), 129.7 (2CH), 125.7 (C_8), 123.7 (2CH), 120.8 (2CH), 116.3 (q, J = 270.1 Hz, CF_3), 50.1 (C_9), 26.2 (C_{14} or C_{15}), 22.8 (C_{14} or C_{15}).

IR (ν, cm^{-1}, $CDCl_3$) 3066, 2929, 1777, 1718, 1591, 1565, 1540, 1490, 1425, 1383, 1380, 1334, 1215, 1175, 1133, 1023.

HRMS (EI+) calculated for $C_{24}H_{15}ClF_3N_5O_4$: 529.0765; Found: 529.0768.

3-((5-Chloro-3-phenoxypyrazin-2-yl)methyl)oxazolidin-2-one (III-27c)



Chemical Formula: $C_{14}H_{12}ClN_3O_3$
Molecular Weight: 305,72

Following the general procedure, the reaction was carried out with xanthate **III-21e** (314 mg, 1.42 mmol) and pyrazine **III-18e** (147 mg, 0.71 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:2 to 1:0) afforded the desired product **III-27c** as a white solid (125 mg, 0.41 mmol, 58% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (s, 1H, H_3), 7.48 – 7.39 (m, 2H), 7.29 – 7.26 (m, 1H, H_8), 7.17 (dd, J = 5.4, 3.4 Hz, 2H), 4.75 (s, 2H, H_9), 4.43 (dd, J = 8.7, 7.3 Hz, 2H, H_{11}), 3.76 (dd, J = 8.7, 7.3 Hz, 2H, H_{10}).

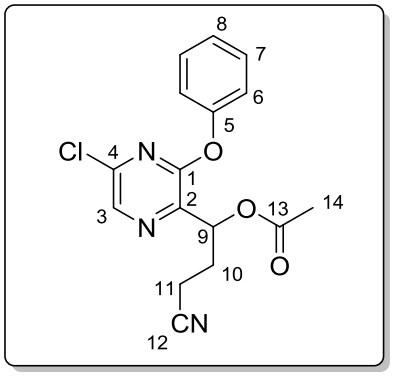
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 159.0 (C_{12}), 156.3 (C), 152.4 (C), 144.6 (C), 139.3 (C), 136.8 (C_3), 129.9 (2CH), 125.9 (C_8), 121.3 (2CH), 62.3 (C_{11}), 45.4 (C_{10}), 44.4 (C_9).

IR (ν, cm^{-1}, $CDCl_3$) 2923, 1755, 1600, 1541, 1490, 1426, 1376, 1277, 1219, 1195, 1184, 1172, 1162, 1114, 1042.

HRMS (EI+) calculated for $C_{14}H_{12}ClN_3O_3$: 305.0567; Found: 305.0555.

mp : 129-131 ℃

1-(5-Chloro-3-phenoxypyrazin-2-yl)-3-cyanopropyl acetate (III-27d)



Chemical Formula: $C_{16}H_{14}ClN_3O_3$
Molecular Weight: 331,76

Following the general procedure, the reaction was carried out with xanthate **III-21e** (327 mg, 1.32 mmol) and pyrazine **III-18e** (137 mg, 0.66 mmol) in 1.3 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 5:1 to 3:1) afforded the desired compound **III-27d** as a colorless oil (141 mg, 0.42 mmol, 64% yield).

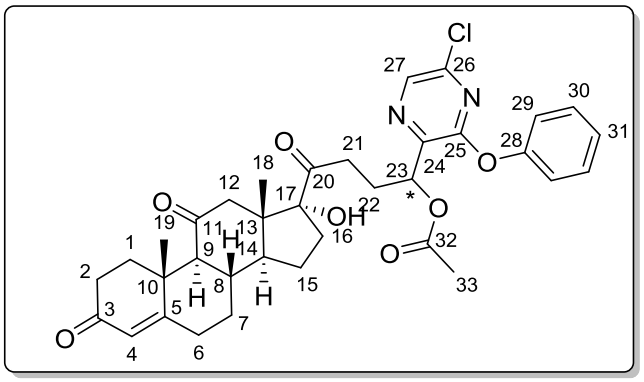
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.24 (s, 1H, H_3), 7.42 (dt, J = 10.6, 2.2 Hz, 2H), 7.28 – 7.25 (m, 1H, H_8), 7.17 (dd, J = 5.4, 3.4 Hz, 2H,), 6.18 (dd, J = 7.0, 5.6 Hz, 1H, H_9), 2.62 – 2.56 (m, 2H, H_{10} or H_{11}), 2.46 – 2.38 (m, 2H, H_{10} or H_{11}), 2.15 (s, 3H, H_{14}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.1 (C_{13}), 156.0 (C), 152.6 (C), 145.6 (C), 140.6 (C), 137.1 (C_3), 129.9 (2CH), 126.0 (C_8), 121.3 (2CH), 118.8 (C_{12}), 69.1 (C_9), 28.5 (C_{10} or C_{11}), 20.8 (C_{14}), 13.7 (C_{10} or C_{11}).

IR (ν, cm^{-1}, $CDCl_3$) 3071, 2940, 1743, 1595, 1538, 1490, 1427, 1372, 1235, 1218, 1172, 1161, 1052, 1024.

HRMS (EI+) calculated for $C_{16}H_{14}ClN_3O_3$: 331.0724; Found: 331.0718.

1-(5-Chloro-3-phenoxypyrazin-2-yl)-4-((*8S,9S,10R,13S,14S,17R*)-17-hydroxy-10,13-dimethyl-3,11-dioxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-4-oxobutyl acetate (III-27e)



Chemical Formula: $C_{35}H_{39}ClN_2O_7$
Molecular Weight: 635,15

Following the general procedure, the reaction was carried out with xanthate[130] (433 mg, 0.79 mmol) and pyrazine (81 mg, 0.39 mmol) in 0.8 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel 60 (SDS, Merck, 15-40 μm) (gradient of toluene/EtOAc = 2:1 to 1:1) afforded the desired product **III-27e** as a white solid (98 mg, 0.15 mmol, 40% yield, 1:1 epimers).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.19 (d, J = 10.4 Hz, 1H, H_{27}), 7.41 (t, J = 7.5 Hz, 2H), 7.26 – 7.22 (m, 1H, H_{31}), 7.20 – 7.14 (m, 2H), 6.10 (dd, J = 7.5, 4.5 Hz, 1H, H_{23}), 5.71 (s, 1H, H_4), 3.22 (br, 1H, *O*H), 3.10 – 2.96 (m, 1H), 2.84 (d, J = 12.3 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.52 – 2.25 (m, 8H), 2.12 (s, 1.5 H, H_{33}, 1st epimer), 2.10 (s, 1.5 H, H_{33}, 2nd epimer), 2.10 – 2.03 (m, 1H), 2.00 – 1.85 (m, 4H), 1.73 – 1.56 (m, 2H), 1.49 – 1.33 (m, 1H), 1.39 (s, 3H, H_{19}), 1.31 – 1.24 (m, 1H), 0.62 (s, 1.5H, H_{18}, 1st epimer), 0.61 (s, 1.5H, H_{18}, 2nd epimer).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 211.0, 210.9 (C=O), 209.6, 209.6 (C=O), 199.9, 170.7, 170.5, 168.8, 155.8, 155.8, 152.7, 152.6, 145.0, 144.9, 142.1, 141.8, 136.9, 136.7, 129.9, 125.8, 124.7, 121.3, 121.3, 89.1, 89.1, 70.0, 69.8, 62.6, 62.6, 51.2, 51.2, 50.3, 49.7, 38.3, 36.6, 36.6, 34.8, 34.6, 34.6, 34.2, 34.1, 33.8, 32.4, 32.3, 26.7, 26.6, 23.5, 21.1, 21.0, 17.3, 16.1, 16.1.

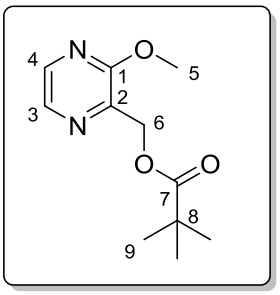
IR (ν, cm^{-1}, $CDCl_3$) 3505, 2941, 1739, 1706, 1667, 1617, 1595, 1539, 1490, 1428,

[130] Debien. L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5118-5121.

1372, 1274, 1235, 1218, 1185, 1172, 1162, 1117, 1071, 1051, 1023.

mp: 97-100 ℃

(3-Methoxypyrazin-2-yl)methyl pivalate (III-27f)



Chemical Formula: $C_{11}H_{16}N_2O_3$
Molecular Weight: 224,26

Following the general procedure, the reaction was carried out with xanthate **III-21p** (544 mg, 2.30 mmol) and pyrazine **III-18i** (127 mg, 1.15 mmol) in 2.3 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 3:2) afforded the desired product **III-27f** as a yellow oil (85 mg, 0.38 mmol, 33% yield), and 26 mg pyrazine **III-18i** (0.24 mmol) was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.09 (d, J = 2.8 Hz, 1H), 8.05 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H, H_6), 3.98 (s, 3H, H_5), 1.24 (s, 9H, H_9).

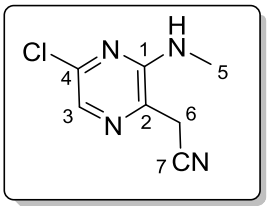
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 178.3 (C_7), 158.5 (C), 141.3 (C), 140.4 (CH), 135.9 (CH), 62.4 (C_6), 53.8 (C_5), 39.0 (C_8), 27.3 ($3C_9$).

IR (ν, cm^{-1}, $CDCl_3$) 2974, 2956, 2931, 2856, 1728, 1549, 1480, 1463, 1452, 1396, 1367, 1284, 1139, 1012.

HRMS (EI+) calculated for $C_{11}H_{16}N_2O_3$: 224.1161; Found: 224.1166.

2-(5-Chloro-3-(methylamino)pyrazin-2-yl)acetonitrile (III-29a)

Following the general procedure, the reaction was carried out with xanthate **III-28a** (478 mg, 2.98 mmol) and pyrazine **III-18a** (214 mg, 1.49 mmol) in 3.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:1 to 0:1) gave two portions. The first portion was further purified by flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:1 to 1:1) afforded the following products:



Chemical Formula: $C_7H_7ClN_4$
Molecular Weight: 182,61

III-29a (60 mg, 0.33 mmol, 22% yield, white solid)

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.79 (s, 1H, H_3), 4.56 (br, 1H, *N*H), 3.75 (s, 2H, H_6), 3.07 (d, J = 4.8 Hz, 3H, H_5).

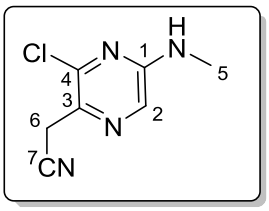
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 152.3 (C_1), 147.5 (C_4), 130.2 (C_3), 129.0 (C_2), 114.9 (C_7), 28.8 (C_5), 22.9 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3470, 2947, 1577, 1541, 1507, 142, 1408, 1375, 1282, 1228, 1209, 1181, 1099.

HRMS (EI+) calculated for $C_7H_7ClN_4$: 182.0359; Found: 182.0364.

mp: 190-191 ℃

2-(3-Chloro-5-(methylamino)pyrazin-2-yl)acetonitrile (III-30a)



Chemical Formula: $C_7H_7ClN_4$
Molecular Weight: 182,61

III-30a (8 mg, 0.04 mmol, 3% yield, light yellow solid)

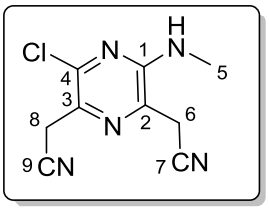
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.78 (s, 1H, H_2), 4.86 (br, 1H, *N*H), 3.90 (s, 2H, H_6), 3.00 (d, J = 5.1 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 154.7 (C_1), 145.7 (C_4), 129.8 (C_3), 129.1 (C_2), 116.4 (C_7), 28.7 (C_5), 23.4 (C_6).

IR (ν, cm^{-1}, $CDCl_3$) 3459, 2948, 1591, 1519, 1415, 1376, 1329, 1144, 1063.

HRMS (EI+) calculated for $C_7H_7ClN_4$: 182.0359; Found: 182.0350.

2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)diacetonitrile (III-31a)



Chemical Formula: $C_9H_8ClN_5$
Molecular Weight: 221,65

III-31a (31 mg, 0.14 mmol, 9% yield, light yellow solid)

^{1}H NMR (δ, ppm) (400 MHz, CD_3CN) 5.66 (br, 1H, *N*H), 3.93 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 2.89 (d, J = 4.7 Hz, 3H, H_5).

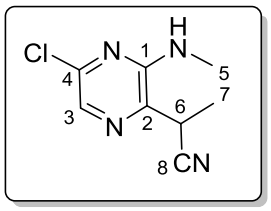
^{13}C NMR (δ, ppm) (101 MHz, CD_3CN) 153.1 (C), 145.4 (C), 132.4 (C), 128.9 (C), 117.6 (C), 116.4 (C), 28.4 (CH_3), 23.5 (CH_2), 23.2 (CH_2).

IR (ν, cm^{-1}, $CDCl_3$) 3468, 1580, 1513, 1411, 1367, 1178, 1025.

HRMS (EI+) calculated for $C_9H_8ClN_5$: 221.0468; Found: 221.0461.

mp: 185-186 ℃

2-(5-Chloro-3-(methylamino)pyrazin-2-yl)propanenitrile (III-29b)



Chemical Formula: $C_8H_9ClN_4$
Molecular Weight: 196,64

Following the general procedure, the reaction was carried out with xanthate **III-28b** (522 mg, 2.98 mmol) and pyrazine **III-18a** (214 mg, 1.49 mmol) in 3.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 8:1 to 4:1) afforded the desired product **III-29b** as a white solid (121 mg, 0.62 mmol, 41% yield), and 95 mg (0.66 mmol) pyrazine **III-18a** was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.80 (s, 1H, H_3), 4.74 (br, 1H, *N*H), 3.89 (q, J = 7.2 Hz, 1H, H_6), 3.06 (d, J = 4.8 Hz, 3H, H_5), 1.70 (d, J = 7.2 Hz, 3H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 151.7 (C), 147.1 (C), 133.3 (C), 129.9 (C_3), 119.3 (C_8), 28.8 (C_5 or C_6), 28.7 (C_5 or C_6), 16.1 (C_7).

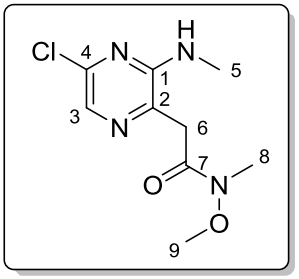
IR (v, cm^{-1}, $CDCl_3$) 3470, 2996, 2946, 1574, 1539, 1505, 1442, 1371, 1310, 1245, 1209, 1191, 1105, 986.

HRMS (EI+) calculated for $C_8H_9ClN_4$: 196.0516; Found: 196.0521.

mp: 142-144 ℃

2-(5-Chloro-3-(methylamino)pyrazin-2-yl)-*N*-methoxy-*N*-methylacetamide (III-29d)

Following the general procedure, the reaction was carried out with xanthate **III-28d** (632 mg, 2.83 mmol) and pyrazine **III-18a** (203 mg, 1.41 mmol) in 2.8 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:1 to 4:1, then diethyl ether/MeOH = 15:1 to 5:1) afforded the single addition product **III-29d** as a white solid (169 mg, 0.69 mmol, 49% yield) and the double addition product **III-31d** as a white solid (52 mg, 0.15 mmol, 11% yield).



Chemical Formula: $C_9H_{13}ClN_4O_2$
Molecular Weight: 244,68

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.68 (s, 1H, H_3), 6.64 (br, 1H, **N**H), 3.89 (s, 2H, H_6), 3.74 (s, 3H, H_9), 3.21 (s, 3H, H_8), 2.98 (d, J = 4.7 Hz, 3H, H_5).

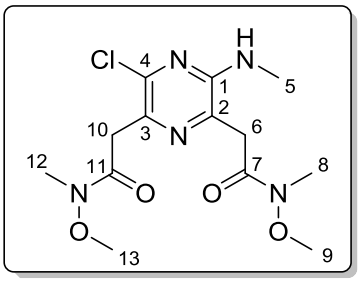
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.3 (C_7), 154.9 (C_1), 146.0 (C_4), 134.9 (C_2), 128.9 (C_3), 62.2 (C_9), 39.0 (C_6), 32.3 (C_8), 28.4 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3345, 2941, 1637, 1588, 1516, 1443, 1391, 1383, 1286, 1231, 1188, 1108, 1004.

HRMS (EI+) calculated for $C_9H_{13}ClN_4O_2$: 244.0727; Found: 244.0731.

mp: 142-143 ℃

2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(N-methoxy-N-methylaceta mide) (III-31d)



Chemical Formula: $C_{13}H_{20}ClN_5O_4$
Molecular Weight: 345,78

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 6.51 (br, 1H, *N*H), 3.94 (s, 2H, H_6 or H_{10}), 3.89 (s, 2H, H_6 or H_{10}), 3.74 (s, 3H, H_9 or H_{13}), 3.70 (s, 3H, H_9 or H_{13}), 3.20 (s, 3H, H_8 or H_{12}), 3.18 (s, 3H, H_8 or H_{12}), 2.97 (d, J = 4.8 Hz, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 171.2 (C_7 or C_{11}), 170.4 (C_7 or C_{11}), 153.9 (C_1), 145.4 (C_4), 134.5 (C_2 or C_3), 133.3 (C_2 or C_3), 62.4 (C_9 or C_{13}), 61.5 (C_9 or C_{13}), 39.0 (C_6 or C_{10}), 37.9 (C_6 or C_{10}), 32.5 (C_8 or C_{12}), 32.3 (C_8 or C_{12}), 28.6 (C_5).

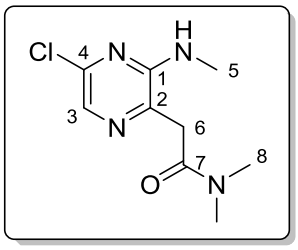
IR (ν, cm^{-1}, $CDCl_3$) 3345, 2969, 2940, 2903, 1639, 1588, 1517, 1443, 1421, 1387, 1372, 1337, 1283, 1172, 1027, 1003.

HRMS (EI+) calculated for $C_{13}H_{20}ClN_5O_4$: 345.1204; Found: 345.1218.

mp: 141-142 ℃

2-(5-Chloro-3-(methylamino)pyrazin-2-yl)-*N*,*N*-dimethylacetamide (III-29e)

Following the general procedure, the reaction was carried out with xanthate **III-28e** (586 mg, 2.83 mmol) and pyrazine **III-18a** (203 mg, 1.41 mmol) in 2.8 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 3:2 to 4:1, then diethyl ether/MeOH = 15:1 to 5/1) afforded the single addition product **III-29e** as a white solid (179 mg, 0.78 mmol, 56% yield) and the double addition product **III-31e** as a white solid (63 mg, 0.20 mmol, 14% yield).



Chemical Formula: $C_9H_{13}ClN_4O$
Molecular Weight: 228,68

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.63 (s, 1H, H_3), 6.87 (s, 1H, *N*H), 3.78 (s, 2H, H_6), 3.18 (s, 3H, H_8), 2.97 (d, J = 4.8 Hz, 3H, H_5), 2.94 (s, 3H, H_8).

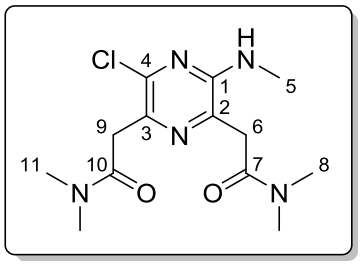
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.0 (C_7), 154.8 (C_1), 146.0 (C_4), 134.7 (C_2), 128.2 (C_3), 41.6 (C_6), 38.4 (C_8), 35.9 (C_8), 28.3 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3341, 2941, 1631, 1591, 1518, 1441, 1404, 1384, 1287, 1230, 1199, 1189, 1116, 1100, 1059, 974.

HRMS (EI+) calculated for $C_9H_{13}ClN_4O$: 228.0778; Found: 228.0768.

mp: 149-150 ℃

2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(*N*,*N*-dimethylacetamide) (III-31e)



Chemical Formula: $C_{13}H_{20}ClN_5O_2$
Molecular Weight: 313,79

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 6.65 (q, J = 5.0 Hz, 1H, *N*H), 3.83 (s, 2H, H_6 or H_9), 3.76 (s, 2H, H_6 or H_9), 3.16 (s, 3H, H_8 or H_{11}), 3.06 (s, 3H, H_8 or H_{11}), 2.97 (s, 3H, H_8 or H_{11}), 2.96 (d, J = 4.8 Hz, 3H, H_5), 2.91 (s, 3H, H_8 or H_{11}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 169.7 (C_7 or C_{10}), 168.9 (C_7 or C_{10}), 153.8 (C_1), 145.1 (C_4), 134.2 (C_2 or C_3), 133.16 (C_2 or C_3), 41.6 (C_6 or C_9), 39.0 (C_6 or C_9), 38.3 (C_8 or C_{11}), 37.6 (C_8 or C_{11}), 35.9 (C_8 or C_{11}), 35.7 (C_8 or C_{11}), 28.5 (C_5).

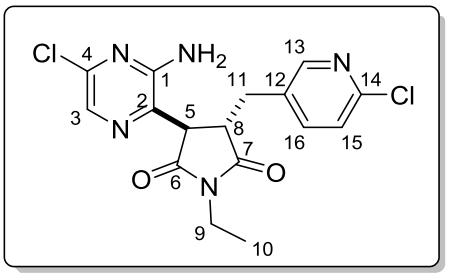
IR (v, cm^{-1}, $CDCl_3$) 3348, 2939, 1633, 1592, 1518, 1402, 1374, 1338, 1288, 1264, 1189, 11134, 1068, 1029.

HRMS (EI+) calculated for $C_{13}H_{20}ClN_5O_2$: 313.1306; Found: 313.1294.

mp: 171-173 ℃

(3,4-*trans*)-3-(3-Amino-5-chloropyrazin-2-yl)-4-((6-chloropyridin-3-yl)methyl)-1-ethylpyrrolidine-2,5-dione (III-29f)

Following the general procedure, the reaction was carried out with xanthate **II-45e** (373 mg, 1.00 mmol) and pyrazine **III-18g** (65 mg, 0.50 mmol) in 1.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:3 to 2:1, then DCM/diethyl ether = 4:1 to 7:3) afforded the single addition product **III-29f** as a white solid (127 mg, 0.33 mmol, 66% yield) and the double addition product **III-31f** as a light brown solid (56 mg, 0.09 mmol, 18% yield).



Chemical Formula: $C_{16}H_{15}Cl_2N_5O_2$
Molecular Weight: 380,23

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.18 (d, J = 2.6 Hz, 1H, H_{Ar}), 7.80 (s, 1H, H_3), 7.46 (dd, J = 8.2, 2.6 Hz, 1H, H_{Ar}), 7.21 (d, J = 8.2 Hz, 1H, H_{Ar}), 5.50 (s, 2H, NH_2), 4.43 (dt, J = 7.2, 5.6 Hz, 1H, H_8), 3.75 (d, J = 5.5 Hz, 1H, H_5), 3.59 – 3.47 (m, 2H, H_9), 3.18 – 3.03 (m, 2H, H_{11}), 1.12 (t, J = 7.2 Hz, 3H, H_{10}).

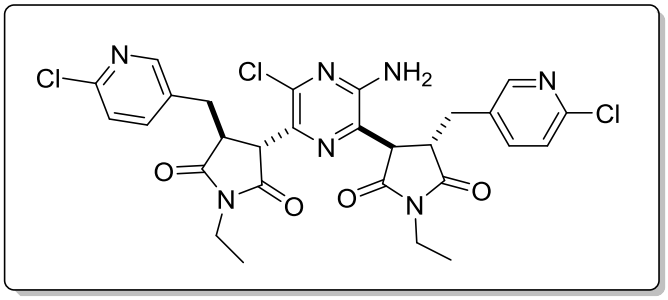
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 177.3 (C_6 or C_7), 176.0 (C_6 or C_7), 154.4 (C_1), 150.6 (C_{Ar}), 150.2 (CH_{Ar}), 146.4 (C_4), 139.6 (CH_{Ar}), 132.6 (C_2), 131.8 (C_3), 131.5 (C_{Ar}), 124.4 (CH_{Ar}), 48.3 (C_5), 43.0 (C_8), 34.5 (C_9), 31.8 (C_{11}), 13.1 (C_{10}).

IR (ν, cm^{-1}, $CDCl_3$) 3461, 3356, 2985, 2941, 1775, 1701, 1617, 1589, 1563, 1533, 1462, 1432, 1405, 1381, 1352, 1227, 1140, 1110, 1049, 1026, 957.

HRMS (EI+) calculated for $C_{16}H_{15}Cl_2N_5O_2$: 379.0603; Found: 379.0598.

mp: 185-186 ℃

4,4'-(3-Amino-5-chloropyrazine-2,6-diyl)bis(3-((6-chloropyridin-3-yl)methyl)-1-ethylpyrrolidine-2,5-dione) (III-31f)



Chemical Formula: $C_{28}H_{26}Cl_3N_7O_4$
Molecular Weight: 630,91

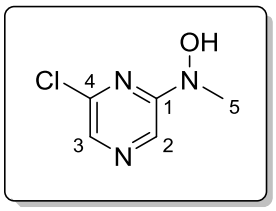
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.22 (dd, J = 5.5, 2.5 Hz, 2H), 8.15 (dd, J = 9.3, 2.5 Hz, 2H), 7.50 – 7.36 (m, 4H), 7.28 – 7.19 (m, 4H), 5.63 (4H), 4.16 – 4.01 (m, 4H), 3.71 (dd, J = 21.0, 5.4 Hz, 2H), 3.64 – 3.47 (m, 8H), 3.30 – 2.93 (m, 10H), 1.12 (m, 12H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 176.9, 176.9, 176.8, 175.4, 175.3, 174.7, 174.4, 153.9, 153.8, 150.8, 150.7, 150.42, 150.38 , 150.2, 150.1, 145.61, 145.57, 139.7, 139.6, 136.6, 136.1, 133.2, 132.9, 131.3, 131.1, 131.0, 124.6, 124.6, 124.4, 124.4, 48.7, 48.6, 48.2, 48.1, 47.9, 47.8, 43.1, 43.0, 34.7, 34.6, 34.51, 34.48, 32.0, 31.9, 31.6, 31.3, 13.2, 13.1, 13.0.

IR (ν, cm^{-1}, $CDCl_3$) 3461, 3352, 2984, 2940, 1778, 1705, 1617, 1588, 1563, 1462, 1445, 1403, 1387, 1352, 1227, 1133, 1111, 1042, 1027.

HRMS (EI+) calculated for $C_{28}H_{26}Cl_3N_7O_4$: 629.1112; Found: not found.

N-(6-Chloropyrazin-2-yl)-*N*-methylhydroxylamine (III-36)



Chemical Formula: $C_5H_6ClN_3O$
Molecular Weight: 159,57

In a sealed tube, 2,6-dichloropyrazine (1.1 g, 7.38 mmol, 1 equiv) was heated with *N*-methylhydroxylamine hydrochloride (0.74 g, 8.86 mmol, 1.2 equiv) in 15 mL absolute ethanol at 80 ℃ for 1 h. The solvent was then removed under reduced pressure. Water was added and the mixture was extracted with dichloromethane for three times. The organic phase was gathered and dried over anhydrous Na_2SO_4. Then the solvent was evaporated and the crude product was further purified by flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 1:1) afforded the desired product **III-36** as a yellow solid (363 mg, 2.27 mmol, 31% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.38 (s, 1H), 7.99 (s, 1H), 6.75 (br, 1H, *O*H), 3.36 (s, 3H, H_5).

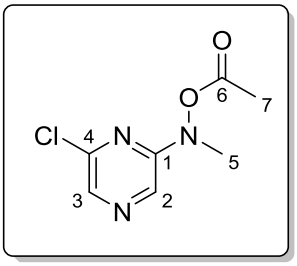
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 158.2 (C), 146.4 (C), 133.9 (CH), 130.1 (CH), 41.3 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3546, 1602, 1561, 1525, 1413, 1397, 1183, 1116.

HRMS (EI+) calculated for $C_5H_6ClN_3O$: 159.0199; Found: 159.0203.

mp: decomposed at 110 ℃

O-Acetyl-*N*-(6-chloropyrazin-2-yl)-*N*-methylhydroxylamine (III-32)



Chemical Formula: $C_7H_8ClN_3O_2$
Molecular Weight: 201,61

A solution of **III-36** (358 mg, 2.24 mmol, 1 equiv), dimethylaminopyridine (5.5 mg, 0.05 mmol, 0.02 equiv) and triethylamine (227 mg, 302 µL, 2.24 mmol, 1 equiv) in dichloromethane (4 mL) was cooled to 0 ℃ prior to slow addition of acetyl chloride (176 mg, 160 µL, 2.24 mmol, 1 equiv). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The solution was washed with saturated sodium hydrogen carbonate aqueous solution, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash chromatography on silica gel (petroleum ether/EtOAc = 3:1) and the desired product **III-32** was obtained as an orange oil (423 mg, 2.10 mmol, 94% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.11 (s, 1H), 8.07 (s, 1H), 3.39 (s, 3H, H_5), 2.25 (s, 3H, H_7).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.3 (C_6), 156.0 (C), 146.6 (C), 135.9 (CH), 129.9 (CH), 40.1 (C_5), 18.9 (C_7).

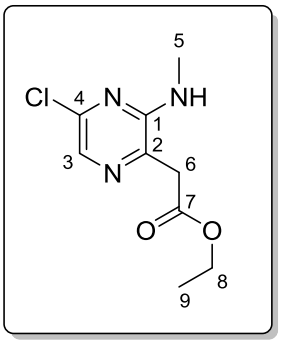
IR (ν, cm^{-1}, $CDCl_3$) 2933, 1792, 1560, 1523, 1412, 1398, 1369, 1175, 1120, 999.

HRMS (EI+) calculated for $C_7H_8ClN_3O_2$: 201.0305; Found: 201.0309.

Ethyl 2-(5-chloro-3-(methylamino)pyrazin-2-yl)acetate (III-41a)

Entry 1: Following the general procedure, the reaction was carried out with xanthate **III-39** (297 mg, 1.42 mmol) and pyrazine **III-18a** (102 mg, 0.71 mmol) in 1.4 mL DCE and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:1 to 1:1) afforded analytical samples of **III-41**.

Entry 2: Following the general procedure, the reaction was carried out with xanthate **III-39** (202 mg, 0.97 mmol) and pyrazine **III-32** (98 mg, 0.49 mmol) in 9.7 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:1 to 1:1) afforded analytical samples of **III-41**.



Chemical Formula: $C_9H_{12}ClN_3O_2$
Molecular Weight: 229,66

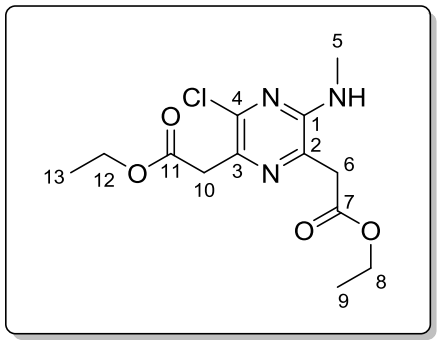
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.72 (s, 1H, H_3), 5.54 (br, 1H, *N*H), 4.17 (q, J = 7.1 Hz, 2H, H_8), 3.70 (s, 2H, H_6), 3.00 (d, J = 4.8 Hz, 3H, H_5), 1.26 (t, J = 7.1 Hz, 3H, H_9).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.1 (C_7), 153.9 (C), 146.3 (C), 133.9 (C), 129.4 (C_3), 62.0 (C_8), 41.1 (C_6), 28.5 (C_5), 14.2 (C_9).

IR (ν, cm^{-1}, $CDCl_3$) 3400, 2985, 2941, 1714, 1578, 1511, 1455, 1379, 1287, 1261, 1224, 1188, 1100, 1026.

HRMS (EI+) calculated for $C_9H_{12}ClN_3O_2$: 229.0618; Found: 229.0610.

Diethyl 2,2'-(3-chloro-5-(methylamino)pyrazine-2,6-diyl)diacetate (III-41c)



Chemical Formula: $C_{13}H_{18}ClN_3O_4$
Molecular Weight: 315,75

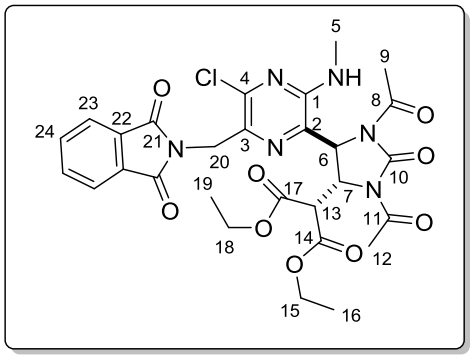
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 5.52 (br, 1H, *N*H), 4.16 (q, J = 6.8 Hz, 2H), 4.14 (q, J = 6.8 Hz, 2H), 3.80 (s, 2H), 3.66 (s, 2H), 2.95 (d, J = 4.8 Hz, 3H, H_5), 1.24 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.4 (C), 170.1 (C), 153.1 (C), 145.7 (C), 133.5 (C), 133.2 (C), 61.9 (CH_2), 61.1 (CH_2), 40.9 (CH_2), 40.0 (CH_2), 28.6 (C_5), 14.3 (CH_3), 14.2 (CH_3).

IR (ν, cm^{-1}, $CDCl_3$) 3398, 2985, 1732, 1582, 1515, 1371, 1191, 1032.

HRMS (EI+) calculated for $C_{13}H_{18}ClN_3O_4$: 315.0986; Found: 315.0982.

Diethyl 2-(1,3-diacetyl-5-(5-chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(methyl amino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)malonate (III-42a)



Chemical Formula: $C_{28}H_{29}ClN_6O_9$
Molecular Weight: 629,02

Following the general procedure, the reaction was carried out with xanthate **III-14** (131 mg, 0.46 mmol) and pyrazine **III-22i** (109 mg, 0.23 mmol) in 0.5 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 1:3) afforded the desired product **III-42a** as a white solid (85 mg, 0.13 mmol, 59% yield) and 30 mg (0.06 mmol) pyrazine was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.88 – 7.85 (m, 2H), 7.78 – 7.73 (m, 2H), 6.83 (br, 1H, *N*H), 5.37 (s, 1H, H_6), 4.94 (d, J = 16.6 Hz, 1H, H_{20a}), 4.86 (d, J = 16.6 Hz, 1H, H_{20b}), 4.43 (d, J = 4.2 Hz, 1H), 4.24 (dddd, J = 18.0, 10.8, 7.2, 3.6 Hz, 2H), 4.11 – 4.00 (m, 2H), 3.97 (d, J = 4.2 Hz, 1H), 3.02 (d, J = 4.6 Hz, 3H, H_5), 2.19 (s, 3H), 2.06 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H).

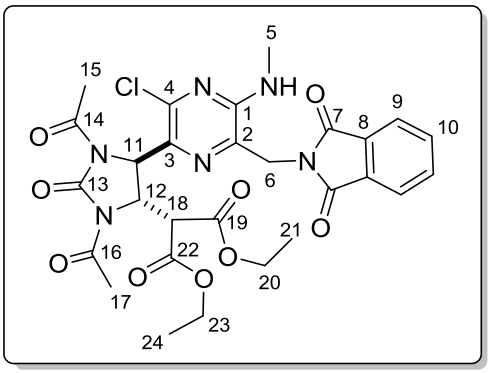
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.7 (C=O), 169.6 (C=O), 168.34 (C=O), 167.83 (C=O), 166.41 (C=O), 151.6 (C), 150.9 (C), 144.7 (C), 134.0 (CH), 133.5 (C), 132.4 (C), 131.3 (C), 123.7 (CH), 62.9 (CH_2), 62.7 (CH_2), 53.9 (CH), 52.5 (C_6), 50.8 (CH), 38.5 (C_{20}), 28.5 (C_5), 23.5 (CH_3), 23.2 (CH_3), 13.9 (CH_3), 13.9 (CH_3).

IR (ν, cm^{-1}, $CDCl_3$) 3385, 2986, 2941, 1774, 1720, 1587, 1516, 1426, 1396, 1373, 1325, 1263, 1203, 1165, 1116, 1036.

HRMS (EI+) calculated for $C_{28}H_{29}ClN_6O_9$: 628.1685; Found: 628.1680.

mp: 166-167 ℃

Diethyl 2-(1,3-diacetyl-5-(3-chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-5-(methyl amino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)malonate (III-42b)



Chemical Formula: $C_{28}H_{29}ClN_6O_9$
Molecular Weight: 629,02

Following the general procedure, the reaction was carried out with xanthate **III-21i** (414 mg, 0.92 mmol, 1.7 equiv) and pyrazine **III-19a** (164 mg, 0.54 mmol, 1.0 equiv) in 1.8 mL DCE (0.5 mmol/mL of xanthate) and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 5:1 to 1:1) afforded the desired product **III-42b** as a white solid (260 mg, 0.41 mmol, 76% yield) and 15 mg (0.05 mmol) pyrazine was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.74 (td, J = 5.2, 2.1 Hz, 2H), 5.93 (br, 1H, *N*H), 5.68 (d, J = 1.7 Hz, 1H, H_{11}), 4.69 (s, 2H, H_6), 4.63 (dd, J = 4.3, 1.7 Hz, 1H, H_{12}), 4.27 – 4.14 (m, 4H), 4.12 (d, J = 4.3 Hz, H_{18}), 3.00 (d, J = 4.7 Hz, 3H, H_5), 2.48 (s, 3H), 2.40 (s, 3H), 1.23 (q, J = 7.2 Hz, 6H).

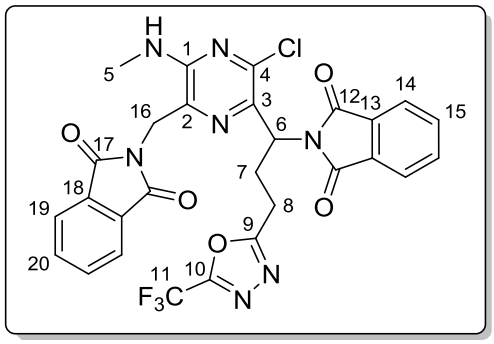
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 171.0 (C=O), 170.0 (C=O), 168.1 (C=O), 166.6 (C=O), 166.3 (C=O), 152.5 (C), 152.1 (C), 144.7 (C), 135.4 (C), 134.5 (2CH), 134.2 (C), 131.9 (C), 123.8 (2CH), 62.3 (CH_2), 62.1 (CH_2), 56.0 (CH), 53.5 (CH), 52.6 (CH), 39.2 (C_6), 28.7 (CH_3), 24.3 (CH_3), 24.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3).

IR (ν, cm^{-1}, $CDCl_3$) 3379, 2985, 1761, 1714, 1584, 1520, 1426, 1389, 1368, 1336, 1264, 1116, 1038.

HRMS (EI+) calculated for $C_{28}H_{29}ClN_6O_9$: 628.1685; Found: 628.1670.

mp: 157-158 ℃

2-(1-(3-Chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-5-(methylamino)pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl)isoindoline-1,3-dione (III-42c)



Chemical Formula: $C_{28}H_{19}ClF_3N_7O_5$
Molecular Weight: 625,95

Following the general procedure, the reaction was carried out with xanthate **III-21b** (200 mg, 0.45 mmol) and pyrazine **III-19a** (89 mg, 0.30 mmol) in 0.9 mL DCE (0.5 mmol/mL of xanthate) and needed 8 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 2:1 to 2:3) afforded the desired product **III-42c** as a white solid (81 mg, 0.13 mmol, 44% yield) and 36 mg (0.12 mmol) pyrazine was recovered.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.83 (dd, J = 5.5, 3.1 Hz, 2H), 7.77 – 7.74 (m, 2H), 7.73 (dd, J = 5.5, 3.0 Hz, 2H), 7.69 (dd, J = 5.6, 3.0 Hz, 2H), 5.79 (br, 1H, *N*H), 5.57 (t, J = 7.2 Hz, 1H, H_6), 4.90 (d, J = 15.2 Hz, 1H, H_{16a}), 4.83 (d, J = 15.2 Hz, H_{16b}), 3.23 – 3.11 (m, 1H), 3.08 (dd, J = 9.5, 5.5 Hz, 1H), 3.04 – 2.95 (m, 1H), 2.99 (d, J = 4.8 Hz, 3H, H_5), 2.71 – 2.59 (m, 1H).

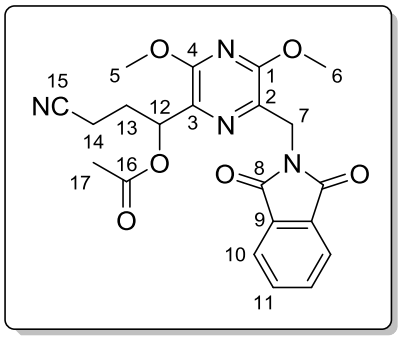
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.7 (C), 168.4 (C), 167.8 (C), 155.4 (q, J = 43.8 Hz, C_{10}), 152.3 (C), 145.4 (C), 134.4 (2CH), 134.2 (2CH), 133.1 (C), 132.7 (C), 132.1 (C), 131.7 (C), 123.7 (2CH), 123.5 (2CH), 116.5 (q, J = 269.9 Hz, CF_3), 50.8 (C_6), 39.6 (C_{16}), 28.6 (C_5), 27.0 (CH_2), 22.8 (CH_2).

IR (ν, cm^{-1}, $CDCl_3$) 3385, 1773, 1716, 1582, 1389, 1371, 1214, 1174, 1134.

HRMS (EI+) calculated for $C_{28}H_{19}ClF_3N_7O_5$: 625.1088; Found: 625.1117.

mp: 99-101 ℃

3-Cyano-1-(6-((1,3-dioxoisoindolin-2-yl)methyl)-3,5-dimethoxypyrazin-2-yl)propyl acetate (III-42d)



Chemical Formula: $C_{21}H_{20}N_4O_6$
Molecular Weight: 424,41

Following the general procedure, the reaction was carried out with xanthate **III-21n** (230 mg, 0.93 mmol) and pyrazine **III-19r** (139 mg, 0.46 mmol) in 1.4 mL DCE (0.66 mmol/mL of xanthate) and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 5:1 to 1:1) afforded the desired product **III-42d** as a white solid (116 mg, 0.27 mmol, 59% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dt, J = 7.0, 3.5 Hz, 2H), 7.77 (td, J = 5.3, 2.1 Hz, 2H), 5.90 (t, J = 5.9 Hz, 1H, H_{12}), 4.96 (d, J = 16.8 Hz, 1H, H_{7a}), 4.89 (d, J = 16.8 Hz, 1H, H_{7b}), 4.01 (s, 3H, H_5 or H_6), 3.94 (s, 3H, H_5 or H_6), 2.26 – 2.14 (m, 2H, H_{14}), 2.14 – 2.03 (m, 1H, H_{13a}), 2.03 – 1.92 (m, 1H, H_{13b}), 1.85 (s, 3H, H_{17}).

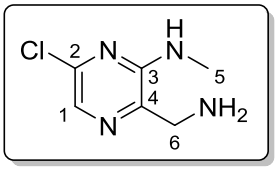
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.1 (C=O), 168.5 (C=O), 155.9 (C), 155.9 (C), 134.3 (CH), 132.4 (C), 129.1 (C), 128.1 (C), 123.5 (CH), 119.3 (CN), 68.1 (C_{12}), 54.1 (C_5 or C_6), 54.0 (C_5 or C_6), 37.8 (C_7), 27.8 (C_{13}), 20.7 (C_{17}), 12.9 (C_{14}).

IR (ν, cm^{-1}, $CDCl_3$) 2990, 2948, 1774, 1718, 1560, 1481, 1455, 1429, 1396, 1342, 1241, 1185, 1110, 1012.

HRMS (EI+) calculated for $C_{21}H_{20}N_4O_6$: 424.1383; Found: 424.1383.

mp: 129-130 ℃.

3-(Aminomethyl)-6-chloro-*N*-methylpyrazin-2-amine (III-43)

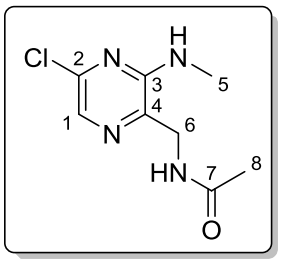


Chemical Formula: $C_6H_9ClN_4$
Molecular Weight: 172,62

Pyrazine **III-18a** (531 mg, 1.75 mmol, 1.0 equiv) and hydrazine monohydrate (176 mg, 170 μL, 3.51 mmol, 2.0 equiv) in 8.8 mL of MeOH were heated at reflux for 3 h. After cooling to 0 ℃, the suspension was filtered and the residue was washed with MeOH. The filtrate was concentrated under reduced pressure. After adding $CHCl_3$, the solid was filtered off and the filtrate was concentrated to afford the desired product **III-43** (105 mg, 0.61 mmol, 35% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.60 (s, 1H, H_1), 7.14 (br, 1H, *N*H), 3.99 (s, 2H, H_6), 2.98 (d, J = 4.9 Hz, 3H, H_5), 1.49 (br, 2H, *N*H_2).
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 154.6 (C_3), 146.0 (C_2), 139.4 (C_4), 127.6 (C_1), 46.7 (C_6), 27.9 (C_5).
IR (ν, cm^{-1}, $CDCl_3$) 3329, 2929, 2858, 1583, 1515, 1408, 1378, 1313, 1238, 1219, 1187, 1103.
mp: 122-124 ℃

N-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)acetamide (III-45)



Chemical Formula: $C_8H_{11}ClN_4O$
Molecular Weight: 214,65

To a solution of amine **III-43** (48 mg, 0.28 mmol, 1.0 equiv) and triethylamine (31 mg, 43 μL, 0.31 mmol, 1.1 equiv) in dichloromethane (2 mL) was added dropwise acetyl chloride (24 mg, 22 μL, 0.31 mmol, 1.1 equiv). After total consumption of the amine, water was added and the organic layer was separated. The water phase was extracted with dichloromethane twice more. The organic phase was gathered and washed with saturated brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 2:1 to 3:1) to give the desired compound **III-45** (34 mg, 0.16 mmol, 57% yield) as a light yellow solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.59 (s, 1H, H_1), 6.59 (br, 1H, *N*H), 6.37 (br, 1H, *N*H), 4.40 (d, J = 6.3 Hz, 2H, H_6), 2.97 (d, J = 4.7 Hz, 3H, H_5), 2.06 (s, 3H, H_8).

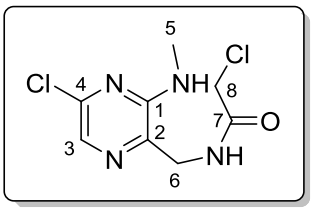
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 171.8 (C_7), 153.4 (C_3), 146.9 (C_2), 136.1 (C_4), 127.6 (C_1), 41.9 (C_6), 28.3 (C_5), 23.2 (C_8).

IR (ν, cm^{-1}, $CDCl_3$) 3446, 3324, 2944, 1663, 1589, 1523, 1385, 1304, 1240, 1217, 1106.

HRMS (EI+) calculated for $C_8H_{11}ClN_4O$: 214.0621; Found: 214.0619.

mp: 176-177 ℃

2-Chloro-*N*-((5-chloro-3-(methylamino)pyrazin-2-yl)methyl)acetamide (III-46)



Chemical Formula: $C_8H_{10}Cl_2N_4O$
Molecular Weight: 249,10

In an NMR tube was added pyrazine **III-43** (17.2 mg, 0.10 mmol, 1 equiv) and triethylamine (25.3 mg, 34.8 μL, 0.25 mmol, 2.5 equiv) in CD_3CN (0.3 mL). After cooling to 0 ℃, chloroacetyl chloride (14.7 mg, 10.4 μL, 0.13 mmol, 1.3 equiv) was added dropwise into the mixture. The solution was then heated to reflux for 4 h. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (EtOAc/petroleum ether = 1:2) to give the desired compound **III-46** as a white solid (18 mg, 0.072 mmol, 72% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.65 (s, 1H, H_3), 7.45 (br, 1H, *N*H), 6.19 (br, 1H, *N*H), 4.46 (d, J = 6.3 Hz, 2H, H_6), 4.12 (s, 2H, H_8), 2.98 (d, J = 4.7 Hz, 3H, H_5).

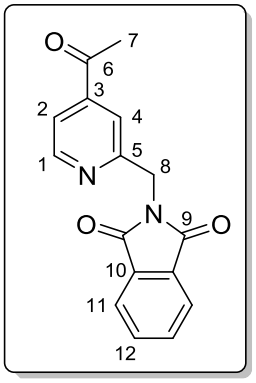
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.7 (C_7), 153.2 (C_1), 147.1 (C_4), 135.0 (C_2), 128.2 (C_3), 42.5 (C_8), 41.9 (C_6), 28.4 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3415, 3342, 2946, 1664, 1587, 1534, 1384, 1310, 1218, 1104.

HRMS (EI+) calculated for $C_8H_{10}Cl_2N_4O$: 248.0232; Found: 248.0244.

2-((4-Acetylpyridin-2-yl)methyl)isoindoline-1,3-dione (III-50a)

Following the general procedure, the reaction was carried out with xanthate **III-14** (389 mg, 1.28 mmol, 1.3 equiv), 4-acetylpyridine (131 mg, 1.08 mmol, 1.0 equiv) and TFA (616 mg, 413 μL, 5.40 mmol, 5.0 equiv) in 1.3 mL ethyl acetate and was stopped after 6 h. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:1 to 2:3) afforded mono-addition product **III-50a** (54 mg, 0.19 mmol, 18% yield) as a white solid and double-addition product **III-51** (42 mg, 0.10 mmol, 9% yield) as a white solid, and 43 mg (0.35 mmol) of the starting 4-acetylpyridine was recovered.



Chemical Formula: $C_{16}H_{12}N_2O_3$
Molecular Weight: 280,28

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.70 (dd, J = 5.1, 0.9 Hz, 1H, H_2), 7.89 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (t, J = 1.2 Hz, 1H, H_4), 7.60 (dd, J = 5.0, 1.6 Hz, 1H, H_2), 5.09 (s, 2H, H_8), 2.61 (s, 3H, H_7).

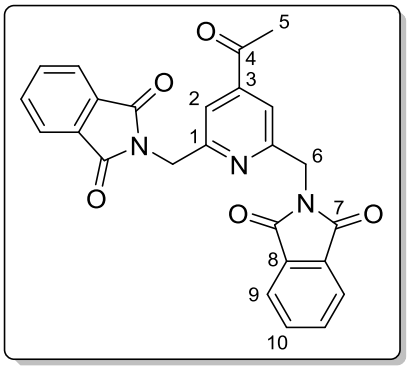
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 197.2 (C_6), 168.2 (C_9), 157.0 (C_5), 151.0 (C_2), 143.7 (C_3), 134.3 (CH), 132.3 (C_{10}), 123.7 (CH), 120.4 (C_1), 119.3 (C_4), 43.0 (C_8), 26.9 (C_7).

IR (ν, cm^{-1}, $CDCl_3$) 1774, 1718, 1701, 1602, 1560, 1470, 1426, 1392, 1362, 1278, 1199, 1188, 1114, 1088.

HRMS (EI+) calculated for $C_{16}H_{12}N_2O_3$: 280.0848; Found: 280.0852.

mp: 135-136 ℃

2,2'-((4-Acetylpyridine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (III-51)



Chemical Formula: $C_{25}H_{17}N_3O_5$
Molecular Weight: 439,43

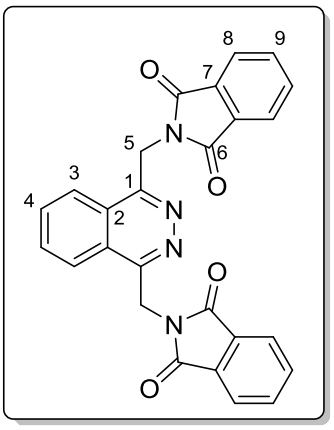
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.75 – 7.67 (m, 8H), 7.57 (s, 2H, H_2), 4.97 (s, 4H, H_6), 2.59 (s, 3H, H_5).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 197.0 (C_4), 167.9 (C_7), 156.7 (C_1), 144.5 (C_3), 134.1 (CH), 132.1 (C_8), 123.5 (CH), 118.0 (C_2), 42.6 (C_6), 27.0 (C_5).

IR (v, cm^{-1}, $CDCl_3$) 1775.1721, 1603, 1567, 1470, 1426, 1392, 1365, 1319, 1301, 1202, 1190, 1111, 1088.

HRMS (EI+) calculated for $C_{25}H_{17}N_3O_5$: 439.1168; Found: 439.1152.

2,2'-(Phthalazine-1,4-diylbis(methylene))bis(isoindoline-1,3-dione) (III-50b)



Chemical Formula: $C_{26}H_{16}N_4O_4$
Molecular Weight: 448,44

Following the general procedure, the reaction was carried out with xanthate **III-14** (422 mg, 1.50 mmol, 3.0 equiv), phthalazine (65 mg, 0.50 mmol, 1.0 equiv) and TFA (285 mg, 191 μL, 2.50 mmol, 5.0 equiv) in 1.5 mL ethyl acetate and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:1 to dichloromethane/ethyl acetate = 4:1) afforded the desired product **III-50b** (91 mg, 0.20 mmol, 40% yield) as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (dd, J = 6.3, 3.2 Hz, 2H), 7.98 (dd, J = 6.3, 3.3 Hz, 2H), 7.82 (dd, J = 5.4, 3.0 Hz, 4H), 7.67 (dd, J = 5.5, 3.1 Hz, 4H), 5.53 (s, 4H, H_5).

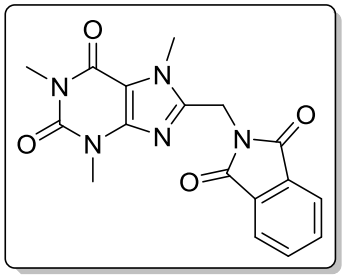
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.1 (C_6), 152.6 (C), 134.1 (CH), 132.8 (CH), 132.5 (C), 124.6 (C), 123.6 (CH), 123.6 (CH), 39.0 (C_5).

IR (ν, cm^{-1}, $CDCl_3$) 3074, 2931, 1774, 1718, 1618, 1602, 1571, 1470, 1425, 1399, 1357, 1257, 1114, 1089.

HRMS (EI+) calculated for $C_{26}H_{16}N_4O_4$: 448.1172; Found: 448.1171.

mp: 300-302 ℃

8-((1,3-Dioxoisoindolin-2-yl)methyl)-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (III-50c)



Chemical Formula: $C_{17}H_{15}N_5O_4$
Molecular Weight: 353,34

Following the general procedure, the reaction was carried out with xanthate **III-14** (422 mg, 1.50 mmol, 3.0 equiv), caffeine (97 mg, 0.50 mmol, 1.0 equiv) in 1.5 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/ethyl acetate = 3:2 to 1:1) afforded the desired product **III-50c** (131 mg, 0.37 mmol, 74% yield) as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dd, J = 5.4, 3.1 Hz, 2H), 7.77 (dd, J = 5.5, 3.0 Hz, 2H), 4.94 (s, 2H), 4.11 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H).

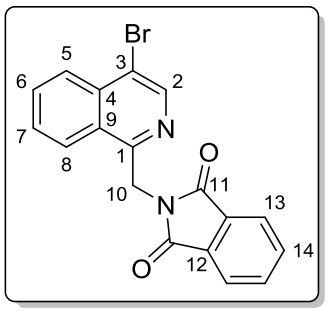
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 167.5 (C), 155.5 (C), 151.7 (C), 147.9 (C), 147.3 (C), 134.6 (CH), 132.0 (C), 123.9 (CH), 108.2 (C), 33.5 (CH_2), 32.3 (CH_3), 30.0 (CH_3), 28.0 (CH_3).

IR (ν, cm^{-1}, $CDCl_3$) 2954, 1776, 1722, 1703, 1657, 1606, 1550, 1470, 1448, 1424, 1390, 1346, 1221, 1087, 1041, 982.

HRMS (EI+) calculated for $C_{17}H_{15}N_5O_4$: 353.1124; Found: 353.1126.

mp: 239-241 ℃

2-((4-Bromoisoquinolin-1-yl)methyl)isoindoline-1,3-dione (III-50d)



Chemical Formula: $C_{18}H_{11}BrN_2O_2$
Molecular Weight: 367,20

Following the general procedure, the reaction was carried out with xanthate **III-14** (422 mg, 1.50 mmol, 3.0 equiv), 4-bromoisoquinoline (104 mg, 0.50 mmol, 1.0 equiv) and TFA (285 mg, 191 μL, 2.50 mmol, 5.0 equiv) in 1.5 mL ethyl acetate and needed 2 h for the reaction to go to completion. Trituration from diethyl ether gave the desired product **III-50d** (111 mg, 0.30 mmol, 60% yield) as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.51 (s, 1H, H_2), 8.21 (dt, J = 8.5, 1.3 Hz, 2H), 7.92 (dd, J = 5.4, 3.1 Hz, 2H), 7.83 (ddd, J = 8.5, 6.9, 1.2 Hz, 1H), 7.79 – 7.70 (m, 3H), 5.49 (s, 2H, H_{10}).

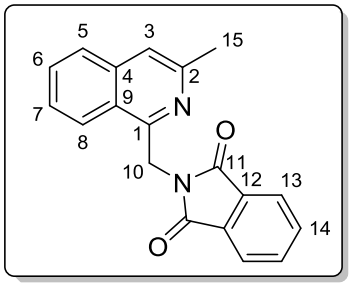
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.6 (C_{11}), 152.7 (C), 143.7 (C_2), 134.9 (C), 134.1 (CH), 132.6 (C), 131.5 (CH), 128.6 (CH), 127.13 (C), 127.08 (CH), 124.2 (CH), 123.7 (CH), 119.4 (C), 40.6 (C_{10}).

IR (v, cm^{-1}, $CDCl_3$) 3074, 2931, 1774, 1718, 1618, 1602, 1571, 1470, 1425, 1399, 1357, 1257, 1114, 1089.

HRMS (EI+) calculated for $C_{18}H_{11}BrN_2O_2$: 366.0004; Found: 366.0008.

mp: 251-252 ℃

2-((3-Methylisoquinolin-1-yl)methyl)isoindoline-1,3-dione (III-50e)



Chemical Formula: $C_{19}H_{14}N_2O_2$
Molecular Weight: 302,33

According to the general procedure, the reaction was carried out with xanthate **III-14** (563 mg, 2.00 mmol), 3-methylisoquinoline (143 mg, 1.00 mmol) and TFA (570 mg, 382 μL, 5.00 mmol) in 2.0 mL EtOAc and needed 3 h for the reaction to go to completion. Purification by flash chromatography on silica gel (EtOAc/petroleum ether = 2:3) afforded the desired product **III-50e** as a white solid (97 mg, 0.32 mmol, 32% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.16 (dq, J = 8.4, 1.0 Hz, 1H), 7.94 (dd, J = 5.5, 3.1 Hz, 2H), 7.80 – 7.73 (m, 3H), 7.65 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.57 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.36 (s, 1H, H_3), 5.52 (s, 2H, H_{10}), 2.46 (s, 3H, H_{15}).

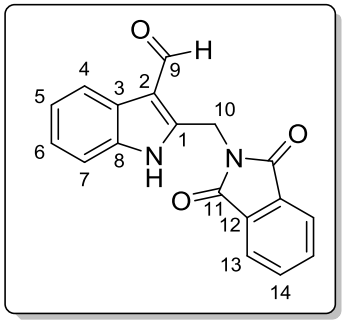
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.8 ($2C_{11}$), 152.2 (C), 150.7 (C), 137.2 (C), 134.0 (2CH), 132.7 (C), 130.0 (CH), 127.0 (CH), 126.5 (CH), 124.1 (C), 123.8 (CH), 123.5 (2CH), 118.3 (CH), 41.1 (C_{10}), 24.4 (C_{15}).

IR (ν, cm^{-1}, $CDCl_3$) 1774, 1716, 1628, 1594, 1571, 1428, 1399, 1113.

HRMS (EI+) calculated for $C_{19}H_{14}N_2O_2$: 302.1055; Found: 302.1044.

mp: 193-194 ℃

2-((1,3-Dioxoisoindolin-2-yl)methyl)-1*H*-indole-3-carbaldehyde (III-50f)



Chemical Formula: $C_{18}H_{12}N_2O_3$
Molecular Weight: 304,31

Following the general procedure, the reaction was carried out with xanthate **III-14** (281 mg, 1.00 mmol, 2.0 equiv), indole-3-carboxaldehyde (73 mg, 0.50 mmol, 1.0 equiv) in 1.0 mL DCE at 50 ℃ and needed 24 h for the reaction to go to completion. After evaporation of the solvent, the residue was triturated from diethyl ether. The desired product **III-50f** (107 mg, 0.35 mmol, 70% yield) was obtained by recrystallization from ethyl acetate as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 10.49 (s, 1H, H_9), 9.33 (br, 1H, *N*H), 8.33 – 8.25 (m, 1H), 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.78 – 7.73 (m, 2H), 7.41 – 7.36 (m, 1H), 7.32 – 7.25 (m, 2H), 5.32 (s, 2H, H_{10}).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 184.9 (C_9), 168.2 (C_{11}), 141.7 (C), 135.4 (C), 134.8 (CH), 131.8 (C_{12}), 125.1 (C), 124.7 (CH), 124.0 (CH), 123.3 (CH), 122.1 (CH), 115.6 (C), 111.5 (CH), 32.1 (C_{10}).

IR (v, cm^{-1}, $CDCl_3$) 3416, 1770, 1716, 1658, 1602, 1456, 1429, 1392, 1362, 1337, 1323, 1157, 1108, 1097, 1016, 990, 959.

HRMS (EI+) calculated for $C_{18}H_{12}N_2O_3$: 304.0848; Found: 304.0834.

mp: 241-242 ℃

Chapter 4: Towards an Inexpensive Radical Methylation and Ethylation of Heteroarenes

General Procedures

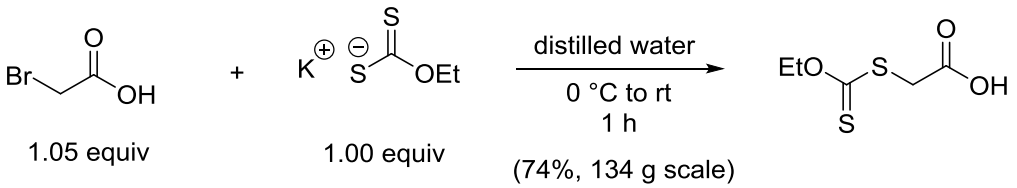
General procedure A for the radical alkylkation

A solution of xanthate (3.0 equiv) and heterocycle (1.0 equiv) in 1,2-dichloroethane or ethyl acetate (1.0 M according to xanthate) was refluxed under nitrogen for 10 min. DLP was added portionwise (20 mol % per hour) until the total consumption of the heterocycle [for substrates that were not completely consumed in 6 h, a seconde addition of xanthate at rt, followed by heating at reflux for 15 min and portionwise addition of DLP (20 mol %) per hour was perfomed]. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel or triturated in the appropriate solvent.

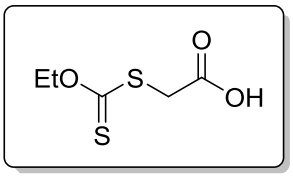
General procedure B for microwave assisted decarboxylation

A solution of the carboxylic acid in *N*,*N*-dimethylacetamide or *N*-methyl-2-pyrrolidone (0.1 M) was irradiated in a microwave reactor at appropriate temperature and the reaction was monitored by TLC plate. After the starting material was totally consumed, the reaction mixture was cooled to room temperature. For reactions with *N*,*N*-dimethylacetamide as the solvent, *N*,*N*-dimethylacetamide was removed under reduced pressure by forming azeotrope with toluene. While for those with *N*-methyl-2-pyrrolidone as the solvent, the reaction mixture was poured into water and extracted twice with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography on silica gel.

2-((Ethoxycarbonothioyl)thio)acetic acid (IV-41)



A solution of 2-bromoacetic acid (145.9 g, 1.05 mol, 1.05 equiv) in distilled water (500 mL) in 1 L Erlenmeyer was cooled to 0 ℃. Potassium *O*-ethylxanthate (160.0 g, 1.00 mol, 1.00 equiv) was added portionwise. The ice bath was then removed and the reaction mixture was stirred for 1 h. The reaction mixture was then cooled down to 0 ℃ and was kept at 0 ℃ until no oil present in the mixture (3 h, if necessary, some crystals of the product could be added to promote crystallization). The crystals were then filtered, washed with cold water and dried above filtration paper in a crystallizer to afford the desired product (143.5 g, 80%), which could be recrystallized from ethyl acetate/cyclohexane (30 mL/500 mL) at 55 ℃ to give the desired product **IV-41** as white crystals (134.2 g, 0.74 mol, 74% yield). The spectra data are in agreement with the literature report.[131]



Chemical Formula: $C_5H_8O_3S_2$
Molecular Weight: 180,24

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.84 (br, 1H), 4.66 (q, J = 7.1 Hz, 2H), 3.96 (s, 2H), 1.43 (t, J = 7.2 Hz, 3H).

^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 212.4, 173.8, 71.0, 37.9, 13.8.

IR (ν, cm^{-1}, $CDCl_3$) 3506, 2990, 2940, 2902, 1719, 1602, 1416, 1365, 1298, 1239, 1151, 1113, 1051.

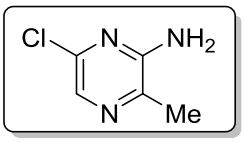
HRMS (EI+) calculated for $C_5H_8O_3S_2$: 179.9915; Found: 179.9923.

mp: 52-53 ℃

---

131 Auty, S. E. R.; Andren, O.; Malkoch, M.; Rannard, S. P. *Chem. Commun.* **2014**, 6574.

6-Chloro-3-methylpyrazin-2-amine (IV-42)



Chemical Formula: $C_5H_6ClN_3$
Molecular Weight: 143,57

According to the general procedure, the reaction was carried out with 2-amino-6-chloropyrazine **III-18g** (130 mg, 1.00 mmol, 1.0 equiv) and xanthate (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 3:1 to 2:1) afforded the desired product **IV-42** as a white solid (46 mg, 0.32 mmol, 32% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.83 (s, 1H), 4.67 (br, 2H), 2.37 (s, 3H).

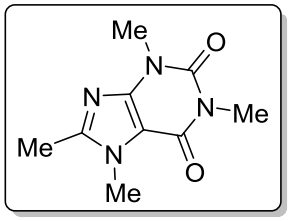
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 152.4, 144.5, 137.4, 131.8, 19.7.

IR (ν, cm^{-1}, $CDCl_3$) 3520, 3413, 1609, 1559, 1542, 1438, 1377, 1268, 1241, 1213, 1033, 990.

HRMS (EI+) calculated for $C_5H_6ClN_3$: 143.0250; Found: 143.0257.

mp: 144-145 ℃

1,3,7,8-Tetramethyl-3,7-dihydro-1*H*-purine-2,6-dione (IV-51a)



Chemical Formula: $C_9H_{12}N_4O_2$
Molecular Weight: 208,22

According to the general procedure, the reaction was carried out with caffeine **IV-50a** (97 mg, 0.50 mmol, 1.0 equiv) and xanthate (271 mg, 1.50 mmol, 3.0 equiv) in ethyl acetate (1.5 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/methanol = 1:0 to 20:1) afforded the desired product **IV-51a** as a white solid (68 mg, 0.33 mmol, 65% yield). The spectra data are in agreement with the literature report.[113]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 3.91 (s, 3H), 3.56 (s, 3H), 3.40 (s, 3H), 2.46 (s, 3H).

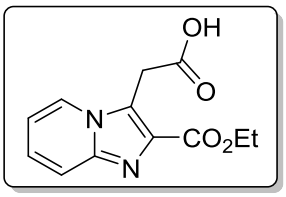
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 155.3, 151.8, 150.8, 148.0, 107.6, 32.0, 29.8, 28.0, 13.2.

IR (ν, cm^{-1}, $CDCl_3$) 2954, 1701, 1654, 1549, 1502, 1469, 1457, 1435, 1397, 1342, 1291, 1220, 1041, 978.

HRMS (EI+) calculated for $C_9H_{12}N_4O_2$: 208.0960; Found: 208.0966.

mp: 211-212 ℃ (lit.: 189-191 ℃)

2-(2-(Ethoxycarbonyl)imidazo[1,2-*a*]pyridin-3-yl)acetic acid (IV-51b)



Chemical Formula: $C_{12}H_{12}N_2O_4$
Molecular Weight: 248,24

According to the general procedure A, the reaction was carried out with imidazopyridine **IV-50b** [132] (190 mg, 1.00 mmol, 1.0 equiv) and xanthate (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL), and needed 4 h for the reaction to go to completion. After removal of the solvent, the residue was triturated with diethyl ether. The desired product **IV-51b** was obtained by recrystallization from methanol/ethyl acetate as a white powder (224 mg, 0.90 mmol, 90% yield).

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 8.35 (dt, J = 7.0, 1.1 Hz, 1H), 7.61 (dt, J = 9.2, 1.1 Hz, 1H), 7.44 (ddd, J = 9.2, 6.7, 1.2 Hz, 1H), 7.06 (td, J = 6.9, 1.2 Hz, 1H), 4.46 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 172.4, 145.6, 128.5, 126.3, 125.6, 118.4, 115.1, 62.1, 30.4, 14.6.

IR (ν, cm^{-1}, Nujol) 3371, 1710, 1694, 1578, 1319, 1297, 1275, 1247, 1223, 1169, 1108, 1028.

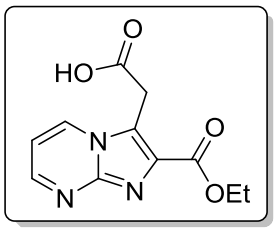
HRMS (EI+) calculated for $C_{12}H_{12}N_2O_4$: 248.0797; Found: 248.0799.

mp: decomposed at 164 ℃.

---

[132] Aginagalde, M.; Vara, Y.; Arrieta, A.; Zangi, R.; Cebolla, V. L.; Delgado-Camon, A.; Cossío, F. P. *J. Org. Chem.* **2010**, *75*, 2776.

2-(2-(Ethoxycarbonyl)imidazo[1,2-*a*]pyrimidin-3-yl)acetic acid (IV-51c)



Chemical Formula: $C_{11}H_{11}N_3O_4$
Molecular Weight: 249,23

According to the general procedure, the reaction was carried out with imidazopyrimidine **IV-50c** (191 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (270 mg, 1.50 mmol, 1.5 equiv) in 1,2-dichloroethane (1.5 mL), and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/methanol = 10:1 to 5:1, with acetic acid (1%) as additive) afforded product **IV-51c** (40 mg, 0.16 mmol, 16% yield) as a pink powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 8.84 (dd, J = 7.0, 1.9 Hz, 1H), 8.70 (dd, J = 4.1, 1.9 Hz, 1H), 7.15 (dd, J = 7.0, 4.1 Hz, 1H), 4.45 (s, 2H), 4.43 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

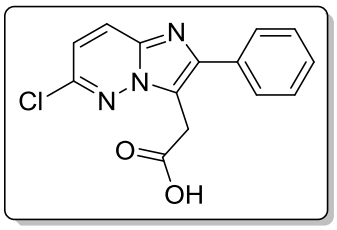
^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) $\underline{C}$OOH not observed, 164.5, 154.4, 148.5, 135.2, 134.3, 124.7, 111.2, 62.3, 30.3, 14.6.

IR (v, cm^{-1}, Nujol) 1709, 1625, 1574, 1509, 1351, 1311, 1267, 1241, 1206, 1181, 1156, 1099.

HRMS (EI+) calculated for $C_{11}H_{11}N_3O_4$: 249.0750; Found: not found.

mp: decomposed at 162 ℃.

2-(6-Chloro-2-phenylimidazo[1,2-*b*]pyridazin-3-yl)acetic acid (IV-51d)



Chemical Formula: $C_{14}H_{10}ClN_3O_2$
Molecular Weight: 287,70

According to the general procedure A, the reaction was carried out with imidazopyrimidine **IV-50d**[133] (115 mg, 0.50 mmol, 1.0 equiv) and xanthate **IV-41** (270 mg, 1.50 mmol, 3.0 equiv) in ethyl acetate (1.5 mL), and needed 3 h for the reaction to go to completion. After removal of the solvent, the residue was triturated with diethyl ether. The desired product **IV-51d** was obtained by recrystallization from methanol/ethyl acetate as a white powder (71 mg, 0.90 mmol, 49% yield).

^{1}H NMR (δ, ppm) (400 MHz, DMSO-d_6) 12.85 (br, 1H), 8.28 (d, J = 9.4 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.52 (dd, J = 8.4, 6.8 Hz, 2H), 7.46 – 7.40 (m, 2H), 4.17 (s, 2H).

^{13}C NMR (δ, ppm) (101 MHz, DMSO-d_6) 170.3, 146.0, 143.6, 136.8, 133.4, 128.9, 128.3, 127.5, 127.3, 119.9, 119.0, 29.7.

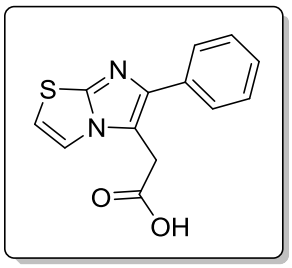
IR (ν, cm^{-1}, Nujol) 1707, 1526, 1355, 1337, 1215, 1201, 1170, 1144, 1109.

HRMS (EI+) calculated for $C_{14}H_{10}ClN_3O_2$: 287.0462; Found: 287.0457.

mp: 230-231 ℃.

133 El Akkaoui, A.; Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2008**, *49*, 2472.

2-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)acetic acid (IV-51e)



Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258,30

According to the general procedure, the reaction was carried out with imidazo[2,1-*b*]thiazole **IV-50e**[134] (200 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in 1,2-dichloroethane (3.0 mL), and needed 3 h for the reaction to go to completion. After removal of the solvent, the residue was triturated with diethyl ether. The desired product **IV-51e** was obtained by recrystallization from acetic acid/ethyl acetate as a white powder (149 mg, 0.58 mmol, 58% yield). The spectra data are in agreement with the literature report.[134]

^{1}H NMR (δ, ppm) (400 MHz, DMSO-d_6) 12.74 (br, 1H), 7.93 (d, J = 4.5 Hz, 1H), 7.73 – 7.60 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 4.5 Hz, 1H), 4.04 (s, 2H).

^{13}C NMR (δ, ppm) (101 MHz, DMSO-d_6) 171.1, 147.6, 143.3, 134.5, 128.6, 127.0, 126.8, 119.2, 116.2, 112.8, 30.9.

IR (ν, cm^{-1}, Nujol) 3110, 1542, 1542, 1342, 1293, 1265, 1136, 1087, 1047, 1031.

HRMS (EI+) calculated for $C_{13}H_{10}N_2O_2S$: 258.0463; Found: 258.0454.

mp: decomposed at 180 ℃ (lit.: 238-240 ℃).

Gram-scale synthesis:

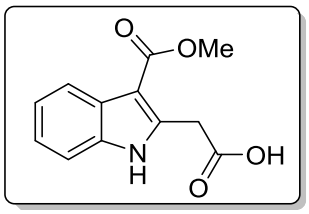
According to the general procedure A, the reaction was carried out with imidazo[2,1-*b*]thiazole (2.00 g, 10.0 mmol, 1.0 equiv) and xanthate (5.41 g, 30.0 mmol, 3.0 equiv) in 1,2-dichloroethane (30 mL), and needed 2.5 h for the reaction to go to completion. After removal of the solvent, the residue was triturated with diethyl ether.

---

[134] Palagiano, F.; Arenare, L.; Luraschil, E.; de Caprariis, P.; Abignente, E.; D'Amico, M.; Filippelli, W.; Rossi, F. *Eur. J. Med. Chem.* **1995**, *30*, 901.

The desired product was obtained by recrystallization from acetic acid/ethyl acetate as a white powder (2.06 g, 8.0 mmol, 80% yield).

2-(3-(Methoxycarbonyl)-1*H*-indol-2-yl)acetic acid (IV-51f)



Chemical Formula: $C_{12}H_{11}NO_4$
Molecular Weight: 233,22

A solution of indole **IV-50f** (175 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL) was refluxed under nitrogen for 10 min. The solution was then cooled down to 60 ℃ (temperature of oil bath) and DLP (100 mol %) was then added. It took 18 h for the reaction to go to completion. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 2:1 to 1:1, with acetic acid (1%) as additive) afforded **IV-51f** as a light brown powder (67 mg, 0.29 mmol, 29% yield).

^{1}H NMR (δ, ppm) (400 MHz, CD_3CN) 10.04 (br, 1H), 8.08 – 7.98 (m, 1H), 7.49 – 7.40 (m, 1H), 7.28 – 7.16 (m, 2H), 4.19 (s, 2H), 3.87 (s, 3H).

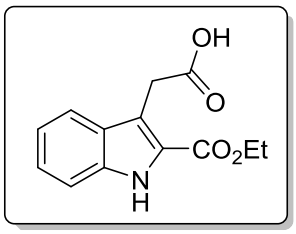
^{13}C NMR (δ, ppm) (101 MHz, CD_3CN) 171.1, 167.0, 141.0, 136.0, 127.4, 123.7, 122.6, 121.9, 112.5, 105.6, 51.4, 33.8.

IR (ν, cm^{-1}, $CDCl_3$) 3286, 2970, 2946, 2880, 2843, 1698, 1658, 1555, 1497, 1456, 1378, 1345, 1270, 1208, 1118, 1094.

HRMS (EI+) calculated for $C_{12}H_{11}NO_4$: 233.0688; Found: 233.0686.

mp: decomposed at 179 ℃.

2-(2-(Ethoxycarbonyl)-1*H*-indol-3-yl)acetic acid (IV-51g)



Chemical Formula: $C_{13}H_{13}NO_4$
Molecular Weight: 247,25

According to the general procedure, the reaction was carried out with indole **IV-50g** (1.89 g, 10.0 mmol, 1.0 equiv) and xanthate **IV-41** (2.70 g, 15.0 mmol, 1.5 equiv) in ethyl acetate (30 mL), and needed 5 h for the reaction to go to completion. After removal of the solvent, the residue was triturated with diethyl ether. The desired product **IV-51g** was obtained by recrystallization from ethanol as a white powder (1.42 g, 5.7 mmol, 57% yield).

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 7.63 (dt, J = 8.2, 1.1 Hz, 1H), 7.43 (dt, J = 8.4, 1.0 Hz, 1H), 7.27 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.09 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.14 (s, 2H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 175.6, 163.6, 137.9, 129.1, 126.2, 125.8, 121.1, 121.0, 116.9, 113.2, 61.7, 31.1, 14.7.

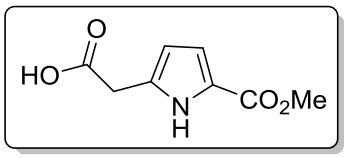
IR (ν, cm^{-1}, Nujol) 3310, 1699, 1682, 1410, 1335, 1262, 1208, 1195, 1130, 1105, 1027.

HRMS (EI+) calculated for $C_{13}H_{13}NO_4$: 247.0845; Found: 247.0841.

mp: 207-209 ℃ (lit.[135]: 208-210 ℃).

[135] Keller, H.; Langer, E.; Lehner, H. *Monatshefte fuer Chemie*, **1977**, *108*, 123.

2-(5-(Methoxycarbonyl)-1*H*-pyrrol-2-yl)acetic acid (IV-51h)



Chemical Formula: $C_8H_9NO_4$
Molecular Weight: 183,16

According to the general procedure A, the reaction was carried out with pyrrole **IV-50h** (250 mg, 2.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 1.5 equiv) in 1,2-dichloroethane (3.0 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 5:1 to 7:3, then dichloromethane/methanol = 10:1, with acetic acid (1%) as additive) afforded product **IV-51h** (139 mg, 0.76 mmol, 38% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 6.79 (d, J = 3.7 Hz, 1H), 6.06 (d, J = 3.8 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 2H).

^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 174.0, 163.2, 132.3, 122.8, 117.1, 110.6, 51.6, 34.0.

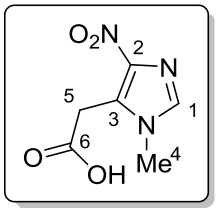
IR (ν, cm^{-1}, $CDCl_3$) 3443, 3275, 2955, 1719, 1602, 1493, 1441, 1337, 1233, 1125, 1042, 1007.

HRMS (EI+) calculated for $C_8H_9NO_4$: 183.0532; Found: 183.0523.

mp: 168-170 ℃.

2-(1-Methyl-4-nitro-1*H*-imidazol-5-yl)acetic acid (IV-51ia)

According to the general procedure, the reaction was carried out with imidazole **IV-50i** (127 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and needed 5 h for the reaction to go to completion. After removal of the solvent, the residue was triturated from diethyl ether. The residue was purified flash chromatography on silica gel (gradient of dichloromethane/methanol = 9:1 to 4:1, with acetic acid (1%) as additive) to give **IV-51ia** (74 mg, 0.40 mmol, 40% yield) as a white powder. The filtrate was concentrated under reduced pressure and flash chromatography on silica gel (gradient of dichloromethane/ethyl acetate = 4:1 to 7:3) afforded **IV-51ib** as a white solid (6 mg, 0.04 mmol, 4% yield).



Chemical Formula: $C_6H_7N_3O_4$
Molecular Weight: 185,14

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 7.71 (s, 1H, H_1), 4.18 (s, 2H, H_5), 3.74 (s, 3H, H_4).

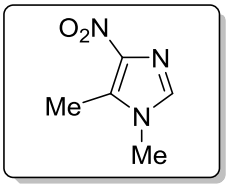
^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 171.5 (C_6), 145.8 (C_2), 137.7 (C_1), 129.8 (C_3), 32.9 (C_4), 30.9 (C_5).

IR (ν, cm^{-1}, Nujol) 1703, 1574.

HRMS (EI+) calculated for $C_6H_7N_3O_4$: 185.0437, M-CO_2, $C_5H_7N_3O_2$: 141.0538; Found: 141.0544.

mp: decomposed at 160 ℃.

1,2-Dimethyl-4-nitro-1*H*-imidazole (IV-51ib)



Chemical Formula: $C_5H_7N_3O_2$
Molecular Weight: 141,13

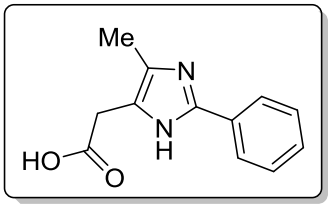
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.34 (s, 1H), 3.65 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 145.0, 134.9, 130.8, 32.4, 10.3.

IR (ν, cm^{-1}, $CDCl_3$) 2959, 2928, 1576, 1504, 1379, 1358, 1289, 1235, 1189, 1058.

HRMS (EI+) calculated for $C_5H_7N_3O_2$: 141.0538; Found: 141.0541.

2-(4-Methyl-2-phenyl-1*H*-imidazol-5-yl)acetic acid (IV-51j)



Chemical Formula: $C_{12}H_{12}N_2O_2$
Molecular Weight: 216,24

According to the general procedure, the reaction was carried out with 4-methyl-2-phenylimidazole **IV-51j** (158 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/methanol = 4:1 to 2:1, with acetic acid (1%) as additive) afforded product **IV-51j** (98 mg, 0.45 mmol, 45% yield) as a light yellow powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 7.89 – 7.79 (m, 2H), 7.54 (dd, J = 5.2, 2.0 Hz, 3H), 3.58 (s, 2H), 2.29 (s, 3H).

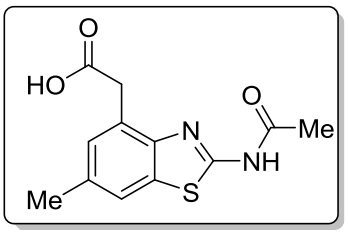
^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 175.4, 144.1, 131.9, 130.5, 128.6, 128.0, 126.9, 126.6, 33.1, 9.4.

IR (ν, cm^{-1}, Nujol) 1748, 1663, 1574, 1455, 1236.

HRMS (EI+) calculated for $C_{12}H_{11}N_2O_2$: 216.0899; Found: not found.

mp: decomposed at 201 ℃.

2-(2-Acetamido-6-methylbenzo[*d*]thiazol-4-yl)acetic acid (IV-51l)



Chemical Formula: $C_{12}H_{12}N_2O_3S$
Molecular Weight: 264,30

According to the general procedure A, the reaction was carried out with benzothiazole **IV-50l** [136] (206 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and xanthate was totally consumed in 4 h. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 2:3, with acetic acid (1%) as additive) afforded the desired product **IV-51l** as a white powder (70 mg, 0.26 mmol, 26% yield), and 75 mg (0.36 mmol) of starting material **IV-50l** was recovered.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 7.56 (s, 1H), 7.15 (s, 1H), 3.97 (s, 2H), 2.43 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 175.6, 171.3, 158.1, 147.3, 134.9, 133.6, 129.7, 128.1, 120.9, 38.1, 22.8, 21.4.

IR (ν, cm^{-1}, Nujol) 3185, 1694, 1568, 1311, 1269, 1240.

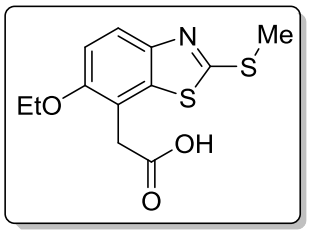
HRMS (EI+) calculated for $C_{12}H_{12}N_2O_3S$: 264.0569; Found: not found.

mp: >250 ℃.

[136] Glennon, R. A.; Gaines, J. J.; Rogers, M. E. *J. Med. Chem.* **1981**, *24*, 766.

2-(6-Ethoxy-2-(methylthio)benzo[*d*]thiazol-7-yl)acetic acid (IV-51ma)

According to the general procedure A, the reaction was carried out with benzothiazole **IV-50m**[137] (225 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in 1,2-dichloroethane (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:10 to 3:2, with acetic acid (1%) as additive) afforded mono-addition product **IV-51ma** (47 mg, 0.17 mmol, 17% yield) as a white powder, and double addition product **IV-51mb** (16 mg, 0.05 mmol, 5% yield) as a white powder.



Chemical Formula: $C_{12}H_{13}NO_3S_2$
Molecular Weight: 283,36

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.74 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.9 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.83 (s, 2H), 2.76 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 176.0, 153.8, 147.8, 138.1, 121.0, 114.9, 111.5, 65.1, 35.8, 16.2, 15.0.

IR (v, cm^{-1}, $CDCl_3$) 3512, 2984, 2933, 1747, 1714, 1596, 1576, 1470, 1403, 1394, 1315, 1261, 1129, 1112, 1059, 1043, 997, 962.

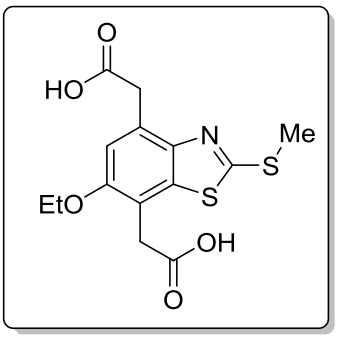
HRMS (EI+) calculated for $C_{12}H_{13}NO_3S_2$: 283.0337; Found: 283.0332.

mp: 170-172 ℃ (ethyl acetate).

---

137 Brown, D. J.; Grigg, G. W.; Iwai, Y.; McAndrew, K. N.; Nagamatsu, T. Van Heeswyck, R. *Austral. J. Chem.* **1979**, ***32***, 2713.

2,2'-(6-Ethoxy-2-(methylthio)benzo[*d*]thiazole-4,7-diyl)diacetic acid (IV-51mb)



Chemical Formula: $C_{14}H_{15}NO_5S_2$
Molecular Weight: 341,40

^{1}H NMR (δ, ppm) (400 MHz, acetone-d_6) 10.84 (s, 2H), 7.17 (s, 1H), 4.15 (q, J = 6.9 Hz, 2H), 4.08 (s, 2H), 3.79 (s, 2H), 2.79 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H).

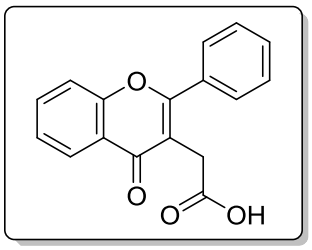
^{13}C NMR (δ, ppm) (101 MHz, acetone-d_6) 172.3, 171.3, 164.9, 154.7, 147.6, 138.4, 128.3, 116.1, 114.2, 65.8, 37.7, 35.6, 15.9, 15.2.

IR (ν, cm^{-1}, Nujol) 1698, 1590, 1494, 1343, 1319, 1245, 1121, 1110, 1048.

HRMS (EI+) calculated for $C_{14}H_{15}NO_5S_2$: 341.0392; Found: 341.0376.

mp: 246-247 ℃.

2-(4-Oxo-2-phenyl-4*H*-chromen-3-yl)acetic acid (IV-51n)



Chemical Formula: $C_{17}H_{12}O_4$
Molecular Weight: 280,28

According to the general procedure A, the reaction was carried out with flavone **IV-50n** (222 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and the reaction needed 4 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 1:2, with acetic acid (1%) as additive) afforded product **IV-51n** (78 mg, 0.28 mmol, 28% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.27 (dd, J = 8.1, 1.6 Hz, 1H), 7.77 – 7.70 (m, 3H), 7.60 – 7.55 (m, 3H), 7.55 – 7.51 (m, 1H), 7.46 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 3.62 (s, 2H).

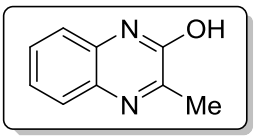
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 179.6, 174.4, 164.5, 156.4, 134.6, 132.1, 131.4, 129.2, 129.0, 126.1, 125.7, 122.3, 118.2, 114.9, 33.5.

IR (ν, cm^{-1}, $CDCl_3$) 3513, 3068, 2929, 2739, 1751, 1714, 1622, 1609, 1587, 1563, 1482, 1469, 1428, 1396, 1306, 1240, 1222, 1161, 1150, 1121.

HRMS (EI+) calculated for $C_{17}H_{12}O_4$: 280.0736, M-CO_2: $C_{16}H_{12}O_2$: 236.0837; Found: 236.0837.

mp: 180-181 ℃

3-Methylquinoxalin-2-ol (IV-53a)



Chemical Formula: $C_9H_8N_2O$
Molecular Weight: 160,18

A solution of 2-quinoxalinol **IV-52a** (145 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-41** (541 mg, 3.00 mmol, 3.0 equiv) in acetic acid (3.0 mL) was heated to 80 ℃ (temperature of oil bath) and DLP was then added portionwise(20 mol % per hour). It took 6 h for the reaction to go to completion. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 3:2, afforded **IV-53a** as a white solid (8 mg, 0.05 mmol, 5% yield). The spectra data are in agreement with the literature report.[113]

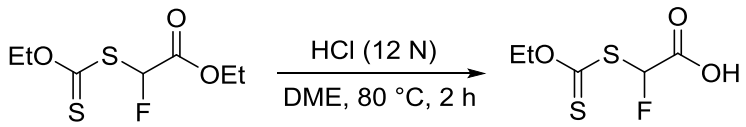
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 11.55 (br, 1H), 7.81 (dd, J = 8.1, 1.4 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.37 – 7.28 (m, 2H), 2.63 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 159.1, 156.7, 132.9, 131.2, 129.8, 128.8, 124.4, 115.6, 21.0.

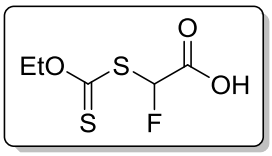
IR (v, cm^{-1}, $CDCl_3$) 3383, 3012, 2965, 2905, 2849, 1670, 1602, 1485, 1429, 1274, 1264, 1189, 1003.

HRMS (EI+) calculated for $C_9H_8N_2O$: 160.0637; Found: 160.0634.

2-((Ethoxycarbonothioyl)thio)-2-fluoroacetic acid (IV-58)



Into a solution of ethyl ethoxythiocarbonylsulfanylfluoroacetate **IV-59**[138] (3.93 g, 17.4 mmol) in dimethoxyethane (17 mL) was added slowly 12 N HCl (17 mL). The mixture was heated in an open flask at 80 ℃ for 2 h (88% of conversion of starting material by ^{1}H NMR of the crude product). The solution was then cooled down to room temperature and concentrated to half volume and was then extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 6:1 to 2:3, with acetic acid (1%) as additive) afforded **IV-58** as a yellow oil (2.28 g, 11.5 mmol, 66% yield).



Chemical Formula: $C_5H_7FO_3S_2$
Molecular Weight: 198,23

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 10.56 (s, 1H), 6.79 (d, J = 49.6 Hz, 1H), 4.73 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 206.4 (d, J = 1.7 Hz), 171.0 (d, J = 27.8 Hz), 93.0 (d, J = 233.4 Hz), 72.0, 13.7.

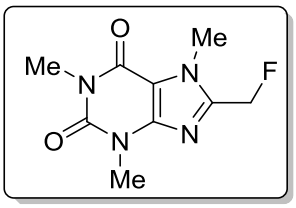
IR (ν, cm^{-1}, $CDCl_3$) 3504, 2989, 1760, 1735, 1369, 1254, 1112, 1042.

HRMS (EI+) calculated for $C_5H_7FO_3S_2$: 197.9821; Found: 197.9809.

---

[138] Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, *71*, 2352.

8-(Fluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (IV-60)



Chemical Formula: $C_9H_{11}FN_4O_2$
Molecular Weight: 226,21

According to the general procedure A, the reaction was carried out with caffeine **IV-50a** (69 mg, 0.35 mmol, 1.0 equiv) and xanthate **IV-58** (210 mg, 1.06 mmol, 3.0 equiv) in ethyl acetate (1.1 mL). After 6 h, another 3.0 equiv of xanthate was added and after 3 h, the reaction didn't evolve. Flash chromatography on silica gel (gradient of ethyl acetate/diethyl ether = 1:1 to 3:2) afforded product **IV-60** (23 mg, 0.10 mmol, 29% yield) as a white powder, and 20 mg (0.10 mmol) of starting material **IV-50a** was recovered.[74]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 5.49 (d, J = 47.9 Hz, 2H), 4.07 (d, J = 1.6 Hz, 3H), 3.57 (s, 3H), 3.41 (s, 3H).

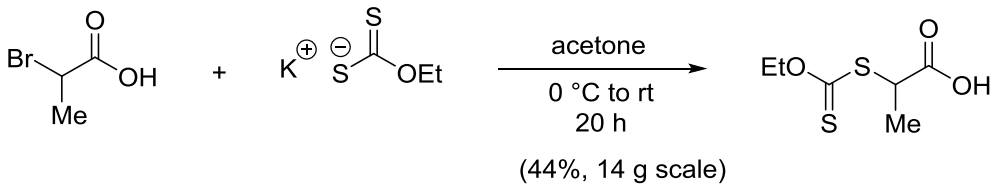
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 155.6, 151.6, 147.4, 146.5 (d, J = 18.9 Hz), 109.1, 75.5 (d, J = 168.7 Hz), 32.5 (d, J = 1.8 Hz), 29.9, 28.1.

IR (ν, cm^{-1}, $CDCl_3$) 2955, 1706, 1660, 1607, 1550, 1467, 1451, 1428, 1407, 1357, 1346, 1294, 1221, 1044, 1013, 991, 980.

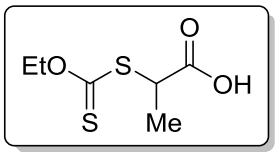
HRMS (EI+) calculated for $C_9H_{11}FN_4O_2$: 226.0866; Found: 226.0862.

mp: 165-167 ℃ (lit.: 155-157 ℃)

2-((Ethoxycarbonothioyl)thio)propanoic acid (IV-63)



Potassium *O*-ethylxanthate (28.4 g, 0.177 mol, 1.05 equiv) was added portionwise to a solution of 2-bromopropionic acid (25.7 g, 0.168 mol, 1.00 equiv) in acetone (170 mL) at 0 ℃ and the mixture was allowed to warm up to room temperature and stirred for 20 h. The solid formed was then filtered off and the filtrate was evaporated to driness. The residue was dissolved in 50 mL dichloromethane and washed with water (100 mL). The aqueous phase was extracted with dichloromethane (50 mL ×2). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The desired product **IV-63** precipitated upon addition of pentane at 0 ℃ as a white powder (14.2 g, 0.073 mol, 44% yield). The spectra data are in agreement with the literature report.[139]



Chemical Formula: $C_6H_{10}O_3S_2$
Molecular Weight: 194,26

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 10.42 (br, 1H), 4.63 (qd, J = 7.1, 0.8 Hz, 2H), 4.38 (q, J = 7.4 Hz, 1H), 1.57 (d, J = 7.4 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 212.2, 177.6, 70.5, 47.7, 17.0, 13.8.

IR (ν, cm^{-1}, $CDCl_3$) 3507, 2987, 2933, 2900, 1752, 1714, 1602, 1453, 1412, 1365, 1292, 1238, 1150, 1113, 1048, 1001.

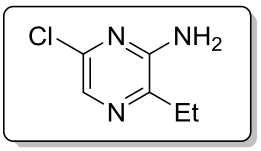
HRMS (EI+) calculated for $C_6H_{10}O_3S_2$: 194.0071; Found: 194.0062.

mp: 41-42 ℃

---

139 Nguyen, T. H.; Paluck, S. J.; McGahran, A. J.; Maynard, H. D. *Biomacromolecules* **2015**, *16*, 2684.

6-Chloro-3-ethylpyrazin-2-amine (IV-64a)



Chemical Formula: $C_6H_8ClN_3$
Molecular Weight: 157,60

According to the general procedure A, the reaction was carried out with 2-amino-6-chloropyrazine **III-18g** (130 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:2 to 1:1) afforded the desired product **IV-64a** as a light yellow solid (116 mg, 0.74 mmol, 74% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.86 (s, 1H), 4.76 (br, 2H), 2.62 (q, J = 7.5 Hz, 2H), 1.31 (t, J = 7.4 Hz, 3H).

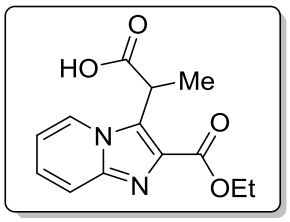
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 151.9, 144.2, 141.6, 131.7, 25.9, 10.6.

IR (ν, cm^{-1}, $CDCl_3$) 3520, 3412, 2978, 2940, 2878, 1608, 1558, 1538, 1464, 1431, 1288, 1212, 1150, 1042, 972.

HRMS (EI+) calculated for $C_6H_8ClN_3$: 157.0407; Found: 157.0411.

mp: 99-100 ℃.

2-(2-(Ethoxycarbonyl)imidazo[1,2-*a*]pyridin-3-yl)propanoic acid (IV-64b)



Chemical Formula: $C_{13}H_{14}N_2O_4$
Molecular Weight: 262,27

A solution of imidazopyridine **IV-50b** (190 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and it took 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:1 to dichloromethane/methanol = 10:1, with acetic acid (1%) as additive) afforded product **IV-64b** (118 mg, 0.45 mmol, 45% yield) as a yellow powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.10 (dd, J = 7.1, 1.2 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.30 – 7.23 (m, 1H), 6.87 (td, J = 6.9, 1.2 Hz, 1H), 5.37 (q, J = 7.4 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.62 (d, J = 7.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H).

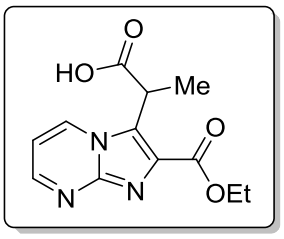
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 175.2, 163.6, 144.2, 131.5, 128.6, 126.7, 125.1, 118.9, 114.1, 61.3, 35.4, 14.3, 14.1.

IR (ν, cm^{-1}, $CDCl_3$) 3508, 2986, 2941, 1749, 1710, 1602, 1557, 1403, 1383, 1280, 1266, 1210, 1173, 1062, 1032.

HRMS (EI+) calculated for $C_{13}H_{14}N_2O_4$: 262.0954; Found: 262.0954.

mp: 90-92 ℃.

2-(2-(Ethoxycarbonyl)imidazo[1,2-*a*]pyrimidin-3-yl)propanoic acid (IV-64c)



Chemical Formula: $C_{12}H_{13}N_3O_4$
Molecular Weight: 263,25

According to the general procedure A, the reaction was carried out with imidazopyrimidine **IV-50c** (191 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in 1,2-dichloroethane (3.0 mL), and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/methanol = 50:1 to 20:1, with acetic acid (1%) as additive) afforded product **IV-64c** (87 mg, 0.33 mmol, 33% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 8.84 (dd, J = 7.1, 1.9 Hz, 1H), 8.69 (dd, J = 4.0, 1.9 Hz, 1H), 7.15 (dd, J = 7.1, 4.0 Hz, 1H), 5.09 (q, J = 7.4 Hz, 1H), 4.42 (qd, J = 7.1, 1.0 Hz, 2H), 1.63 (d, J = 7.4 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H).

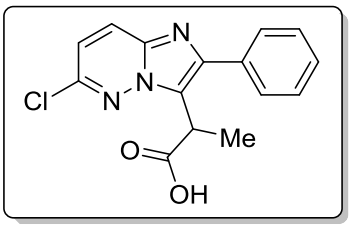
^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 174.7, 164.5, 154.3, 148.3, 135.3, 133.5, 129.4, 111.3, 62.4, 36.3, 15.0, 14.6.

IR (v, cm^{-1}, Nujol) 3104, 1917, 1710, 1620, 1566, 1505, 1421, 1321, 1256, 1233, 1214, 1159, 1110, 1075, 1064, 1023.

HRMS (EI+) calculated for $C_{12}H_{13}N_3O_4$: 263.0906; Found: not found.

mp: decomposed at 160 ℃.

2-(6-Chloro-2-phenylimidazo[1,2-*b*]pyridazin-3-yl)propanoic acid (IV-64d)



Chemical Formula: $C_{15}H_{12}ClN_3O_2$
Molecular Weight: 301,73

According to the general procedure A, the reaction was carried out with imidazopyrimidine **IV-50d** (230 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and it took 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 1:2, with acetic acid (1%) as additive) afforded product **IV-64d** (105 mg, 0.35 mmol, 35% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, DMSO-d_6) 12.66 (br, 1H), 8.26 (d, J = 9.4 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.56 – 7.48 (m, 2H), 7.46 – 7.41 (m, 1H), 7.39 (d, J = 9.4 Hz, 1H), 4.49 (q, J = 7.3 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H).

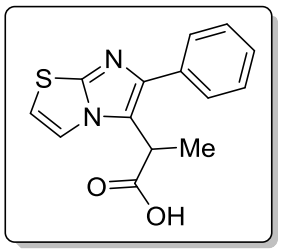
^{13}C NMR (δ, ppm) (101 MHz, DMSO-d_6) 172.5, 145.6, 143.1, 136.6, 133.6, 128.8, 128.3, 128.1, 127.4, 125.0, 118.7, 34.9, 13.8.

IR (ν, cm^{-1}, Nujol) 1704, 1522, 1352, 1318, 1257, 1110, 1092.

HRMS (EI+) calculated for $C_{15}H_{12}ClN_3O_2$: 301.0618; Found: 301.0605.

mp: decomposed at 246 ℃.

2-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)propanoic acid (IV-64e)



Chemical Formula: $C_{14}H_{12}N_2O_2S$
Molecular Weight: 272,32

According to the general procedure A, the reaction was carried out with imidazo[2,1-*b*]thiazole **IV-50e** (200 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in 1,2-dichloroethane (3.0 mL), and needed 4 h to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 3:2 to dichloromethane/methanol = 20:1, with acetic acid (1%) as additive) afforded product **IV-64e** (176 mg, 0.65 mmol, 65% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, CD_3OD) 7.82 (d, J = 4.5 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.49 – 7.43 (m, 2H), 7.41 – 7.35 (m, 1H), 7.18 (d, J = 4.5 Hz, 1H), 4.29 (q, J = 7.4 Hz, 1H), 1.55 (d, J = 7.4 Hz, 3H).

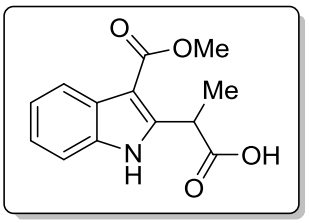
^{13}C NMR (δ, ppm) (101 MHz, CD_3OD) 175.7, 150.9, 145.2, 135.2, 129.63, 129.60, 128.9, 122.9, 120.9, 114.0, 37.6, 16.1.

IR (ν, cm^{-1}, Nujol) 3107, 1704, 1338, 1308, 1247, 1222, 1137, 1098, 1078, 1068.

HRMS (EI+) calculated for $C_{14}H_{12}N_2O_2S$: 272.0619; Found: 272.0622.

mp: decomposed at 180 ℃.

2-(3-(Methoxycarbonyl)-1*H*-indol-2-yl)propanoic acid (IV-64f)



Chemical Formula: $C_{13}H_{13}NO_4$
Molecular Weight: 247,25

According to the general procedure A, the reaction was carried out with indole **IV-50f** (175 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (291 mg, 1.50 mmol, 1.5 equiv) in 1,2-dichloroethane (1.5 mL). After 6 h, another 1.5 equiv of xanthate was added and the reaction needed 6 h to go to completion. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 1:2, with acetic acid (1%) as additive) afforded product **IV-64f** (145 mg, 0.59 mmol, 59% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 9.70 (br, 1H), 8.08 – 7.98 (m, 1H), 7.41 (ddd, J = 7.2, 3.7, 2.2 Hz, 1H), 7.26 (dd, J = 6.1, 3.1 Hz, 2H), 4.91 (q, J = 7.2 Hz, 1H), 4.02 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H).

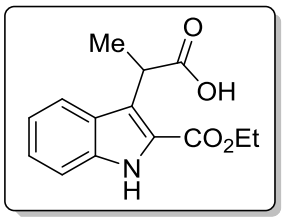
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 175.8, 168.6, 144.0, 135.0, 126.1, 123.6, 122.5, 121.6, 111.7, 104.8, 52.1, 38.2, 16.6.

IR (ν, cm^{-1}, $CDCl_3$) 3454, 3308, 2990, 2953, 1757, 1691, 1636, 1536, 1457, 1389, 1363, 1332, 1285, 1265, 1206, 1137, 1121, 1066.

HRMS (EI+) calculated for $C_{13}H_{13}NO_4$: 247.0845; Found: 247.0852.

mp: 137-138 ℃.

2-(2-(Ethoxycarbonyl)-1*H*-indol-3-yl)propanoic acid (IV-64g)



Chemical Formula: $C_{14}H_{15}NO_4$
Molecular Weight: 261,28

According to the general procedure A, the reaction was carried out with ethyl indole-2-carboxylate **IV-50g** (189 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (233 mg, 1.20 mmol, 1.2 equiv) in 1,2-dichloroethane (1.2 mL). After 6 h, another 1.2 equiv of xanthate was added and it took 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 4:1 to 2:1, with acetic acid (1%) as additive) afforded product **IV-64g** (210 mg, 0.80 mmol, 80% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.98 (s, 1H), 7.73 (dq, J = 8.2, 0.9 Hz, 1H), 7.39 (dt, J = 8.3, 1.0 Hz, 1H), 7.32 (ddd, J = 8.2, 6.8, 1.1 Hz, 1H), 7.12 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 4.89 (q, J = 7.2 Hz, 1H), 4.45 – 4.36 (m, 2H), 1.63 (d, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H).

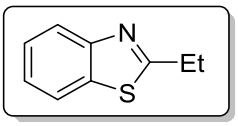
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 179.5, 162.2, 136.0, 126.5, 125.9, 123.3, 122.0, 121.5, 120.7, 112.2, 61.4, 36.4, 17.3, 14.5.

IR (ν, cm^{-1}, $CDCl_3$) 3463, 2987, 1747, 1708, 1602, 1546, 1435, 1380, 1325, 1238, 1153, 1105, 1061..

HRMS (EI+) calculated for $C_{14}H_{15}NO_4$: 261.1001; Found: 261.0999.

mp: 131-133 ℃.

2-Ethylbenzo[*d*]thiazole (IV-64h)



Chemical Formula: C_9H_9NS
Molecular Weight: 163,24

According to the general procedure A, the reaction was carried out with benzothiazole **IV-50k** (135 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (1.5 mL). After 6 h, another 3.0 equiv of xanthate was added and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:10 to 1:8) afforded the desired product **IV-64h** as a colorless oil (36 mg, 0.22 mmol, 22% yield). The spectra data are in agreement with the literature report.[140]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.00 – 7.94 (m, 1H), 7.84 (ddd, J = 8.0, 1.3, 0.7 Hz, 1H), 7.45 (ddd, J = 8.2, 7.2, 1.3 Hz, 1H), 7.34 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 3.15 (q, J = 7.6 Hz, 2H), 1.48 (t, J = 7.6 Hz, 3H).

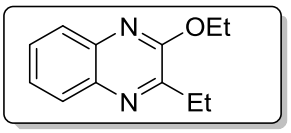
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 173.7, 153.4, 135.2, 126.0, 124.7, 122.6, 121.6, 27.9, 14.0.

IR (ν, cm^{-1}, $CDCl_3$) 3069, 2979, 2938, 1599, 1518, 1457, 1438, 1311, 1279, 1239, 1173, 1157, 1068, 1015.

HRMS (EI+) calculated for C_9H_9NO: 163.0456; Found: 163.0464.

[140] Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948.

2-Ethoxy-3-ethylquinoxaline (IV-64i)



Chemical Formula: $C_{12}H_{14}N_2O$
Molecular Weight: 202,26

According to the general procedure A, the reaction was carried out with quinoxaline **IV-52c** (174 mg, 1.00 mmol, 1.0 equiv) and xanthate **IV-64i** (583 mg, 3.00 mmol, 3.0 equiv) in ethyl acetate (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and it took 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 20:1 to 10:1) afforded product **IV-64i** (107 mg, 0.53 mmol, 53% yield) as a white powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.97 – 7.92 (m, 1H), 7.78 (ddd, J = 8.2, 1.5, 0.5 Hz, 1H), 7.58 (ddd, J = 8.3, 7.0, 1.6 Hz, 1H), 7.51 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.99 (q, J = 7.5 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.5 Hz, 3H).

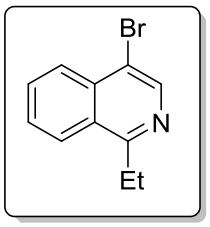
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 156.2, 152.6, 140.0, 138.6, 128.8, 128.3, 126.8, 126.2, 62.3, 27.1, 14.6, 11.7.

IR (ν, cm^{-1}, $CDCl_3$) 3068, 2982, 2939, 1582, 1461, 1423, 1378, 1327, 1314, 1265, 1225, 1183, 1161, 1139, 1050, 1032.

HRMS (EI+) calculated for $C_{12}H_{14}N_2O$: 202.1106; Found: 202.1104.

mp: 66-67 ℃

4-Bromo-1-ethylisoquinoline (IV-64j)



Chemical Formula: $C_{11}H_{10}BrN$
Molecular Weight: 236,11

According to the general procedure A, the reaction was carried out with 4-bromoisoquinoline **IV-55p** (208 mg, 1.00 mmol, 1.0 equiv), xanthate **IV-63** (583 mg, 3.00 mmol, 3.0 equiv) and TFA (137 mg, 92 μL, 1.2 mmol, 1.2 equiv) in 1,2-dichloroethane (3.0 mL). After 6 h, another 3.0 equiv of xanthate was added and it took 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 10:1 to 4:1) afforded product **IV-64j** (80 mg, 0.34 mmol, 34% yield) as a colorless oil.

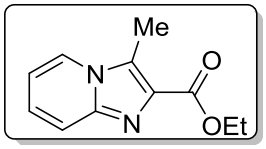
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.62 (s, 1H), 8.22 – 8.12 (m, 2H), 7.78 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.65 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 3.30 (q, J = 7.5 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 162.9, 143.7, 134.9, 131.1, 128.1, 128.0, 126.9, 125.7, 117.9, 28.5, 13.6.

IR (v, cm^{-1}, $CDCl_3$) 3075, 2977, 2937, 2878, 1617, 1568, 1497, 1465, 1386, 1312, 1264, 1242, 1183, 1058, 1015.

HRMS (EI+) calculated for $C_{11}H_{10}BrN$: 234.9997; Found: 234.9980.

Ethyl 3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (IV-65a)



Chemical Formula: $C_{11}H_{12}N_2O_2$
Molecular Weight: 204,23

According to the general procedure B, the reaction was carried out with acid **IV-51b** (124 mg, 0.50 mmol) in *N*,*N*-dimethylacetamide (5 mL) and heated at 180 ℃ for 10 min. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:3 to 1:5) afforded product **IV-65a** (90 mg, 0.44 mmol, 88% yield) as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dt, J = 7.0, 1.2 Hz, 1H), 7.65 (dt, J = 9.1, 1.2 Hz, 1H), 7.22 (ddd, J = 9.2, 6.7, 1.3 Hz, 1H), 6.89 (td, J = 6.8, 1.2 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 2.79 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H).

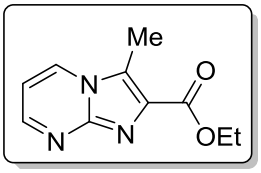
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 164.4, 144.0, 126.4, 125.4, 123.4, 119.2, 113.5, 61.0, 14.6, 9.5.

IR (v, cm^{-1}, $CDCl_3$) 2983, 2929, 2857, 1709, 1567, 1507, 1445, 1405, 1377, 1362, 1277, 1259, 1227, 1162, 1097, 1058.

HRMS (EI+) calculated for $C_{11}H_{12}N_2O_2$: 204.0899; Found: 204.0905.

mp: 34-36 ℃.

Ethyl 3-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate (IV-65b)



Chemical Formula: $C_{10}H_{11}N_3O_2$
Molecular Weight: 205,22

According to the general procedure B, the reaction was carried out with acid **IV-51c** (43 mg, 0.17 mmol) in *N*,*N*-dimethylacetamide (1.7 mL) and heated at 180 ℃ for 10 min. Flash chromatography on silica gel (gradient of dichloromethane/methanol = 20:1 to 15:1) afforded product **IV-65b** (25 mg, 0.12 mmol, 71% yield) as a light green solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.64 (dd, J = 4.0, 2.0 Hz, 1H), 8.27 (dd, J = 6.9, 2.0 Hz, 1H), 6.96 (dd, J = 6.9, 4.0 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 2.80 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H).

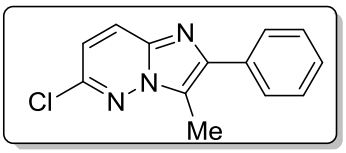
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 164.1, 151.5, 146.8, 133.5, 131.3, 124.9, 109.6, 61.3, 14.5, 9.1.

IR (v, cm^{-1}, $CDCl_3$) 2984, 2940, 1710, 1623, 1558, 1530, 1503, 1444, 1409, 1386, 1374, 1345, 1299, 1247, 1227, 1153, 1089, 1061, 1020.

HRMS (EI+) calculated for $C_{10}H_{11}N_3O_2$: 205.0851; Found: 205.0837.

mp: 182-184 ℃.

6-Chloro-3-methyl-2-phenylimidazo[1,2-*b*]pyridazine (IV-65c)



Chemical Formula: $C_{13}H_{10}ClN_3$
Molecular Weight: 243,69

According to the general procedure B, the reaction was carried out with acid **IV-51d** (99 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (4.0 mL) and heated at 180 ℃ for 20 min and then 200 ℃ for 50 min. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:3) afforded product **IV-65c** (57 mg, 0.23 mmol, 58% yield) as a yellow solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.89 (d, J = 9.3 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.52 – 7.46 (m, 2H), 7.42 – 7.36 (m, 1H), 7.02 (d, J = 9.3 Hz, 1H), 2.77 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 146.4, 143.7, 137.0, 134.2, 128.9, 128.2, 128.1, 126.3, 122.6, 117.6, 9.7.

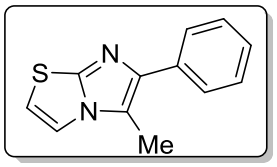
IR (ν, cm^{-1}, $CDCl_3$) 3065, 1713, 1602, 1579, 1548, 1520, 1485, 1443, 1401, 1348, 1313, 1295, 1219, 1171, 1134, 1116, 1082.

HRMS (EI+) calculated for $C_{13}H_{10}ClN_3$: 243.0563; Found: 243.0563.

mp: 131-133 ℃.

5-Methyl-6-phenylimidazo[2,1-*b*]thiazole (IV-65d)

According to the general procedure B, the reaction was carried out with acid **IV-51e** (103 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (4.0 mL) and heated at 200 ℃ for 70 min and 220 ℃ for 10 min. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 3:7 to 1:0) afforded product **IV-65d** (37 mg, 0.17 mmol, 43% yield) as a white powder, and side-product **IV-66** (53 mg, 0.19 mmol, 46% yield) as light yellow oil.



Chemical Formula: $C_{12}H_{10}N_2S$
Molecular Weight: 214,29

The spectra data are in agreement with the literature report.[141]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.75 – 7.68 (m, 2H), 7.43 (dd, J = 8.4, 7.0 Hz, 2H), 7.32 – 7.27 (m, 2H), 6.82 (d, J = 4.5 Hz, 1H), 2.60 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 147.6, 143.3, 135.2, 128.6, 127.4, 126.9, 117.7, 116.8, 112.3, 10.9.

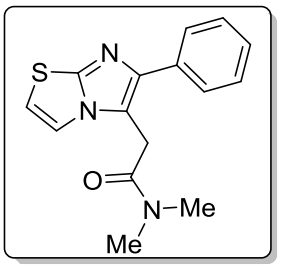
IR (ν, cm^{-1}, $CDCl_3$) 3119, 3064, 2921, 1603, 1542, 1494, 1484, 1471, 1388, 1367, 1320, 1258, 1142, 1073, 1016.

HRMS (EI+) calculated for $C_{12}H_{10}N_2S$: 214.0565; Found: 214.0566.

mp: 125-126 ℃ (lit.: 109-111 ℃).

141 Wu, F.; Hou, R.; Wang, H.; Kang, I.; Chen, L. *J. Chin. Chem. Soc.* **2011**, *58*, 663.

N,*N*-Dimethyl-2-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)acetamide (IV-66)



Chemical Formula: $C_{15}H_{15}N_3OS$
Molecular Weight: 285,37

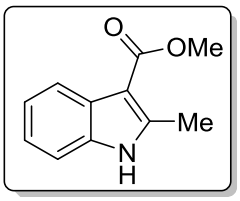
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.67 (d, J = 4.5 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.46 – 7.40 (m, 2H), 7.36 – 7.30 (m, 1H), 6.78 (d, J = 4.5 Hz, 1H), 4.04 (s, 2H), 2.91 (s, 3H), 2.78 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 168.5, 149.5, 144.8, 134.8, 128.8, 128.1, 127.6, 119.3, 115.6, 111.9, 37.6, 35.9, 31.0.

IR (ν, cm^{-1}, $CDCl_3$) 3120, 3034, 2935, 1643, 1605, 1541, 1492, 1468, 1444, 1401, 1370, 1324, 1261, 1119.

HRMS (EI+) calculated for $C_{15}H_{15}N_3OS$: 285.0936; Found: 285.0934.

Methyl 2-methyl-1*H*-indole-3-carboxylate (IV-65e)



Chemical Formula: $C_{11}H_{11}NO_2$
Molecular Weight: 189,21

According to the general procedure B, the reaction was carried out with acid **IV-51f** (47 mg, 0.20 mmol) in *N*,*N*-dimethylacetamide (2.0 mL) and heated at 180 ℃ for 10 min and 200 ℃ for 10 min. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:5 to 1:4) afforded product **IV-65e** (30 mg, 0.16 mmol, 80% yield) as a white powder. The spectra data are in agreement with the literature report.[142]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.43 (br, 1H), 8.16 – 8.06 (m, 1H), 7.34 – 7.28 (m, 1H), 7.25 – 7.17 (m, 2H), 3.94 (s, 3H), 2.75 (s, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 166.7, 144.1, 134.6, 127.2, 122.5, 121.9, 121.4, 110.6, 104.6, 50.9, 14.4.

IR (ν, cm^{-1}, $CDCl_3$) 3459, 3061, 2996, 2951, 1691, 1602, 1554, 1460, 1444, 1421, 1271, 1233, 1200, 1118, 1093.

HRMS (EI+) calculated for $C_{11}H_{11}NO_2$: 189.0790; Found: 189.0781.

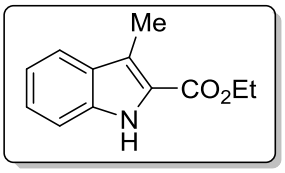
mp: 163-165 ℃ (lit.[143] = 161-163 ℃).

142 Tanimori, S.; Ura, H.; Kirihata, M. *Eur. J. Org. Chem.* **2007**, *24*, 3977.
143 Nguyen, H. H.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 362.

Ethyl 3-methyl-1*H*-indole-2-carboxylate (IV-65f)

Entry 1: According to the general procedure B, the reaction was carried out with acid **IV-51g** (99 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (4.0 mL) and heated at 220 ℃ for 30 min. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:5 to 2:1) afforded product **IV-65f** (32 mg, 0.16 mmol, 39% yield) as a white powder, and side-product **IV-67** (48 mg, 0.17 mmol, 44% yield) as a white powder.

Entry 2: According to the general procedure B, the reaction was carried out with acid **IV-51g** (99 mg, 0.40 mmol) in *N*-methyl-2-pyrrolidone (4.0 mL) and was heated at 230 ℃ for 70 min. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:4) afforded product **IV-65f** (54 mg, 0.27 mmol, 66% yield) as a white powder.



Chemical Formula: $C_{12}H_{13}NO_2$
Molecular Weight: 203,24

The spectra data are in agreement with the literature report.[144]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.74 (br, 1H), 7.67 (dq, J = 8.1, 1.0 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.15 (ddd, J = 8.0, 6.7, 1.3 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 162.8, 136.0, 128.7, 125.7, 123.6, 120.9, 120.3, 120.0, 111.7, 60.8, 14.6, 10.1.

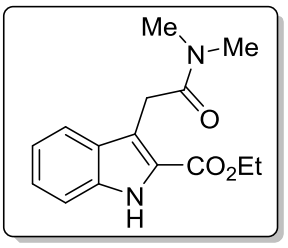
IR (v, cm^{-1}, $CDCl_3$) 3464, 3064, 2985, 2939, 1693, 1580, 1560, 1450, 1380, 1334, 1322, 1311, 1244, 1188, 1130, 1093, 1057, 1017.

HRMS (EI+) calculated for $C_{12}H_{13}NO_2$: 203.0946; Found: 203.0949.

mp: 134-135 ℃ (lit.: 130-132 ℃).

144 Yang, Q.-Q.; Marchini, M.; Xiao, W.-J.; Ceroni, P.; Bandini, M. *Chem. - Eur. J.* **2015**, *21*, 18052.

Ethyl 3-(2-(dimethylamino)-2-oxoethyl)-1*H*-indole-2-carboxylate (IV-67)



Chemical Formula: $C_{15}H_{18}N_2O_3$
Molecular Weight: 274,32

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.85 (br, 1H), 7.80 (dd, J = 8.1, 1.0 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.13 (ddd, J = 8.1, 6.7, 1.3 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.27 (s, 2H), 3.10 (s, 3H), 2.97 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H).

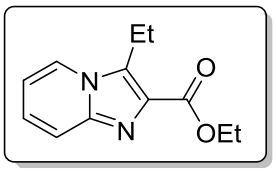
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 170.8, 162.0, 136.0, 128.3, 125.9, 123.6, 121.7, 120.7, 117.8, 111.8, 61.0, 37.6, 35.9, 31.1, 14.5.

IR (v, cm^{-1}, $CDCl_3$) 3465, 2984, 2938, 1705, 1644, 1602, 1555, 1448, 1399, 1326, 1314, 1238, 1180, 1130, 1093, 1024.

HRMS (EI+) calculated for $C_{15}H_{18}N_2O_3$: 274.1317; Found: 274.1316.

mp: 151-152 ℃.

Ethyl 3-ethylimidazo[1,2-*a*]pyridine-2-carboxylate (IV-68a)



Chemical Formula: $C_{12}H_{14}N_2O_2$
Molecular Weight: 218,26

According to the general procedure B, the reaction was carried out with acid **IV-64b** (105 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (4.0 mL) and heated at 180 ℃ for 10 min. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 7:3 to 3:1) afforded product **IV-68a** (63 mg, 0.29 mmol, 72% yield) as a light brown oil.

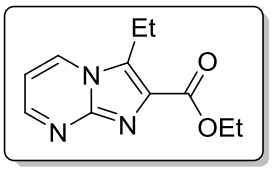
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (dt, J = 7.0, 1.2 Hz, 1H), 7.66 (dt, J = 9.2, 1.1 Hz, 1H), 7.21 (ddd, J = 9.2, 6.7, 1.2 Hz, 1H), 6.87 (td, J = 6.8, 1.2 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 3.32 (q, J = 7.5 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 164.2, 144.0, 132.2, 131.8, 125.3, 123.3, 119.4, 113.4, 61.0, 17.1, 14.6, 12.2.

IR (ν, cm^{-1}, $CDCl_3$) 2982, 2937, 2877, 1709, 1602, 1560, 1508, 1462, 1401, 1384, 1364, 1279, 1219, 1163, 1100, 1090, 1058, 1019.

HRMS (EI+) calculated for $C_{12}H_{14}N_2O_2$: 218.1055; Found: 218.1046.

Ethyl 3-ethylimidazo[1,2-*a*]pyrimidine-2-carboxylate (IV-68b)



Chemical Formula: $C_{11}H_{13}N_3O_2$
Molecular Weight: 219,24

According to the general procedure B, the reaction was carried out with acid **IV-64c** (79 mg, 0.30 mmol) in *N*,*N*-dimethylacetamide (3.0 mL) and heated at 180 ℃ for 10 min. Flash chromatography on silica gel (dichloromethane/methanol = 20:1) afforded product **IV-68b** (47 mg, 0.21 mmol, 71% yield) as a light brown powder.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.65 (dd, J = 4.0, 2.0 Hz, 1H), 8.30 (dd, J = 7.0, 2.0 Hz, 1H), 6.95 (dd, J = 6.9, 3.9 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.32 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.6 Hz, 3H).

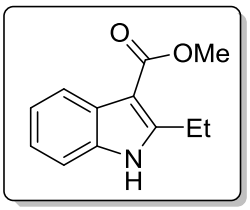
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 163.9, 151.5, 146.8, 132.9, 131.2, 130.7, 109.6, 61.3, 16.8, 14.5, 12.4.

IR (v, cm^{-1}, $CDCl_3$) 2983, 2938, 2878, 1710, 1623, 1602, 1552, 1504, 1434, 1408, 1351, 1268, 1220, 1152, 1094, 1058, 1019.

HRMS (EI+) calculated for $C_{11}H_{13}N_3O_2$: 219.1008; Found: not found.

mp: 145-147 ℃.

Methyl 2-ethyl-1*H*-indole-3-carboxylate (IV-68c)



Chemical Formula: $C_{12}H_{13}NO_2$
Molecular Weight: 203,24

According to the general procedure B, the reaction was carried out with acid **IV-64f** (99 mg, 0.40 mmol) in *N*,*N*-dimethylacetamide (4.0 mL) and heated at 180 ℃ for 10 min. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:4) afforded product **IV-68c** (66 mg, 0.32 mmol, 81% yield) as a colorless needle. The spectra data are in agreement with the literature report.[145]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.50 (br, 1H), 8.11 (ddt, J = 6.9, 1.5, 0.7 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.26 – 7.18 (m, 2H), 3.94 (s, 3H), 3.21 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 166.5, 149.8, 134.6, 127.3, 122.5, 121.9, 121.6, 110.8, 103.7, 50.9, 21.5, 13.4.

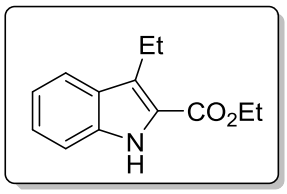
IR (ν, cm^{-1}, $CDCl_3$) 3459, 3061, 2979, 2951, 2876, 1692, 1548, 1490, 1461, 1447, 1363, 1343, 1329, 1270, 1226, 1196, 1118, 1097, 1058.

HRMS (EI+) calculated for $C_{12}H_{13}NO_2$: 203.0946; Found: 203.0938.

mp: 74-55 ℃ (pentane) (lit. = 72-73 ℃).

145 Kaneko, C; Fujii, H; Kawai, S.; Yamamoto, A.; Hashiba, K.; Kimata, T.; Hayashi, R.; Somei, M. *Chem. Pharm. Bull.* **1980**, *28*, 1157.

Ethyl 3-ethyl-1*H*-indole-2-carboxylate (IV-68d)



Chemical Formula: $C_{13}H_{15}NO_2$
Molecular Weight: 217,27

According to the general procedure B, the reaction was carried out with acid **IV-64g** (56 mg, 0.21 mmol) in *N*-methyl-2-pyrrolidone (2.1 mL) and heated at 260 ℃ for 60 min. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:5) afforded product **IV-68d** (28 mg, 0.13 mmol, 61% yield) as colorless needle. The spectra data are in agreement with the literature report.[146]

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.72 (br, 1H), 7.70 (dq, J = 8.1, 0.9 Hz, 1H), 7.38 (dt, J = 8.3, 1.0 Hz, 1H), 7.32 (ddd, J = 8.2, 6.8, 1.1 Hz, 1H), 7.14 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 3.14 (q, J = 7.5 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.5 Hz, 3H).

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 162.6, 136.0, 127.8, 127.0, 125.6, 122.9, 120.9, 120.0, 111.8, 60.8, 18.2, 15.6, 14.6.

IR (ν, cm^{-1}, $CDCl_3$) 3463, 2975, 2934, 2873, 1711, 1693, 1577, 1555, 1464, 1452, 1380, 1328, 1312, 1266, 1240, 1185, 1132, 1097, 1085, 1019.

HRMS (EI+) calculated for $C_{13}H_{15}NO_2$: 217.1103; Found: 217.1101.

mp: 119-121 ℃ (lit.[147]: 112-114 ℃).

146 Du, X.; Ghosh, A.; Stanley, L. M. *Org. Lett.* **2014**, *16*, 4036.

147 Piscitelli, F.; Ligresti, A.; La Regina, G.; Coluccia, A.; Morera, L.; Allara, M.; Novellino, E.; Di Marzo, V.; Silvestri, R. *J. Med. Chem.* **2012**, *55*, 5627.

université PARIS-SACLAY | ÉCOLE DOCTORALE INTERFACES Approches Interdisciplinaires : Fondements, Applications et Innovation

Titre : Application des Xanthates à la Synthèse des Azaindanes et à la Fonctionnalisation C-H des Hétéroaromatiques

Mots clés : chimie radicalaire, xanthates, fonctionnalisation C-H, azaindanes, hétéroaromatiques

Résumé: Cette thèse décrit les nouvelles applications de la chimie radicalaire des xanthates développée au laboratoire. Nous nous sommes intéressés en particulier par la fonctionalisation d'hétéroaromatiques en utilisant la chimie radicalaire des xanthates.

Dans ce cadre, une approche modulaire de la preparation des azaindanes a été d'abord dévéloppée. Reposant sur la capacité de xanthates de se faire le médiateur de l'addition intermoléculaire sur des alcènes et de la cyclisation intramoléculaire sur des pyridines, cette méthode a permis la synthèse de nombreuses azaindanes contenant des groups fonctionnels très intéressants.

La puissance de la chimie radicalaire des xanthates a été prouvé par l'alkylations intermoléculares de pyrazines et bien d'autres hétéroaromatiques. Pyrazines hautement fonctionalisés ont été préparés dans des condtions réactionelles très douces. Finalement, l'addition de xanthate carboxyméthyle sur des hétéroaromatiques a été devéloppée, donnant des acides arylacétiques. Les hétéroaromatiques méthylés ont été préparés par les décarboxylations des intermédiares acides arylacétiques. La fluorométhylation et éthylation ont été également développées.

Title: Application of Xanthates to the Synthesis of Azaindanes and to the C-H Functionalization of Heteroaromatics

Key words: radical chemistry, xanthates, C-H functionnalization, azaindanes, heteroaromatics

Summary: This thesis describes the new applications of radical xanthate chemistry developed in the laboratory. In particular, we focused on the functionalization of heteroaromatics using xanthate chemistry.

In this framework, a modular approach to the preparation of azaindanes was first developed. Based on the ability of xanthates to mediate both intermolecular addition to alkenes and intramolecular cyclization onto pyridines, this method allowed the synthesis of many azaindanes containing very interesting functional groups.

The power of xanthate radical chemistry has been proven by the intermolecular alkylation of pyrazines and several other heteroaromatics. Highly functionalized pyrazines were prepared in very mild reaction conditions. Finally, the addition of carboxymethyl xanthate to heteroaromatics was developed, affording arylacetic acids. The methylated heteroaromatics were prepared by the decarboxylations of the intermediate arylacetic acids. Fluoromethylation and ethylation have also been developed.