Synthesis and reactivity of 3-acetyl-2-aminothiophenes

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Thèse

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Synthesis and reactivity of 3-acetyl-2-aminothiophenes

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JURY

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Contents

List of abbreviations

Abs	Absolute
Anal	Analytical
Atm	Atmospheric
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Ca	Circa = approximately
Calcd	Calculated
CAN	Cerium ammonium nitrate
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
HRMS	High resolution mass
ESI	Electron spray ionization
LHMDS	lithium hexamethyldisilazide
MeOH	Methanol
MHz	Megahertz
ml	Milliliter
Mol	Mole
mp	Melting Point
NMR	Nuclear magnetic resonance
***p*(*o*-tolyl)$_3$**	Tris(*o*-tolyl)phosphine
Pd(AcO)$_2$	Palladium(II) acetate

$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
pH	Potential of hydrogen
PPh_3	Triphenylphosphine
ppm	Part per million
***t*BuOK**	Potassium *tert*-butoxide
TEA	Triethylamine
temp	Temperature
TLC	Thin layer chromatography
Tmeda	Tetramethylethylenediamine
UV	Ultraviolent
VH	Vilsmeier-Haack
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Résumé de la thèse

Un intérêt grandissant pour le système thiéno[2,3-*b*] pyridine est apparu ces trois dernières décennies. De nombreux chercheurs ont présentés des composés basés sur ce système comme traitement possible de l'anxiété et de la dépression, comme bactéricide, contre l'inflammation et la leishmania, la malaria et les maladies auto-immunes. Les ortho-amino acyl thiophènes sont des produits de départ possible pour synthétiser ces motifs. L'accès à ce type de composés sera la première étape de ce travail.

Nous décrivons ici la première synthèse de 3-acétyl-2-aminothiophènes en utilisant la réaction à 3 composants de Gewald. Ces composés montrent différents modes de cyclisation dans le cas de traitement avec le réactif de Vilsmeier-Haack. comparé au ortho aminoacétophénones, leurs analogues benzéniques. Ceci semble ête du à la présence du noyau thiophénique. Cette réaction a permis l'accès à de nouveaux dérivés 4-chlorothiéno[2,3-*b*]pyridines . Ces derniers ont été couplés via la réaction de Buchwald-Hartwig catalysée par le palladium.à des anilines avec des rendements moyens à bons.

D'autre part, les 4-chloro-3-formylthiéno[2,3-*b*]pyridines ont été préparés par réaction du réactif de Vilsmeier-Haack sur les acétamido thiophènes correspondants dans les conditions classiques. Ces dérivés ne sont pas accessibles sans la protection de l'amine et non plus à partir des dérivés chlorés en 4.

La synthèse de 4-méthylthiéno[2,3-*b*]pyridines a pu être réalisée par réaction des 3-acétyl-2-aminothiophènes avec des cétones dans les conditions de Friedländer.

Abstract of the thesis

Significant interest in the thieno[2,3-*b*]pyridine nucleus has arisen during the last three decades. Many researchers have reported the use of compounds based on this scaffold as a possible treatment of anxiety and depression, bacterial infection, inflammation, leishmaniasis, malaria and autoimmune diseases. Ortho-amino acyl thiophenes are possible starting material allowing to reach the thienopyridine structure. Access to these compounds was our first task for this thesis.

We report here the first synthesis of 3-acetyl-2-aminothiophene by using the three-component Gewald reaction. These compounds exhibit a different mode of cyclisation in the reaction with Vilsmeier–Haack reagent than that reported for the reaction with *o*-aminoacetophenone, which could be ascribed to the influence of the thiophene nucleus. This simple, two-step reaction allows the construction of some novel 4-chlorothieno[2,3-*b*]pyridine derivatives from very simple building unit while which reacted further with aniline by palladium-catalysed *C*–*N* cross-coupling to give the coupled product in moderate to high yield.

On other hand, 4-chloro-3-formylthieno[2,3-*b*]pyridine derivatives were synthesized by reaction between protected 3-acetyl-2-aminothiophenes and vilsmeier-Haack reagent under normal conditions. These products were not accessible neither without *N*-protection of the starting materials nor by reaction between the reagent and 4-chlorothieno [2,3-*b*]pyridine under any condition.

Some derivatives of 4-methylthieno[2,3-*b*]pyridine were prepared by reaction between 3-acetyl-2-aminothiophene and some ketones under Friedländer condition.

General introduction

Introduction générale

Le thiophène est un élément de construction important pour des agents thérapeutiques et des applications industrielles (optique non-linéaire…).

Notre laboratoire a acquis au long des années une grande expérience dans la synthèse du noyau thiophénique en utilisant différentes approches. Dans ce travail nous décrivons une nouvelle synthèse de thiophène ; les 3-acétyl-2-aminothiophènes et l'étude de la réactivité de ces dérivés afin qu'ils soient utilisables par la suite pour la formation de molécules plus complexes.

Le premier but de notre travail était la synthèse des thiophènes fonctionnalisés. Dans le chapitre 1, nous décrivons la préparation des 3-acétyl-2-aminothiophènes par l'utilisation de la réaction de Gewald aux dépens de la cyanoacétone. Une autre synthèse de thiophènes est aussi décrite dans ce chapitre permettant la formation du noyau à partir du cétènes dithioacétal préparé à partir de la cyanoacétone.

La proximité des 2 groupements fonctionnels (amino et acétyle) sur le thiophène permet d'envisager le composé comme point de départ pour de nombreux autres dérivés en utilisant diverses réactions. Dans le chapitre 2, nous explorons cette réactivité par action du réactif de Vilsmeier-Haack en ciblant la synthèse de thiénopyridines. Nous comparons cette réactivité à celle des o-aminoacétophénones.

Afin de mieux comprendre le mécanisme de la cyclisation avec le réactif de Vilsmeier-Haack, nous proposons de protéger l'amine par alcoylation pour voir si l'accès à des thiénopyridines différentes est possible. Ceci est décrit dans le chapitre 3.

Dans le chapitre 4, la possibilité supplémentaire de condensation vers des polycycles, la réaction de Friedländer, est utilisée. Des conditions douces y seront recherchés pour celle-ci.

Les chlorothiénopyridines attendues précédemment seront étudiées dans le cas de l'amination par substitution nucléophile aromatique dans différentes conditions (directe, Ullmann et Buchwald-Hartwig). Tous ces couplages seront présentés dans le chapitre 5.

General introduction

Thiophene is very important building block in many chemical products used as pharmaceutical agents or industrial applications (non-linear optics…).

In our laboratory, we have long experience in synthesizing thiophene containing compounds using diversity of synthetic approach. In current work, we report a novel synthesis of thiophene derivatives; 3-acetyl-2aminothiophenes and also the study of their reactivity in order to use them as a launch point of many final products via different synthetic pathways.

The first task of our project was the synthesis of functionalized thiophenes. In chapter one we described how to prepare 3-acetyl-2aminothiophene using the simple classical Gewald's reaction starting from cyanoacetone. Another synthesis of thiophenes is described starting from cyanoacetone dithioacetals.

Neighbourhood of two functional group (amino and acetyl) on the thiophene ring qualified them to be the base of synthesis many novel derivatives applying different organic reactions. In chapter 2 we explore the reactivity of 3-acetyl-2aminothiophenes in reaction with Vilsmeier-Haack reagent looking for access to thienopyridines. We made a comparison to the reactivity of o-aminoacetophenones.

In a trial for more comprehension of the mechanism of cyclization with Vilsmeier-Haack reagent, we decided to protect the amino group to see whether the reaction is behaving differently and the access to functionalized thienopyridines is possible. This is described in chapter 3.

In chapter 4, another utilization of the reactivity of our starting material through application of Friedländer reaction is studied. Smooth conditions for the reaction are searched for.

As chlorothienopyridines will be available from the former studies, we are looking at the reactivity of chlorine atom to nucleophilic amination using different reactions (Ullmann coupling, Buchwald-Hartwig coupling…). All these coupling are described in chapter 5.

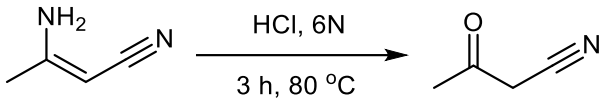
Chapter 1 – Synthesis of 3-acetyl-2-aminothiophenes

Résumé chapitre 1: Synthèse des 3-acétyl 2-aminothiophènes

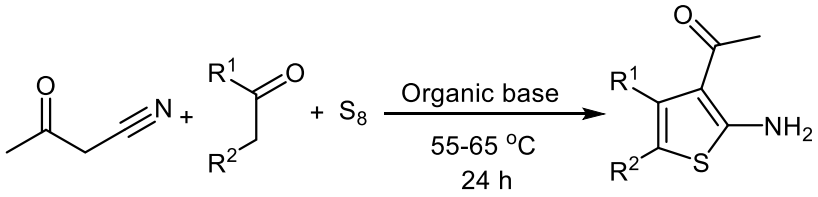
Le thiophène est un hétérocycle important qui possède des possibilités biologiques intéressantes. En fait il est considéré comme un bioisostère du benzène et peut ainsi remplacer ce dernier dans des structures actives. Un certain nombre de médicament à base de thiophène existe d'ailleurs Ticlopidine, Clopidogrel…). Des dérivés benzocondensés du thiophène sont présents aussi dans la pharmacopée (Raloxifène, Olazapine…).

Dans une première partie, les différentes méthodes d'accès au thiophène sont décrites (Paal-Knorr, Fiesselmann, Gewald, à partir de béta-chloroacroléïne, à partir de cétènes dithioacétals).

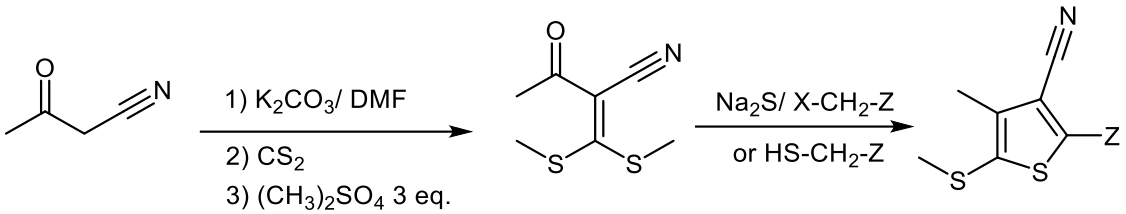
La méthode de Gewald est une méthode a 3 composants permettant un accès facile au noyau thiophénique fonctionnalisé par une amine et un nitrile ou un ester. La méthode décrite dans ce travail permet l'extension à une fonctionnalisation par une amine t un groupement acétyle. Le réactif de départ est la cyanoacétone préparée par hydrolyse d'amino-crotononitrile.



La condensation se fait dans les conditions mises au point concernant température et base utilisée (pipéridine la plus efficace) :



Cette cyano-acétone permet aussi l'accès à des thiophènes via le cétène dithioacétal:


O
N
1) K_2CO_3/ DMF
2) CS_2
3) $(CH_3)_2SO_4$ 3 eq.
O
N
S
S
Na_2S/ X-CH_2-Z
or HS-CH_2-Z
N
Z
S
S

1 Synthesis of 3-acetyl-2-thiophenes

1.1 Introduction

Thiophene is a very important building block of many heterocycles which possesses pharmacological characteristics. Wide varieties of drugs are containing thiophene in their structure, e.g. antiplatelet aggregation tetrahydrothieno[3,2-*c*]pyridine: ticlopidine® and clopidogrel®,[1] estrogen receptor modulator Benzo[*b*]thiophenes: Raloxifene®[2] and antipsychotic thieno[2,3-*b*][1,5]benzodiazepine: olanzapine®.[3]

Other nucleus like thieno[2,3-*b*]pyridine has provoked a great interest as a possible treatment of anxiety and depression,[4] bacterial infection,[5] inflammation,[6] leishmaniasis,[7] malaria[8] and autoimmune diseases.[9] Tacrine like thiophene was reported as a possible alternative of Tacrine in treatment of Alzheimer disease.[10]

[1] G. J. Hankey, C. L. Sudlow, and D. W. Dunbabin, "Thienopyridine Derivatives (Ticlopidine, Clopidogrel) versus Aspirin for Preventing Stroke and Other Serious Vascular Events in High Vascular Risk Patients," *The Cochrane Database of Systematic Reviews*, no. 2 (2000): CD001246, doi:10.1002/14651858.CD001246; Robert T. Dorsam and Satya P. Kunapuli, "Central Role of the P2Y12 Receptor in Platelet Activation," *The Journal of Clinical Investigation* 113, no. 3 (February 2004): 340–45, doi:10.1172/JCI20986.

[2] Isabel C. F. R. Ferreira et al., "Evaluation of the Antioxidant Properties of Diarylamines in the Benzo[*b*]thiophene Series by Free Radical Scavenging Activity and Reducing Power," *Bioorganic & Medicinal Chemistry Letters* 16, no. 5 (March 1, 2006): 1384–87, doi:10.1016/j.bmcl.2005.11.035.

[3] H. Y. Meltzer and H. C. Fibiger, "Olanzapine: A New Typical Antipsychotic Drug," *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 14, no. 2 (February 1996): 83–85, doi:10.1016/0893-133X(95)00197-L.

[4] Mervyn Thompson and Roger Martin, Cns Active Tetrahydrobenzothienopyridines, issued May 14, 1993, https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1993009122.

[5] E Bakhite A et al., "Synthesis and Reactions of New Thienopyridines, Pyridothieniopyrimidines and Pyridothienotriazines," *Bull. Korean Chem. Soc.* 23 (2002): 1709.

[6] Tsuneo Yasuma et al., Thienopyridine Derivatives and Their Use as Anti-Inflammatory Agents, WO0164685 (A3), issued August 8, 2002, https://worldwide.espacenet.com/publicationDetails/biblio;jsessionid=hDr9+iU3s6a2txAHInX0lV1f.espacenet_levelx_prod_3?FT=D&date=20020808&DB=&locale=&CC=WO&NR=0164685A3&KC=A3&ND=1; Kuncha Madhusudana et al., "Anti-Inflammatory Potential of Thienopyridines as Possible Alternative to NSAIDs," *European Journal of Pharmacology* 678, no. 1–3 (March 5, 2012): 48–54, doi:10.1016/j.ejphar.2011.12.019.

[7] Luiz C. S. Pinheiro, "Searching for New Antileishmanial Lead Drug Candidates: Synthesis, Biological and Theoretical Evaluations of Promising thieno[2,3-*b*] Pyridine Derivatives," *Journal of Microbiology and Antimicrobials* 4, no. 1 (January 2012), doi:10.5897/JMA11.109.

[8] Andreas Masch and Conrad Kunick, "Selective Inhibitors of Plasmodium Falciparum Glycogen Synthase-3 (PfGSK-3): New Antimalarial Agents?," *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, SI: IPK 2014, 1854, no. 10, Part B (October 2015): 1644–49, doi:10.1016/j.bbapap.2015.03.013.

[9] Diane Boschelli et al., Thieno[2,3-*b*]pyridine-5-Carbonitriles as Protein Kinase Inhibitors, WO2007038519 (A1), issued April 5, 2007, https://worldwide.espacenet.com/publicationDetails/biblio?FT=D&date=20070405&DB=&locale=&CC=WO&NR=2007038519A1&KC=A1&ND=1.

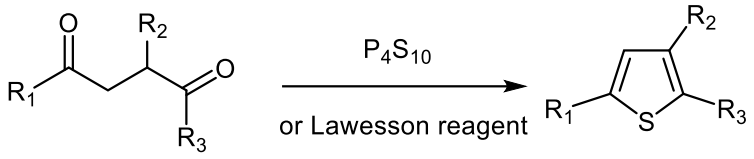
[10] Pierre Seck et al., "Synthesis of New Selenophene and Thiazole Analogues of the Tacrine Series," *Arkivoc* 3 (2012): 431–441; David Thomae, Gilbert Kirsch, and Pierre Seck, "Synthesis of Selenophene Analogues of the Tacrine Series: Comparison of Classical Route and Microwave Irradiation," *Synthesis* 2008, no. 10 (May 2008): 1600–1606, doi:10.1055/s-2008-1067001.

1.1.1 Synthesis of thiophene

Thiophene was discovered as a contaminant of benzene by Victor Meyer in 1883.[11] Many synthetic route has been established in organic synthesis since this date. Some examples of synthesis are described below

1.1.1.1 Paal- Knorr synthesis

By this Mode of synthesis, thiophene **2** could be obtained by a reaction between 1,4-dicarbonyl derivatives **1** and sulphur source (P_4S_{10} or Lawesson's reagent) (Scheme 1).[12]

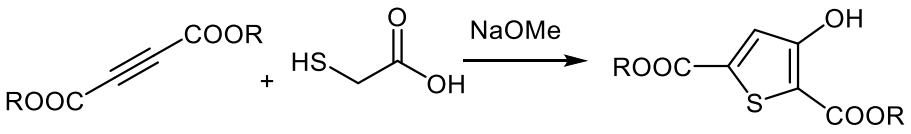


1 **2**

Scheme 1 Paal-Knorr synthesis of thiophene

1.1.1.2 Fiesselmann thiophene synthesis

By basic treatment, thiophene **5** could be obtained from reaction of α,β-acetylenic esters **3** with thioglycolic acid **4** (Scheme 2).[13]



3 **4** **5**

Scheme 2 Fiesselmann thiophene Synthesis

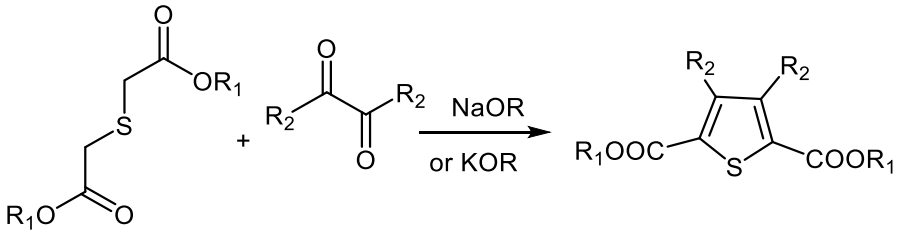
[11] Victor Meyer, "Ueber Den Begleiter Des Benzols Im Steinkohlentheer," *Berichte Der Deutschen Chemischen Gesellschaft* 16, no. 1 (January 1, 1883): 1465–78, doi:10.1002/cber.188301601324.

[12] H. Z. Lecher et al., "The Phosphonation of Aromatic Compounds with Phosphorus Pentasulfide," *Journal of the American Chemical Society* 78, no. 19 (October 1, 1956): 5018–22, doi:10.1021/ja01600a058; E. Campaigne and William O. Foye, "The Synthesis of 2,5-Diarylthiophenes," *The Journal of Organic Chemistry* 17, no. 10 (October 1, 1952): 1405–12, doi:10.1021/jo50010a023.

[13] "Fiesselmann Thiophene Synthesis," in *Name Reactions* (Springer Berlin Heidelberg, 2006), 230–32, doi:10.1007/3-540-30031-7_103.

1.1.1.3 The Hinsberg Synthesis

Condensation between 1,2-diketones **7** and thiodiglycolate **6** led to synthesizing of thiophene carboxylic acids **8**, sodium or potassium ethoxides served as catalyst (Scheme 3).[14]



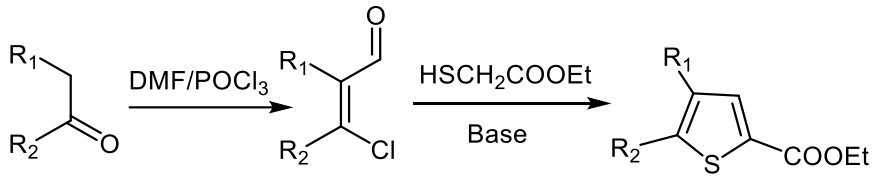
6 **7** **8**

Scheme 3 Hinsberg thiophene Synthesis

1.1.2 Synthesis of thiophene using multicomponents reaction

1.1.2.1 General synthesis of 2-functionalized thiophene

A synthetic pathway was established by reacting β-chloroacroline derivatives **10** with Ethyl thioglycolate for synthesizing 2-ethyl carboxylate derivatives of thiophene **11**[15], compound **10** were obtained by Arnold; who synthesized it in a reaction between α methylene containing ketone **10** and Vilsmeier-Haack reagent (Scheme 4).[16]



9 **10** **11**

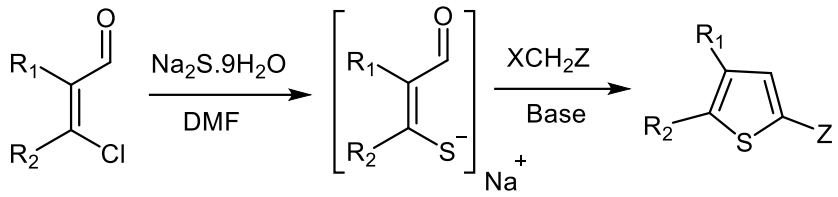
Scheme 4 General synthesis of 2-functionalized thiophene.

[14] O. Hinsberg, "Synthetische Versuche Mit Thiodiglykolsäureester," *Berichte Der Deutschen Chemischen Gesellschaft* 43, no. 1 (January 1, 1910): 901–6, doi:10.1002/cber.191004301153.

[15] S. Hauptmann et al., "Eine Neue Synthese Substituierter Thiophene Und Pyrrole," *Tetrahedron Letters* 9, no. 11 (January 1, 1968): 1317–19, doi:10.1016/S0040-4039(01)98945-2.

[16] Z. Arnold and J. Žemlička, "Synthetische Reaktionen von Dimethylformamid IV. Darstellung von β-Chlorvinylaldehyden Aus Carbonylverbindungen," *Collection of Czechoslovak Chemical Communications* 24, no. 7 (1959): 2385–92, doi:10.1135/cccc19592385.

This reaction has been extended to a three component reaction in one pot by our group, $Na_2S.9H_2O$ was the sulphur source. It reacted with β-chloroacrolein derivatives **10** in DMF to produce an intermediate that cyclized *in situ* with an activated halide in basic medium producing the thiophene **12** as the final output.[17]

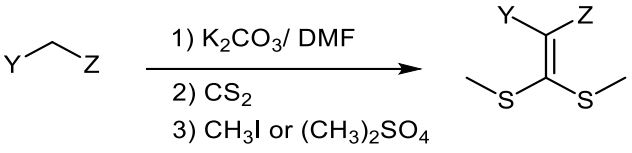


10 **12**

Z= electron withdrawing group

Scheme 5 Synthesis of 2-functionalized thiophene.

Similarly, ketene dithioacetal is a key intermediate in synthesis of many aromatic heterocycles, especially thiophenes.[18] It was prepared for the first time by Freund[19], our laboratory has long tradition in preparation of such kind of products using DMF as a solvent, and potassium carbonate as catalysing base. Methyl iodide or dimethylsulphate are the reagents in use as methylating agent (Scheme 6).



13 **14**

Y, Z are electron withdrawing groups

Scheme 6 General synthesis of ketene dithioacetal,

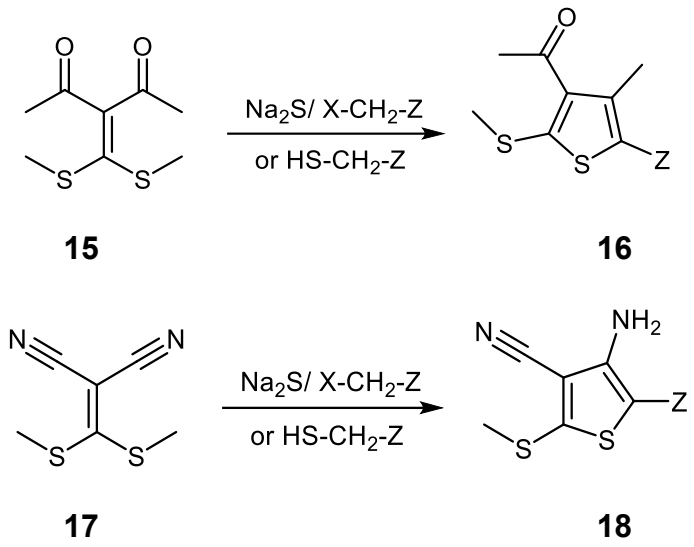
To cyclize compound **14**, two pathways were reported: one by combination between sodium sulfide and activated halide, second synthetic pathway by reaction of ketene

[17] Paul Cagniant and Gilbert Kirsch, "Méthode Générale de Synthèse de Composés Thiophénique Simples Ou Complexes Alcoylés, Arylés Ou Fonctionnalisés en Position-2," *C. R. Acad. Sc. Paris*, C, 281 (1975): 35–38.

[18] Geoffroy Sommen, Alain Comel, and Gilbert Kirsch, "A Convenient Synthesis of 2,3,4,5-Functionalized Thieno[2,3-*b*]thiophenes.," *ChemInform* 34, no. 28 (July 15, 2003), doi:10.1002/chin.200328120.

[19] Erich Freund, "Über Die Einwirkung von Schwefelkohlenstoff Auf Nitro-Methan," *Berichte Der Deutschen Chemischen Gesellschaft (A and B Series)* 52, no. 3 (March 8, 1919): 542–44, doi:10.1002/cber.19190520307.

dithioacetal with thioglycolate. Both synthetic pathways are promoted by basic catalysis. Sodium sulfide or thioglycolate are serving as the source of Sulphur in the furnished thiophene (Scheme 7).[20]

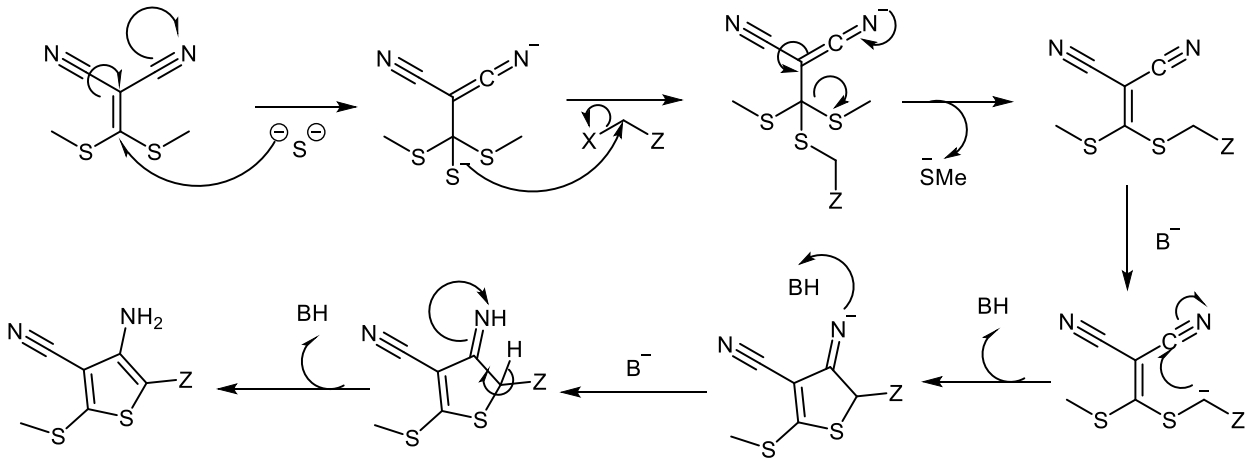


Scheme 7 Cyclization of ketene dithioacetal into thiophene

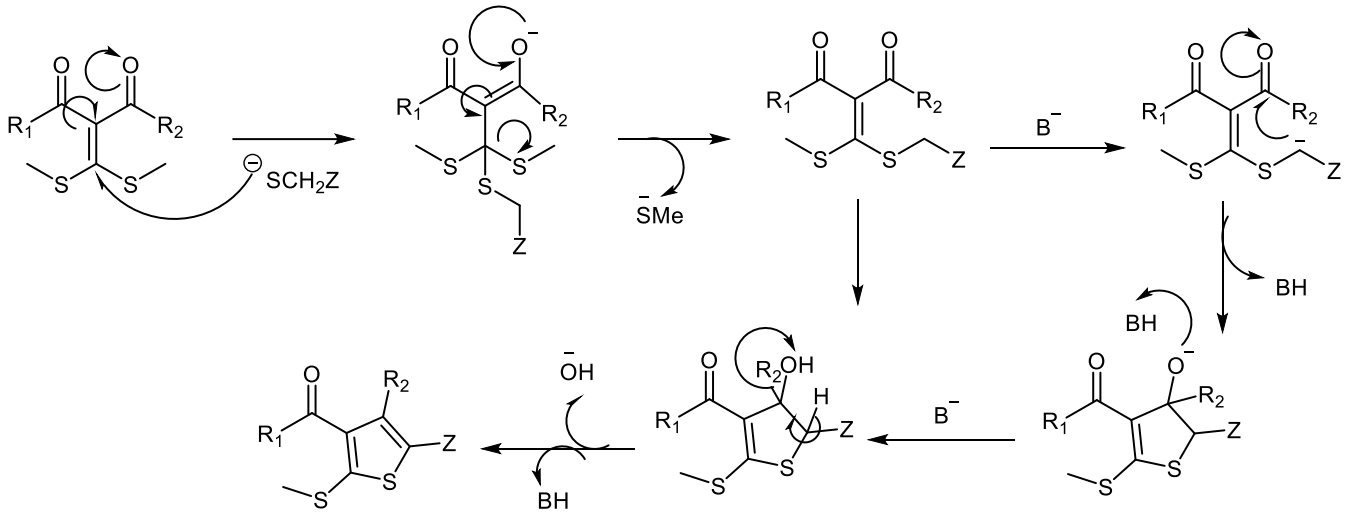
The reaction mechanisms are depicted in Scheme 8 and Scheme 9; in which 1,4 Michael addition of the negative charge of sodium sulfide or the thioglycolate leads to formation of S-alkylated intermediate upon elimination of the methylsulfanyl group. These addition-elimination take place in two steps in case of thioglycolate or three steps with sodium sulphide. The last intermediate goes toward thiophene through cyclization according to Claisen, Thorpe-Ziegler or Dieckmann reaction to form the thiophene ring.[21]

[20] Yoshinori Tominaga, Jiann-Kuan Luo, and Raymond N. Castle, "The Reaction of Methyl 3-Amino-4-Cyano-5-Methylthiothiophene-2-Carboxylate with Dmad. A New Synthesis of Polyfunctionalized Quinolines," *Journal of Heterocyclic Chemistry* 31, no. 4 (July 1, 1994): 771–73, doi:10.1002/jhet.5570310413; Kenneth J. Wilson et al., "Synthesis of Thiophene-2-Carboxamidines Containing 2-Amino-Thiazoles and Their Biological Evaluation as Urokinase Inhibitors," *Bioorganic & Medicinal Chemistry Letters* 11, no. 7 (April 9, 2001): 915–18, doi:10.1016/S0960-894X(01)00102-0; M. Augustin, W. -D. Rudorf, and U. Schmidt, "Thiophene Durch S-Alkylierung," *Tetrahedron* 32, no. 24 (January 1, 1976): 3055–61, doi:10.1016/0040-4020(76)80166-4; Sommen, Comel, and Kirsch, "A Convenient Synthesis of 2,3,4,5-Functionalized Thieno[2,3-*b*]thiophenes."

[21] Vladimir G. Granik, Alexander V. Kadushkin, and Jürgen Liebscher, "Synthesis of Amino Derivatives of Five-Membered Heterocycles by Thorpe-Ziegler Cyclization," in *Advances in Heterocyclic Chemistry*, ed. Alan R. Katritzky, vol. 72 (Academic Press, 1998), 79–125.



Scheme 8



Scheme 9

1.1.3 Synthesis of aminothiophene

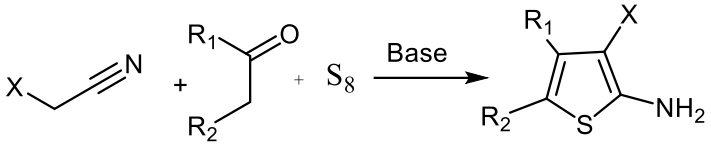
1.1.3.1 Synthesis of 2-aminothiophene by Gewald's reaction

In 1966 Karl Gewald established a new synthetic pathway for synthesizing 2-aminothiophene by applying one-pot reaction in which a carbonyl compound containing a methylene group in the α-position reacts with elemental sulphur and activated nitriles to

produce 2-aminothiophene.[22] It was considered so brilliant to enclose the inert sulphur within a heterocyclic nucleus and force it to react.[23]

Gewald three component reaction has been accomplished using different kinds of carbonyl product which containing free methylene group in position α, the most common activated nitriles were malononitrile, cyanoacetic ester and primary cyanoacetamide.[24]

This reaction has been widely applied since it was discovered to result in many derivatives including different electron-withdrawing groups in the 3-position (e.g., CN, COOR, $CONH_2$ and COPh) (Scheme 10).[25]



19 **20** **21**

X= electron withdrawing group e.g., CN, COOR, $CONH_2$ and COPh

Scheme 10 General scheme of Gewald synthesis

1.1.3.1.1 Mechanism of Gewald reaction[26]

As it illustrated in Scheme 11, the reaction consists of Knoevenagel condensation between the carboyl containing compound and the activated nitrile which is followed by ring closure accomplished by sulphur atom attacking the cyano carbon.[27]

[22] Karl Gewald, Elfriede Schinke, and Horst Böttcher, "Heterocyclen Aus CH-Aciden Nitrilen, VIII. 2-Amino-Thiophene Aus Methylenaktiven Nitrilen, Carbonylverbindungen Und Schwefel," *Chemische Berichte* 99, no. 1 (January 1, 1966): 94–100, doi:10.1002/cber.19660990116.

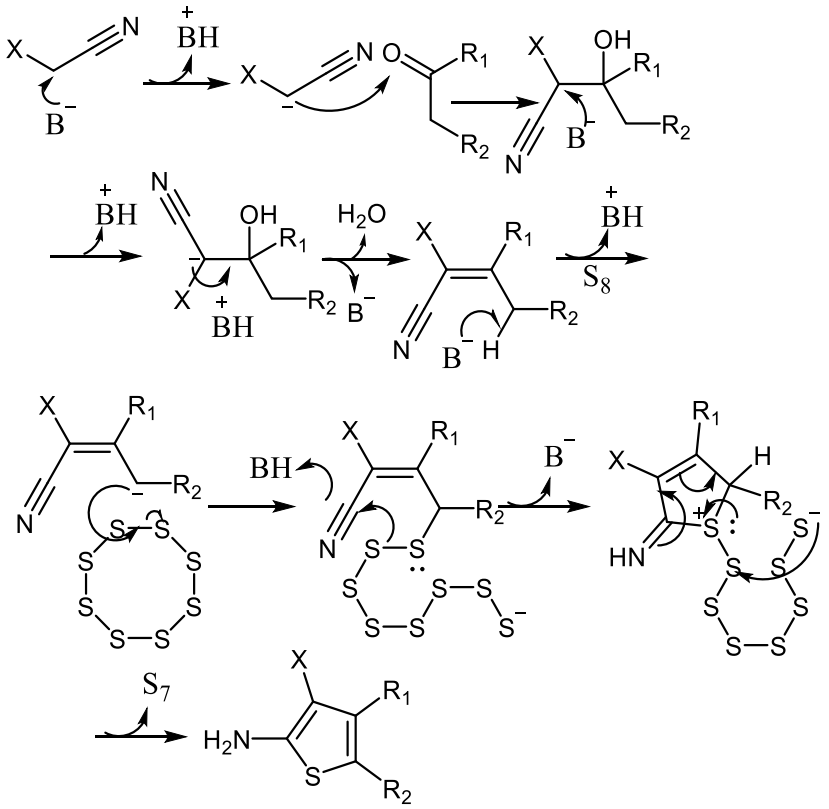
[23] Yijun Huang and Alexander Dömling, "The Gewald Multicomponent Reaction," *Molecular Diversity* 15, no. 1 (February 2011): 3–33, doi:10.1007/s11030-010-9229-6.

[24] Roland Mayer and K. Gewald, "The Action of Carbon Disulfide and Sulfur on Enamines, Ketimines, and CH Acids," *Angewandte Chemie International Edition in English* 6, no. 4 (April 1, 1967): 294–306, doi:10.1002/anie.196702941; Huang and Dömling, "The Gewald Multicomponent Reaction."

[25] M. S. Manhas et al., "Synthesis of Thieno- and Furo-Pyrimidinethiones," *Journal of the Chemical Society C: Organic*, no. 14 (January 1, 1969): 1937–39, doi:10.1039/J39690001937; K.-J Hwang and N.-K Choi, "A Facile Synthesis of 2-Aminothiophene Derivatives," *Bull. Korean Chem. Soc.* 12 (1991): 121; J D Ramanathan et al., "Biological-Activity Of Some 2-Amino 4, 5, 6, 7-tetrahydrobenzo[*b*]thiophenes and Their Derivatives," *Journal of the Indian Chemical Society* 55, no. 8 (1978): 822–825; P. Richter, D. Oertel, and F. Oertel, "Synthese von 3-Alkyl-5-phenyl-2-thioxo-3*H*-1,2-dihydro-cycloalka[4,5]thieno[2,3-*e*][1,2,4]triazepinen," *Pharmazie* 43, no. 11 (1988): 753–755.

[26] Huang and Dömling, "The Gewald Multicomponent Reaction."

[27] Norton P. Peet et al., "Mechanistic Observations in the Gewald Syntheses of 2-Aminothiophenes," *Journal of Heterocyclic Chemistry* 23, no. 1 (January 1, 1986): 129–34, doi:10.1002/jhet.5570230126.

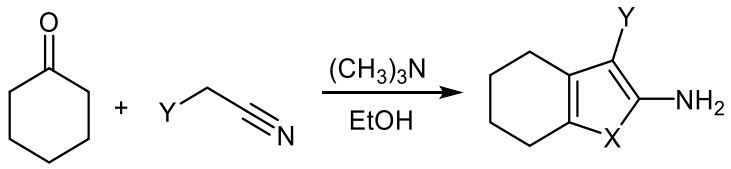


Scheme 11 Mechanism of Gewald reaction

1.1.3.1.2 Modified Gewald reaction

1.1.3.1.2.1 Synthesis of tellurophene and selenophene

Tellurophene and selenophene **24** were accessible *via* Gewald procedure by replacement elemental sulphur by tellurium or selenium (Scheme 12).[28]



22 **23** **24**

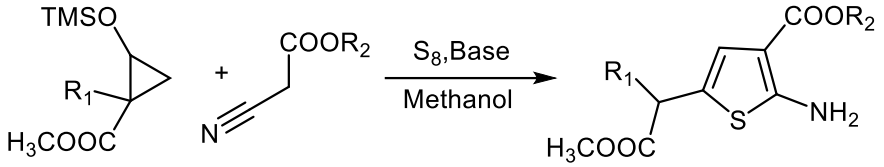
X= Se or Te while Y = COOEt, $CONH_2$ or CN.

Scheme 12 Synthesis of tellurophene and selenophene;

[28] Jirí Šibor and Pavel Pazdera, "Syntheses of Some New Five-Membered Heterocycles Containing Selenium and Tellurium," *Molecules* 1, no. 10 (February 4, 1997): 157–62, doi:10.1007/s007830050031.

1.1.3.1.2.2 Synthesis of 2-amnothiophene derivatives by employing methyl 2-siloxycyclopropanecarboxylates

Methyl 2-siloxycyclopropanecarboxylates **25** replaced the carbonyl compound in reaction with the activated nitrile **26** (Scheme 13).[29]

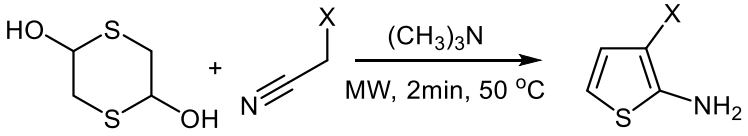


25 **26** **27**

Scheme 13

1.1.3.1.2.3 Microwave assisted two component Gewald synthesis

Dithiane (thioacetaldehyde dimer) **28** reacted with activated nitrile compound **29** under microwave assisted condition to give the thiophene product **30** in very short time (2 minutes) and in good yield in comparison with classical synthesis (Scheme 14).[30]



28 **29** **30**

X= electron withdrawing group

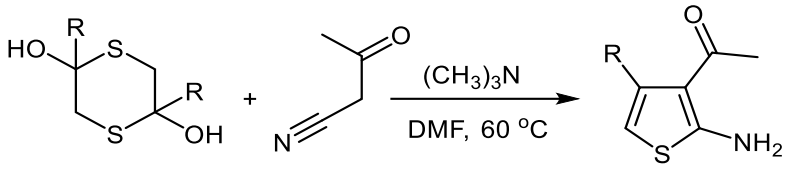
Scheme 14 Microwave assisted two component Gewald synthesis

[29] Hülya Özbek, Ivana Veljkovic, and Hans-Ulrich Reissig, "Gewald Synthesis of Aminothiophene Carboxylic Acids Providing New Dipeptide Analogues," *Synlett* 2008, no. 20 (December 2008): 3145–48, doi:10.1055/s-0028-1087243.

[30] Stéphanie Hesse, Enrico Perspicace, and Gilbert Kirsch, "Microwave-Assisted Synthesis of 2-Aminothiophene-3-Carboxylic Acid Derivatives, 3H-thieno[2,3-*d*]pyrimidin-4-One and 4-chlorothieno[2,3-*d*]pyrimidine," *Tetrahedron Letters* 48, no. 30 (July 23, 2007): 5261–64, doi:10.1016/j.tetlet.2007.05.136.

1.1.3.1.2.4 Two components Gewald synthesis of 3-acetyl-2-aminothiophenes

In 2006, Eller *et al.* introduced the first derivative having an acetyl group in the 3-position **33** by following a two-component pathway involving cyanoacetone **32** and 1,4-dithiane **31** (the source of sulphur at the same time).[31]



31 **32** **33**

Scheme 15 Two component Gewald synthesis of 3-acetyl-2-aminothiophenes.

Among various pathways of synthesizing thiophene, Gewald synthesis is very convenient synthetic procedure for production of 2-aminothiophene. Classic Gewald reaction was applied to produce different electron withdrawing group in position 3 (e.g., CN, COOR, $CONH_2$ and COPh). Some Modified techniques has been processed in order to improve yield (e.g., Microwave) or to obtain certain products. First Synthesis of 3-acetyl-2-aminothiophenes was approached by Eller *et al*. in 2006.[32]

1.1.4 Synthesis of 3-aminothiophene

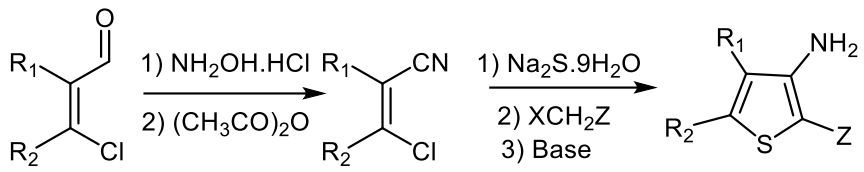
1.1.4.1 Starting from β-chloroacrolein

β-chloroacrolein **10** could be involved in multicomponent reaction with hydroxyl amine hydrochloride and acetic anhydride to give acrylonitrile **34** which consequently reacted with sodium sulphide and activated halide to give 3-aminothiophene **35** in basic condition (Scheme 40).[33]

[31] Gernot A. Eller and Wolfgang Holzer, "First Synthesis of 3-Acetyl-2-Aminothiophenes Using the Gewald Reaction," *Molecules (Basel, Switzerland)* 11, no. 5 (2006): 371–76.

[32] Ibid.

[33] H. M. Sampath Kumar et al., "Efficient One-Pot Preparation of Nitriles from Aldehydes Using N-Methyl-Pyrrolidone," *Synthesis* 1999, no. 04 (April 1999): 586–87, doi:10.1055/s-1999-3450; Zhijun Wang, Richard Neidlein, and Claus Krieger, "A New Approach to the Synthesis of Heteroannulated 3,1-Oxazin-4-Ones from β-Enamino Esters and Phosgeneiminium Salts," *Synthesis* 2000, no. 02 (2000): 255–58, doi:10.1055/s-2000-6249; Sommen, Comel, and Kirsch, "A Convenient Synthesis of 2,3,4,5-Functionalized Thieno[2,3-*b*]thiophenes."

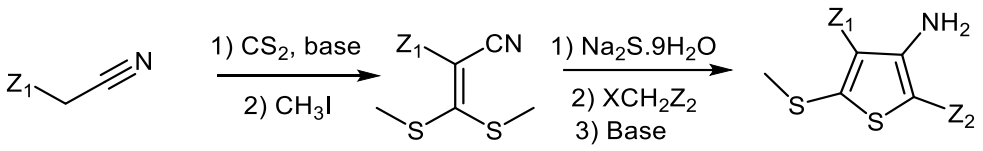


10 **34** **35**

Scheme 16

1.1.4.2 From malononitrile and cyanoacetate

Another multicomponent example is synthesis of 3-aminothiophene **38** starting from cyano group containing compound (malononitrile or cyanoacetate) **36** in two step reaction (Scheme 17).[34]



36 **37** **38**

Z_1 = CN or COOR, Z_2 = electron withdrawing group

Scheme 17

1.2 Results and Discussion

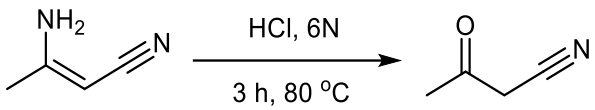
1.2.1 Synthesis of 3-acetyl-2-aminothiophenes by application of three component Gewald synthesis

A typical three-component Gewald reaction was applied in which cyanoacetone, a carbonyl compound, and elemental sulphur reacted to produce 3-acetyl-2-aminothiophene derivatives.

1.2.1.1 Synthesis of Cyanoacetone

Cyanoacetone **32** is colorless unstable oily liquid. It has to be freshly prepared in every time of performing the reaction and very shortly before launching it.

[34] Sommen, Comel, and Kirsch, "A Convenient Synthesis of 2,3,4,5-Functionalized Thieno[2,3-*b*]thiophenes."



39 **32**

Scheme 18 Synthesis of cyanoacetone

Cyanoacetone **32** was prepared from (*E*,*Z*)-3-aminocrotonitrile **39** by stirring in 6N HCl solution for 3 h (Scheme 18).[35]

Cyanoacetone **32** was serving as the activated nitrile as it contains cyano and acetyl group on the two sides of activated methylene group.

1.2.1.2 Selection of suitable catalyzing amine

By surveying the literature, many organic amines has been used as basic catalysis; morpholine, piperidine, trimethylamine… etc. From our experiments, we can arrange the bases in decreasing order according to their efficiency as the followinwing: piperidine > triethylamine > morpholine.

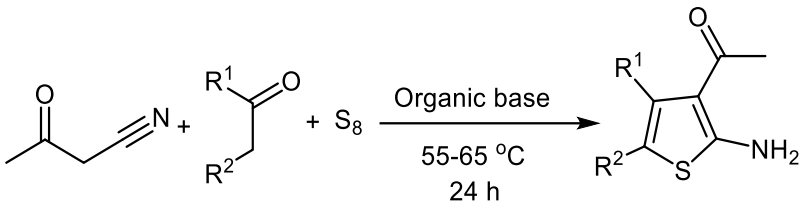
1.2.1.3 Selection of the solvent

Ethanol, methanol and DMF were the most reported solvent in use. Both ethanol and methanol was performing well during our reaction. We did not notice any effect on yield upon changing of the solvent.

1.2.1.4 Reactivity of ketones

This type of reaction were applied for wide ranges of ketones, nearly 40 different kinds of carbonyl derivatives were tried. Few examples gave products in yield varying from 8-86% depending on kind of ketones (Table 1). The time of the reaction was adjusted to be 24 hours which was found optimum, the temperature was between 55-65 °C. Increasing the time of the reaction or temperature beyond the fore mentioned values were found to decrease the yield or led to produce an oily solution upon treatment with ice and water (Scheme 19).

[35] John Mccall, Robert Kelly, and Donna Romero, Heterocyclic Compounds for the Inhibition of Pask, WO/2012/149157, issued November 2, 2012, https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2012149157&recNum=154&docAn=US2012035209&queryString=(%20&.



32 **40** **41**

Scheme 19 General method of 3-acetyl-2-amino-thiophene

1.2.1.4.1 Alicyclic ketones

The best results were obtained from alicyclic ketones. The site of substitution on the ketone governed the output. 2-substitution as in case of 2-methylcyclohexanone, 2-chlorocyclohexanone and 2-acetylcyclohexanone gave no reaction in contrarily to 3-methyl, 4-methyl and 4-tert-butyl-cyclohexanone (Table 1). Also multi substitution in more than one site (3,3,5-timethylcyclohexanone) and Aromatic substitution (in case of alpha and beta tetralone) did not give any results. It appeared that, the liberty of alpha methylene on both sides of the ketone is very crucial in order to complete the reaction. Increasing the number of the member of the ring beyond seven caused failure of achievement of the reaction, cyclooctanone and cyclododecanone gave no products.

In investigation of ^{1}H NMR results of the products, it was found that the common features between all spectra were those indicating the two functional group; the sharp singlet of methyl group of acetyl moiety and broad singlet which interpreted for NH_2 group. Compounds **49**, **51** and **53**, showed interesting mode of H-H coupling. Due to the presence of asymmetric carbon in position 5 for **49** and in position 6 for the last two.

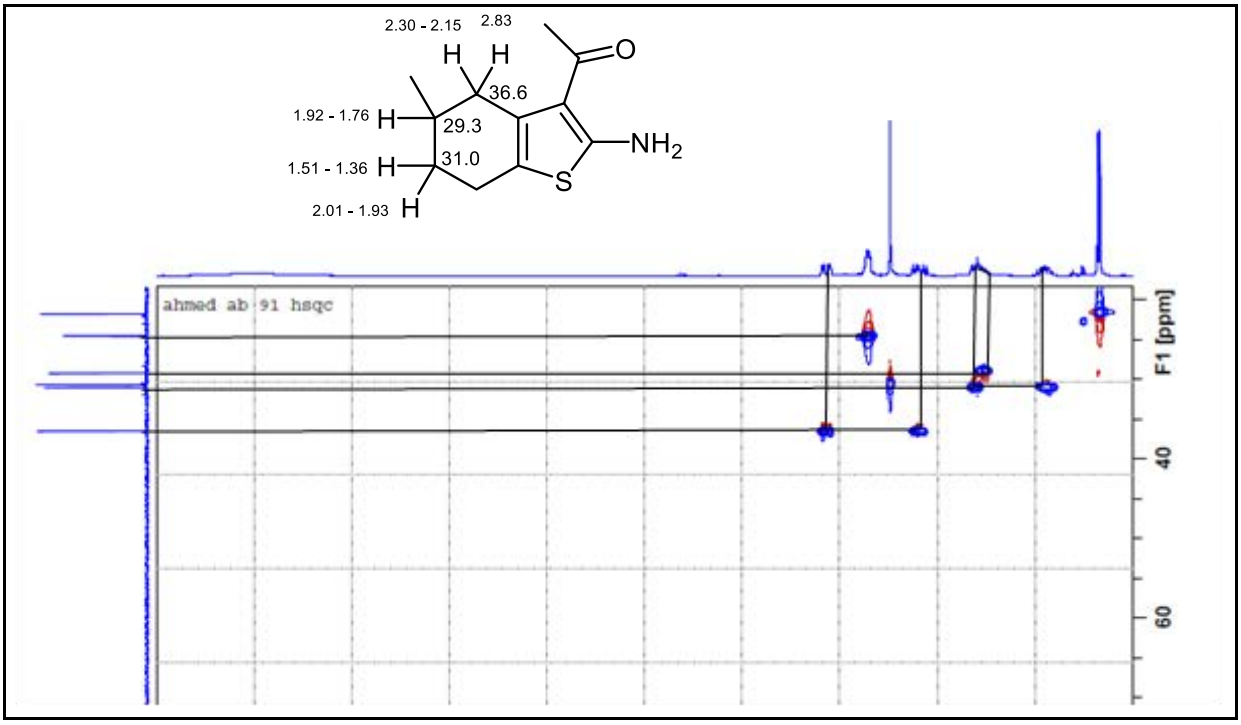


Figure 1 2D type of NMR (HSQC) of compound **49**

Each aliphatic proton surrounding the centre of asymmetry resonating solely and quite distinctive from the other carried on same carbon. Correlating the peaks to every proton done using 2D type of NMR. HSQC and HMBC were employed to identify C-H direct and indirect coupling. For compound **49**; proton with chemical shift δ = 1.51 – 1.36 ppm was found to be carried on carbon which had δ = 31.0 ppm while the other proton appeared more deshielded in δ = 2.01 – 1.93 ppm. Carbon with chemical shift of 36.6 ppm had its protons separated (δ = 2.30 – 2.15 and 2.83 ppm). Sole hydrogen signals was found at δ = 1.92 – 1.76 ppm (Figure 1).

Same techniques were applied for **51** and **53** and in case of **51** it revealed that the single proton on carbon of δ = 27.8 ppm had chemical shift of 1.47 – 1.35 ppm and carbon with δ = 29.2 ppm had protons viewed at region of δ = 2.72 – 2.61, 2.85 – 2.76 ppm while protons of carbon at δ = 32.9 ppm were in the area of δ = 2.21 – 2.12, 2.61 – 2.54 ppm (Figure 2).

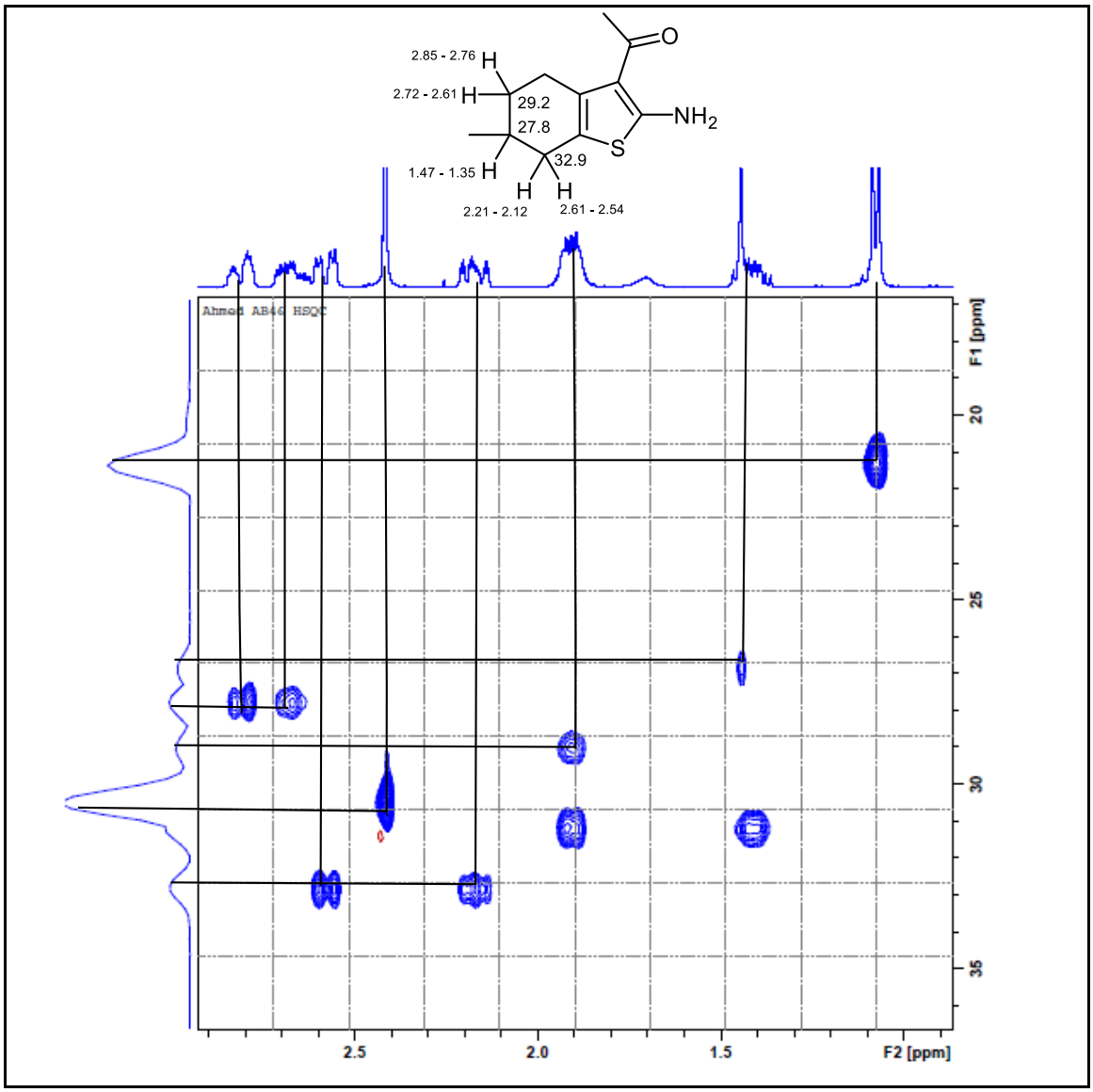


Figure 2 2D type of NMR (HSQC) of compound **51**

53 exhibited some difference from the previously investigated examples; protons on the aliphatic region had different chemical shifts even for those which are not adjacent to the asymmetric centre (δ = 26.3 ppm). Protons which are attached to it were resonating around 2.57 – 2.49 ppm and 2.37 – 2.28 ppm, the lone proton (on carbon with chemical shift = 44.9 ppm) appeared at 1.56 – 1.46 ppm meanwhile the asymmetric centre neighbours which were carbon with chemical shift of 24.7 and 29.2 ppm had their protons appeared at region of 2.07 – 2.00, 1.40 – 1.28 and 2.66 – 2.60, 2.88 ppm respectively (Figure 3).

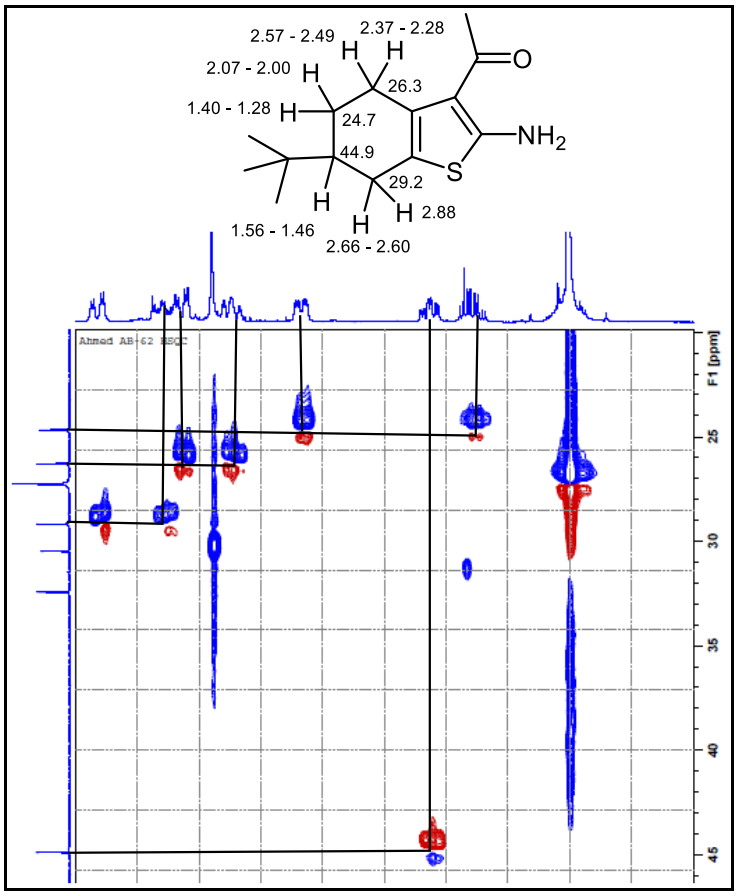


Figure 3 2D type of NMR (HSQC) of compound **53**

1.2.1.4.2 Aliphatic ketones

Among several normal aliphatic ketones which were tried, few examples only succeeded in giving moderate to low yield, increasing the length of the chain had influence on decreasing the reactivity of the reactant. The yields were inversely proportional with the length of the chain (36, 30 and 8 % for reaction with butanone **56**, 2-hexanone **58** and 2-octanone **60** respectively) (Table 1). Branching of the ketone skeleton or presence of substituent on the chain resulted in abolishment of the reactivity of the ketone. This could be attributed to the free rotation of the long chain which may hamper the ring closure during formation of the thiophene ring.

1.2.1.4.3 Heterocyclic ketones

The presence of heteroatoms helped in augmenting the yields (66 and 72 % of the products of the reaction with 1-methylpiperidin-4-one **64** and tetrahydro-4*H*-thiopyran-4-

one **62** respectively) (Table 1). When the member of the ring decreased than six, unidentified products was separated. Substitution on any site of the ring produced in no products.

1.2.1.4.4 Diketones

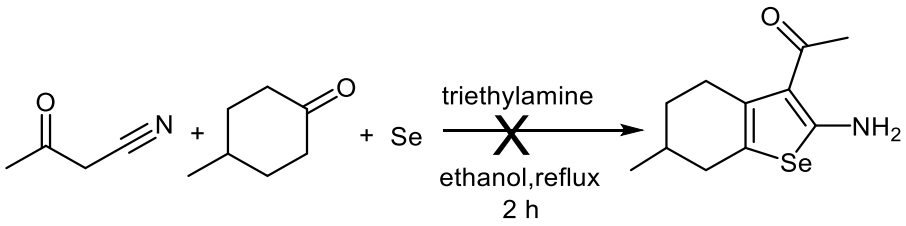
No products were obtained from reaction of cyanoacetone, S_8 with the diketones, neither normal aliphatic nor alicyclic ketones reacted to give the desired products.

1.2.1.4.5 Aldehydes

In reaction of heptanal with other reactants under Gewald's conditions, no product was identified.

1.2.2 Synthesis trial of 3-acetyl-2-aminoselenophene by application of three component Gewald synthesis

To extend our varities of the products, a trial was done to replace elemental sulphur with selenium to produce selenophene rather than thiophene.[36] 4-methylcyclohexanone **42**, selenium and cyanoacetone **32** were the three components of the reaction in presence of excess of triethylamine as catalyst in ethanol. The reaction was refluxed for two hours. When the reaction was treated by ice and water, selenium was separated and no formation of product was detected (Scheme 20).



32 **42** **43**

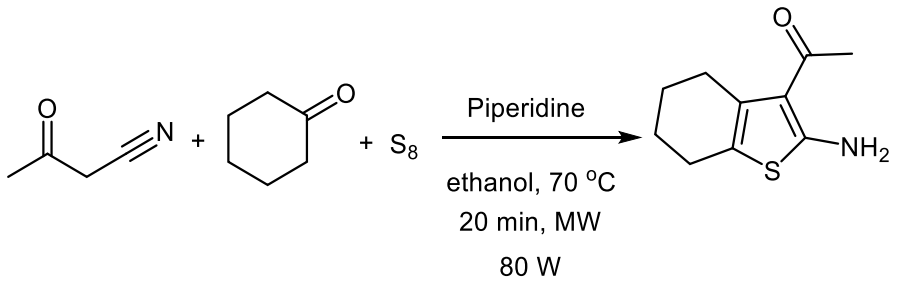
Scheme 20 Synthesis trial of 3-acetyl-2-aminoselenophene

1.2.3 Application of microwave assisted Gewald synthesis

Microwave assisted synthesis was tried to investigate the effect of this technique on the yield and to shorten the reaction time. Cyclohexanone **44** (1 mmol), activated nitrile

[36] Seck et al., "Synthesis of New Selenophene and Thiazole Analogues of the Tacrine Series," 2012.

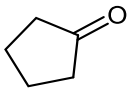
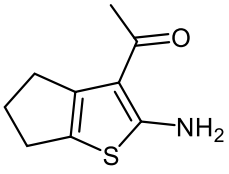
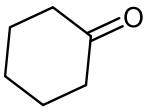
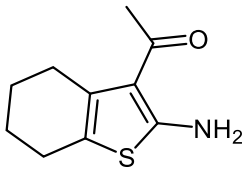
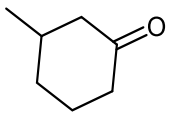
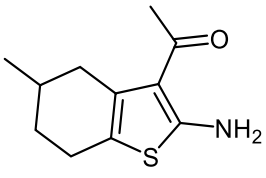
32 (1.2 mmol) and elemental sulphur (1.2 mmol) was dissolved in ethanol, 1.2 mmol of piperidine was used for catalyzing the reaction. The parameter of the apparatus was adjusted to be: temperature = 70 °C, (Pmax = 80 W) and the reaction time was 20 minutes (Scheme 21).[37] The reaction was done in open vessel, no improvement in yield was observed in comparison with the classic technique. The only advantage is shortening of the reaction time from 24 hours to 20 minutes, but the output scale was not practical.



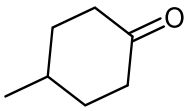
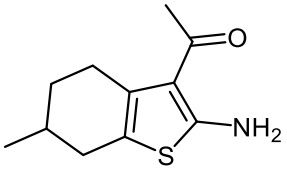
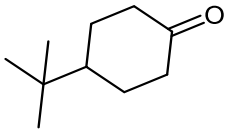
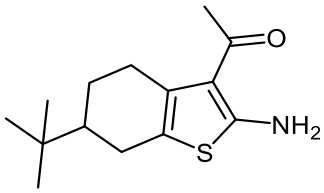
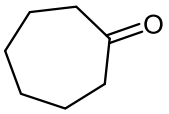
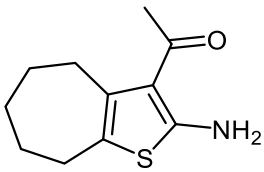
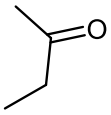
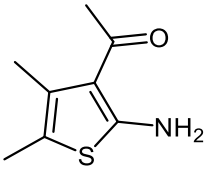
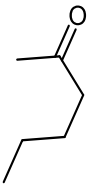
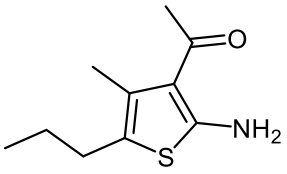
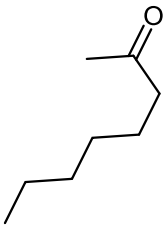
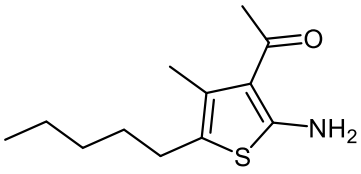
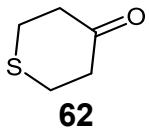
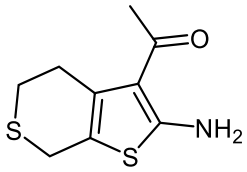
32 **44** **45**

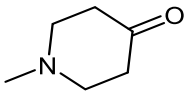
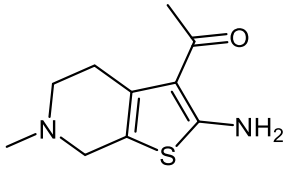
Scheme 21

Table 1 Products and yield of Gewald's reaction.

Ketone	Thiophenes	Yield
 **46**	 **47**	61%
 **44**	 **45**	58%
 **48**	 **49**	30%

[37] Germain Revelant et al., "Microwave-Assisted Synthesis of 5-Substituted 2-Aminothiophenes Starting from Arylacetaldehydes," *Synthesis* 2011, no. 18 (September 2011): 2935–40, doi:10.1055/s-0030-1261032.

 **50**	 **51**	28%
 **52**	 **53**	86%
 **54**	 **55**	32%
 **56**	 **57**	36%
 **58**	 **59**	30%
 **60**	 **61**	8%
 **62**	 **63**	72%

 **64**	 **65**	66%

1.2.4 Synthesis of 2-(methylthio)thiophene-3-carbonitrile derivatives

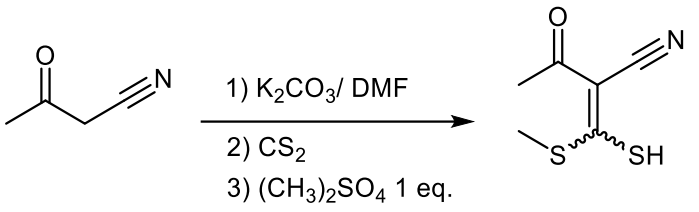
1.2.4.1 Synthesis of 2-(bis(methylthio)methylene)-3-oxobutanenitrile

Cyanoacetone **32** was an attractive subject as starting material to be involved in the multicomponent synthesis of functionalized thiophene in two step reactions. It contains active methylene group confined between cyano group and acetyl group, the direction of cyclization in the second step toward one of these two electron withdrawing groups was the key question of our synthesis.

It was prepared just a while before the 3-components reaction started by the way described before in Scheme 18.

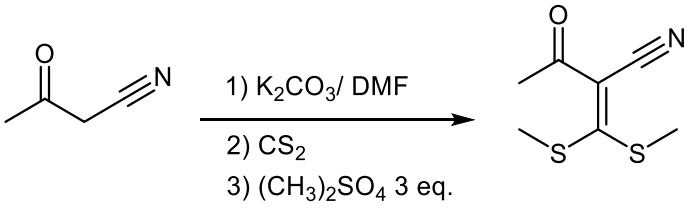
Afterward, it was dissolved in DMF with potassium carbonate and stirred for two hours in room temperature. Carbon disulfide (3 equivalents) was added and the reaction temperature was retained in room temperature for additional two hours. Finally, one equivalent of dimethyl sulfate was added and the reaction mixture was agitated for four hours, after treatment with ice and water, a product was obtained.

When this product was investigated by ^{1}H and ^{13}C NMR, the structure appeared to be (*E,Z*)-2-(mercapto(methylthio)methylene)-3-oxobutanenitrile **66** (Scheme 22), only one methyl group was added to one side. When the number of equivalent was increased to three equivalents and upon application of the same procedure, the desired product 2-(bis(methylthio)methylene)-3-oxobutanenitrile **67** was obtained as sole product (Scheme 23).



32 **66**

Scheme 22

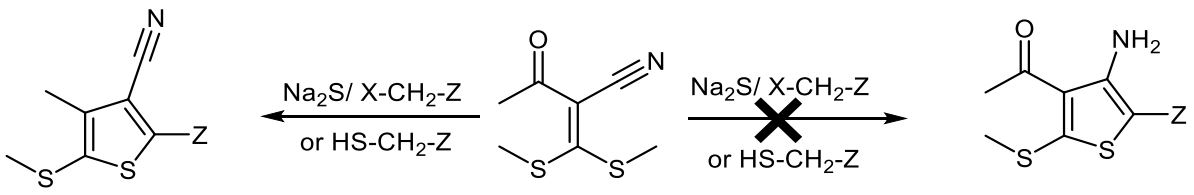


32 **67**

Scheme 23

1.2.4.2 Cyclization

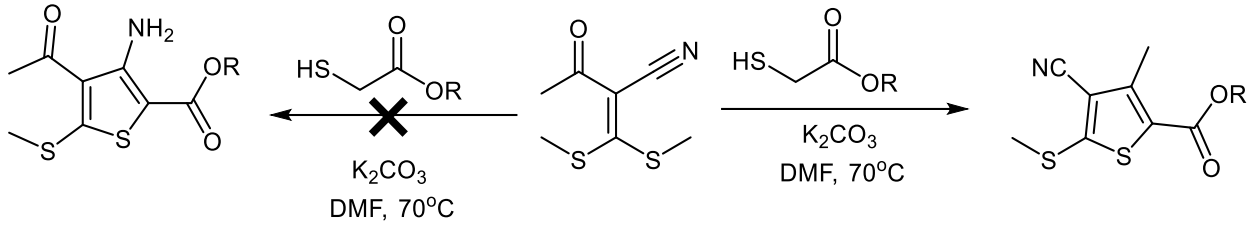
Two possibilities of cyclization were proposed; one of them is similar to what explained in Scheme 8, and acetylaminothiophene nucleus was predicted, or on the other side (Scheme 9) and in this case cyanothiophene was expected to be formed. Sodium sulfide was dissolved in DMF and the solution heated till 70 °C for dissolution of the salt, compound **67** was added and the solution was kept at stirring for one hour at 70 °C. Activated halide was added and after stirring for 30 minutes, potassium carbonate was introduced and the stirring was left for additional one hour at 70 °C. When the solution treated with water, a precipitate of thiophene was collected by filtration. Studying of the structure using NMR tools indicated the formation of compound **68** (Scheme 24).



68 **67** **69**

Scheme 24

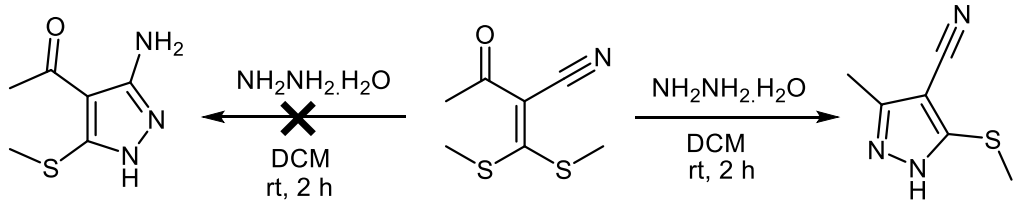
No traces of compound **69** were identified, replacement sodium sulfide and activated halide with thioglycolate did not lead to the other cyclization (Scheme 25), also changing of the catalytic base to DBU did not result in formation of compound **69** (Scheme 24).



70 **67** **71**

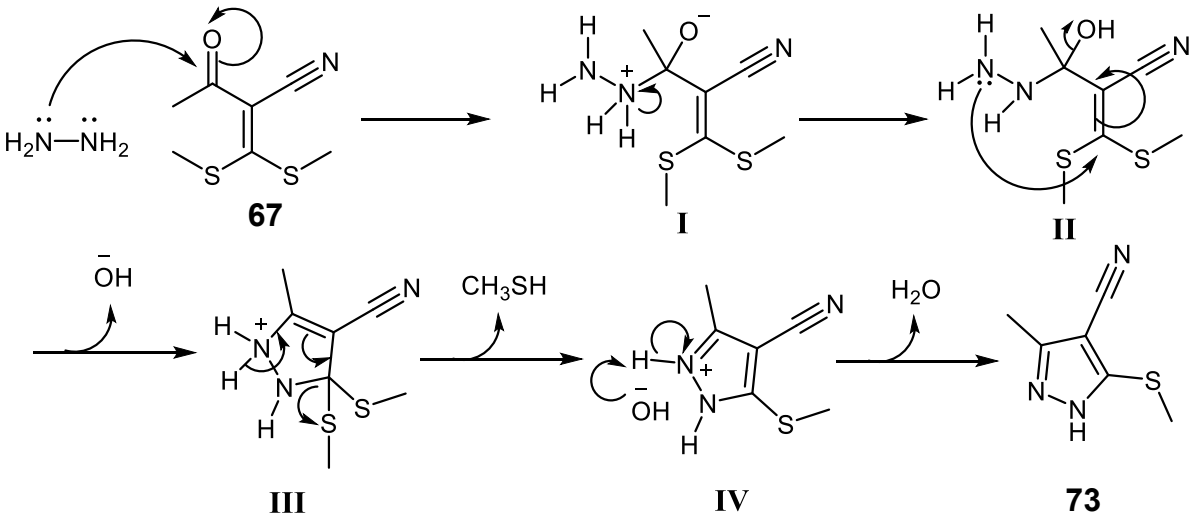
Scheme 25

The mode of cyclization of 2-(bis(methylthio)methylene)-3-oxobutanenitrile **67** was further explored by hydrazine hydrate to investigate the direction of the cyclization whether it is changing or not (Scheme 26).



72 **67** **73**

Scheme 26

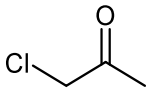
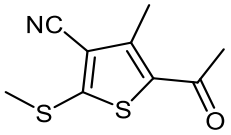
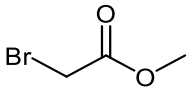
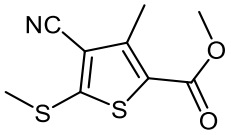
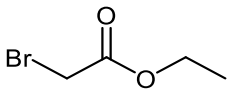
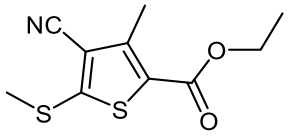
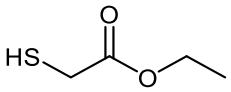
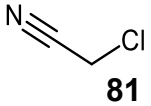
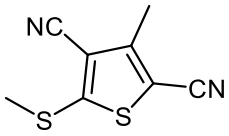


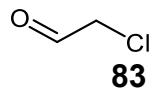
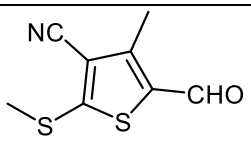
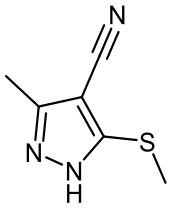
Scheme 27

Compound **67** was mixed with one equivalent of hydrazine hydrate in dichloromethane, at room temperature. The reaction mixture was stirred and followed by TLC. After the accomplishment of the reaction (ca 2 hours) the pyrazole **73** obtained had the same mode of ring closure as the only obtained product (Scheme 26) (Table 2).

The mechanism could be described by the nucleophilic attack of one nitrogen atom of hydrazine on the carbonyl carbon followed by another nitrogen attack on the carbon which restrained between two sulphur atoms for ring closure. This accompanied by delocalization of the double bond and followed by loss of water and methanethiol molecule to provide the final product **73** (Scheme 27).

Table 2 Products of the reaction between 2-(bis(methylthio)methylene)-3-oxobutanenitrile **67** and activated halide, thioglycolate and hydrazine hydrate

Reagent	Product	Yield
 **74**	 **75**	10%
 **76**	 **77**	36%
 **78**	 **79**	78%
 **80**		46%
 **81**	 **82**	44%

 **83**	 **84**	Traces
$NH_2NH_2.H_2O$	 **73**	98%

1.3 Conclusion

Gewald's procedure has not described before to produce 3-acetyl containing thiophene by three components method and the first synthesis of 3- acetyl-2-aminothiophene by using such way was introduced. Many trials were applied to produce varieties of this nucleus but only few examples of ketones were reactive. The sensitivity of cyanoacetone and rapid decomposition of it, may be one of description of the low reactivity of such kind of reaction. Yield of alicyclic ketones and their reactivity were observed to be higher than normal aliphatic one, which could be attributed to the free rotation of unchained ends of the aliphatic ketone may halt the ring closure.

Diketones and substituted or branched aliphatic ketones did not respond to the reaction. Assisted microwave synthesis was helpful only in decreasing the reaction time, but did not help in increasing the yield. Replacement elemental Sulphur with selenium and application of the reported procedure did not produce selenophene.

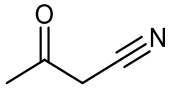
Ketene dithioacetal (2-(bis(methylthio)methylene)-3-oxobutanenitrile **67**) prepared from cyanoacetone was another option for synthesizing thiophene nucleus. The mode of cyclization of it was observed to be on the direction of carbonyl carbon and cyanothiophene was obtained, using hydrazine hydrate to produce pyrazole from same starting compound did not lead to any change in the pattern of cyclization. The necleophilic attack on carbonyl carbon end to formation of cyanopyrazole.

1.4 Experimental part

All solvents and reagents were purchased from commercial sources unless otherwise noted. Melting points were determined with a Büchi 530 digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using Me4Si as the internal standard. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High-resolution mass spectra were measured with a Micro-Tof-Q98 instrument in ESI mode. Column chromatography was performed using silica gel (60M, 0.04–0.063 mm). Thin-layer chromatography (TLC) was performed using silica gel plates (POLYGRAM SIL G/UV254, 0.20 mm), which were visualised under UV light.

Cyanoacetone (32)

(*E,Z*)-3-Aminocrotonitrile (10 g, 0.12 mol) was dissolved in 6N HCl (28.5 mL), and the solution was stirred and heated to 80 °C for 3 hours. The reaction mixture was cooled, extracted several times with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under *vacuo*.



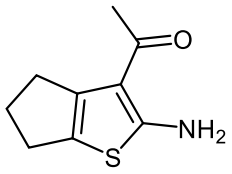
Yield: 5 g (53%); colourless liquid.

1H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 2 H), 2.28 (s, 3 H).

3-Acetyl-2-aminothiophene Derivatives; General Procedure

Carbonyl compound (0.025 mol) was added to freshly prepared cyanoacetone (0.03 mol) in either MeOH or EtOH (40 ml). Sublimed sulphur S_8 (0.03 mol) and piperidine (0.03 mol) were added and the mixture was stirred and heated to 55–65 °C for 24 h. Ice was then added and the formed precipitate was filtered under vacuum and washed with water. The obtained solid was crystallised from a suitable solvent, with the exception of 57 and 63, which were collected directly without further purification.

1-(2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-yl)ethanone (47)



Yield: 61%; brown solid (toluene); mp 230 °C

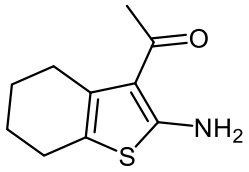
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.82 (s, 2 H), 2.92 – 2.87 (m, 2 H), 2.78 – 2.72 (m, 2 H), 2.44 – 2.38 (m, 2 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.7, 168.6, 141.0, 121.3, 112.2, 31.74, 29.1, 28.7, 27.3.

HRMS (ESI): *m/z* calcd for $[C_9H_{11}NOS + Na]^+$: 204.0454; found: 204.0464.

Anal Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 60.14; H, 6.10, N, 7,48; S, 17.25.

1-(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (45)



Yield: 58%; brown solid (toluene); mp 114-117 °C

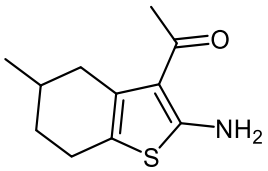
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.94 (s, 2 H), 2.74 – 2.67 (m, 2 H), 2.58 – 2.52 (m, 2 H), 2.42 (s, 3 H), 1.86 – 1.79 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.1, 163.9, 130.6, 117.6, 115.8, 30.7, 28.1, 24.7, 23.1, 22.9.

HRMS (ESI): *m/z* calcd for $[C_{10}H_{13}NOS + Na]^+$: 218.0610; found: 218.0602.

Anal Calcd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.17; O, 8.19; S, 16.42. Found: C, 61.85; H, 6.65, N, 6.86; S, 16.18.

1-(2-Amino-5-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (49)



Yield: 28%; greenish solid (Abs. ethanol); mp 180-182°C

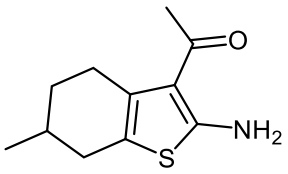
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (s, 2 H), 2.83 (dd, *J* = 15.6, 4.5 Hz, 1 H), 2.60 – 2.53 (m, 2 H), 2.42 (s, 3 H), 2.30 – 2.15 (m, 1 H), 2.01 – 1.76 (m, 2 H), 1.51 – 1.36 (m, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.0, 164.3, 130.6, 117.3, 115.7, 36.6, 31.0, 30.6, 29.3, 24.5, 22.1.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{15}NOS + Na]^+$: 232.0767; found: 232.0784.

Anal Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.84; H, 7.12; N, 6.53; S, 15.12.

1-(2-Amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3 yl)ethanone (51)



Yield: 28%; greenish solid (cyclohexane); mp 127 °C

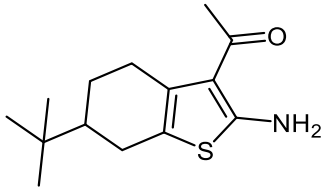
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.79 (s, 2 H), 2.85 – 2.76 (m, 1 H), 2.72 – 2.61 (m, 1 H), 2.61 – 2.54 (m, 1 H), 2.41 (s, 3 H), 2.21 – 2.12 (m, 1 H), 1.95 – 1.86 (m, 2 H), 1.47 – 1.35 (m, 1 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.0, 164.2, 130.2, 117.2, 115.6, 32.9, 31.3, 30.6, 29.2, 27.8, 21.4.

HRMS (ESI): *m/z* calcd for $[C_9H_{16}OS\text{-}H + Na]^+$: 232.0767; found: 232.0801.

Anal Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.61; H, 7.19; N, 6.88; S, 15.75.

1-(2-Amino-6-(tert-butyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (53)



Yield: 86%; beige-brown solid (cyclohexane); mp 155-158 °C

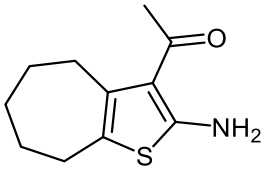
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (s, 1 H), 2.88 (ddt, *J* = 15.9, 4.7, 1.8 Hz, 1 H), 2.66 – 2.49 (m, 2 H), 2.40 (s, 3 H), 2.37 – 2.28 (m, 1 H), 2.07 – 2.00 (m, 1 H), 1.56 – 1.46 (m, 1 H), 1.40 – 1.28 (m, 1 H), 0.94 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.0, 164.2, 130.6, 118.3, 115.5, 44.9, 32.4, 30.5, 29.2, 27.2, 26.3, 24.7

HRMS (ESI): *m/z* calcd for $[C_{14}H_{21}NOS + Na]^+$: 274.1207; found: 274.1236.

Anal Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57; S, 12.76. Found: C, 66.41; H, 8.42; N, 5.55; S, 13.03.

1-(2-Amino-5,6,7,8-tetrahydro-4Hcyclohepta[*b*]thiophen-3 yl)ethanone (55)



Yield: 32%; brown solid (toluene); mp 129-130 °C

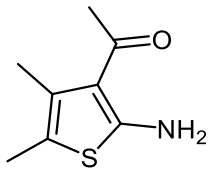
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.62 (s, 2 H), 2.87 – 2.79 (m, 2 H), 2.61 – 2.59 (m, 2 H), 2.43 (s, 1 H), 1.89 – 1.83 (m, 2 H), 1.75 – 1.64 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.6, 161.4, 136.1, 121.1, 118.5, 31.7, 31.0, 29.8, 28.4, 27.6, 26.6.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{15}NOS + Na]^+$: 232.0767; found: 232.0778.

Anal Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; O, 7.64; S, 15.32. Found: C, 62.99; H, 7.13; N, 7.11; S, 15.08.

1-(2-Amino-4,5-dimethylthiophen-3-yl)ethanone (57)



Yield: 36%; brown solid; mp 154-157 °C

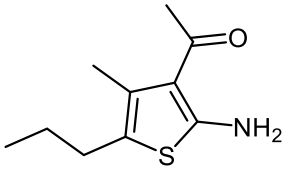
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 (s, 2 H), 2.46 (s, 3 H), 2.23 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.4, 163.1, 128.4, 117.0, 113.8, 30.6, 15.8, 12.6.

HRMS (ESI): *m/z* calcd for $[C_8H_{11}NOS + H]^+$: 170.634; found: 170.0633; calcd for $[C_8H_{11}NOS+Na]+$: 192.0454; found: 192.0456.

Anal Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28; S, 18.95. Found: C, 56.65; H, 6.41; N, 9.07; S, 19.07.

1-(2-Amino-4-methyl-5-propylthiophen-3-yl)ethanone (59)



Yield: 30%; brown solid (cyclohexane); mp 113-115 °C

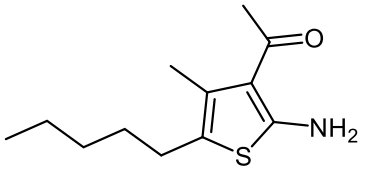
1H NMR (400 MHz, CDCl3) δ = 6.89 (brs, 2 H), 2.56 (t, *J* = 7.6 MHz, 2 H), 2.47 (s, 3 H), 2.24(s, 3 H), 1.57 (m, 2 H), 0.96 (t, *J* = 7.2, 3 H).

13C NMR (100 MHz, CDCl3) δ = 194.4, 163.3, 128.0, 120.0, 13.6, 117.0, 30.6, 29.2, 24.4, 15.86.

HRMS (ESI): *m/z* calcd for $[C_{10}H_{15}NOS + Na]^+$: 220.0767; found: 220.0781.

Anal Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.55; H, 7.58; N, 7.20; S, 16.70.

1-(2-Amino-4-methyl-5-pentylthiophen-3-yl)ethanone (61)



Yield: 8%; greenish solid (cyclohexane); mp 112-113 °C

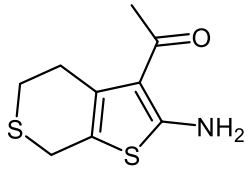
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.59 – 2.53 (m, 2 H), 2.46 (s, 3 H), 2.24 (s, 3 H), 1.58 – 1.51 (m, 2 H), 1.39 – 1.28 (m, 4 H), 0.92 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.4, 163.4, 127.9, 120.3, 117.04, 31.3, 30.9, 27.3, 22.5, 15.8, 14.02.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{19}NOS\text{-}H + Na]^+$: 247.0993; found: 247.1001.

Anal Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22; S, 14.23. Found: C, 64.01; H, 8.34; N, 6.17; S, 14.35.

1-(2-Amino-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-yl)ethanone (63)



Yield: 72% brownish solid; mp 167-170 °C

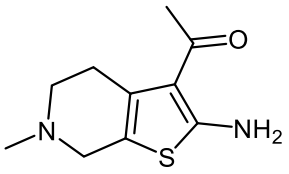
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.96 (s, 2 H), 3.62 (t, *J* = 1.6 Hz, 2 H), 3.02 (ddd, *J* = 5.8, 4.6, 1.2 Hz, 2 H), 2.93 (t, *J* = 5.5 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.9, 163.1, 130.5, 116.2, 113.6, 31.0, 29.8, 26.1, 25.4.

HRMS (ESI): *m/z* calcd for $[C_9H_{11}NOS_2 + H]^+$: 214.0355; found: 214.0353.

Anal Calcd for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20; N, 6.57; S, 30.06. Found: C, 50.35; H, 5.16; N, 6.75; S, 29.44.

1-(2-Amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)ethanone (65)



Yield: 66% black solid (dichloromethane/methanol); mp 149-151 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (s, 2 H), 3.24 (s, 2 H), 2.73 (t, *J* = 5.7 Hz, 2 H), 2.57 (t, *J* = 5.7 Hz, 2 H), 2.31 (s, 3 H), 2.29 (s, 3 H).

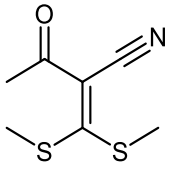
13C NMR (100 MHz, DMSO-d_6): δ = 192.2, 164.6, 113.3, 128.5, 113.21, 53.0, 52.0, 45.1, 30.1, 27.7.

HRMS (ESI): *m/z* calcd for $[C_{10}H_{14}N_2OS + H]^+$: 211.0900; found: 211.0891.

Anal Calcd for $C_{10}H_{14}N2OS.H_2O$: C, 52.54; H, 7.06; N, 12.25; S, 14.02. Found: C, 52.48; H, 7.01; N, 12.62; S, 14.04.

2-(bis(methylthio)methylene)-3-oxobutanenitrile (67)

Freshly prepared cyanoacetone (3.5 g, 0.042 mol) was dissolved with K_2CO_3 (5.8 g, 0.042 mol) in 40 ml DMF, the solution was stirred for two hours in room temperature. Carbon disulfide (9.5 g, 0.13 mol) was added while the reaction mixture was stirred in room temperature for another two hours. Afterward, dimethyl sulfate (15.9 g, 0.13 mol) was added and the stirring continued till 4 hours, after treatment with ice and water, a product was obtained as precipitate, filtered under *vacuo* and crystallized from cyclohexane (5.3 g, yield 72%).



Yield: 72%; brown solid (cyclohexane); mp 60 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.80 (s, 3 H), 2.60 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.1, 181.5, 118.3, 106.2, 30.9, 21.1, 18.9.

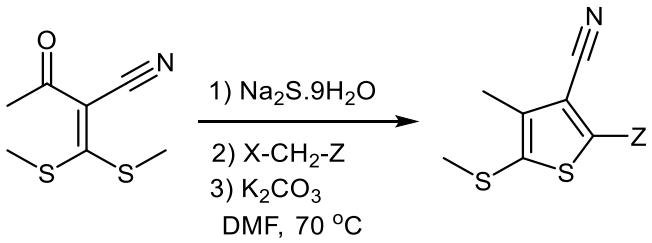
HRMS (ESI): *m/z* calcd for $[C_7H_9NOS_2 + H]^+$: 188.0198; found: 188.0226. For $[C_7H_9NOS_2 + Na]^+$: 210.0018; found: 210.0069.

Anal Calcd for $C_7H_9NOS_2$: C, 44.89; H, 4.84; N, 7.48; S, 34.24. Found: C, 45.03; H, 4.86; N, 7.40; S, 34.23.

4-Methyl-2-(methylthio)thiophene-3-carbonitrile derivatives, general procedure

Method A

Compound **67** (20 mmol) and $Na_2S.9H_2O$ (20 mmol) was dissolved in 40 ml DMF and the solution was stirred at 70 °C for one hour. Activated halide (40 mmol, 2 equivalent) was added and after stirring for 30 minutes at 70 °C, potassium carbonate (20 mmol) was introduced and the stirring was left for additional one hour at 70 °C. When the solution quenched with ice and water, solid precipitate of thiophene was appeared and collected by filtration through vacuum.

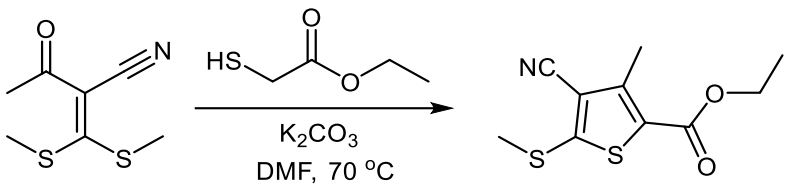


67 **68**

Scheme 28

Method B

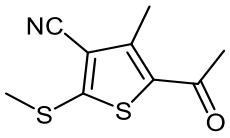
Compound **67** (20 mmol) was dissolved in 40 ml DMF, ethyl thioglycolate **80** (20 mmol) and potassium carbonate (20 mmol) were added to the solution which stirred at 70 °C for three hour. Precipitate of the product was formed by decomposition of the reaction solution in ice and water, it was filtered under vacuum, washed by water and dried to give compound **79**; yield, 46%



67 **79**

Scheme 29

5-Acetyl-4-methyl-2-(methylthio)thiophene-3-carbonitrile (75)

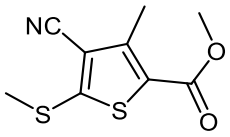


Yield: 10%

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.71 (s, 3 H), 2.64 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.9, 157.5, 145.7, 136.1, 113.3, 112.3, 29.6, 18.4, 15.8.

Methyl 4-cyano-3-methyl-5-(methylthio)thiophene-2-carboxylate (77)



Yield: 36%; beige-brown solid; mp 122 °C

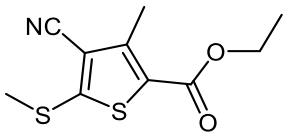
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.90 (s, 3 H), 2.70 (s, 3 H), 2.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.9, 155.7, 146.5, 125.1, 113.1, 112.8, 62.4, 18.9, 14.9.

HRMS (ESI): *m/z* calcd for $[C_9H_9NO_2S_2 + H]^+$: 228.0147; found: 228.0174. For $[C_9H_9NO_2S_2 + Na]^+$: 249.9967; found: 249.9992.

Anal Calcd for $C_9H_9NO_2S_2.3\%H_2O$: C, 46.13; H, 4.20; N, 5.97; S, 27.36. Found: C, 47.56; H, 3.97; N, 6.18; S, 26.09.

Ethyl 4-cyano-3-methyl-5-(methylthio)thiophene-2-carboxylate (79)



Yield: 78% (method A), 46% (method B); yellow solid; mp 114 °C.

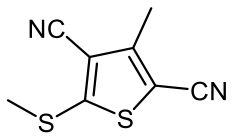
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.36 (q, *J* = 7.1 Hz, 2 H), 2.70 (s, 3 H), 2.63 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.7, 147.5, 126.1, 113.4, 111.8, 61.4, 18.5, 14.9, 14.3.

HRMS (ESI): *m/z* calcd for $[C_{10}H_{11}NO_2S_2 + H]^+$: 242.0304; found: 242.0344. For $[C_{10}H_{11}NO_2S_2 + Na]^+$: 264.0123; found: 264.0156.

Anal Calcd for $C_{10}H_{11}NO_2S_2.2\%H_2O$: C, 48.77; H, 4.72; N, 5.68; S, 26.04. Found: C, 48.88; H, 4.56; N, 5.75; S, 25.51.

3-Methyl-5-(methylthio)thiophene-2,4-dicarbonitrile (82)



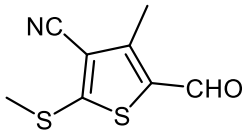
Yield: 44%; brown solid; mp 122 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.63 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4, 151.4, 112.6, 112.1, 110.5, 104.6, 18.9, 15.1.

HRMS (ESI): *m/z* calcd for $[C_8H_6N_2S_2 + H]^+$: 195.0045; found: 195.0075.

5-Formyl-4-methyl-2-(methylthio)thiophene-3-carbonitrile (84)



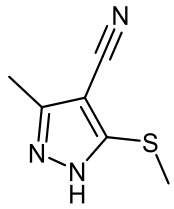
Yield: traces; solid

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.81 (s, 1 H), 2.64 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.7, 163.0, 162.5, 148.9, 135.9, 112.7, 18.3, 13.3.

3-Methyl-5-(methylthio)-1*H*-pyrazole-4-carbonitrile (73).

Compound **67** (0.2 g, 1.14 mmol) was mixed with hydrazine hydrate (0.07 g, 1.14 mmol) in dichloromethane at room temperature. The reaction mixture was stirred and followed by TLC. After 2 hours the pyrazole **73** was obtained by extraction using ethyl acetate and dried by Na_2SO_4 *anhyd* and concentrated under vacuum. The product was purified by silica gel column chromatography (EtOAc–cyclohexane, 1:3) for maximum purity.



Yield: 96%; white solid; mp 45 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.59 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.0, 149.0, 113.3, 93.2, 16.0, 11.0.

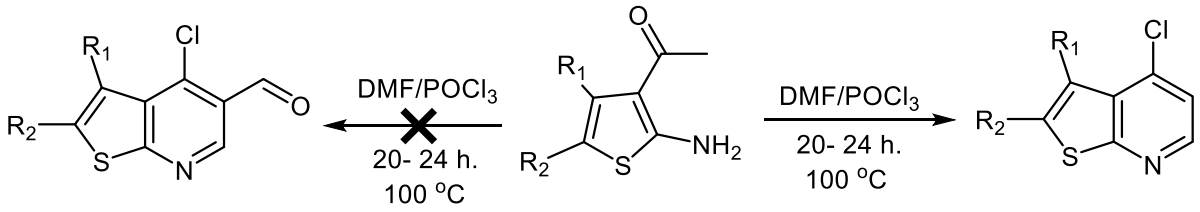
Anal Calcd for $C_6H_7N_3S.1.5\%H_2O$: C, 46.56; H, 4.67; N, 27.15; S, 20.72. Found: C, 46.21; H, 4.40; N, 27.16; S, 20.15.

Chapter 2 - Reactivity of 3-acetyl-2-aminothiophenes in reaction with Vilsmeier-Haack reagent

Résumé chapitre 2: Réactivité des 3-acétyl -2-aminothiophènes par rapport au réactif de Vilsmeier-Haack.

Comme l'accès aux 3-acétyl 2-amino thiophènes est possible par la méthode développée, il est intéressant d'étudier la réactivité de ce type de composé par rapport aux 2 fonctions présentes et à leur proximité. Un certain nombre de réactions a été décrit sur des amino-acétyl-thiophènes obtenus par d'autres méthodes. Parmi ces réactions, la diazotation, la condensation avec des isocyanates et des béta-cétoesters, la réaction de Friedländer ont été étudiées. Dans les 3 derniers cas, la condensation conduit à des systèmes de type quinoléinique. Nous nous sommes intéressés à la réaction de Vilsmeier-Haack-Arnold réalisée aux dépens de nos composés. En effet cette réaction devait conduire à des dérivés quinoléiniques si on compare aux o-amino acétophénones qui donnent ce résultat.

Le réactif de Vilsmeier-Haack a été utilisé sur nos dérivés. La mise au point des conditions a permis la synthèse de chloro-thiénopyridines et non celle de chloro-thiénopyridines carbaldéhydes comme cela se passe pour les o-amino-acétophénones.



2 Reactivity of 3-acetyl-2-aminothiophenes in reaction with Vilsmeier-Haack reagent.

2.1 Introduction

The neighbourhood of the acetyl and amino group on the skeleton of the annulated thiophenes was anticipated to make them reactive. The main motivation was to investigate the impact of thiophene ring on the behaviour and reactivity of the compounds toward certain reagents involving both functional group.

2.1.1 Chemistry of 3-acetyl-2-aminothiophenes derivative

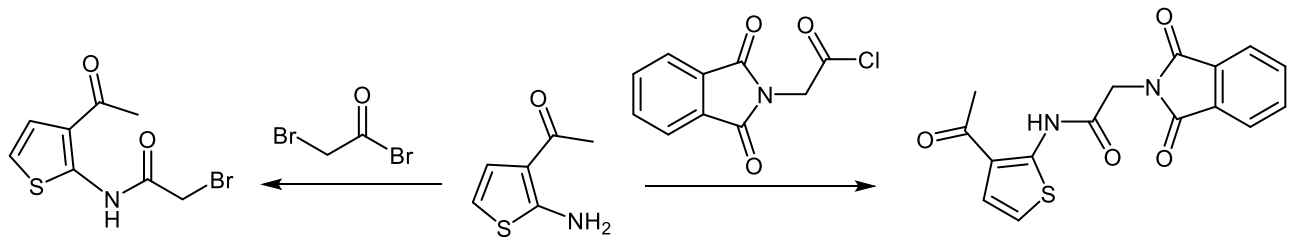
There are few examples of 3-acetyl-2-aminothiophenes reactions were reported in the literatures, some of them were carried out on the amino group or on both acetyl and amino group for quninoline or thienopyrimidine synthesis by cyclization.

2.1.1.1 Reaction of amino group

2.1.1.1.1 Reaction with acetyl halogenides

Some acetamide were prepared by reaction with different types of acetyl halides (Scheme 30). The starting compounds **86** in this reaction were prepared by the method mentioned in

Scheme 15.[38]



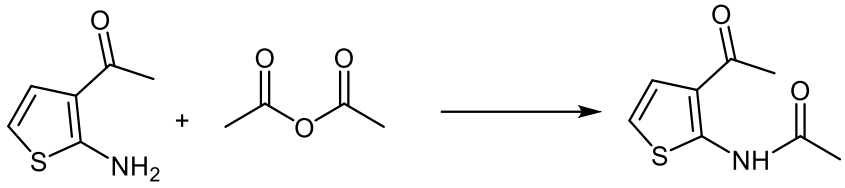
85 **86** **87**

Scheme 30

[38] Gernot A. Eller and Wolfgang Holzer, "Synthesis and Detailed Spectroscopic Characterization of Two Novel *N*-(3-acetyl-2-thienyl)acetamides," *Molbank* 2006, no. 6 (December 1, 2006): M520, doi:10.3390/M520.

2.1.1.1.2 Acetylation

Amino group reacted with acetic anhydride by the well-known procedure, to form acetylated analogue **89** (Scheme 31).[39]

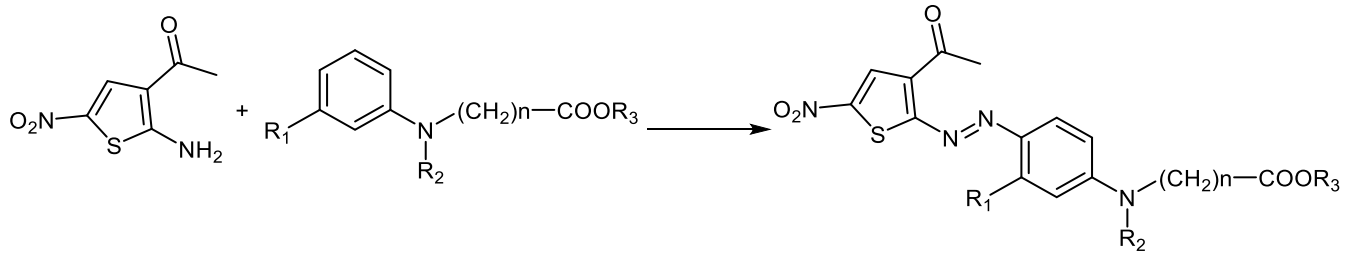


86 **88** **89**

Scheme 31

2.1.1.1.3 Azo coupling

Some red-light blue azo disperse dyes were prepared by azo coupling between 2-amino-3-acetyl-5-nitrothiophene and compounds **91** (Scheme 32).[40]



90 **91** **92**

Scheme 32

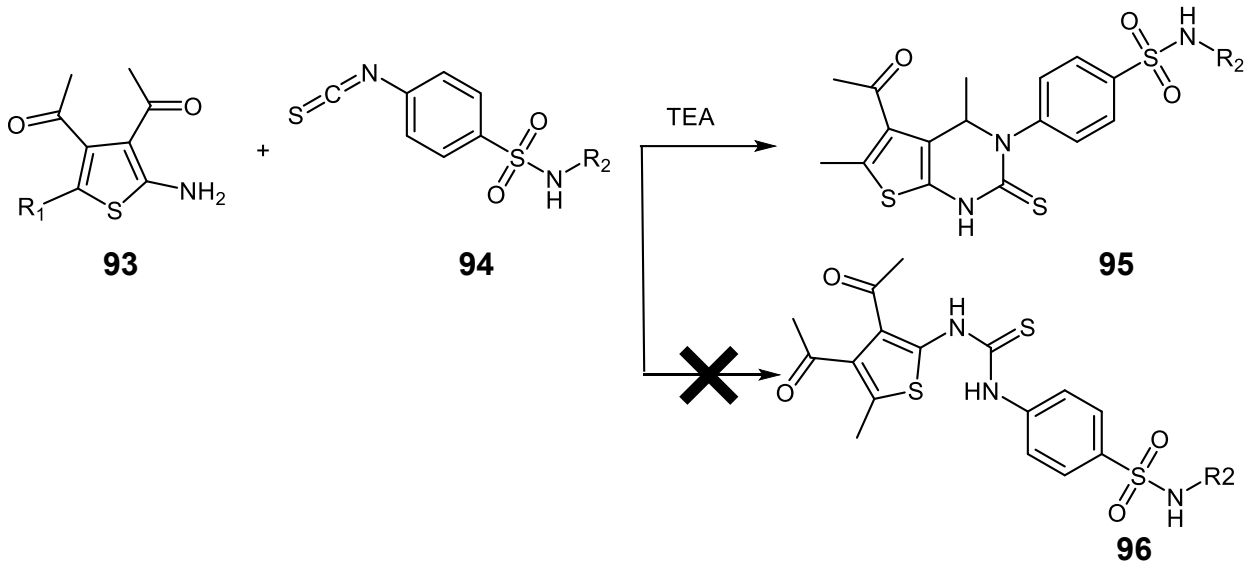
[39] Eller and Holzer, "First Synthesis of 3-Acetyl-2-Aminothiophenes Using the Gewald Reaction."

[40] Haiyu Li, Red-light blue azo disperse dye with high color development strength and preparation method therefor, CN105238094 (A), issued January 13, 2016.

2.1.1.1.4 Cyclisation

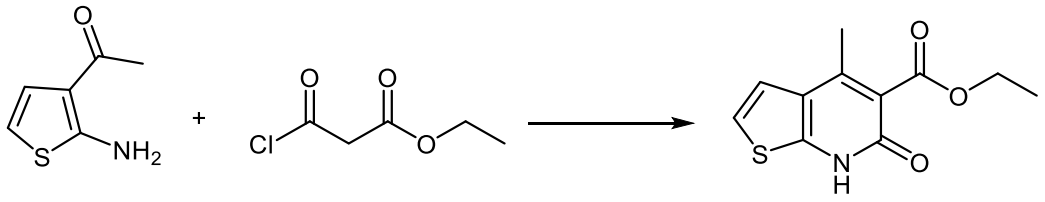
2.1.1.1.4.1 Reaction with isothiocyanate

Functionalized thiophene **93** reacted with of isothiocyanato sulfonamide derivatives **94** and produced thienopyrimidine **95** derivative instead of the other possibility **96** (Scheme 33).[41]



Scheme 33

2.1.1.1.4.2 Reaction with β-keto ester



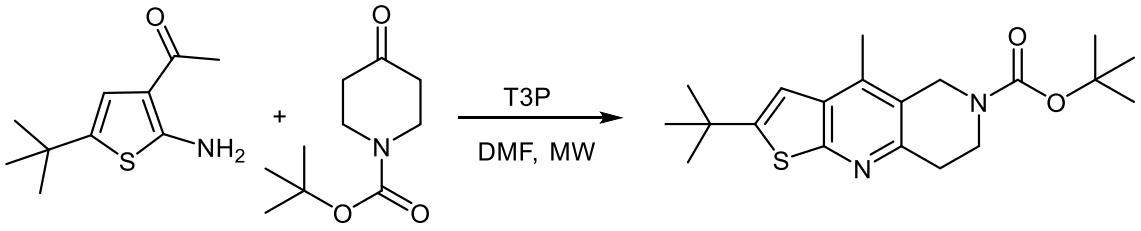
Scheme 34

[41] Hala M. Aly, "Synthesis and Antitumor Activity of Some Novel Pyrazole and Thienopyrimidine Derivatives," *Phosphorus, Sulfur, and Silicon and the Related Elements* 185, no. 1 (December 29, 2009): 211–21, doi:10.1080/10426500902758410.

3-Acetyl-2-aminothiophenes **86** underwent cyclization when reacted with β-keto ester **97** to produce the qunioline analogues **98** (Scheme 34).[42]

2.1.1.1.4.3 Friedländer cyclization

Propylphosphonic anhydride (T3P®) was used as catalytic agent in condensation between 1-(2-amino-5-(*tert*-butyl)thiophen-3-yl)ethan-1-one **99** and Boc protected piperidin-4-one **100**, by Friedländer reaction and quinolone **101** was obtained (Scheme 35).[43]



99 **100** **101**

Scheme 35

2.1.2 Vilsmeier-Haack reaction

Vilsmeier–Haack reaction is very practical method for versatile synthetic purposes. [44] The Vilsmeier–Haack reagent ($POCl_3$/DMF) has been widely used in formylation, chlorination and cyclisation processes.[45]

2.1.2.1 Formylation

Vilsmeier–Haack reaction was initially established for formylation purposes of activated aromatic compounds (Scheme 36).[46]

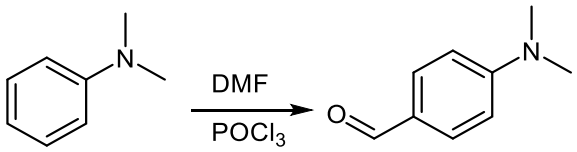
[42] Sven KUHNERT et al., United States Patent Application: 0140148478 -Heteroquinoline-3-Carboxamides As Kcnq2/3 Modulators, 20140148478, issued A1.

[43] John Kallikat Augustine, Agnes Bombrun, and Srinivasa Venkatachaliah, "An Efficient Catalytic Method for the Friedländer Annulation Mediated by Peptide Coupling Agent Propylphosphonic Anhydride (T3P®)," *Tetrahedron Letters* 52, no. 50 (December 14, 2011): 6814–18, doi:10.1016/j.tetlet.2011.10.048.

[44] A. Vilsmeier and A. Haack, "Über Die Einwirkung von Halogenphosphor Auf Alkyl-Formanilide. Eine Neue Methode Zur Darstellung Sekundärer Und Tertiärer *P* -Alkylamino-Benzaldehyde," *Berichte Der Deutschen Chemischen Gesellschaft (A and B Series)* 60, no. 1 (January 12, 1927): 119–22, doi:10.1002/cber.19270600118.

[45] Weike Su et al., "Recent Progress in the Use of Vilsmeier-Type Reagents," *Organic Preparations and Procedures International* 42, no. 6 (November 12, 2010): 503–55, doi:10.1080/00304948.2010.513911.

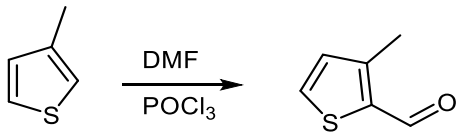
[46] Vilsmeier and Haack, "Über Die Einwirkung von Halogenphosphor Auf Alkyl-Formanilide. Eine Neue Methode Zur Darstellung Sekundärer Und Tertiärer *P* -Alkylamino-Benzaldehyde."



102 **103**

Scheme 36

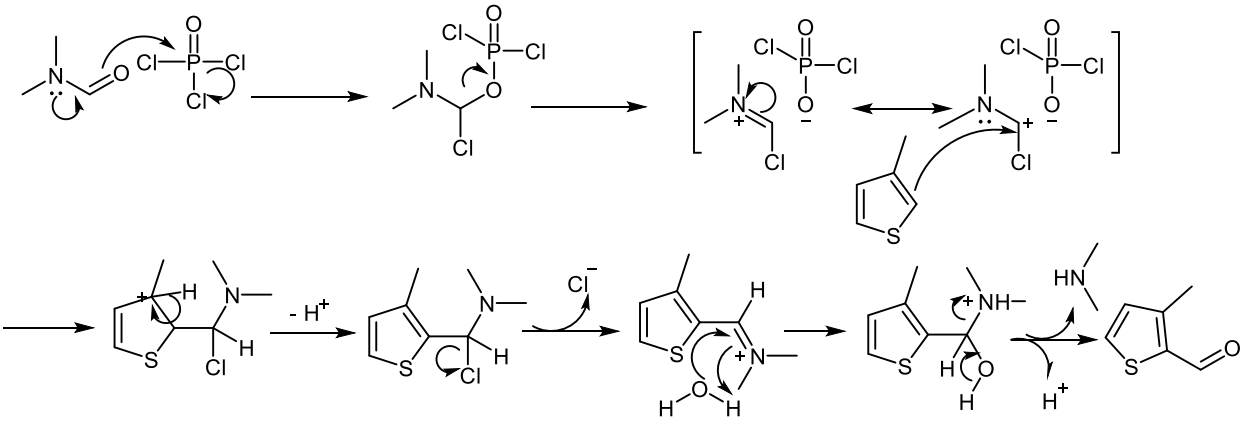
It used also for formylation of the aromatic heterocycles, as in the next example (Scheme 37), in which 3-methylthiophene **104** gave 3-methylthiophene-2-carbaldehyde **105** as major product (Scheme 37).[47]



104 **105**

Scheme 37

2.1.2.1.1 Mechanism of formylation[48]



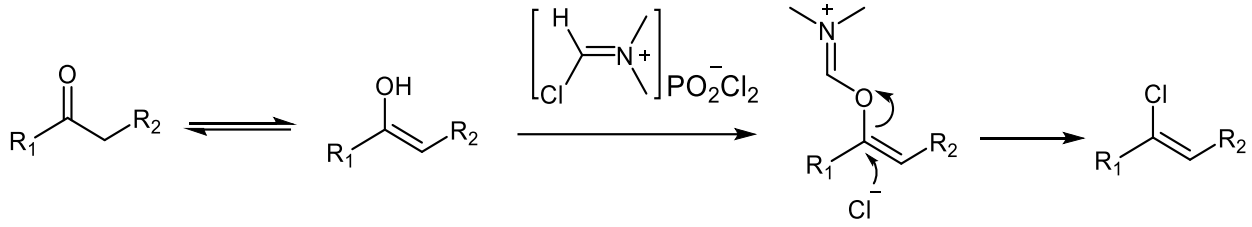
Scheme 38

[47] Otto Meth-Cohn and Mark Ashton, "Regioselective Electrophilic formylation—3-Substituted Thiophenes as a Case Study," *Tetrahedron Letters* 41, no. 15 (April 8, 2000): 2749–52, doi:10.1016/S0040-4039(00)00254-9.

[48] Gurnos Jones and Stephen P. Stanforth, "The Vilsmeier Reaction of Non-Aromatic Compounds," in *Organic Reactions* (John Wiley & Sons, Inc., 2004).

2.1.2.2 Chlorination

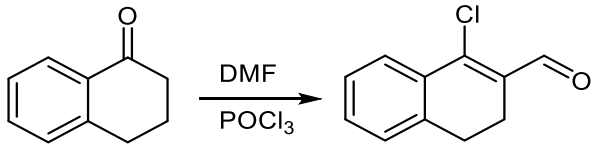
Oxygen of carbonyl compound could be replaced by chlorine atom *via* electrophilic attack of VH reagent (Scheme 39).[49]



Scheme 39

2.1.2.3 Chloroformylation

Ketones could react with VH reagent to yield β-chloroacrolein[50] (Scheme 40) (another example of this sort of reaction was described within chapter one in thiophene synthesis introduction in Scheme 4.



106 **107**

Scheme 40

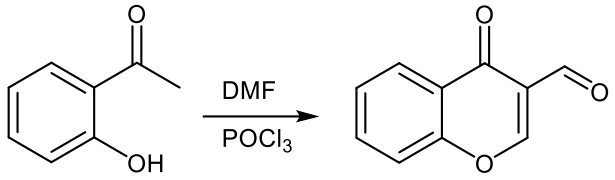
2.1.2.4 Cyclisation

The preparation of 3-formylchromone **109** from *o*-hydroxyacetophenone **108** (Scheme 41) and 3-formylquinoline **111** from *o*-aminoacetophenone **110**

[49] Annamaria Lilienkampf, Mikael P. Johansson, and Kristiina Wähälä, "(Z)-1-Aryl-1-Haloalkenes as Intermediates in the Vilsmeier Haloformylation of Aryl Ketones," *Organic Letters* 5, no. 19 (September 18, 2003): 3387–90, doi:10.1021/ol034914c; Su et al., "Recent Progress in the Use of Vilsmeier-Type Reagents"; A. F. Mironov et al., "A New, Convenient Synthesis of Pyrrolylacetylenes," *Synthesis* 1979, no. 07 (1979): 533–35, doi:10.1055/s-1979-28749.

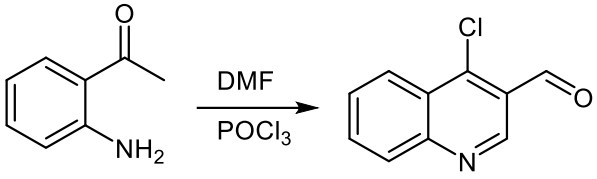
[50] Arnold and Žemlička, "Synthetische Reaktionen von Dimethylformamid IV. Darstellung von β-Chlorvinylaldehyden Aus Carbonylverbindungen"; G. Jagath Reddy et al., "Synthesis of Pyrazolo[1,5-*a*]pyrimido[4,3-*d*] Benzopyrans and 2-Pyrazolo[1,5-*a*]pyrimidinylphenols from the Reaction of 5(3)-Amino Pyrazoles," *Heterocyclic Communications* 9, no. 5 (2011): 453–456, doi:10.1515/HC.2003.9.5.453.

(Scheme 42) through such reactions in one step starting, was reported.[51]



108 **109**

Scheme 41



110 **111**

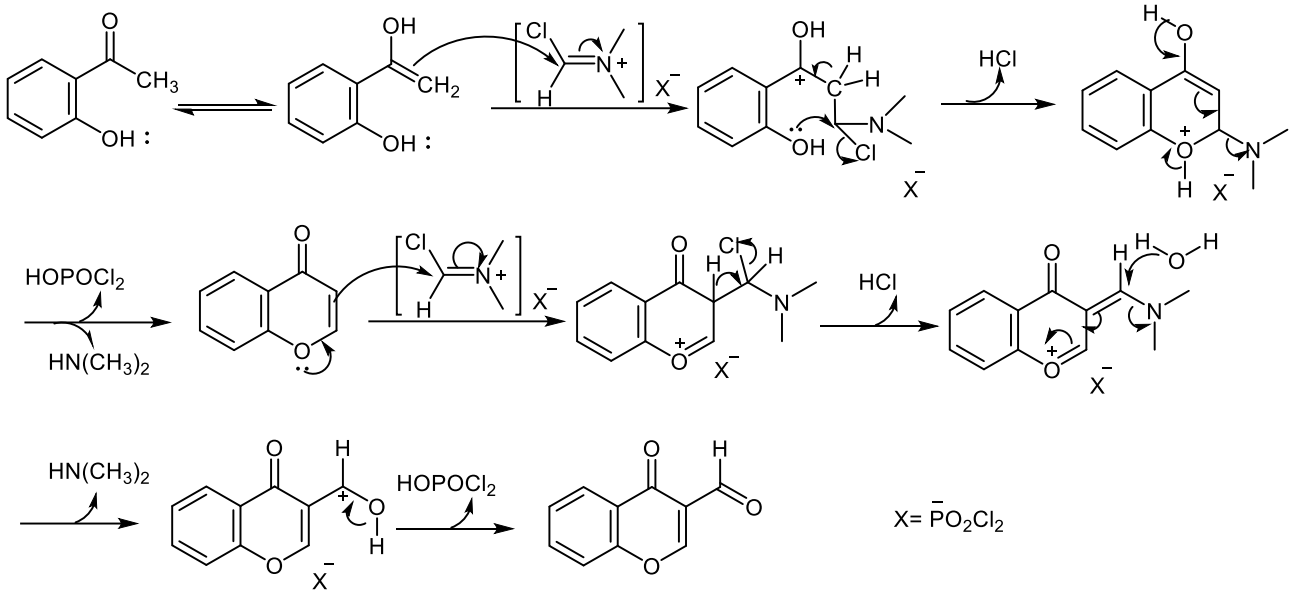
Scheme 42

2.1.2.4.1 Mechanism of cyclization

Two attacks of VH reagent are assumed to happen. Firstly, the enol form acts as nucleophilic and linked to the carbon of the iminium ion, one HCl moiety left and after intramolecular delocalization of the double bond, the lone pair of electrons of the hydroxyl group neutralize the positive charge of the carbon atom which results in ring closure. One molecule of phosphorodichloridic acid and dimethyl amine leaves and neutral molecule is obtained. The double bond of the last intermediate spontaneously attacks another molecule of the iminium salt, after losing HCl and dimethyl amine respectively, the product is hydrolyzed by water molecule and phosphorodichloridic acid separated (Scheme 43).[52]

[51] Horst Harnisch, "Chromon-3-Carbaldehyde," *Justus Liebigs Annalen Der Chemie* 765, no. 1 (January 3, 1973): 8–14, doi:10.1002/jlac.19727650103; Akira Nohara, Tomonobu Umetani, and Yasushi Sanno, "A Facile Synthesis of Chromone-3-Carboxaldehyde, Chromone-3-Carboxylic Acid and 3-Hydroxymethylchromone," *Tetrahedron Letters* 14, no. 22 (January 1973): 1995–98, doi:10.1016/S0040-4039(01)96102-7; Carla I Nieto et al., "An Experimental and Theoretical NMR Study of NH-Benzimidazoles in Solution and in the Solid State: Proton Transfer and Tautomerism," *Beilstein Journal of Organic Chemistry* 10 (July 16, 2014): 1620–29, doi:10.3762/bjoc.10.168.

[52] K. C Rajanna et al., "Kinetics and Mechanism of Vilsmeier-Haack Synthesis of 3-Formyl Chromones Derived from O-Hydroxy Aryl Alkyl Ketones: A Structure Reactivity Study," *Tetrahedron* 52, no. 10 (March 4, 1996): 3669–82, doi:10.1016/0040-4020(96)00043-9.



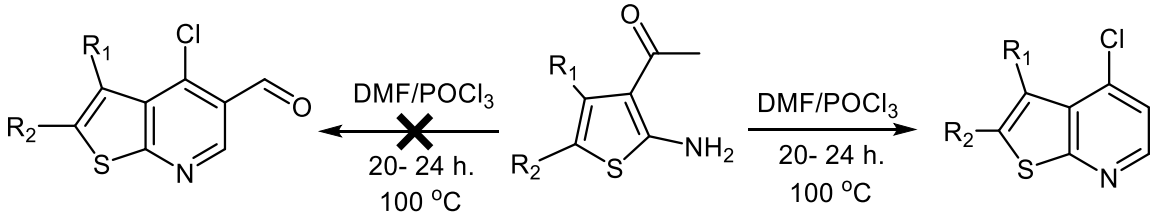
Scheme 43

2.2 Results and discussion

Vilsmeier–Haack–Arnold reaction was applied to achieve the cyclisation of 3-acetyl-2-aminothiophenes which prepared by Gewald's reaction. This step was inspired from cyclization of *o*-hydroxyacetophenone **108** and *o*-aminoacetophenone **110**, which were previously mentioned in Scheme 41 and Scheme 42. The impact of replacement of a benzene ring with thiophene in aforementioned cyclisation has not been investigated before. To study this reaction, we decided to use the 3-acetyl-2-amino thiophene, as a starting material. The influence of the thiophene nucleus on the reaction is clear (

Scheme **44**).

Several trials were applied to achieve the cyclisation, optimization of reaction conditions; temperature, time of the reaction, number of Vilsmeier–Haack reagent equivalents, mode of addition and the treatment of the reaction mixture at the end of the reaction was very critical and seen to be effective on the occurrence of the reaction, sort of the products and the yield.



112 **41** **113**

Scheme 44

2.2.1 Reaction temperature

By working in the reported conditions of 60 °C for five hours,[53] an unknown product was separated as a major component. Increasing the time of the reaction did not help. When the temperature was elevated to 100 °C for five hours, a mixture of the desired compound and an unknown by-product were obtained.

2.2.2 Time of the reaction

After adjustment of the temperature to be 100 °C, five hours of reaction working did not help to get the desired compound exclusively. Increasing the time made no difference in the result.

2.2.3 Number of the Vilsmeier–Haack reagent of equivalents

The number of equivalents of the VH reagent was found to have great influence upon the completion of the reaction. Using large excess of the reagent, caused the treatment of the reaction with ice and water to be very violent and exothermic due to presence of great extent of unreacted $POCl_3$. Decreasing the number of equivalents down certain limit gave uncomplete transformation.

2.2.4 Mode of reagent addition

The mode of addition was also found to govern both the type of product formed and the yield. Addition of the reagent over seven hours found to be the best solution to

[53] Nieto et al., "An Experimental and Theoretical NMR Study of NH-Benzimidazoles in Solution and in the Solid State."

maximize the yield of the required product and to decrease the undefined product to the minimum.

In conclusion, addition of the reagent over seven hours at 100 °C then stirring the reaction mixture overnight at the same temperature appeared to be the best reaction conditions.. The reaction followed by TLC, and mostly the starting material was consumed between 20 to 24 hours. The reaction mixture was treated with ice and water, pH of the reaction adjusted to neutral by ammonium acetate. The reaction mixture was extracted with EtOAc several times and the residue was adsorbed on silica and the product was obtained in pure form after running of flash silica gel column chromatography (EtOAc–cyclohexane, 1:9). Recrystallization of all products was done by mixture of (MeOH–H_2O, 1:1).

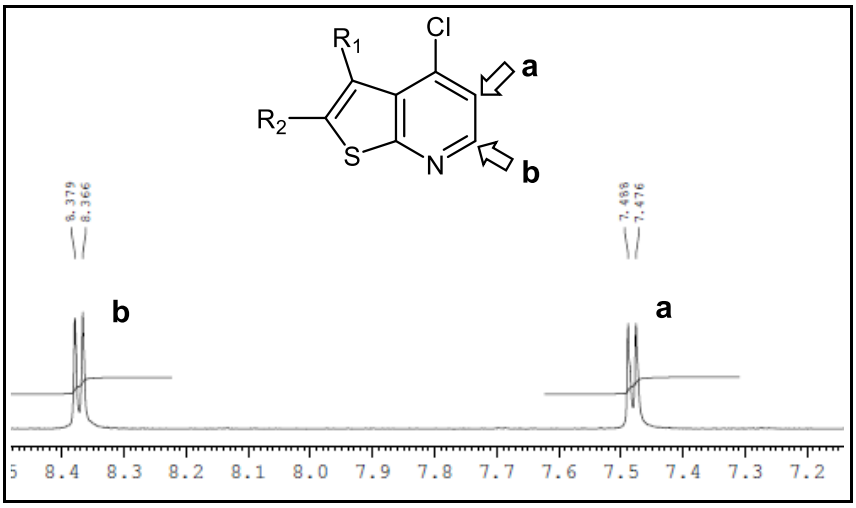


Figure 4 ^{1}H NMR spectrum of 4-chlorothieno[2,3-*b*]pyridine derivatives.

The output of the reaction were surprisingly different from what we expected, the analysis of ^{1}H NMR results showed absence of formyl proton and no indication of presence of singlet signals characterized for the proton of quinolone ring which adjacent to the nitrogen atom (Figure 4).

In contrast, two doublet signals was identified and the coupling constant of them referred to that they are coupling with each other. This pattern of NMR spectrum proved formation of formyl free product (Figure 4).

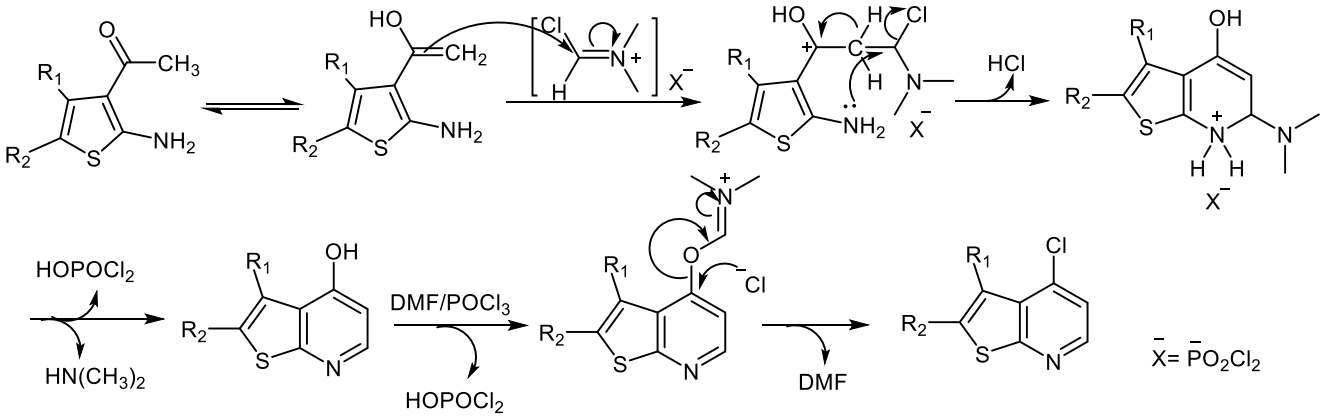
The replacement of the benzene ring with a thiophene ring is likely to have an impact on the final products, and may prevent further attack of the Vilsmeier–Haack reactant (Scheme 43).

2.2.5 Mechanism

Mechanism of the cyclization is postulated to be happened by one or two attacks of VH reagent:

2.2.5.1 The first pathway

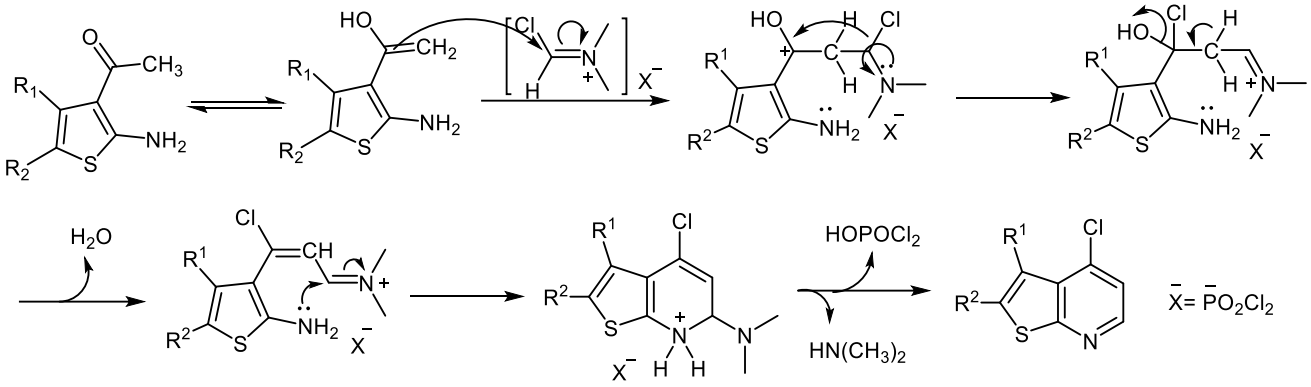
It may occur through the enol form which can be attacked by the reagent to form an intermediate, which losses HCl and proceeds through intramolecular cyclization till quinone which finally reacts in its enol form with another molecule of the reagent to give the final product (Scheme 45).



Scheme 45

2.2.5.2 The second pathway

Second assumption, is also possible by losing one water molecule from the fourth intermediate, afterward, it is consequently cyclized through two steps to give directly the final product (Scheme 46).



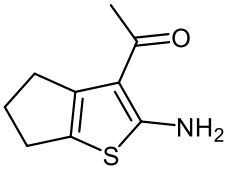
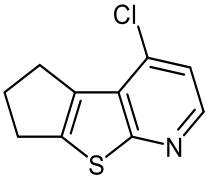
Scheme 46

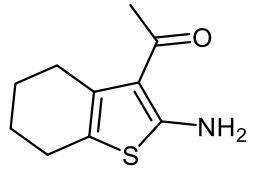
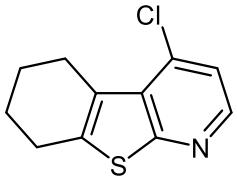
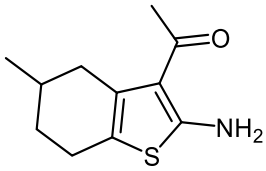
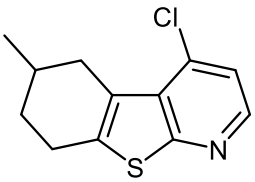
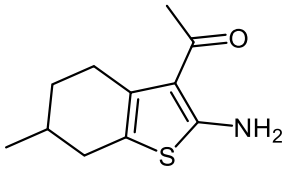
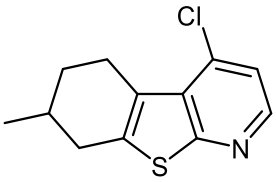
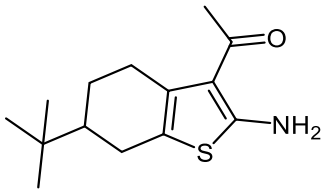
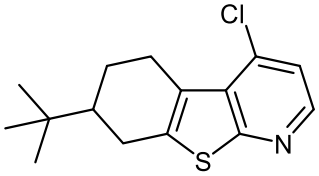
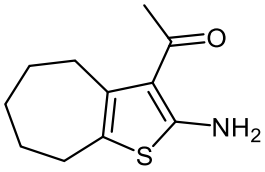
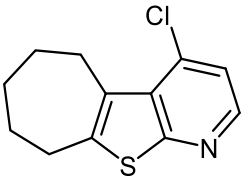
All the reactants gave yields from low to moderate, with the exception of **63** and **65**, which gave undefined mixtures on TLC, without any major component. Attempts to separate pure compounds from these mixtures by using flash chromatography failed (Table 3).

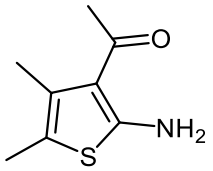
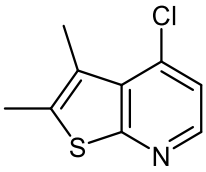
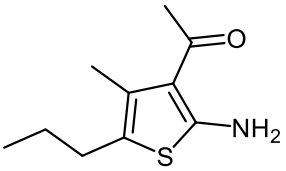
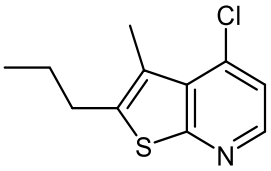
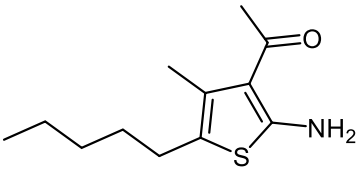
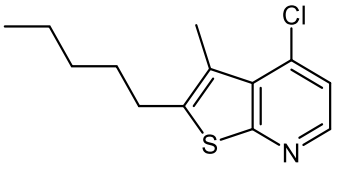
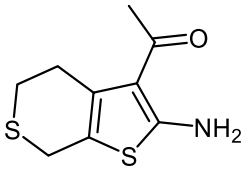
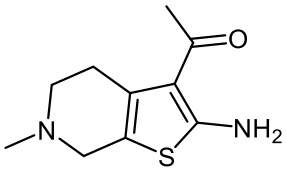
2.3 Conclusion

Thiophene compounds exhibited a different mode of cyclisation in the reaction with Vilsmeier–Haack reagent than that reported for the reaction with *o*-aminoacetophenone, which could be ascribed to the influence of the thiophene nucleus.

Table 3 Product of reaction between 3-acetyl-3-aminothiophene and VH reagent

Thiophenes	Thieno[2,3-*b*]pyridine	Yield
 **47**	 **114**	30%

 **45**	 **115**	43%
 **49**	 **116**	36%
 **51**	 **117**	36%
 **53**	 **118**	80%
 **55**	 **119**	53%

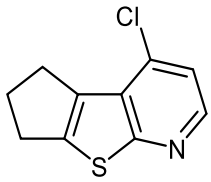
 **57**	 **120**	10%
 **59**	 **121**	25%
 **61**	 **122**	36%
 **63**		No product
 **65**		No product

2.4 Experimental part

4-Chlorothieno[2,3-*b*]pyridine Derivatives; General Procedure

For preparation of the Vilsmeier reagent, $POCl_3$ (2.5 mL) was dropped into DMF (10 mL) at 0 °C over 15 min with stirring. The starting materials (2.5 mmol) was dissolved in a minimum amount of DMF and the Vilsmeier reagent was added dropwise over 7 hours to the stirred solution at 100 °C. The reaction mixture was stirred at 100 °C. The progress of the reaction was monitored by TLC until the consumption of the starting material was complete (ca. 20–24 h), then the reaction mixture was treated with ice and water, neutralised with ammonium acetate and extracted with EtOAc several times. The product was obtained in pure form after purification by silica gel column chromatography (EtOAc–cyclohexane, 1:9) followed by recrystallization (MeOH–H_2O, 1:1).

4-Chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (114)



Yield: 156 mg (30%); white solid; mp 123 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

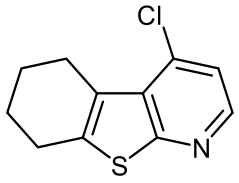
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 5.1 Hz, 1 H), 7.17 (d, *J* = 5.1 Hz, 1 H), 3.17 – 3.07 (m, 2 H), 3.03 – 2.92 (m, 2 H), 2.47 – 2.37 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 145.0, 144.0, 137.1, 136.7, 128.2, 120.0, 30.1, 29.9, 27.3.

HRMS (ESI): *m/z* calcd for $[C_{10}H_8ClNS + H]^+$: 210.0144; found: 210.0142.

Anal. Calcd for $C_{10}H_8ClNS \cdot H_2O$: C, 55.55; H, 4.06; N, 6.47; S′ 14.88. Found: C, 55.20; H, 4.03; N, 6.28; H, 14.66.

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (115)



Yield: 240 mg (43%); white solid; mp 67 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

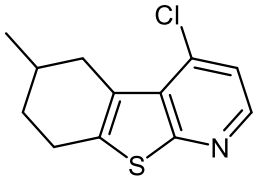
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 3.16 (dd, *J* = 5.8, 2.7 Hz, 2 H), 2.89 (t, *J* = 4.2 Hz, 2 H), 1.98 – 1.85 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.0, 144.8, 139.1, 137.9, 130.6, 127.8, 120.8, 26.7, 26.1, 22.5.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{10}ClNS + Na]^+$: 246.0115; found: 246.0133.

Anal Calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; N, 6.26; S, 14.33. Found: C, 59.70; H, 4.58; N, 6.48; S, 14.08.

4-Chloro-6-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (116)



Yield: 213 mg (36%); white solid; mp 112–115 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

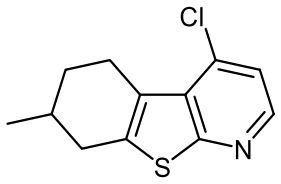
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 3.40 (dd, *J* = 17.4, 5.6 Hz, 1 H), 2.97 – 2.89 (m, 2 H), 2.64 – 2.56 (m, 1 H), 2.03 – 1.92 (m, 2 H), 1.60 – 1.48 (m, 1 H), 1.17 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.6, 145.1, 138.6, 137.6, 130.3, 127.8, 120.7, 35.0, 30.6, 28.9, 25.9, 21.7.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{13}ClNS]^+$: 238.0452; found: 238.0456.

Anal Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 60.44; H, 5.11; N, 5.82; S, 13.03.

4-Chloro-7-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (117)



Yield: 213 mg (36%); white solid; mp 54–56 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

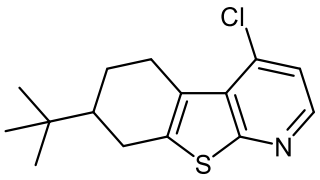
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.22 (d, *J* = 5.1 Hz, 1 H), 3.38 – 3.29 (m, 1 H), 3.08 – 2.90 (m, 2 H), 2.56 – 2.46 (m, 1 H), 2.07 – 1.96 (m, 2 H), 1.57 – 1.47 (m, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.5, 145.2, 138.5, 137.6, 130.2, 127.4, 120.7, 35.1, 30.7, 28.8, 26.5, 21.3.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{12}ClNS + H]^+$: 238.0452; found: 238.0463.

Anal Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 60.89; H, 5.13; N, 6.02; S, 13.07.

7-(*tert*-butyl)-4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (118)



Yield: 558 mg (80%); white solid; mp 75–77 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

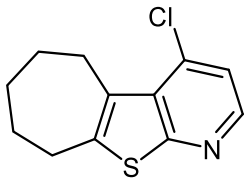
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 4.8 Hz, 1 H), 7.23 (d, *J* = 4.8 Hz, 1 H), 3.50 – 3.40 (m, 1 H), 2.97 – 2.89 (m, 2 H), 2.70 – 2.60 (m, 1 H), 2.19 – 2.12 (m, 1 H), 1.66 – 1.60 (m, 1 H), 1.49 – 1.34 (m, 1 H), 1.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.5, 145.2, 140.0, 137.5, 130.2, 127.8, 120.7, 44.5, 32.4, 27.8, 27.7, 27.2, 24.2.

HRMS (ESI): *m/z* calcd for $[C_{15}H_{18}ClNS + H]^+$: 280.0921; found: 280.0929.

Anal Calcd for $C_{15}H_{18}ClNS$: C, 64.38; H, 6.48; N, 5.01; S, 11.46. Found: C, 63.93; H, 6.55; N, 5.06; S, 10.96.

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*b*]pyridine (119)



Yield: 313 mg (53%); white solid; mp 60–63 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

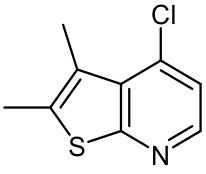
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 5.0 Hz, 1 H), 7.25 (d, *J* = 5.0 Hz, 1 H), 3.45 – 3.38 (m, 2 H), 3.00 – 2.94 (m, 2 H), 1.99 – 1.91 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6, 144.9, 143.4, 137.4, 133.1, 130.3, 121.4, 32.0, 30.1, 28.3, 27.1, 26.60.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{12}ClNS + H]^+$: 238.0452; found: 238.0458.

Anal. Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 61.01; H, 5.38; N, 6.06; S, 13.48.

4-Chloro-2,3-dimethylthieno[2,3-*b*]pyridine (120)



Yield: 49 mg (10%); white solid; mp 69–72 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

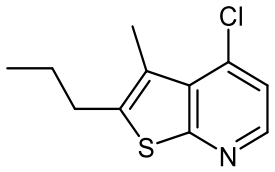
1H NMR (400 MHz, DMSO-d_6) δ = 8.37 (d, *J* = 5.1 Hz, 1 H), 7.48 (d, *J* = 5.1 Hz, 1 H), 3.33 (s, 3 H), 2.53 (s, 3 H).

13C NMR (100 MHz, DMSO-d_6) δ = 160.8, 145.8, 136.7, 135.6, 129.8, 125.3, 121.2, 14.3, 13.7.

HRMS (ESI): *m/z* calcd for $[C_9H_8ClNS + H]^+$: 198.0139; found: 198.0141.

Anal Calcd for $C_9H_8ClNS.H_2O$ (3%): C, 53.04; H, 4.20; N, 6.87; S, 15.70. Found: C, 53.34; H, 3.94; N, 7.00; S, 15.31.

4-Chloro-3-methyl-2-propylthieno[2,3-*b*]pyridine (121)



Yield: 141 mg (25%); white solid; mp 36–38 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

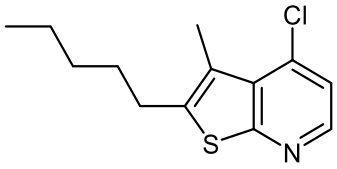
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 5.1 Hz, 1 H), 7.24 (d, *J* = 5.1 Hz, 1 H), 2.86 (t, *J* = 7.6 Hz, 2 H), 2.60 (s, 3 H), 1.80 – 1.76 (m, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0, 145.2, 141.4, 137.9, 130.9, 125.3, 121.0, 30.4, 24.2, 14.7, 13.8.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{12}ClNS + H]^+$: 226.0452; found: 226.0456.

Anal Calcd for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 6.20; S, 14.20. Found: C, 58.70; H, 5.48; N, 6.38; S, 13.87.

4-Chloro-3-methyl-2-pentylthieno[2,3-*b*]pyridine (122)



Yield: 228 mg (36%); white solid; mp 36–38 °C (MeOH–H2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37 (d, J = 5.1 Hz, 1 H), 7.47 (d, J = 5.1 Hz, 1 H), 2.87 (t, J = 7.6 Hz, 2 H), 2.53 (s, 3 H), 1.63 (t, J = 8 Hz, 2 H), 1.37 – 1.30 (m, 4H), 0.90 – 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0, 145.2, 141.7, 137.8, 130.9, 125.1, 121.0, 31.4, 30.6, 28.4, 22.4, 14.7, 14.0.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{16}ClNS + H]^+$: 254.0765; found: 254.0770.

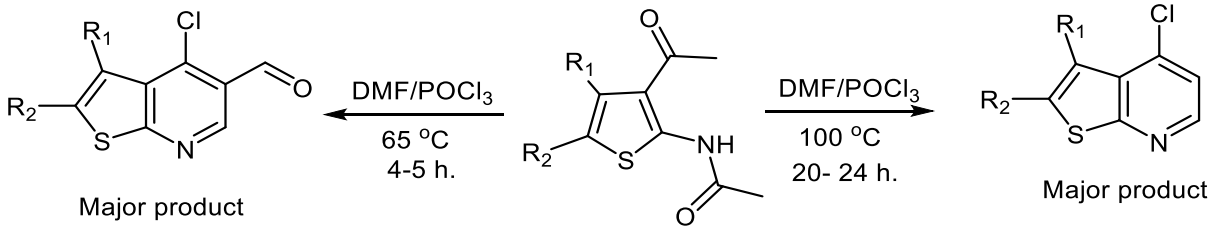
Anal Calcd for $C_{13}H_{16}ClNS$: C, 61.52; H, 6.35; N, 5.52; S, 12.63. Found: C, 61.82; H, 6.45; N, 5.60; S, 12.18.

Chapter 3 - Reactivity of *N*-protected 3-acetyl-2-aminothiophenes in reaction with Vilsmeier-Haack reagent

Résumé chapitre 3: Réactivité des 3-acétyl-2-alcoylamino-thiophènes par rapport au réactif de Vilsmeier-Haack.

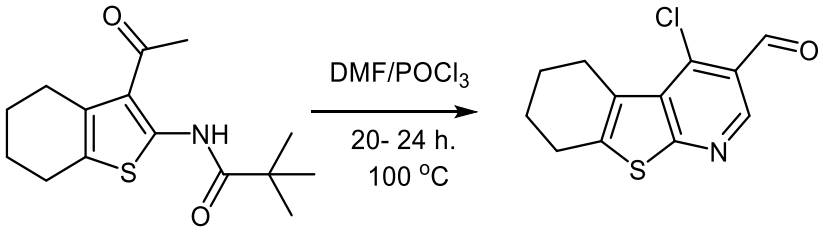
Le 2-acétamidothiophène a pu dans les conditions de Vilsmeier-Haack-Arnold être transformé en 4-chloro-3-formylthiénopyridine. Nous nous sommes donc intéressés à la réaction des 3-acétyl-2-acétamidothiophènes dans ces conditions. Ces derniers sont préparés de manière classique par reflux dans l'anhydride acétique.

Lorsque les dérivés sont mis en présence du réactif de Vilsmeier-Haack et suivant les conditions réactionnelles (Température-temps), les produits obtenus sont différents en proportions.



Il faut signaler que l'action du réactif de Vilsmeier-Haack sur le dérivé chloré ne conduit pas à l'aldéhyde.

Il est à signaler que la même réaction faite sur l'amide pivaloylé ne donne que le dérivé chloro-aldéhydique dans des conditions fortes.



3 Reactivity of *N*-protected 3-acetyl-2-aminothiophenes in reaction with Vilsmeier-Haack reagent

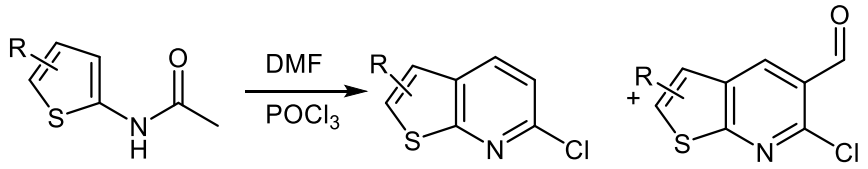
3.1 Introduction

In the previous chapter we explained the reaction between, 3-acetyl-2-amino thiophene and Vilsmeier–Haack reagent. The products was free from formyl group and all efforts to prolong the time of the reaction, increasing the number of reagent equivalents or increasing the temperature in order to force the occurrence of the second attack of the reagent to form the formyl derivatives went in vain (

Scheme **44**).

3.1.1 Reaction of 2-acetamido-5 substituted thiophenes

2-Acetamido-5 substituted thiophene **123**, reported to react with VH reagent under normal conditions to give mixture of products, when the conditions of the reaction adjusted to certain parameters, either **124** or **125** were formed by application of harsh condition (Scheme 47).[54]



123 **124** **125**

Scheme 47

124 could be obtained by reflux of the reaction mixture from 6 – 12 hours (depending on kind of the derivatives), number of moles used for DMF and $POCl_3$ were 1 and 3 respectively, in presence of 1,1,2,2-tetrachloroethane or dichloroethane as a solvent.[55]

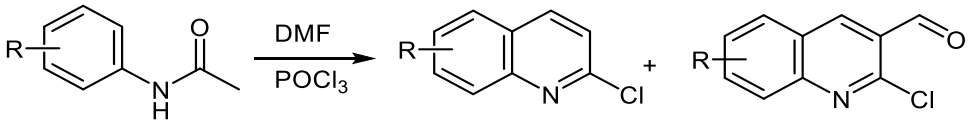
[54] O. Meth-Cohn and Bramha Narine, "A Versatile New Synthesis of Quinolines, Thienopyridines and Related Fused Pyridines," *Tetrahedron Letters* 19, no. 23 (January 1, 1978): 2045–48, doi:10.1016/S0040-4039(01)94745-8.

[55] Ibid.

While **125** was approachable by solvent free synthesis, and the equivalent of the reagent was increased by one and half time (DMF; 3 moles and $POCl_3$: 7 moles), the time of reflux was between 1.5 - 4 hours.[56]

3.1.2 Reaction of acetanilides

Similarly, *m*-methoxy-, *m*-methyl-, 3,4-dimethoxy-, and 3,4,5-trimethoxy-acetanilide reacted under the previously mentioned conditions, with changing in reflux time to be between 4 - 6 hours in case of **127** and 1.5-6 hours in case of **128**. Solvent which was used to produce quinolone free product was 1,1,2,2-tetrachloroethane (Scheme 48).[57]



126 **127** **128**

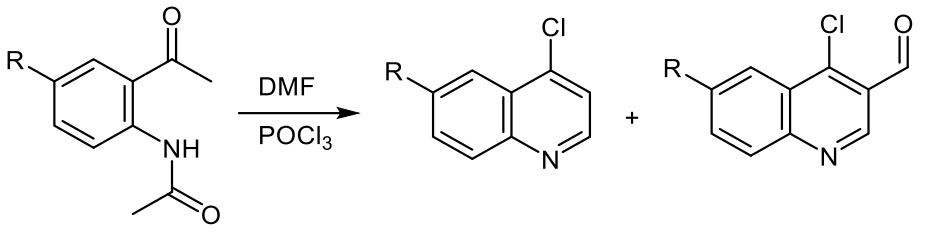
Scheme 48

When **126** was one of following derivatives: (R = H, 6, 7 or 8 Methyl acetanilide and 6 or 7 methoxyacetanilide), **128** could be synthesized as only product by heating **126** with 2.5 equivalent of DMF and 7 equivalent of phosphoryl chloride at 75 °C, by changing the derivative. For some derivatives which contained 3-SMe, 2,4-Me_2 and 3,4-OMe_2 and 3,4,5-OMe_3, compound **128** was only accessible by reflux from 1.5 to 6 hours.[58]

3.1.3 Reaction of *N*-protected aminoacetophenone

In 1997, various derivatives of 4-chloroquinolines **130** and 4-chloro-3-formylquinoline **131** were prepared by acetylation of amino group of *o*-aminoacetophenone **129** under Vilsmeier- Haack condition (Scheme 49).[59]

[56] Ibid.
[57] Ibid.
[58] Otto Meth-Cohn, Bramha Narine, and Brian Tarnowski, "A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part II.," *Tetrahedron Letters* 20, no. 33 (January 1, 1979): 3111–14, doi:10.1016/S0040-4039(01)95334-1.
[59] R. R. Amaresh and P. T. Perumal, "A Novel One-Pot Synthesis of 4-Chloro-3-Quinolinecarboxaldehydes, 4-Chloroquinolines and 4-Chloro-3-Ethylquinolines Using Vilsmeier Reagent," *Indian Journal of Chemistry Sections A and B* 36, no. 7 (February 15, 1997): 541–44.



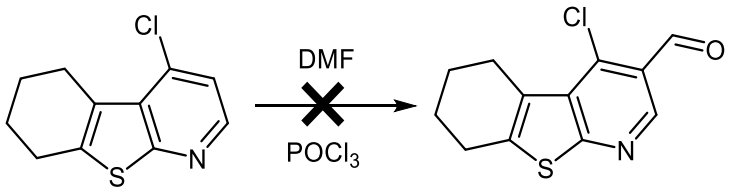
129 **130** **131**

Scheme 49

Noteworthy that the formyl free products were obtained as traces (0 – 14% yield) in mixture with major products **131** .the temperature of the reaction was 90 °C (Scheme 49).[60]

3.2 Results and discussion

In synthesis of 4-chlorothieno[2,3-*b*]pyridine, formyl analogue was not attainable by any mean.[61] Formylation was not obtained when compound **115** was subjected to VH reagent at different heating condition (65–100 ºC) which is expected from pyridine as an electron deficient nucleus (Scheme 50).



115 **132**

Scheme 50

We assumed that the thiophene ring stabilize the pyridine moiety by its inductive effect which prevented it from attack another iminium ion of VH reagent, to test our assumption and to make approach toward comprehension of reaction mechanism, we

[60] Ibid.

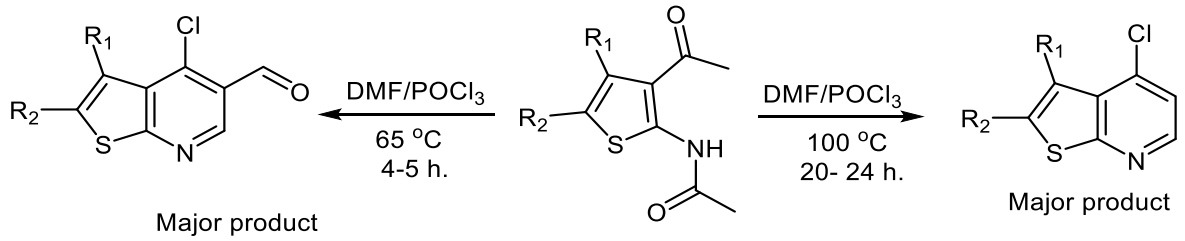
[61] Ahmed Abdelwahab, Atef Hanna, and Gilbert Kirsch, "Synthesis of Novel 3-Acetyl-2-Aminothiophenes and Investigation of Their Behaviour in the Reaction with Vilsmeier–Haack Reagent," *Synthesis* 48, no. 17 (June 10, 2016): 2881–88, doi:10.1055/s-0035-1561459.

decided to construct *N*-protected starting materials. This protection was intended to be done by electron withdrawing group, like acetyl or pivaloyl groups.

N-acetylated analogue was simply prepared by well-known procedure[62] of refluxing gently with acetic anhydride. Compounds **59** and **61** required certain modification of the procedure. For these last two, thiophene was concurrently dissolved with one equivalent of acetyl chloride in excess of acetic anhydride and stirred at 35 °C as maximum temperature, after 30 minutes the starting material was completely transformed to product which was treated with water and extracted with ethyl acetate. It was subsequently exposed to flash column purification (EtOAc–cyclohexane, 1:3) for maximum purity.

The previous procedure was not suitable for compound **63** to obtain complete reaction, mixture of starting material and product were obtained regardless the reaction time. Increasing the reaction temperature led to produce a lot of by-products. When the compound was dissolved in dichloromethane, excess of acetic anhydride, 3 equivalent of acetyl chloride and 3 equivalent of triethyl amine were added then the reaction mixture was gently refluxed for 30 hours, the complete reaction was achieved.

These *N*-acetylated analogues were treated by VH reagent under three different condition of temperature: room temperature, at 65 °C and at 100 °C.



112 **133** **113**

Scheme 51

[62] Arthur I. Vogel, *Textbook of Practical Organic Chemistry 5th Ed*, accessed October 31, 2016, p: 1273.

These *N*-acetylated products were treated by Vilsmeier-Haack reagent at 65 ºC and 100 ºC. At each temperature we used two equivalents of reagent; same equivalent of preparation of chlorothienopyridine (

Scheme **44**) or double amount. Addition of the reagent was done at once or dropwise over nearly 7 hours. It was found that every alteration of VH reagent amount and mode of addition at different temperatures led to different yields and products (Table 4).

3.2.1 Room temperature

Chloroformylthienopyridine **112** was synthesized as major product, chlorothienoderivatives **113** also obtained in lesser yield, the reaction time in this case need to be beyond 48-72 hours in order to obtain maximum productivity and the number of equivalent of VH reagent was same to which was used in

Scheme **44**.

3.2.2 At 65 °C

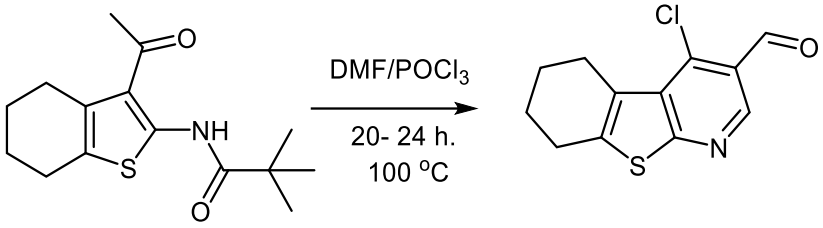
When same previously used reagent equivalent was applied, chlorothienopyridine **113** was the major product in low yield, while formylated product **112** was traces. When this amount was doubled and added at once, yield of formylated product **112** raised to be around 94% - 32%) while unformylated compounds **113** were 25% to 0% in 4-5 hours. Dropping the reagent over long period of time resulted in excessive decrease in the yield of both products, the reagent amount made no difference (Table 4).

3.2.3 At 100 °C

The reagent was dropped over long period of time (5-7 hours) and the reaction left under stirring for 20-24 hours.[6] Maximum yield of chlorothienopyridines **113** was obtained. When the same amount of the reagent was added at once, yields of both folmylated **112** and non-formylated compounds **113** were dramatically decreased, but the formylated product **112** was in greater amount.

Pivaloyl derivative **134** was exposed to the same reaction condition of synthesis of chlrothienopyridine[6] and formylated product **132** was the only output of this reaction

(yield, 42%), the same protected analogue gave no reaction at room temperature and 19% yield only at 65 °C using doubled amount of reagent (Scheme 52).



134 **132**

Scheme 52

Working with the procedure we described[63] and the same percentage of reactants with the new starting material gave us a considerable improvement in the yield of chlorothienopyridine **113** in addition to cleaner reaction, while addition of double amount of the reagent at one time to the reactant led to formation of formylated analogue **112** as major product and exclusively in some cases, the reaction time in this case was decreased to be 4-5 hours (Table 4).

Differently from reported before,[64] acetyl group was not involved in cyclization. It is suggested to play role by its electron withdrawing capability, which may result in stabilizing the double bond in intermediate **IV** (Scheme 53) making it more prone to another iminum ion attack. In contrary to the reaction of acetanilides **129**,[65] in which *N*-acetylation allowed synthesizing the 4-chloroquinoline **130** in low yield or had no influence. Using higher amount of the reagent, may result in rapid reaction and cyclization so acetyl group leaves the reactant after accomplishment of another nucleophilic attack (intermediate **VII**) (Scheme 53). Additionally, acetyl group protection is stable toward deacetylation at 65 °C. In contrast, lower quantity of the reagent added dropwise and

[63] Abdelwahab, Hanna, and Kirsch, "Synthesis of Novel 3-Acetyl-2-Aminothiophenes and Investigation of Their Behaviour in the Reaction with Vilsmeier–Haack Reagent."

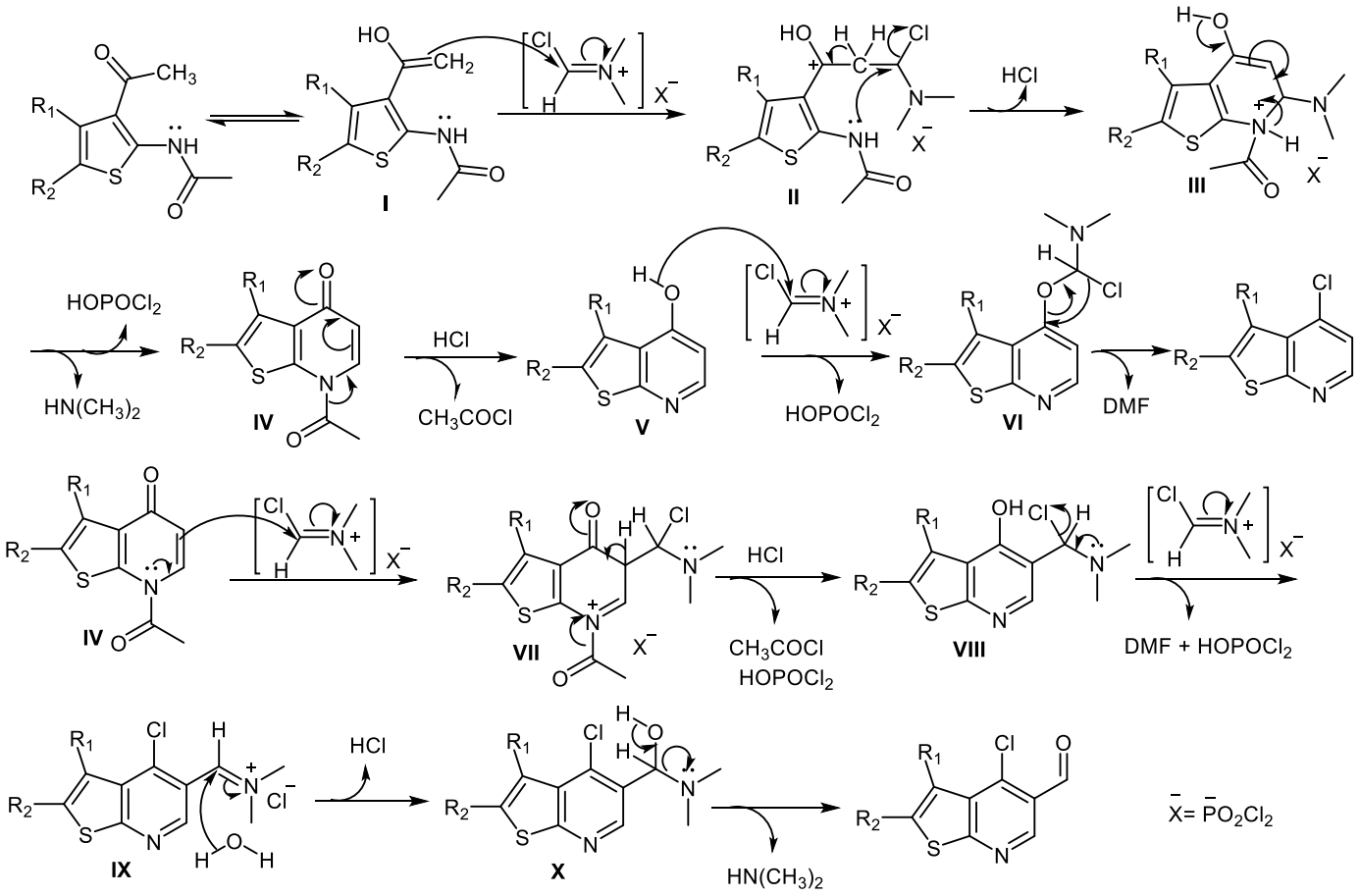
[64] Meth-Cohn and Narine, "A Versatile New Synthesis of Quinolines, Thienopyridines and Related Fused Pyridines."

[65] Amaresh and Perumal, "A Novel One-Pot Synthesis of 4-Chloro-3-Quinolinecarboxaldehydes, 4-Chloroquinolines and 4-Chloro-3-Ethylquinolines Using Vilsmeier Reagent."

higher temperature (100 °C) gives chance to departure of the acetyl group in the acidic media. This made the amino group free at the early stage of the reaction and pyridine seems like not susceptible to the excessive iminium ion.

By the way, pivaloyl group is more stable than acetyl group. Working under higher temperature (100 ºC), and with the normal reagent quantity gave only the formylated product, that may emphasize our suggestion.

3.2.4 Mechanism



Scheme 53

The mechanism of reaction is postulated to occur by two possible routes. First mode of cyclization in which the acetyl group leaves just prior to the chlorination (intermediate

IV). One HCl molecule help in liberation of acetyl group as acetyl chloride. The second pathway is assumed to happen at lower temperature, in which the acetyl group departure is retarded to allow the non-resonating double bond of pyridine ring (intermediate **VII**) to attack another iminium ion. The chlorination occurs afterward by third molecule of VH reagent (intermediate **VIII, IX)**. This last intermediate transformed to the final product by water treatment at the end of the reaction (

Scheme **53**).

All the products structure were verified by ^{1}H NMR and ^{13}C NMR; in ^{1}H NMR spectra; two sharp singlets appeared in region around 10.5 and 8.7 ppm which are characteristic for the formyl proton and the single proton of the pyridine ring respectively (Figure 5), while the formyl carbon appeared in region of 189 – 188 ppm.

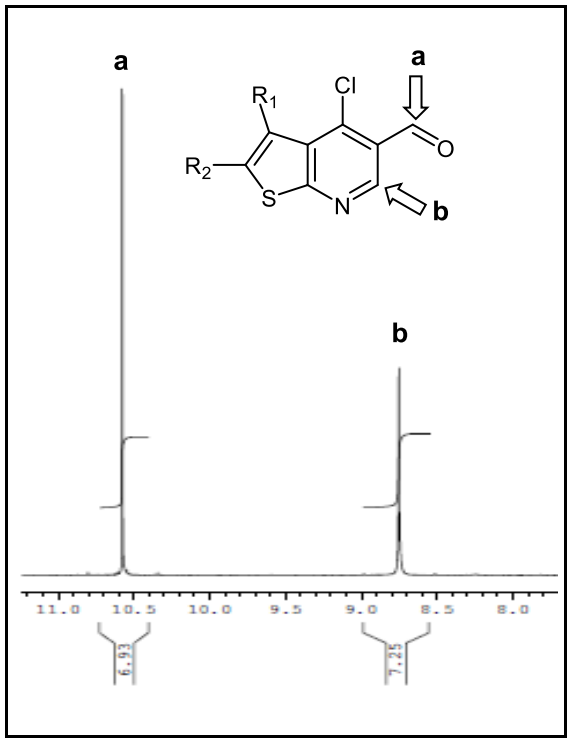
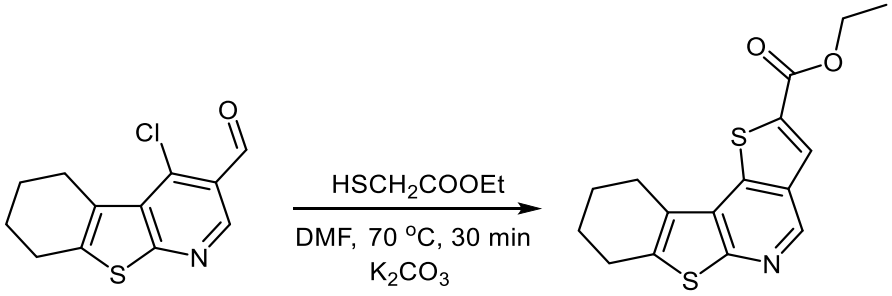


Figure 5 ^{1}H NMR spectrum of 4-chloro-3-formylthieno[2,3-*b*]pyridine derivatives.

HRMS (ESI) was also used for more structure confirmation, it was noticed that all analysed compounds showed molecular ion: $[M + H + CH_3OH]^+$ as base peak

concurrently with $[M + H]^+$ and as only viewed molecular ion in case of **144**. Compound **148** exhibited splitting of the formyl group and the produced molecular ion were $[M\text{-}CHO + H]^+$ and $[M + H + CH_3OH]^+$. Appearance of methanol adduct in all measured compounds may be attributed to a possibly formed hydrogen bond between the formyl group and the hydroxyl group of the alcohol (the used solvent in mass analysis).

To explore the reactivity of the obtained products we applied the method described by Hauptmann *et al.*[66] for compound **132**, it exhibited high reactivity and the reaction was accomplished within 30 minutes at 70°C (Scheme 54).



132 **135**

Scheme 54

3.3 Conclusion

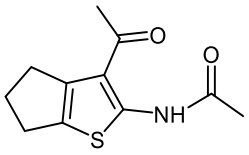
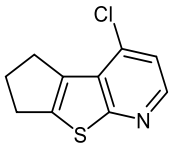
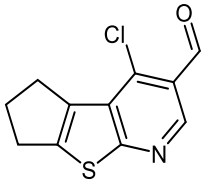
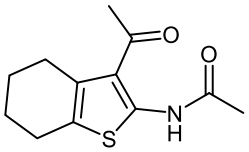
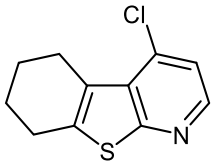
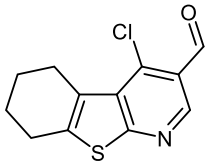
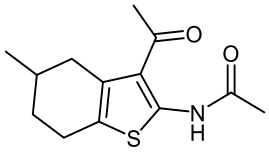
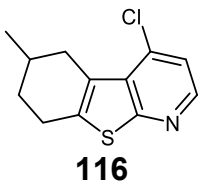
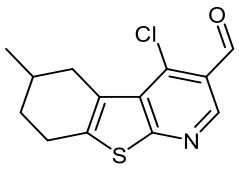
We reported here new synthetic pathway of both 4-chlorothieno[2,3-*b*]pyridine and 4-chloro-3-formylthieno[2,3-*b*]pyridine by application of *N*-protection. This acylation helped increasing the yield of unformylated products and introduction of mild synthesis of novel 4-chloro-3-formylthieno[2,3-*b*]pyridine. Directing the reaction toward one of the two products could be considered as controllable by modification the conditions of the reaction; temperature, mode of addition (which was found very crucial) and amount of the reagent. Differently from what reported before for synthesis of chloroquinoline, our product appeared to behave completely in opposite way. Chloroquinoline is formed as traces when acetamido acetophenone was used while chlorothieno[2,3-*b*]pyridin was formed by using of 3-acetyl-2-aminothiophene. Protection of the amino group of the last,

[66] Hauptmann et al., "Eine Neue Synthese Substituierter Thiophene Und Pyrrole."

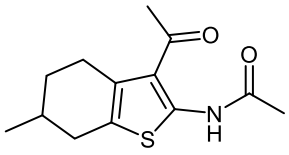
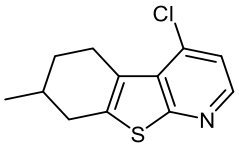
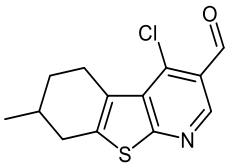
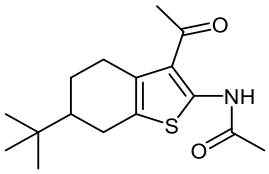
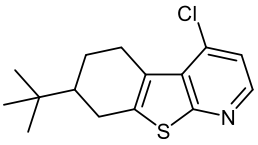
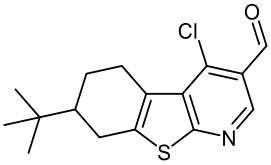
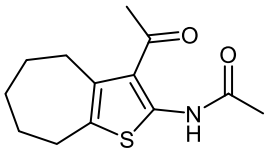
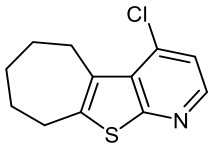
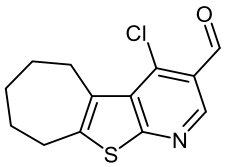
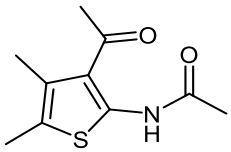
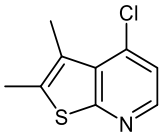
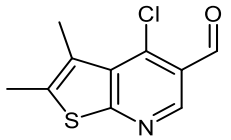
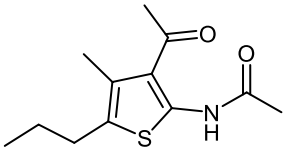
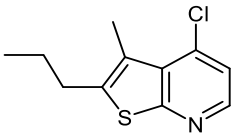
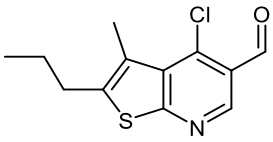
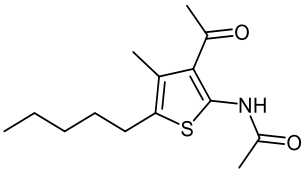
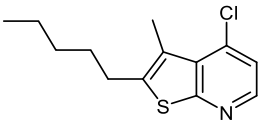
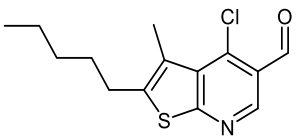
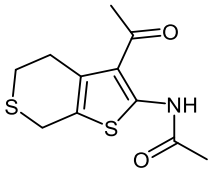
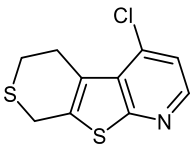
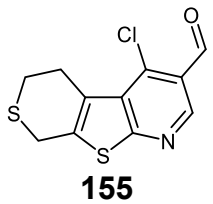
made the production of formylated product reachable which is the normal result of this procedure with *o*-aminoacetopenone and *o*-hydroxyacetophenone.

N-protection provides us more knowledge about the mechanisms of cyclization and chlorination of 3-acetyl-2-aminothiophene. These two processes more reasonable to happen by two attacks of iminium ion rather than one. In case of our previous proposal; that cyclization and chlorination take places by only one nucleophilic attack,[67] *N*-acetylation is supposed to produce merely chlrothienopyridine rather than 3-formyl derivatives.

Table 4 Products and yields of VH reaction with N-protected 3-acetyl-2-aminothiophenes at 65 °C and 100 °C

N-protected 3-acetyl-2-aminothiophenes	Thieno[2,3-*b*]pyridine	Yield 65 °C	Yield 100 °C	4-Chloro-3-formylthieno[2,3-*b*]pyridine	Yield 65 °C	Yield 100 °C
 **136**	 **114**	0%	21%	 **137**	94%	9%
 **138**	 **115**	25%	58%	 **132**	60%	0%
 **139**	 **116**	0%	48%	 **140**	86%	30%

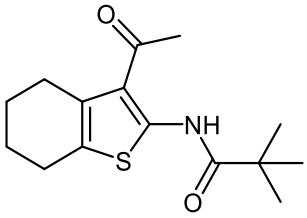
[67] Ibid.

 **141**	 **117**	11%	54%	 **142**	65%	9%
 **143**	 **118**	23%	30%	 **144**	32%	22%
 **145**	 **119**	14%	70%	 **146**	53%	traces
 **147**	 **120**	0%	55%	 **148**	63%	traces
 **149**	 **121**	10%	85%	 **150**	77%	0%
 **151**	 **122**	15%	36%	 **152**	62%	19%
 **153**	 **154**	23%	11%	 **155**	43%	0%

3.4 Experimental part

N-(3-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)pivalamide (134)

Pivaloyl chloride (0.92 g, 7.7 mmol) was added to 10 ml of dichloromethane in which 1-(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone **45** (1g, 5.1 mmol) was previously dissolved, triethyl amine (0.78 g, 7.7 mmol) was added and the solution was stirred at room temperature for 3 hours, afterward the solution was dried under vacuum to evaporate the solvent and the residue was dissolved in acetone and the precipitation was provoked by addition of ice and water. The solution was left for 30 minutes for allowing maximum precipitation, the solid was collected by filtration under vacuum and washed by water, the solid was of sufficient purity to be used without further purification (yield: 1.16 g; 81%)



Yield: 81%; grey solid; mp 112-116 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.79 (s, 1 H), 2.85 – 2.70 (m, 2 H), 2.71 – 2.66 (m, 2 H), 2.54 (s, 3 H), 1.89 – 1.80 (m, 4 H), 1.35 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 176.8, 149.8, 129.4, 127.1, 120.9, 39.3, 31.3, 27.5, 27.3, 24.5, 23.1, 22.7.

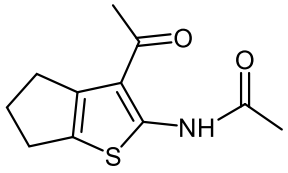
HRMS (ESI): *m/z* calcd for $[C_{15}H_{21}NO_2S + Na]^+$: 302.1185; found: 302.1202. For $[C_{15}H_{21}NO_2S + K]^+$: 318.0925; found: 318.0946.

Anal Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.47. Found: C, 64.92; H, 7.48; N, 4.93; S, 11.46.

N-(3-acetylthiophen-2-yl)acetamide derivatives (136 - 147), general procedure

1 g of 3-acetyl-2-aminothiophene derivatives was dissolved in 3 ml of acetic anhydride, the mixture was refluxed gently for 10-15 minutes, and quenched with water/ice, and then the solution was boiled gently, to breakdown the leftover acetic anhydride, the formed solid was filtered under vacuum and washed with water, dried and recrystallized in appropriate solvent if it needed.

N-(3-acetyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)acetamide (136)



Yield: 1.03 g (84%); green solid; mp 117-119 °C

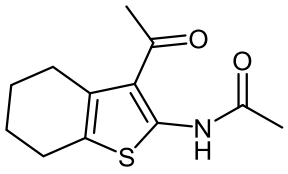
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.01 (s, 1 H), 2.96 – 2.85 (m, 2 H), 2.82 – 2.63 (m, 2 H), 2.42 – 2.33 (m, 5 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.1, 167.7, 153.0, 140.0, 133.0, 116.8, 31.4, 29.8, 28.6, 28.0, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{13}NO_2S + Na]^+$: 246.0565; found: 246.0567.

Anal Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; O, 14.33; S, 14.36. Found: C, 58.87; H, 5.88; N, 6.03; S, 14.47.

N-(3-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (138)



Yield: 1.17 g (96%); brown solid; mp 100-103 °C; (cyclohexane).

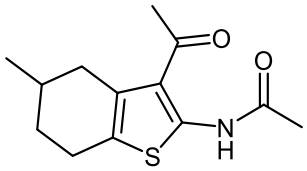
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.36 (s, 1 H), 2.83 – 2.76 (m, 2 H), 2.71 – 2.65 (m, 2 H), 2.52 (s, 3 H), 2.28 (s, 3 H), 1.89 – 1.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 167.8, 148.9, 129.3, 127.2, 120.8, 31.4, 27.5, 24.5, 23.8, 23.1, 22.6.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{15}NO_2S + H]^+$: 238.0896; found: 238.0921.

Anal Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.72; H, 6.34; N, 5.96; S, 13.48.

_N_-(3-acetyl-5-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (139)



Yield: 1 g (83%); brown solid; mp 148 °C (cyclohexane).

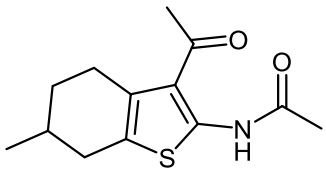
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.35 (s, 1H), 2.95 – 2.89 (m, 1 H), 2.76 – 2.66 (m, 2 H), 2.53 (s, 3 H), 2.27 (s, 3 H), 2.05 – 1.85 (m, 3 H), 1.56 – 1.37 (m, 1 H), 1.13 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 169.2, 150.6, 130.8, 128.3, 122.1, 37.4, 32.9, 32.2, 30.8, 25.7, 25.2, 23.2.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + Na]^+$: 274.0872; found: 274.0882.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; O, 12.73; S, 12.76. Found: C, 62.40; H, 6.76; N, 5.59; S, 12.68

_N_-(3-acetyl-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (141)



Yield: 1.19 g (99%); beige-brown solid; mp 120-122 °C (cyclohexane).

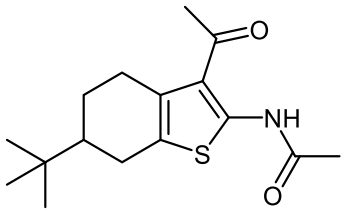
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.36 (s, 1 H), 2.94 – 2.85 (m, 1 H), 2.80 – 2.68 (m, 2 H), 2.52 (s, 3 H), 2.35 – 2.21 (m, 4 H), 2.02 – 1.86 (m, 2 H), 1.55 – 1.37 (m, 1 H), 1.10 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 167.8, 149.1, 129.0, 126.9, 120.6, 32.6, 31.4, 31.3, 28.9, 27.3, 23.8, 21.3.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + Na]^+$: 274.0872; found: 274.0890.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.03; H, 6.82; N, 5.53; S, 12.70.

_N_-(3-acetyl-6-(tert-butyl)-4,5,6,7-tetrahydrobenzo[_b_]thiophen-2-yl)acetamide (143)



Yield: 1.17 (82%); beige-brown solid; mp 141-143 °C (cyclohexane).

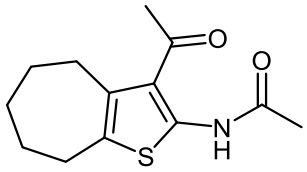
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.26 (s, 1 H), 2.96 – 2.83 (m, 1 H), 2.72 – 2.49 (m, 2 H), 2.43 (s, 3 H), 2.39 – 2.30 (m, 1 H), 2.19 (s, 3 H), 2.08 – 1.88 (m, 1 H), 1.53 – 1.32 (m, 1 H), 1.32 – 1.03 (m, 1 H), 0.88 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 167.8, 149.5, 127.5, 124.1, 120.1, 53.2, 52.3, 45.23, 31.1, 29.7, 27.7, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{16}H_{23}NO_2S + Na]^+$: 316.1342; found: 316.1338.

Anal Calcd for C, 65.49; H, 7.90; N, 4.77; S, 10.93. Found: C, 65.51; H, 7.92; N, 5.26; S, 10.95.

_N_-(3-acetyl-5,6,7,8-tetrahydro-4_H_-cyclohepta[_b_]thiophen-2-yl)acetamide (145)



Yield: 1 g (83%); beige-brown solid; mp 75-78 °C (EtOH 96%).

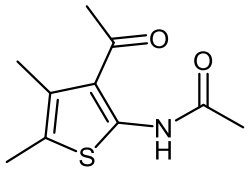
^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.90 (s, 1 H), 2.93 – 2.90 (m, 2 H), 2.76 – 2.73 (m, 2 H), 2.53 (s, 3 H), 2.25 (s, 3 H), 1.92 – 1.86 (m, 2 H), 1.75 – 1.64 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.5, 167.6, 145.7, 135.0, 131.4, 123.1, 31.9, 31.6, 29.3, 28.4, 27.6, 26.7, 23.71.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + H]^+$: 252.1058; found: 252.1049.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.56; H, 6.70; N, 5.45; S, 12.65.

_N_-(3-acetyl-4,5-dimethylthiophen-2-yl)acetamide (147)



Yield: 1 g (81%); brown solid; mp 115-119 °C (EtOH 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.29 (s, 1 H), 2.55 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 167.7, 147.9, 127.3, 123.8, 121.9, 31.3, 23.8, 15.3, 12.5 (s).

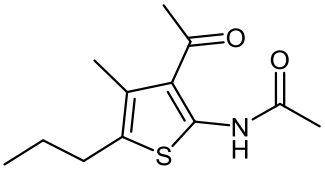
HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + H]^+$: 234.0565; found: 234.0572.

Anal Calcd for C, 56.85; H, 6.20; N, 6.63; O, 15.14; S, 15.17. Found: C, 56.85; H, 6.16; N, 6.98; S, 15.14.

N-(3-acetylthiophen-2-yl)acetamide derivatives (149, 151), general procedure

Compounds **59** or **61** (5.1 mmol) and acetyl chloride (0.4 g, 5.1 mmol) was dissolved and stirred in excess of acetic anhydride at 35 °C. After 30 minutes the solution was treated with water and ice and heated to decompose the acetic anhydride and then extracted with ethyl acetate. It was subsequently exposed to flash column purification (EtOAc–cyclohexane, 1:3) for maximum purity.

N-(3-acetyl-4-methyl-5-propylthiophen-2-yl)acetamide (149)



Yield: 1 g (82%); brown solid; mp 58-60 °C; R_f = 0.54 (EtOAc–cyclohexane, 1:3).

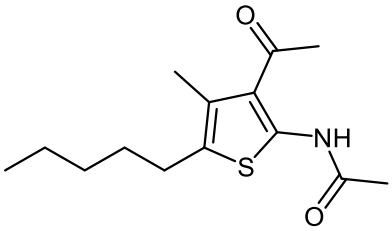
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.28 (s, 1 H), 2.67 – 2.63 (m, 2 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 1.70 – 1.59 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.2, 167.7, 148.3, 129.7, 127.0, 122.0, 31.4, 29.3, 24.4, 23.8, 15.3, 13.7.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{17}NO_2S + Na]^+$: 262.0872; found: 262.0909.

Anal Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.02; H, 7.10; N, 5.80; S, 13.12.

N-(3-acetyl-4-methyl-5-pentylthiophen-2-yl)acetamide (151)



Yield; 1.32 g (97%); brown solid; mp 40 °C; R_f = 0.53 (EtOAc–cyclohexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.31 (s, 1 H), 2.66 (t, *J* = 7.7 Hz, 2 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 1.66 – 1.54 (m, 2 H), 1.38 – 1.29 (m, 4 H), 0.96 – 0.85 (m, 3 H).

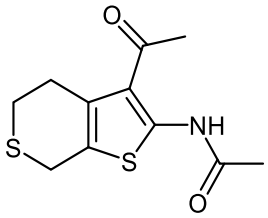
^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 167.7, 148.2, 130.0, 126.8, 122.0, 31.4, 31.3, 30.9, 27.3, 23.8, 22.4, 15.3, 14.0.

HRMS (ESI): *m/z* calcd for $[C_{14}H_{21}NO_2S + H]^+$: 268.1366; found: 268.1369.

Anal Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.75; H, 7.89; N, 5.41; S, 12.08.

_N_-(3-acetyl-4,7-dihydro-5_H_-thieno[2,3-_c_]thiopyran-2-yl)acetamide (153)

Compound **63** (1g, 4.6 mmol) dissolved in 10 ml of dichloromethane, excess of acetic anhydride, acetyl chloride (1.08 g, 13.8 mmol) and triethyl amine (1.4 g, 13.8 mmol) were added and the reaction mixture was gently refluxed for 30 hours, the solvent was evaporated and residue dissolved in acetone and treated by ice and water. The reaction mixture was boiled for decomposing the acetic anhydride and the formed precipitate was filtered under vacuum and washed with water and crystallized from EtOH-H_2O.



Yield; 1 g (84%); brown solid; mp 132-135 °C (EtOH 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (s, 1 H), 3.76 (s, 2 H), 3.10 (t, *J* = 5.8 Hz, 2 H), 2.97 (t, *J* = 5.8 Hz, 2 H), 2.53 (s, 3 H), 2.29 (s, 3 H).

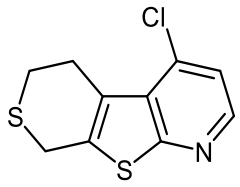
^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.5, 167.9, 148.5, 129.1, 123.2, 121.3, 31.7, 29.2, 26.3, 25.4, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{13}NO_2S_2 + H]^+$: 256.0460; found: 256.0460.

Anal Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49; S, 25.11. Found: C, 51.94; H, 5.67; N, 5.17; S, 25.56.

4-chloro-5,8-dihydro-6H-thiopyrano[4',3':4,5]thieno[2,3-*b*]pyridine (154)

Compounds **154** was prepared from **153** (0.3 g, 1.2 mmol) by same procedure reported before.



Yield: 31 mg (11%); colorless solid; mp 154 °C R_f = 0.29 (EtOAc–cyclohexane, 1:9).

1H NMR (400 MHz, CDCl3) δ 8.34 (d, J = 5.0 Hz, 1 H), 7.26 (d, J = 5.0 Hz, 1 H), 3.93 (s, 2 H), 3.51 – 3.43 (m, 2 H), 3.03 (t, J = 5.2 Hz, 2 H).

13C NMR (100 MHz, CDCl3) δ = 161.1, 145.9, 138.1, 134.7, 130.4, 127.5, 121.2, 28.7, 26.6, 25.9.

HRMS (ESI): *m/z* calcd for $[C_{10}H_8ClNS_2 + H]^+$: 241.9859; found: 241.9864.

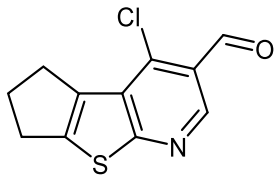
Anal Calcd for $C_{10}H_8ClNS_2$; C, 49.68; H, 3.34; N, 5.79; S, 26.52. Found: C, 49.99; H, 3.60; N, 5.52; S, 26.85

4-chloro-3-formylthieno[2,3-*b*]pyridine, general procedure

Vilsmeier-Haack reagent was prepared by previously mentioned method, in this case the amount of the reagent was: 5 ml of $POCl_3$, and 20 mL of DMF for 2.5 mmol of the starting material. The reagent was added to the thiophene at one time, and stirred at 65 °C for 4-5 hours. At the end of the reaction, the solution was decomposed by mixture of ice and water and neutralized by sodium acetate, in case of formation of precipitate, filtration under vacuum was applied, the obtained solid was dissolved in ethyl acetate and washed 2-3 times with water, the residue was purified by silica gel column chromatography (EtOAc–cyclohexane, 1:9), otherwise the solution was directly extracted by ethyl acetate, and purified by the same way.

For preparation of 4-chlorothieno[2,3-*b*]pyridine, same previously mentioned procedure and reactant amount were employed (Chapter 2).

4-Chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (137)



Yield: 560 mg (94%); White solid; mp 160 -163 °C (cyclohexane); R_f = 0.36 (EtOAc–cyclohexane, 1:9).

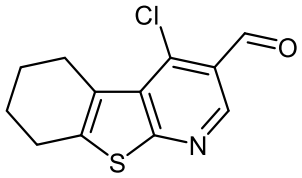
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 = (s, 1 H), 8.76 (s, 1 H), 3.21 – 3.13 (m, 2 H), 3.04 – 2.96 (m, 2 H), 2.50 – 2.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.7, 171.0, 146.0, 145.3, 140.4, 137.4, 128.1, 124.2, 30.1, 27.4.

HRMS (ESI): *m/z* calcd for $[C_{11}H_8ClNOS + H]^+$: 238.0088; found: 238.0122.

Anal Calcd for $C_{11}H_8ClNOS$: C, 55.58; H, 3.39; N, 5.89; S, 13.49. Found: C, 56.35; H, 3.44; N, 5.82; S, 13.10.

[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (132)



Yield: 346 mg (60%); White solid; mp 162-165 °C (cyclohexane); ; R_f = 0.36 (EtOAc–cyclohexane, 1:9).

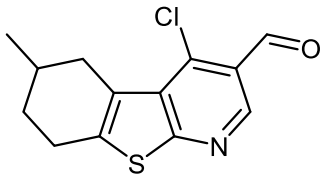
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.77 (s, 1 H), 3.15 – 3.12 (m, 2 H), 2.84 – 2.80 (m, 2 H), 1.95 – 1.78 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.1, 166.4, 145.7, 141.2, 140.7, 130.0, 128.8, 124.3, 26.9, 26.3, 22.4, 22.3.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{10}ClNOS + H]^+$: 252.0244; found: 252.0266.

Anal Calcd for $C_{12}H_{10}ClNOS$: C, 57.26; H, 4.00; N, 5.56; S, 12.74. Found: C, 57.89; H, 4.28; N, 5.30; S, 12.22.

4-Chloro-6-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (140)



Yield: 571 mg (86%); White solid; mp 148-152 °C (cyclohexane); ; R_f = 0.40 (EtOAc–cyclohexane, 1:9).

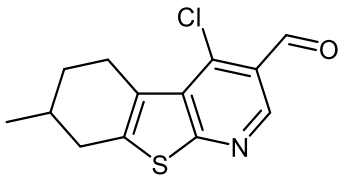
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.76 (s, 1 H), 3.41 – 3.31 (m, 1 H), 2.90 – 2.81 (m, 2 H), 2.61 – 2.54 (m, 1 H), 1.99 – 1.83 (m, 2 H), 1.53 – 1.43(m, 2 H), 1.10 (d, *J* = 6.5 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl3) δ = 189.0, 166.3, 145.4, 141.4, 140.6, 130.2, 128.9, 124.4, 35.2, 30.3, 28.9, 26.1, 21.6.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.0397.

Anal Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H, 4.55; N, 5.27; S, 12.06. Found: C, 58.82; H, 4.56; N, 5.11; S, 12.00.

4-Chloro-7-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (142)



Yield: 429 mg (65%); White solid; mp 148 -152 °C (cyclohexane) ; R_f = 0.36 (EtOAc–cyclohexane, 1:9).

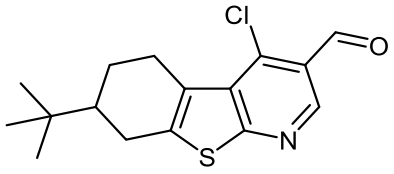
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.55 (s, 1 H), 8.80 (s, 1 H), 3.34 – 3.30(m, 1 H), 3.08 – 2.91 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.55 – 2.34 (m, 1 H), 2.01 – 1.86 (m, 2 H), 1.51 – 1.41 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.1, 166.6, 145.7, 141.2, 140.3, 129.9, 128.5, 124.4, 34.2, 30.6, 28.6, 26.7, 21.2.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.04201.

Anal Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H, 4.55; N, 5.27; S, 12.06. Found: C, 58.59; H, 4.54; N, 5.12; S, 11.92.

7-(*tert*-butyl)-4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (144)



Yield: 246 mg (32%); White solid; mp 190-192 °C (cyclohexane); ; R_f = 0.40 (EtOAc–cyclohexane, 1:9).

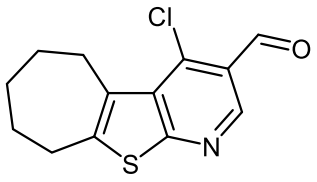
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.55 (s, 1 H), 8.77 (s, 1 H), 3.50 – 3.35 (m, 1 H), 2.96 – 2.80 (m, 2 H), 2.63 – 2.55 (m, 1 H), 2.18 – 2.01 (m, 1 H), 1.58 – 1.50 (m, 2 H), 1.41 – 1.31 (m, 1 H), 0.92 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0, 166.6, 145.6, 141.4, 141.1, 129.8, 128.8, 124.3, 44.4, 32.4, 28.0, 27.9, 27.2, 24.1.

HRMS (ESI): *m/z* calcd for $[C_{16}H_{18}ClNOS + H + CH_4O]^+$: 340.1133; found: 340.11691.

Anal Calcd for $C_{16}H_{18}ClNOS$: C, 62.43; H, 5.89; N, 4.55; S, 10.41. Found: C, 62.43; H, 5.90; N, 4.50; S, 10.35.

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (146)



Yield: 350 mg (53%); yellow solid; mp 120-122 °C (cyclohexane); ; R_f = 0.38 (EtOAc–cyclohexane, 1:9).

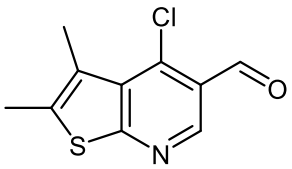
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.58 (s, 1 H), 8.75 (s, 1 H), 3.41 – 3.33 (m, 2 H), 2.94 – 2.86 (m, 2 H), 1.95 – 1.80 (m, 2 H), 1.76 – 1.67 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.3, 165.4, 145.3, 145.1, 141.3, 134.3, 129.9, 124.7, 31.7, 30.1, 28.4, 26.9, 26.4.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.0429.

Anal Calcd for $C_{13}H_{12}ClNOS$: 58.75; H, 4.55; N, 5.27; S, 12.06. Found: 58.62; H, 4.50; N, 5.15; S, 12.22.

4-Chloro-2,3-dimethylthieno[2,3-*b*]pyridine-5-carbaldehyde (148)



Yield: 354 mg (63%); yellow solid; mp 216-218 °C (cyclohexane); ; R_f = 0.29 (EtOAc–cyclohexane, 1:9).

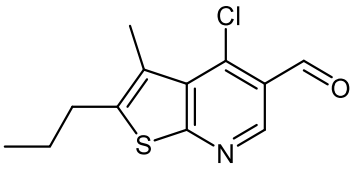
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.56 (s, 1 H), 8.77 (s, 1 H), 2.55 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0, 165.8, 145.7, 141.4, 137.3, 126.8, 14.8, 14.1.

HRMS (ESI): *m/z* calcd for $[C_{10}H_8ClNOS – CHO + H]^+$: 198.0139; found: 198.0165.

Anal Calcd for $C_{10}H_8ClNOS$: C, 53.22; H, 3.57; N, 6.21; S, 14.21. Found: C, 53.25; H, 3.60; N, 6.04; S, 14.17.

4-Chloro-3-methyl-2-propylthieno[2,3-*b*]pyridine-5-carbaldehyde (150)



Yield: 487 mg (77%); White solid; mp 102-105 °C; ; R_f = 0.38 (EtOAc–cyclohexane, 1:9).

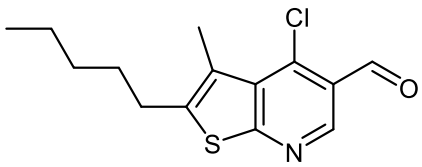
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.67 (s, 1 H), 8.88 (s, 1 H), 2.89 (t, *J* = 7.6 Hz, 2 H), 2.67 (s, 3 H), 1.85 – 1.69 (m, 4 H), 1.06 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.2, 166.1, 145.7, 143.2, 141.6, 130.5, 126.4, 124.4, 30.5 24.2, 15.0, 13.7.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{12}ClNOS + H]^+$: 254.0401; found: 254.0419.

Anal Calcd for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.77; N, 5.52; S, 12.63. Found: C, 56.71; H, 4.79; N, 5.35; S, 12.48.

4-Chloro-3-methyl-2-pentylthieno[2,3-*b*]pyridine-5-carbaldehyde (152)



Yield: 436 mg (62%); White solid; mp 65-67 °C (EtOH-H_2O); ; R_f = 0.42 (EtOAc–cyclohexane, 1:9).

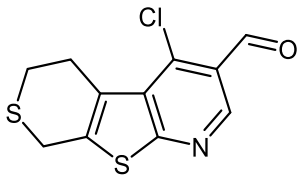
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.65 (s, 1 H), 8.87 (s, 1 H), 2.89 (t, *J* = 7.6 Hz, 2 H), 2.64 (s, 3 H), 1.80 – 1.66 (m, 2 H), 1.45 – 1.35 (m, 4 H), 0.97 – 0.88 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 189.2, 166.1, 145.7, 143.5, 141.5, 130.5, 126.2, 124.5, 31.4, 30.5, 28.5, 22.4, 15.0, 13.92.

HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}ClNOS + H]^+$: 282.0719; found: 282.0732

Anal Calcd for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; Cl, 12.58; N, 4.97; S, 11.38. Found: C, 59.97; H, 5.23; N, 5.25; S, 11.60.

4-Chloro-5,8-dihydro-6*H*-thiopyrano[4',3':4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (155)



Yield: 289 mg (43%); yellow solid; mp 180 °C (cyclohexane); R_f = 0.29 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.81 (s, 1 H), 3.86 (s, 2 H), 3.46 (t, *J* = 5.9 Hz, 2 H), 2.97 (t, *J* = 5.9 Hz, 2 H).

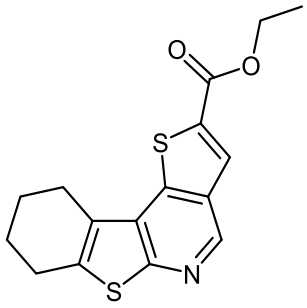
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8, 165.35, 146.6, 141.6, 136.5, 130.0, 128.6, 124.6, 28.9, 26.7, 25.9.

HRMS (ESI): *m/z* calcd for $[C_{11}H_8ClNOS_2 + H]^+$: 269.9814; found: 269.9821.

Anal Calcd for $C_{11}H_8ClNOS_2$: C, 48.98; H, 2.99; Cl, 13.14; N, 5.19; O, 5.93; S, 23.77. Found: C, 49.00; H, 3.14; N, 5.92; S, 23.47.

Ethyl 7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*b*]thieno[2,3-*d*]pyridine-2-carboxylate (156)

Compound **132** (0.1 g, 0.4 mmol) was dissolved with ethyl thioglycolate (0.05 g, 0.4 mmol) in DMF (3 ml) and potassium carbonate (0.06 g, 0.4 mmol) was introduced. The solution was stirred for 30 minutes at 70°C. The reaction mixture was treated by ice and water. If precipitate was formed; it was filtered under vacuum, washed and dried, otherwise the solution was extracted by ethyl acetate and dried by Na_2SO_4 *anhyd* and concentrated under vacuum. The precipitate or the residue was recrystallized from ethanol.



Yield: 69 mg (55%); white solid; mp 168 °C (ethanol 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.97 (s, 1 H), 8.24 (s, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 3.07 – 3.03 (m, 2 H), 2.98 – 2.95 (m, 2 H), 2.08 – 1.95 (m, 4 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.3, 155.3, 142.8, 142.6, 138.5, 133.4, 132.6, 129.3, 127.6, 127.3, 61.9, 25.7, 25.3, 23.0, 22.4, 14.3.

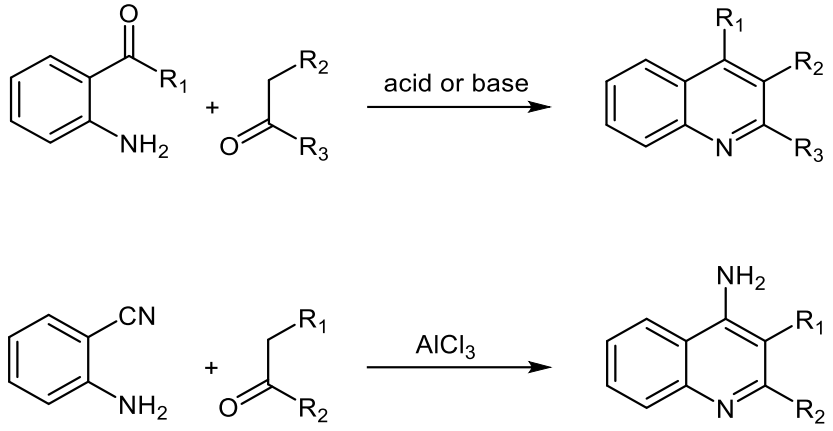
HRMS (ESI): *m/z* calcd for $[C_{16}H_{15}NO_2S_2 + H]^+$: 318.0617; found: 318.0626.

Anal Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.54; H, 4.76; N, 4.41; S, 20.20. Found: C, 60.72; H, 4.72; N, 4.80; S, 20.13.

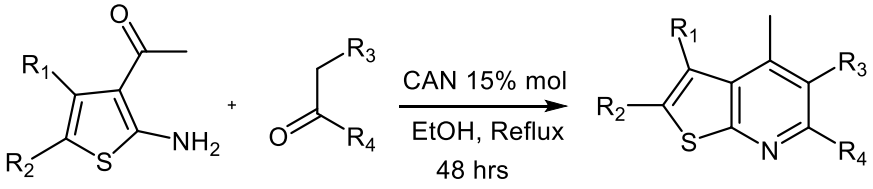
Chapter 4 - Reactivity of 3-acetyl-2-aminothiophenes in Friedländer condensation reaction

Résumé chapitre 4: Réactivité des 3-acétyl-2-aminothiophènes dans la condensation de Friedländer.

La réaction de Friedländer permet de préparer des quinoléines par condensation d'o-aminobenzaldéhyde, d'o-aminoacétophénone et d'anthranilonitrile avec des cétones α-méthyléniques catalysée par des acides de Lewis.Cette réaction a été utilisée pour la synthèse de la Tacrine®, médicament utilisé pour combattre Alzheimer mais abandonné maintenant. Cette réaction a été étudiée au laboratoire pour la synthèse d'analogues thiophéniques de Tacrine® par condensation d'o-amino thiophène- carbonitrile.



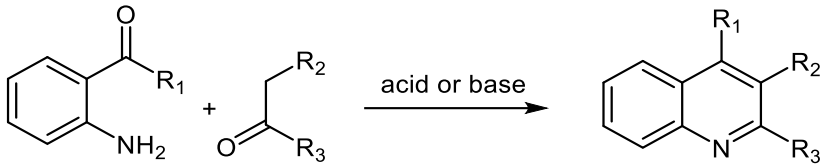
Les dérivés o-amino-acétylthiophènes préparés ont été utilisés pour cette condensation. Celle-ci a été effectuée par catalyse avec le bnitrate de cérium et d'ammonium en milieu éthanol à reflux et à permis la synthèse de nouvelles thiénopyridines.



4 Reactivity of 3-acetyl-2-aminothiophenes in Friedländer condensation reaction.

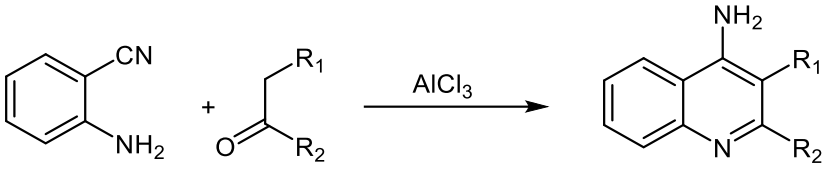
4.1 Introduction

One of the reaction which is applicable for 3-acetyl-2-aminothiophenes is the Friedländer reaction (see chapter 2). In this chapter we are going to describe the reaction and discuss our own results. Friedländer condensation is an acid or base catalyzed condensation– cyclodehydration reaction.



157 **158** **159**

Scheme 55



160 **161** **162**

Scheme 56

This reaction takes place between an aromatic ortho-aminoaryl ketone/aldehyde (Scheme 55). or ortho-aminobenzonitril (Scheme 56) with reactive active methylene compounds to afford quinolines or heteroannulated pyridines such as poly-substituted quinolone[68], sugar-based quinolones, sugar-based naphthyridines, sugar-based

[68] Alireza Hasaninejad et al., "Synthesis of Poly-Substituted Quinolines via Friedländer Hetero-Annulation Reaction Using Silica-Supported P2O5 under Solvent-Free Conditions," *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)* 30, no. 1 (April 1, 2011): 73–81; Mustapha C. Mandewale et al., "Developments in Quinoline Synthesis: A Review," *Heterocyclic Letters* 5, no. 3 (2015): 475–88.

xanthones[69], 1,8-naphthyridine[70], 1,10-phenanthrolines[71], selenophene analogue, thiazole analogue[72] oxazolopyridine[73], benzopyranopyridines.[74]

This reaction is generally carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of base or under heating at 150-220 °C in the absence of catalyst. In order to improve the generality of Friedländer method, some acids catalyst, such as hydrochloric acid[75], *p*-toluenesulfonic acid[76], dodecylphosphonic acid[77], sulphuric acid-modified PEG-600013[78] have been employed. Also, modified methods,

[69] Subbiah Nagarajan et al., "Regioselective Facile One-Pot Friedländer Synthesis of Sugar-Based Heterocyclic Biomolecules," *Carbohydrate Research* 345, no. 14 (September 23, 2010): 1988–97, doi:10.1016/j.carres.2010.07.016.

[70] K. Mogilaiah, M. Prashanthi, and S. Kavitha, "Lithium Chloride as an Efficient Catalyst for Friedlander Synthesis of 1,8-Naphthyridines via the Use of Microwave Irradiation and Pestle/Mortar.," *ChemInform* 37, no. 19 (May 9, 2006), doi:10.1002/chin.200619139; Baskar Nammalwar et al., "ChemInform Abstract: Quinoline- and 1,8-Naphthyridine-3-Carboxylic Acids Using a Self-Catalyzed Friedlaender Approach.," *ChemInform* 45, no. 39 (September 23, 2014): no-no, doi:10.1002/chin.201439179.

[71] Serafino Gladiali et al., "Friedländer Synthesis of Chiral Alkyl-Substituted 1,10-Phenanthrolines," *The Journal of Organic Chemistry* 66, no. 2 (January 1, 2001): 400–405, doi:10.1021/jo0009806.

[72] David Thomae, Gilbert Kirsch, and Pierre Seck, "Synthesis of Selenophene Analogues of the Tacrine Series: Comparison of Classical Route and Microwave Irradiation," *Synthesis* 2008, no. 10 (May 2008): 1600–1606, doi:10.1055/s-2008-1067001; Pierre Seck, David Thomae, and Gilbert Kirsch, "Synthesis of Substituted Amino-Cycloalkyl[*b*]thieno-[3,2-*e*]pyridines," *Journal of Heterocyclic Chemistry* 45, no. 3 (May 1, 2008): 853–57, doi:10.1002/jhet.5570450333; Pierre Seck et al., "Synthesis of New Selenophene and Thiazole Analogues of the Tacrine Series," *Arkivoc* 3 (2012): 431–441.

[73] Maria do Carmo Carreiras et al., "Synthesis and Friedlander Reactions of 5-Amino-4-Cyano-1, 3-Oxazoles," *Heterocycles*, 2007, 2249–2262.

[74] Zeba N. Siddiqui, "One Pot Synthesis of New Benzopyranopyridines via Friedlander Condensation," *Tetrahedron Letters* 53, no. 37 (September 12, 2012): 4974–78, doi:10.1016/j.tetlet.2012.07.013.

[75] Guan-Wu Wang, Cheng-Sheng Jia, and Ya-Wei Dong, "Benign and Highly Efficient Synthesis of Quinolines from 2-Aminoarylketone or 2-Aminoarylaldehyde and Carbonyl Compounds Mediated by Hydrochloric Acid in Water," *Tetrahedron Letters* 47, no. 7 (February 13, 2006): 1059–63, doi:10.1016/j.tetlet.2005.12.053.

[76] Cheng-Sheng Jia et al., "Rapid and Efficient Synthesis of Poly-Substituted Quinolines Assisted by P-Toluene Sulphonic Acid under Solvent-Free Conditions: Comparative Study of Microwave Irradiation versus Conventional Heating," *Organic & Biomolecular Chemistry* 4, no. 1 (December 15, 2006): 104–10, doi:10.1039/B513721G; Pradip K. Bhowmik et al., "Photoactive Amorphous Molecular Materials Based on Bisquinoline Diamines and Their Synthesis by Friedländer Condensation Reaction," *Journal of Photochemistry and Photobiology A: Chemistry* 283 (June 1, 2014): 45–55, doi:10.1016/j.jphotochem.2014.03.021.

[77] Nagarajan et al., "Regioselective Facile One-Pot Friedländer Synthesis of Sugar-Based Heterocyclic Biomolecules"; Soheila Ghassamipour and Razieh Ghashghaei, "Zirconium Dodecylphosphonate Promoted Synthesis of Xanthene Derivatives by Condensation Reaction of Aldehydes and β-Naphthol or Dimedone in Green Media," *Monatshefte Für Chemie - Chemical Monthly* 146, no. 1 (August 20, 2014): 159–63, doi:10.1007/s00706-014-1277-7.

[78] Mohammad Ali Zolfigol et al., "Solid-Supported Sulfonic Acid-Containing Catalysts Efficiently Promoted One-Pot Multi-Component Synthesis of β-Acetamido Carbonyl Compounds," *Journal of Chemical Sciences* 124, no. 2 (April 14, 2012): 501–8, doi:10.1007/s12039-011-0210-4.

using Lewis acids[79], inorganic salts[80], ionic liquids[81], branched catalysts[82] have been reported for this reaction.

4.1.1 Mechanism of reaction

Two viable reaction mechanisms exist for Friedländer condensation reaction (

Scheme **57**). In the first mechanism 2-amino substituted carbonyl compound **I** and reactive active methylene compound **II** reacts in a rate-limiting to aldol adduct **III**. This intermediate loses water in an elimination reaction to unsaturated carbonyl compound and then loses water again in imine formation to quinoline derivative **V**. In the second mechanism the first step is Schiff base **VI** formation followed by aldol reaction to **VII** and elimination to quinoline derivative **V**.[83]

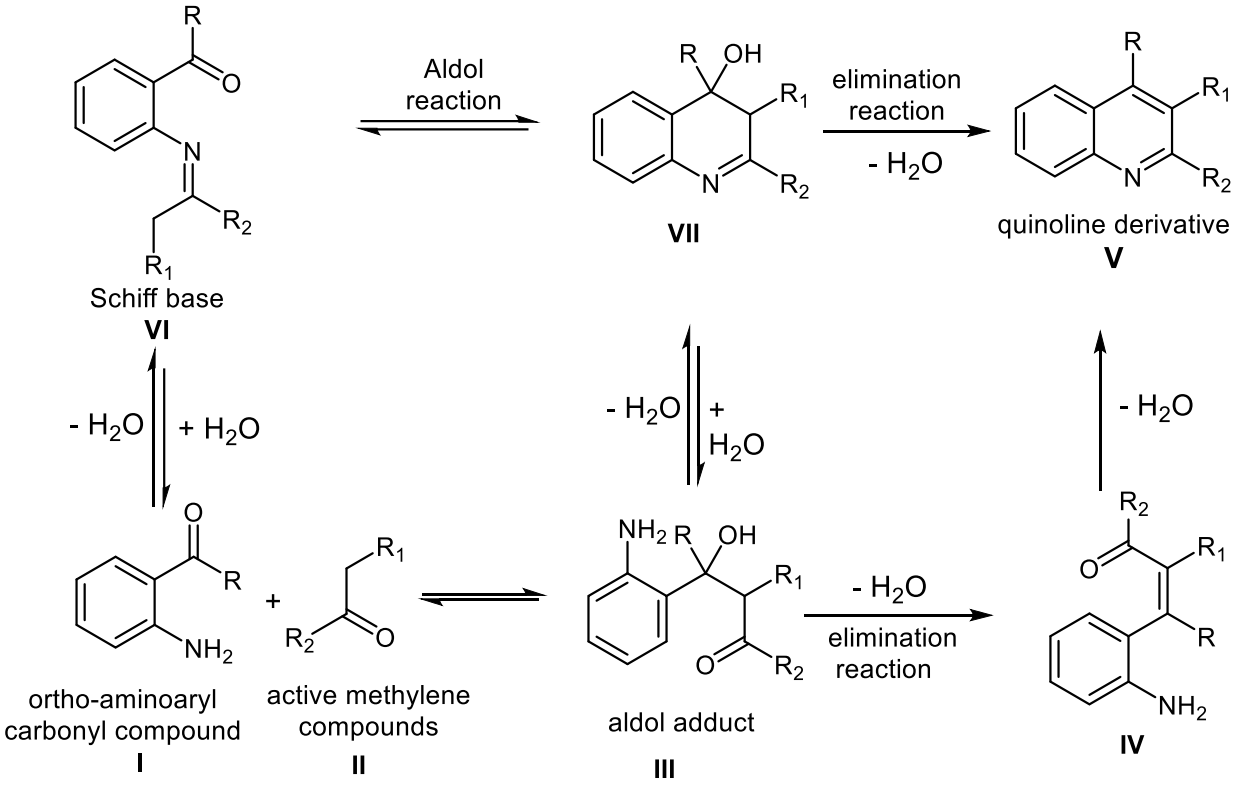
[79] Mogilaiah, Prashanthi, and Kavitha, "Lithium Chloride as an Efficient Catalyst for Friedlander Synthesis of 1,8-Naphthyridines via the Use of Microwave Irradiation and Pestle/Mortar."; ibid.; Jessé S. da Costa et al., "Lewis Acid Promoted Friedländer Condensation Reactions between Anthranilonitrile and Ketones for the Synthesis of Tacrine and Its Analogues," *Journal of the Brazilian Chemical Society* 20, no. 8 (2009): 1448–54, doi:10.1590/S0103-50532009000800009; Ebrahim Soleimani et al., "An Efficient Approach to Quinolines via Friedländer Synthesis Catalyzed by Cuprous Triflate," *Chemical & Pharmaceutical Bulletin* 58, no. 2 (February 2010): 212–13; Brahmayya, "Synthesis of Quinolines and Their In Vitro Antioxidant Activities under Solvent Free Conditions by Using the SiO2-Zn-MgO as a Novel and Reusable Catalyst," *Journal of Applied Pharmaceutical Science*, October 28, 2012, doi:10.7324/JAPS.2012.21008.

[80] U. V. Desai et al., "A Highly Efficient Synthesis of Trisubstituted Quinolines Using Sodium Hydrogensulfate on Silica Gel as a Reusable Catalyst," *Arkivoc* 15 (2006): 198–204; Y. Venkateswarlu, S. Ramesh Kumar, and P. Leelavathi, "A Simple and Efficient Protocol for the Synthesis of Quinolines Catalyzed by Chloramines-T," *Org Commun* 5, no. 3 (2012): 120.

[81] Mohammad Abdollahi-Alibeik and Marjan Pouriayevali, "Nanosized MCM-41 Supported Protic Ionic Liquid as an Efficient Novel Catalytic System for Friedlander Synthesis of Quinolines," *Catalysis Communications* 22 (May 2012): 13–18, doi:10.1016/j.catcom.2012.02.004; Morteza Shiri et al., "A New and Facile Access to the 2-(Indol-3-Yl)-3-Nitriloquinolines Based on Friedländer Annulations," *Tetrahedron* 68, no. 30 (July 29, 2012): 6059–64, doi:10.1016/j.tet.2012.05.006.

[82] Lei Fang et al., "Homogeneous Catalysis, Heterogeneous Recycling: A New Family of Branched Molecules with Hydrocarbon or Fluorocarbon Chains for the Friedländer Synthesis of Quinoline under Solvent-Free Conditions," *Tetrahedron* 69, no. 51 (December 23, 2013): 11004–9, doi:10.1016/j.tet.2013.10.029.

[83] Joseph M Muchowski and Michael L Maddox, "Concerning the Mechanism of the Friedländer Quinoline Synthesis," *Canadian Journal of Chemistry* 82, no. 3 (March 1, 2004): 461–78, doi:10.1139/v03-211.

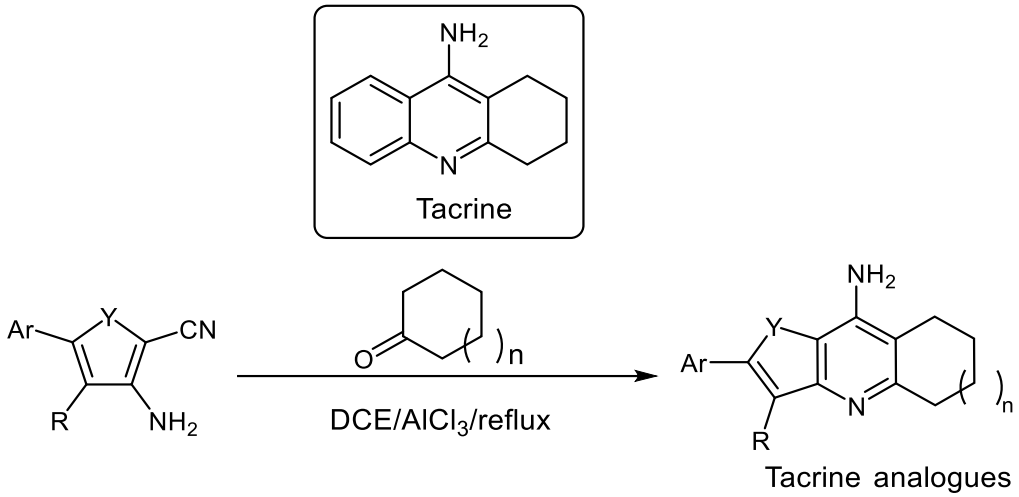


Scheme 57

Thomae *et al*., 2007[84] and 2008[85] reported synthesis of substituted thiophenes and selenophenes analogues of Tacrine; (former treatment of Alzheimer's disease) *via* Friedländer condensation of 3-amino2-cyano-5-arylthiophene and/or 3-amino-2-cyano-5-arylselenophene with some cyclic ketone in dichloroethane and in the presence of Lewis acid $AlCl_3$ (Scheme 58).

[84] David Thomae, Gilbert Kirsch, and Pierre Seck, "Synthesis of Thiophene Analogues of the Tacrine Series," *Synthesis* 2007, no. 7 (April 2007): 1027–32, doi:10.1055/s-2007-965944.

[85] Thomae, Kirsch, and Seck, "Synthesis of Selenophene Analogues of the Tacrine Series," May 2008.

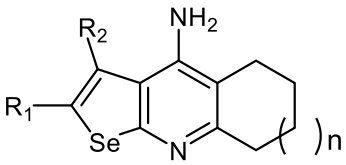


163 **164**

Y= S or Se; n= 0-2; Ar= C_6H_5, C_6H_4Cl-*p* or C_6H_5OMe-*p*

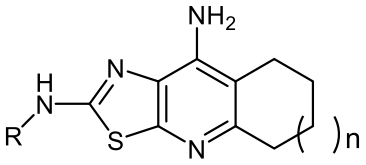
Scheme 58 Synthesis of Tacrine analogues.

Also, Seck *et al*., 2012 demonstrated some new cycloalkene-fused selenolo[3,2-*e*]pyridines **165** and tetrahydro[1,3]thiazolo[5,4-*b*]quinolines **166** derivatives *via* Friedländer condensation of 2-aminoselenophene-3-carbonitriles and 5-amino-1,3-thiazole-4-carbonitriles with cycloalkanones in the presence of aluminium chloride in dichloroethane.[86]



a, n = 1; $R^1 = R^2 = CH_3$
b, n = 0; $R^1 = R^2 = (CH_2)_4$
c, n = 1; $R^1 = R^2 = (CH_2)_4$
d, n = 2; $R^1 = R^2 = (CH_2)_4$
e, n = 1; $R^1 = R^2 = (CH_2)_5$

165



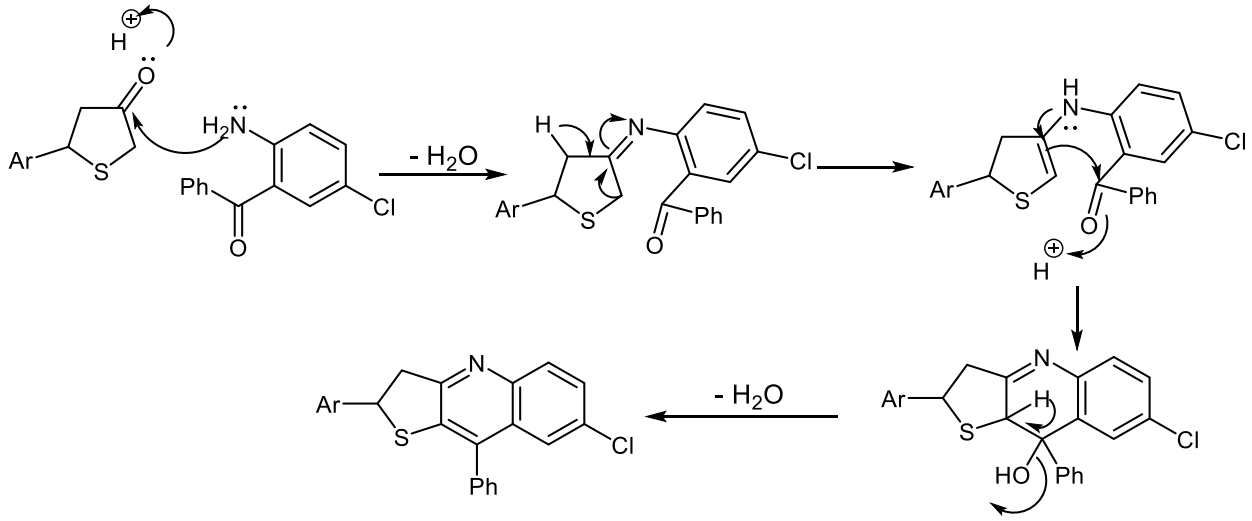
a, n = 0; R = C_6H_5
b, n = 1; R = C_6H_5
c, n = 2; R = C_6H_5
d, n = 0; R = $C_6H_4OCH_3$-*p*
e, n = 1; R = $C_6H_4OCH_3$-*p*
f, n = 2; R = $C_6H_4OCH_3$-*p*

166

7-Chloro-2-(2,4-dichlorophenyl) and 2-(3-nitrophenyl)-9-phenyl-2,3-dihydro-thieno-[3,2-*b*]quinolones which displayed anti-tubercular activity with MIC of 0.90 and 0.95 μM against MTB and MDR-TB respectively, were synthesized regioselectively by Friedländer

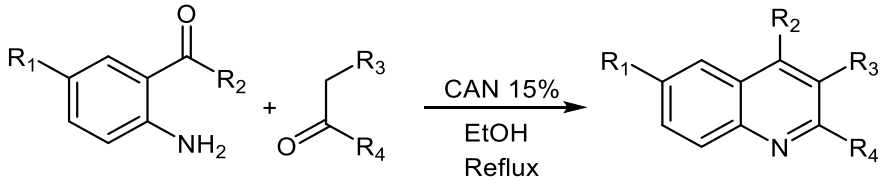
[86] Seck et al., "Synthesis of New Selenophene and Thiazole Analogues of the Tacrine Series," 2012.

annulation of 5-aryldihydro-3(2*H*)-thiophenones and 2-amino-5-chloro-benzophenone in the presence of Lewis acid; CF_3COOH in good yields under microwave irradiation at 100°C (Scheme 59).[87]



Scheme 59

Cerium ammonium nitrate (CAN) was an alternative catalyst employed by Carlos Menéndez and his coworker, to avoid harsh condition of acidic and basic catalyst. It was involved in catalytic amount and provided cheap, stable and non-toxic advantages.



167 **168** **169**

Scheme 60

The aniline derivatives were refluxed with active methylene containing ketones for different periods of time according to type of derivatives, the accomplishment of the

[87] Kamaraj Balamurugan et al., "A Microwave-Assisted, Facile, Regioselective Friedländer Synthesis and Antitubercular Evaluation of 2,9-Diaryl-2,3-Dihydrothieno-[3,2-*b*]quinolines," *European Journal of Medicinal Chemistry* 45, no. 2 (February 2010): 682–88, doi:10.1016/j.ejmech.2009.11.011.

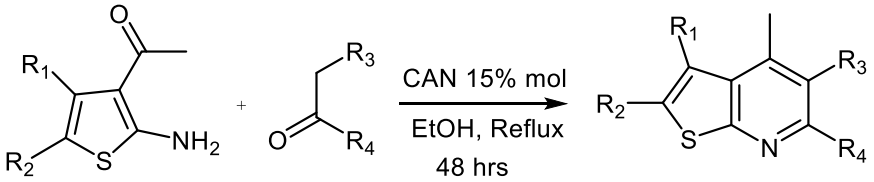
reaction was followed by TLC and the product was purified by column chromatography (Scheme 60). [88]

4.2 Results and discussion

Friedländer condensation introduced us an additional pathway for synthesis of thieno[2,3-*b*]pyridine. This perspective is allowed by 3-acetyl-2-aminothiophene due to adjacency of both amino and acetyl group. Wide varieties of derivatives could be obtainable, by different α methylene containing carbonyl compound.

Despite the different behaviour of thiophene ring in certain reaction from aryl compound, it still behaves similarly in other cases. Friedländer condensation was reported as an applicable synthesis on thiophene and thiazole rings in presence of $AlCl_3$.[89]

In previously described examples of Friedländer condensation including thiophene, cyano group was the functional group on which the reaction took place. In our example, the acetyl group replaced the cyanide moiety and cerium ammonium nitrate (CAN),[90] was the catalyst of choice.



41 **168** **170**

Scheme 61

The procedure, reported by V. Sridharan *et al* was mainly followed. The time of the reaction was determined by continuous following of the reaction using TLC. The reactants were mixed in same equivalency and refluxed in absolute ethanol. It was noticed that, whatever the time of reaction, thiophenes were not consumed completely. The catalyst

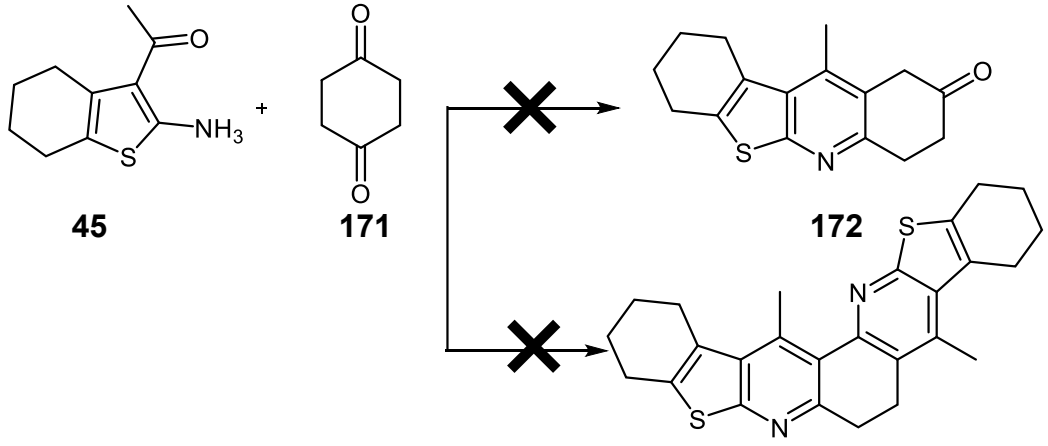
[88] Vellaisamy Sridharan et al., "Cerium(IV) Ammonium Nitrate Is an Excellent, General Catalyst for the Friedländer and Friedländer−Borsche Quinoline Syntheses: Very Efficient Access to the Antitumor Alkaloid Luotonin A," *The Journal of Organic Chemistry* 74, no. 15 (August 7, 2009): 5715–18, doi:10.1021/jo900965f.

[89] Seck et al., "Synthesis of New Selenophene and Thiazole Analogues of the Tacrine Series," 2012; Seck, Thomae, and Kirsch, "Synthesis of Substituted Amino-Cycloalkyl[*b*]thieno-[3,2-*e*]pyridines"; Thomae, Kirsch, and Seck, "Synthesis of Selenophene Analogues of the Tacrine Series," May 2008.

[90] Sridharan et al., "Cerium(IV) Ammonium Nitrate Is an Excellent, General Catalyst for the Friedländer and Friedländer−Borsche Quinoline Syntheses."

effect appeared to be the same at all molar amounts, increasing the molar percentage from reported amount (15 mol%) to 30% did not make any effect on accomplishment of the reaction (Scheme 61) (Table 5).

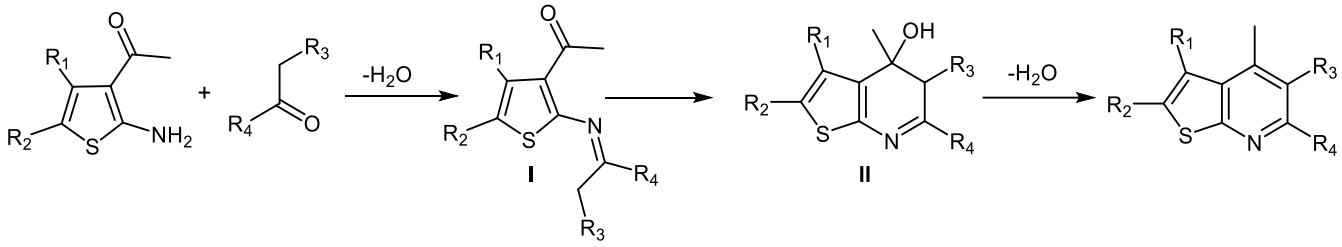
The examples which tried through the practical work gave yield from low to moderated, compounds **63**, **65** were not reactive, which gave another hint about influence of the heteroatom in the fused cycle upon the reactivity of the thiophene. It is worth to be mentioned that when the Friedländer reaction was tried between the 3-acetyl-2-aminothiophe **45** and diketone **171**, unknown products were obtained (Scheme 62).



Scheme 62

4.2.1 Mechanism of the reaction

From the two previously mentioned plausible mechanisms (Scheme 57), we are picking up one of them to explain the condensation process, this mechanism consists in two kind of condensation, Schiff and aldol. Firstly the amino group condensed with the carbonyl oxygen and the molecule losses the first water molecule and Schiff base (I) is formed (Scheme 63).



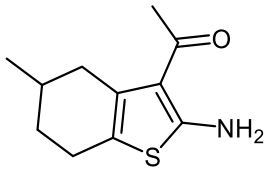
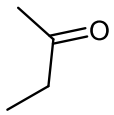
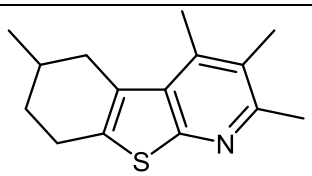
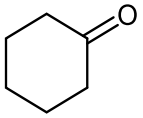
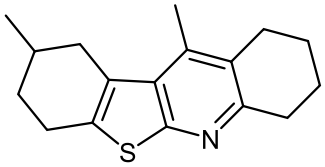
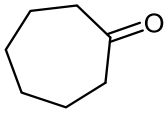
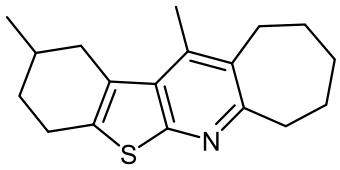
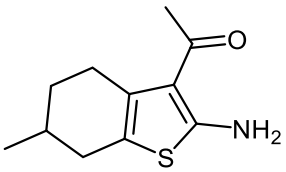
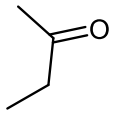
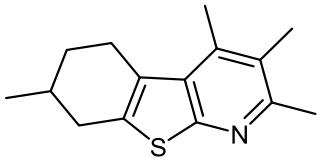
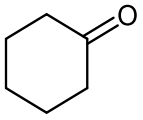
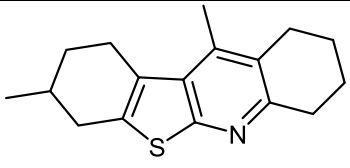
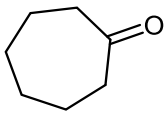
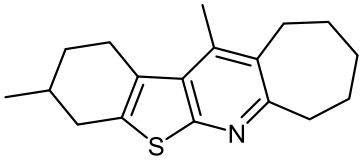
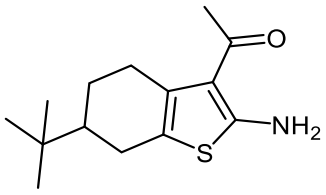
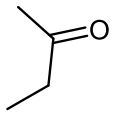
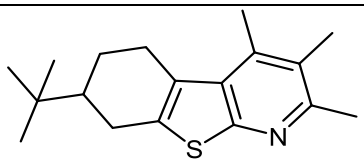
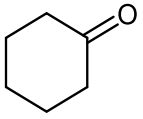
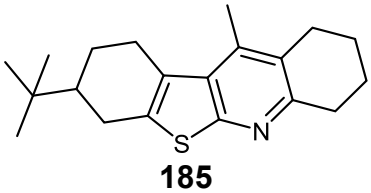
41 **168** **170**

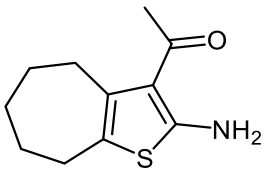
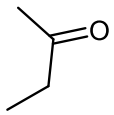
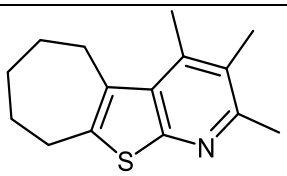
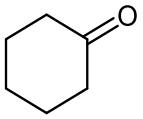
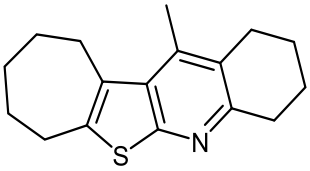
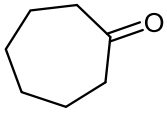
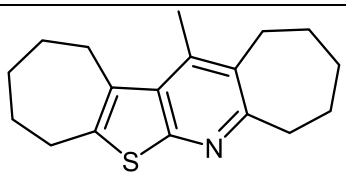
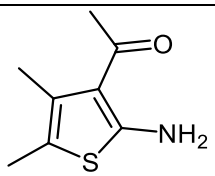
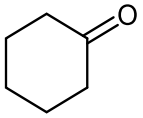
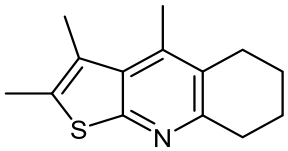
Scheme 63

Secondly, the cyclization process occurs through two steps, as the carbonyl carbon attacks the active methylene of the carbonyl compound to form an intermediate **II** which subsequently losses the second water molecule to afford the final product **170** (Scheme 63).

Table 5 Products and the yields Friedländer condensation between of 3-acetyl-2-aminothiophenes and ketones.

Thiophenes	Ketone	4-methylthieno[2,3-*b*]pyridine	Yield
	56	**174**	17%
47	**44**	**175**	26%
	54	**176**	46%
45	**44**	**177**	38%

 **49**	 **56**	 **178**	47%
	 **44**	 **179**	39%
	 **54**	 **180**	33%
 **51**	 **56**	 **181**	9%
	 **44**	 **182**	39%
	 **54**	 **183**	21%
 **53**	 **56**	 **184**	26%
	 **44**	 **185**	29%

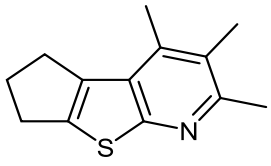
 **55**	 **56**	 **186**	34%
	 **44**	 **187**	21%
	 **54**	 **188**	22%
 **57**	 **44**	 **189**	20%

4.3 Experimental part

4-Methylthieno[2,3-*b*]pyridine, general procedure

2 Mmol of thiophene was dissolved in 5 ml of absolute ethanol, 3 mmol of ketone and 15 mol% of cerium ammonium nitrate (CAN) were added. The reaction mixture was refluxed for 48 hours, then the solution was treated by ice and water, extracted by EtOAc, dried over Na_2SO_4 *anhyd* and concentrated under vacuum. The residue was purified by flash column chromatography using (cyclohexane – EtOAc, 9:1) as eluent.

,3,4-Trimethyl-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (174)



Yield: 17%; yellow solid; mp 148 °C.

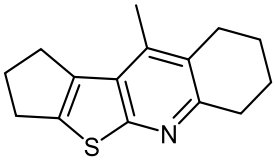
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.19 – 3.07 (m, 2 H), 3.02 (t, *J* = 7.4 Hz, 2 H), 2.61 (s, 3 H), 2.56 (s, 3 H), 2.53 – 2.45 (m, 2 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1, 152.4, 140.7, 139.6, 136.7, 128.2, 126.2, 30.9, 29.7, 27.5, 23.2, 16.1, 14.7.

HRMS (ESI): *m*/*z* calcd for $[C_{13}H_{15}NS + H]^+$: 218.0998; found: 218.0997.

Anal. Calcd for $C_{13}H_{15}NS$: C, 71.85; H, 6.96; N, 6.45; S, 14.75. Found: C, 71.35; H, 7.20; N, 6.99; S, 14.00.

10-Methyl-2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]quinolone (175)



Yield: 26%; orange solid; mp 114-116 °C.

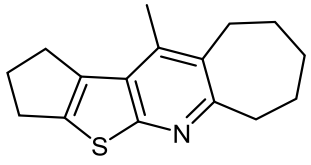
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 – 3.06 (m, 2 H), 3.06 – 2.94 (m, 2 H), 2.78 – 2.74 (m, 2 H), 2.56 – 2.39 (m, 5 H), 2.03 – 1.69 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 153.3, 140.3, 139.3, 136.5, 127.8, 126.8, 33.4, 30.9, 29.8, 27.4, 26.0, 23.2, 22.9, 15.0.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{17}NS + H]^+$: 244.1154; found: 244.1143.

Anal. Calcd for $C_{15}H_{17}NS$: C, 74.03; H, 7.04; N, 5.76; S, 13.17. Found: C, 74.04; H, 7.44; N, 5.79; S, 12.76.

11-Methyl-1,2,3,6,7,8,9,10-octahydrocyclohepta[*b*]cyclopenta[4,5]thieno[3,2-*e*]pyridine (176)



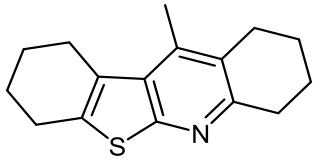
Yield: 46%; white solid; mp 148-150 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.18 – 3.08 (m, 4 H), 3.04 – 3.00 (m, 2 H), 2.94 – 2.85 (m, 2 H), 2.59 (s, 3 H), 2.55 – 2.29 (m, 2 H), 1.92 – 1.86 (m, 2 H), 1.78 – 1.70 (m, 2 H), 1.68 – 1.63 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.3, 159.4, 140.5, 137.9, 136.9, 132.7, 128.1, 38.9, 32.1, 31.1, 29.8, 28.1, 27.5, 27.4, 26.8, 15.8.

HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{19}NS + H]^+$: 258.1311; found: 258.1312.

11-Methyl-1,2,3,4,7,8,9,10-octahydrobenzo[4,5]thieno[2,3-*b*]quinolone (177)



Yield: 38%; yellow solid; mp 116-118 °C.

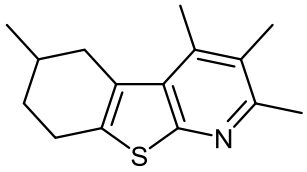
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.02-3.00 (m, 4 H), 2.88-2.84 (m, 2 H), 2.76-2.73 (m, 2 H), 2.55 (s, 3H), 1.94 – 1.84 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.1, 153.3, 140.2, 135.2, 130.6, 127.8, 126.8, 33.4, 28.1, 26.3, 26.2, 23.4, 23.2, 22.8, 22.6, 15.4.

HRMS (ESI): *m*/*z* calcd for $[C_{16}H_{19}NS + H]^+$: 258.1304; found: 258.1311.

Anal. Calcd for $C_{16}H_{19}NS$: C, 74.66; H, 7.44; N, 5.44; S, 12.46. Found: C, 74.05; H, 7.44; N, 5.70; S, 12.38.

2,3,4,6-Tetramethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (178)



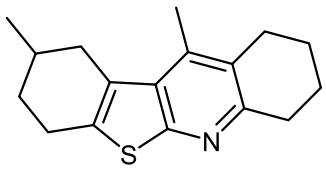
Yield: 47%; orange solid; mp 100-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.19 – 3.14 (m, 1 H), 2.91 – 2.88 (m, 2 H), 2.61 (s, 3 H), 2.60 (s, 3 H), 2.58 – 2.46 (m, 1 H), 2.28 (s, 3 H), 2.02 – 1.84 (m, 2 H), 1.57 – 1.47 (m, 1 H), 1.15 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.1, 152.5, 140.4, 135.1, 130.8, 127.5, 126.2, 34.3, 31.3, 28.8, 27.8, 23.4, 21.3, 16.4, 14.9.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{19}NS + H]^+$: 246.1311; found: 246.1339.

2,11-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzo[4,5]thieno[2,3-*b*]quinolone (179)



Yield: 39%; yellow solid; mp 88 °C.

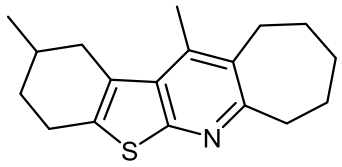
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.25 – 3.09 (m, 1 H), 3.04 – 2.99 (s, 2 H), 2.91 – 2.87 (m, 2 H), 2.79 – 2.72 (m, 2 H), 2.73 – 2.59 (m, 1 H), 2.56 (s, 3 H), 2.01 – 1.71 (m, 6 H), 1.60 – 1.43 (m, 1 H), 1.15 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.90, 152.9, 140.9, 135.2, 130.8, 127.7, 126.6, 36.6, 30.7, 29.4, 26.3, 26.0, 23.3, 22.7, 22.3, 21.8, 15.6.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{21}NS + H]^+$: 272.1467; found: 272.1469.

Anal. Calcd for $C_{17}H_{21}NS$: C, 75.23; H, 7.80; N, 5.16; S, 11.81. Found: C, 75.03; H, 7.69; N, 5.46; S, 12.19.

2,12-Dimethyl-2,3,4,7,8,9,10,11-octahydro-1*H*-benzo[4,5]thieno[2,3-*b*]cyclohepta[*e*]pyridine (180)

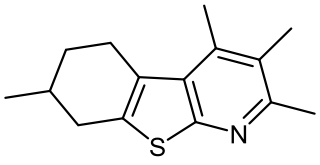


Yield: 33%; white solid; mp 120-122 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.15 – 3.02 (m, 3 H), 2.88 – 2.72 (m, 4 H), 2.57 (s, 3 H), 2.53 – 2.35 (m, 1 H), 1.93 – 1.71 (m, 3 H), 1.69 – 1.59 (m, 2 H), 1.59 – 1.53 (m, 2 H), 1.49 – 1.34 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 150.3, 139.1, 135.4, 133.0, 128.0, 127.4, 36.7, 31.9, 30.7, 29.7, 29.4, 28.0, 27.2, 26.7, 26.0, 21.8, 16.4.

2,3,4,7-Tetramethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (181)



Yield: 9%; orange solid; mp 158-160 °C.

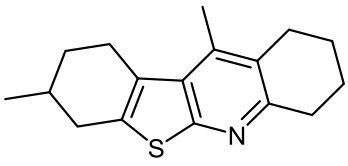
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.13 – 2.98 (m, 1 H), 2.97 – 2.75 (m, 2 H), 2.53 (s, 3H), 2.51 (s, 3 H), 2.43 – 2.37 (m, 1 H) 2.20 (s, 3 H), 2.05 – 1.86 (m, 2 H), 1.46 – 1.36 (m, 1 H), 1.03 (d, *J* = 6.5 Hz, 3 H).

13C NMR (100 MHz, CDCl3) δ = 157.0, 152.5, 140.2, 135.2,130.8, 127.5, 126.2, 34.3, 31.3, 28.8, 27.8, 23.5, 21.3, 16.4, 14.9.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{20}NS + H]^+$: 246.1311; found: 246.1311.

Anal. Calcd for $C_{15}H_{19}NS.5\%H_2O$: C, 69.75; H, 7.97; N, 5.42; S, 12.41. Found: C, 69.72; H, 7.69; N, 5.84; S, 12.44.

3,11-Dimethyl-1,2,3,4,7,8,9,10-octahydrobenzo[4,5]thieno[2,3-*b*]quinolone (182)



Yield: 39%; white solid; mp 120-122 °C.

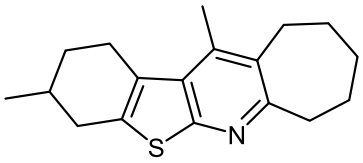
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.18 – 3.08 (m, 1 H), 3.03 – 2.99 (m, 2 H), 2.96 – 2.85 (m, 1 H), 2.77 – 2.73 (m, 2 H), 2.55 (s, 1 H), 2.52 – 2.44 (m, 1 H), 2.02 – 1.94 (m, 2 H), 1.94 – 1.83 (m, 5 H), 1.56 – 1.45 (m, 1 H), 1.12 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.1, 153.3, 140.2, 134.90, 130.4, 127.4, 126.8, 34.3, 33.4, 31.3, 28.8, 27.8, 26.3, 23.4, 22.8, 21.3, 15.4.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{21}NS + H]^+$: 272.1467; found: 272.1474.

Anal. Calcd for $C_{17}H_{21}NS.2\%H_2O$: C, 73.72; H, 7.86; N, 5.05; S, 11.57. Found: C, 73.21; H, 7.60; N, 5.62; S, 11.58.

12-Methyl-2,3,4,7,8,9,10,11-octahydro-1*H*-benzo[4,5]thieno[2,3-*b*]cyclohepta[*e*]pyridine (183)



Yield: 21%; white solid; mp 126-128 °C.

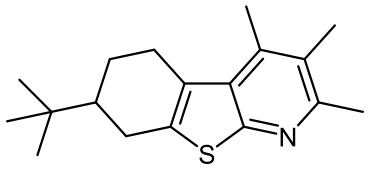
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.23 – 3.02 (m, 3 H), 3.05 – 2.78 (m, 4 H), 2.65 (s, 3 H), 2.57 – 2.40 (m, 1 H), 2.02 – 1.97 (m, 2 H), 1.93 – 1.79 (m, 2 H), 1.75 – 1.62 (m, 4 H), 1.55 – 1.45 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4, 157.1, 138.8, 135.2, 132.9, 130.6, 127.7, 38.8, 34.4, 32.0, 31.4, 28.8, 28.0, 27.9, 27.3, 26.8, 21.3, 16.2.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{23}NS + H]^+$: 286.1624; found: 286.1644.

Anal. Calcd for $C_{18}H_{23}NS$: C, 75.74; H, 8.12; N, 4.91; S, 11.23. Found: C, 76.02; H, 8.08; N, 5.60; S, 11.62.

7-(*tert*-Butyl)-2,3,4-trimethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (184)



Yield: 26%; orange solid; mp 134-136 °C.

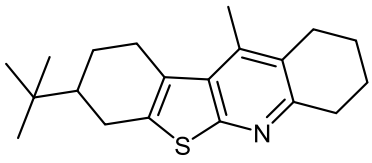
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.24 – 3.19 (m, 1 H), 2.94 – 2.87 (m, 2 H), 2.63 (m, 1 H), 2.64 (s, 3 H), 2.61 (s, 3 H), 2.29 (s, 3 H), 2.15 – 2.10 (m, 1 H), 1.60 (m, 1 H), 1.49 – 1.33 (m, 1 H), 0.98 (s, 9 H).

^{13}C NMR (100 MHz, CDCl3) δ = 157.4, 152.6, 140.1, 136.1, 130.6, 127.8, 126.1, 44.5, 32.4, 31.9, 29.7, 27.8, 27.4, 24.8, 23.6, 22.7, 16.2, 14.9.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{25}NS+ H]^+$: 288.1780; found: 288.1771.

Anal. Calcd for $C_{18}H_{25}NS$: C, 75.21; H, 8.77; N, 4.87; S, 11.15. Found: C, 74.11; H, 8.74; N, 5.35; S, 10.94.

3-(*tert*-Butyl)-11-methyl-1,2,3,4,7,8,9,10-octahydrobenzo[4,5]thieno[2,3-*b*]quinolone (185)



Yield: 29%; orange solid; mp 86-88 °C.

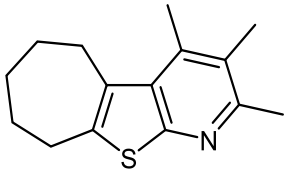
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.26 – 3.14 (m, 1 H), 3.07 – 2.96 (m, 2 H), 2.96 – 2.80 (m, 2 H), 2.78 – 2.69 (m, 2 H), 2.70 – 2.56 (m, 1 H), 2.53 (s, 3 H), 2.17 – 2.04 (m, 1 H), 1.97 – 1.79 (m, 4 H), 1.65 – 1.53 (m, 1 H), 1.48 – 1.34 (m, 1 H), 0.98 (s, 9 H).

^{13}C NMR (100 MHz, CDCl3) δ = 158.1, 152.3, 140.7, 135.9, 131.0, 127.2, 126.4, 44.5, 32.4, 31.9, 29.7, 28.5, 27.8, 27.4, 24.8, 23.6, 22.7, 22.1, 20.8, 16.2.

HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{27}NS + H]^+$: 314.1937; found: 314.1977.

Anal. Calcd for $C_{20}H_{27}NS.2\%H_2O$: C, 75.09; H, 8.73; N, 4.37; S, 10.02. Found: C, 75.30; H, 8.58; N, 4.91; S, 9.99.

2,3,4-Trimethyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*b*]pyridine (186)



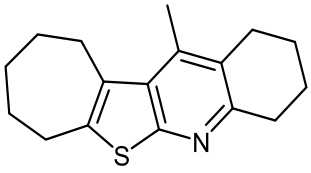
Yield: 34%; orange solid; mp 84-86 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.18–316 (m, 2 H), 2.93–2.91 (m, 2 H), 2.64 (s, 3 H), 2.61 (s, 3 H), 2.31 (s, 3 H), 1.96–1.90 (m, 2 H), 1.84 – 1.69 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.5, 152.6, 139.6, 139.5, 133.3, 131.5, 126.2, 31.7, 29.7, 29.5, 27.2, 26.6, 23.7, 17.1, 15.1.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{19}NS + H]^+$: 246.1311; found: 246.1306.

12-Methyl-2,3,4,7,8,9,10,11-octahydro-1*H*-cyclohepta[4,5]thieno[2,3-*b*]quinolone (187)



Yield: 21%; orange solid; mp 77-78 °C.

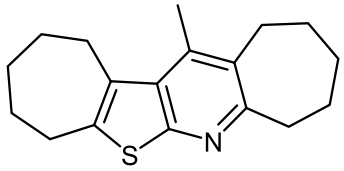
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.24 – 3.10 (m, 2 H), 3.05 – 2.92 (m, 2 H), 2.92 (dd, *J* = 12.0, 6.5 Hz, 2 H), 2.84 – 2.72 (m, 2 H), 2.58 (s, 3 H), 1.95 – 1.83 (m, 6 H), 1.83 – 1.65 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 152.7, 140.4, 133.9, 131.8, 127.1, 126.9, 33.0, 32.0, 29.5, 29.4, 27.3, 26.5, 23.3, 22.6, 22.4, 16.1.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{21}NS + H]^+$: 272.1467; found: 272.1472.

Anal. Calcd for $C_{17}H_{21}NS.2\%H_2O$: C, 73.72; H, 7.86; N, 5.05; S, 11.57. Found: C, 75.38; H, 7.61; N, 5.91; S, 11.92.

13-Methyl-1,2,3,4,5,8,9,10,11,12-decahydrocyclohepta[4,5]thieno[2,3-*b*]cyclohepta[*e*]pyridine (188)



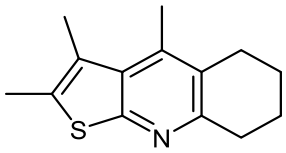
Yield: 22%; brown solid; mp 164-166 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.19 – 3.13 (m, 2 H), 3.14 – 3.08 (m, 2 H), 2.97 – 2.89 (m, 4 H), 2.66 (s, 3 H), 1.95 – 1.84 (m, 4 H), 1.83 – 1.70 (m, 6 H), 1.68 – 1.63 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.09, 156.5, 140.1, 138.7, 133.6, 133.1, 131.8, 38.5, 31.9, 31.7, 29.8, 29.6, 28.2, 27.3, 26.8, 26.6, 17.1.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{23}NS + Na]^+$: 308.1443; found: 308.1439.

2,3,4-Trimethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolone (189)



Yield: 20%; white solid; mp 97-100 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.06 – 2.91 (m, 2 H), 2.75 – 2.65 (m, 2 H), 2.55 (s, 3 H), 2.41 (s, 3 H), 2.38 (s, 3 H), 1.90 – 1.70 (m, 4 H).

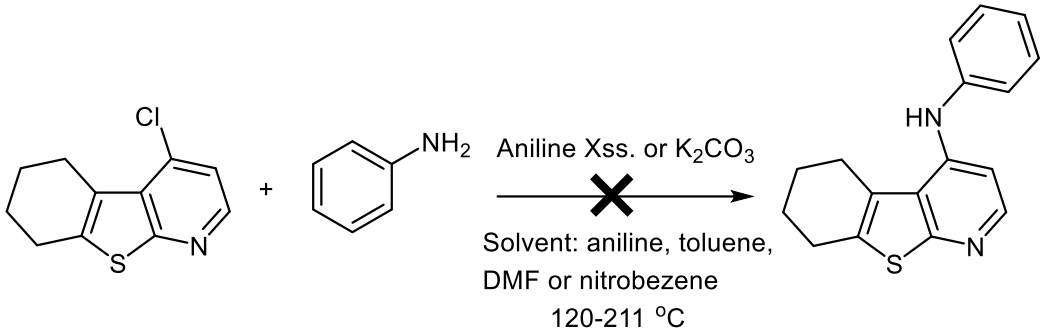
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.5, 150.9, 138.7, 133.0, 132.3, 126.0, 125.6, 30.7, 29.7, 26.0, 22.7, 20.8, 15.4, 14.1.

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{17}NS + H]^+$: 232.1154; found: 232.1136.

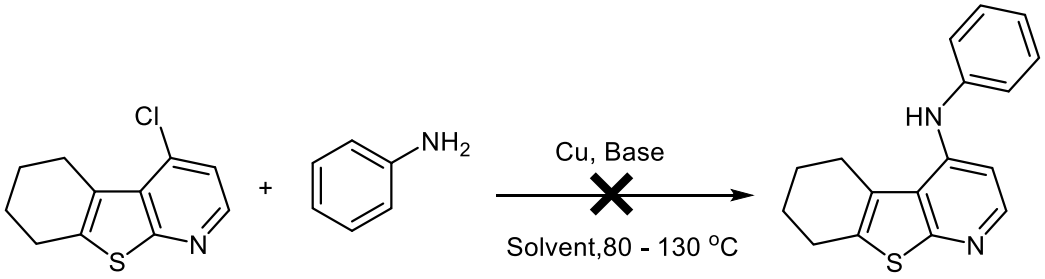
Chapter 5- *C-N* coupling between 4-chlorothieno[2,3-*b*]pyridine derivatives and aromatic amines

Résumé chapitre 5: Couplage *C-N* entre les 4-chlorothiéno[2,3-*b*]pyridines et les anilines

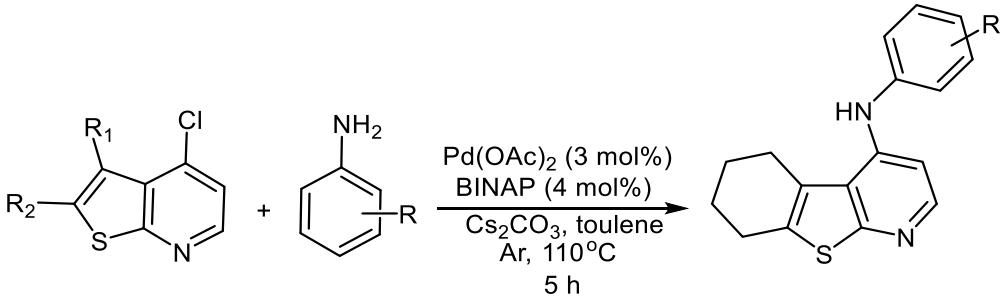
En possession d'analogues quinoléiniques chlorés, il était intéressant d'étudier leur réactivité dans le cadre de réaction de substitution nucléophile aromatique. Une brève introduction sur ce type de réaction ainsi que celles catalysées par les métaux de transition est présentée. Divers essais ont été faits, de manière directe, dans les conditions d'Ullmann et de Buchwald-Hartwig. Si les deux premières n'ont pas donné de résultats, la dernière méthode a permis le couplage avec des anilines.



Condensation directe



Condensation d'Ullmann



Couplage Buchwald-Hartwig

5 *C-N* coupling between 4-chlorothieno[2,3-*b*]pyridine Derivatives and aromatic amines

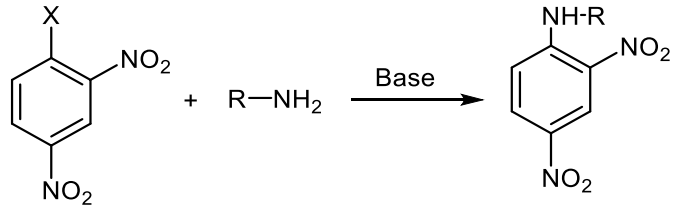
5.1 Introduction

Synthesis of 4-chlorothieno[2,3-*b*]pyridine derivatives have introduced another perspective in their chemistry. Presence of chlorine atom, was motivation of more lead structure development and alteration. The liability of these atom would pave a new path toward synthesizing more derivatives, hopefully some of them will have certain biological activity.

To explore the reactivity of chlorine atom, thienopyridines were exposed to nucleophilic substitution using different amines. This substitution was tried in different conditions, simple nucleophilic substitution, of Ullmann coupling conditions and Buchwald-Hartwig cross coupling.

5.1.1 Nucleophilic substitution

Reaction between amines and aromatic halide need more drastic condition than that described for alkyl halide. The substitution to be accomplished needs at least one of activating group to facilitate the replacement of the halogen e.g. nitro group (Scheme 64).[91]



190 **191** **192**

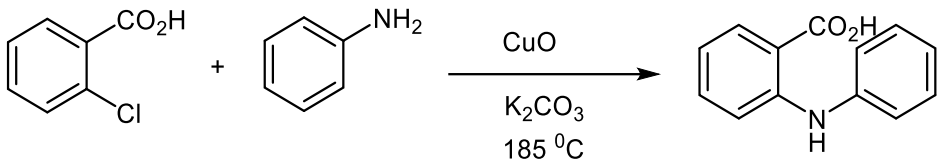
Scheme 64

5.1.2 Ullmman reaction

Ullmann reaction has become one of the general methods for (*C-N*) bond formations *via* the copper-mediated coupling of aryl and vinyl halides to aromatic nitrogen

[91] Vogel, *Textbook of Practical Organic Chemistry 5th Ed*.

heterocycles or amines and amides (Scheme 65).[92] It has been applied in the synthesis of natural products compounds with medicinal importance,[93] in pharmaceuticals[94] and their applications in materials research as well as in the synthesis of dyes.[95]



193 **194** **195**

Scheme 65

5.1.2.1 Mechanism

The role of copper as a catalyst is generally believed to take part in successive oxidative addition, transmetallation, and reductive elimination reactions (Scheme 66).[96]

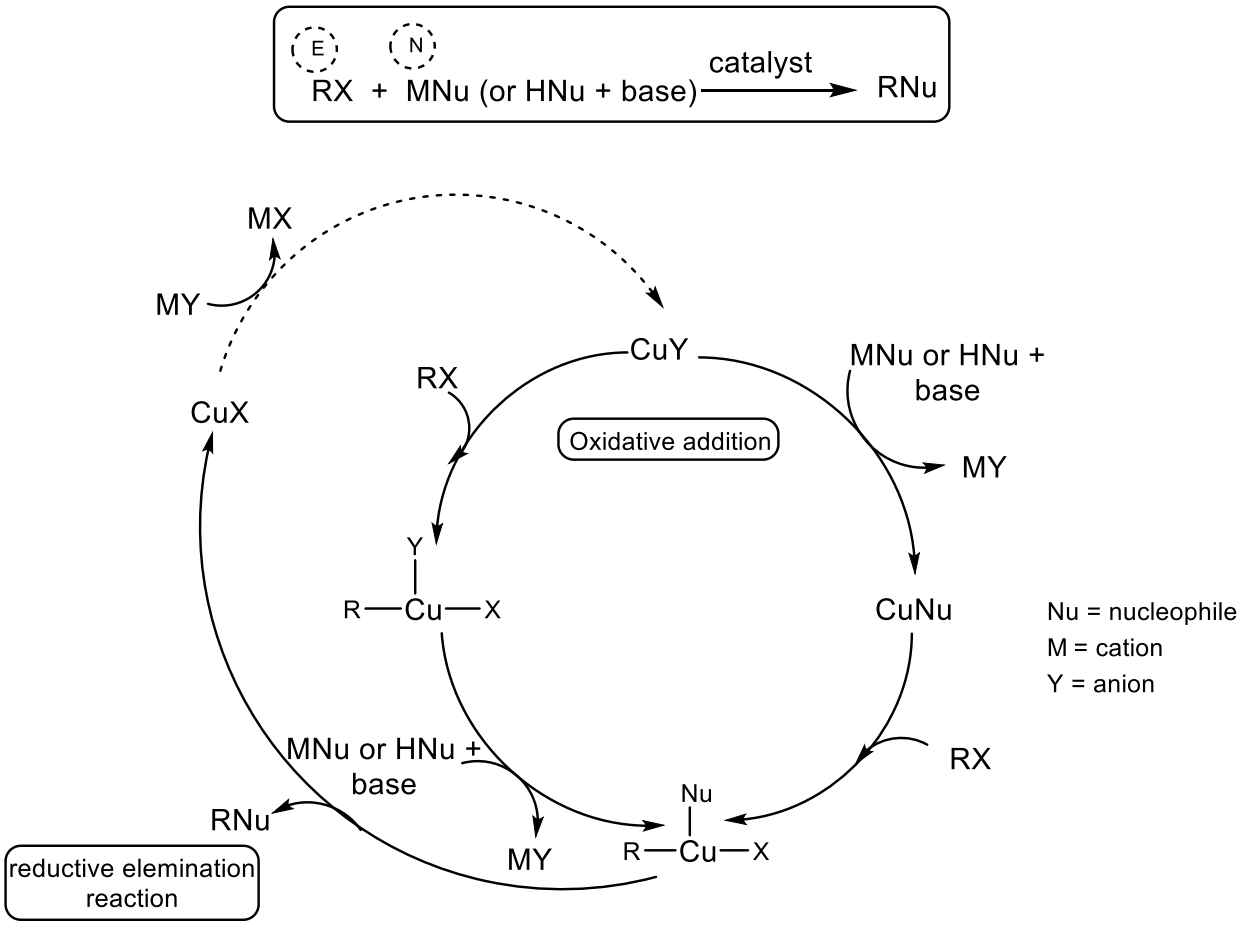
[92] F. Ullmann, "Ueber Eine Neue Bildungsweise von Diphenylaminderivaten," *Berichte Der Deutschen Chemischen Gesellschaft* 36, no. 2 (April 1, 1903): 2382–84, doi:10.1002/cber.190303602174.

[93] Hongwei Jin et al., "Copper-Catalyzed Cascade Reactions of N-(2-Bromoallyl)amines with $KHCO_3$ as the C1 Source: An Efficient Process for the Synthesis of Oxazolidin-2-Ones," *RSC Advances* 4, no. 51 (June 19, 2014): 26990–92, doi:10.1039/C4RA02304H.

[94] M. Romero et al., "Preparation of N-Arylpiperazines and Other N-Aryl Compounds from Aryl Bromides as Scaffolds of Bioactive Compounds," *Tetrahedron* 62, no. 38 (September 18, 2006): 9010–16, doi:10.1016/j.tet.2006.07.011; Madhu R. Sharma and M. M. V. Ramana, "KF/Al_2O_3Mediated Synthesis of N-Arylamines and Their Antifungal Activity," *Int. J. Pharm. Sci. Rev. Res* 23, no. 2 (2013): 155–163.

[95] Enas M. Malik et al., "Ullmann Reactions of 1-Amino-4-Bromoanthraquinones Bearing Various 2-Substituents Furnishing Novel Dyes," *Dyes and Pigments* 131 (August 2016): 33–40, doi:10.1016/j.dyepig.2016.03.023.

[96] F. Ullmann, "Ueber Eine Neue Bildungsweise von Diphenylaminderivaten," *Berichte Der Deutschen Chemischen Gesellschaft* 36, no. 2 (April 1, 1903): 2382–84, doi:10.1002/cber.190303602174.



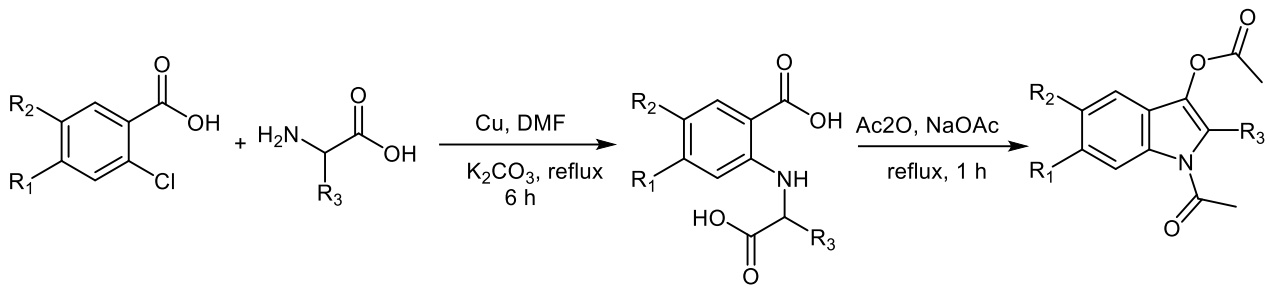
Scheme 66 The reaction mechanism of Ullmman cross coupling reaction

5.1.2.2 Ligand-free Ullmann synthesis

In our group, we developed simple method of synthesizing 2-Substituted 3-acetoxy-1-acetyl-1*H*-indoles **199** in only two steps *via* Ullmann coupling between chlorobenzoic acid **196** and amino acids **197** and using copper powder and DMF (Scheme 67).[97] Wolf *et al* made coupling between bromobenzoic acid **200** and aniline derivatives **201** in presence of catalytic amount of copper powder and Cu_2O

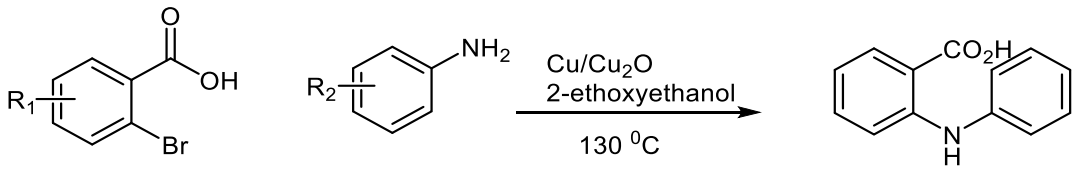
[97] Alexander Balbuzano-Deus et al., "A Simple Procedure for the Preparation of 6-Chloro-3-Acetoxy-1-Acetylindole," *Organic Preparations and Procedures International* 38, no. 1 (February 1, 2006): 87–88, doi:10.1080/00304940609355983; Juan Rodriguez Dominguez, Xiao Gang, and Gilbert Kirsch, "The Ullmann Coupling between 2-Chlorobenzoic Acids and Amino Acids; A Valuable Reaction for Preparing 2-Substituted 1-Acetyl-1*H*-Indol-3-yl Acetates-," *Synthesis* 2009, no. 14 (July 2009): 2345–48, doi:10.1055/s-0029-1216851.

Scheme 68).[98]



196 **197** **198** **199**

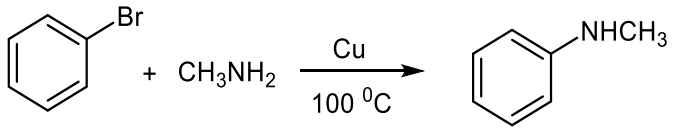
Scheme 67



200 **201** **202**

Scheme 68

In aqueous medium and open air and inert environment, several derivatives of bromobenzene were coupled with methyl amine solution, the copper catalyses were elemental copper, copper (I) oxide Cu_2O or copper (II) oxide CuO. This reaction was proceeded without bases or by presence of triethyl amine, sodium carbonate potassium carbonate or tripotassium phosphate (Scheme 69).[99]



203 **204** **205**

Scheme 69

[98] Christian Wolf et al., "Regioselective Copper-Catalyzed Amination of Bromobenzoic Acids Using Aliphatic and Aromatic Amines," *The Journal of Organic Chemistry* 71, no. 8 (April 1, 2006): 3270–73, doi:10.1021/jo060034a.

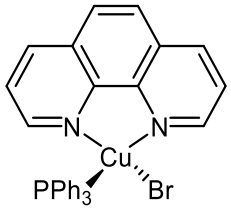
[99] Jiao Jiao et al., "A Facile and Practical Copper Powder-Catalyzed, Organic Solvent- and Ligand-Free Ullmann Amination of Aryl Halides," *The Journal of Organic Chemistry* 76, no. 4 (February 18, 2011): 1180–83, doi:10.1021/jo102169t.

5.1.2.3 Role of ligand

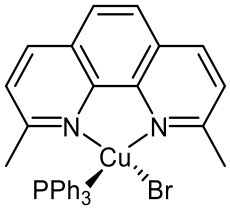
The Ullmann reaction showed a lot of disadvantages; high temperature and need of high boiling polar solvents (Scheme 65) could be overcome by using of copper-ligand complexes.[100]

Development of ligands for Ullmann type copper catalysed coupling reactions has been done to improve reaction conditions with wider substrate scope. Therefore, extensive research efforts have been devoted to promote alternative ligands to run over the limitations of copper catalysed reactions in Ullmann type couplings in order to reduce the catalyst loadings and increase the yields using moderate reaction conditions.[101]

In 2001, in an effort for increase the copper (I) salts solubility in the organic solvent and hence increasing their catalytic capacity, Cu(phen)(PPh_3)Br **206** and Cu(neocup)(PPh3)Br **207** were prepared and performed will in *C-N* coupling (Scheme 70).[102]



206



207

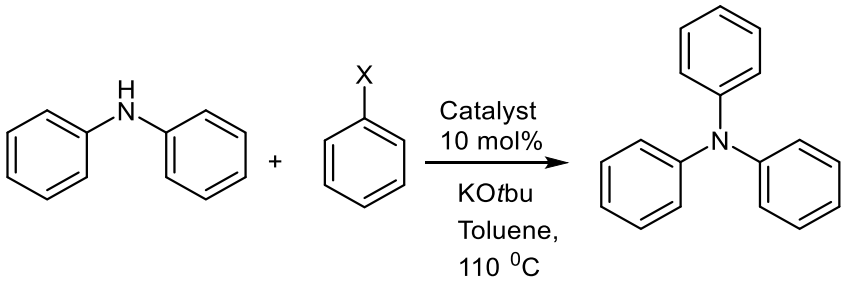
Kwong *et al*., 2002[103] reported a mild, practical Cu-catalyzed amination of functionalized aryl iodides using ethylene glycol, propylene and butylene glycols as ligands and isopropanol as the solvent in open air medium (Scheme 71).

[100] Irina P. Beletskaya and Andrei V. Cheprakov, "Copper in Cross-Coupling Reactions: The Post-Ullmann Chemistry," *Coordination Chemistry Reviews*, Vignettes of Homogeneous Catalysis, 248, no. 21–24 (December 2004): 2337–64, doi:10.1016/j.ccr.2004.09.014.

[101] Ibid.; Florian Monnier and Marc Taillefer, "Catalytic C-C, C-N, and *C-O* Ullmann-Type Coupling Reactions: Copper Makes a Difference," *Angewandte Chemie International Edition* 47, no. 17 (April 14, 2008): 3096–99, doi:10.1002/anie.200703209.

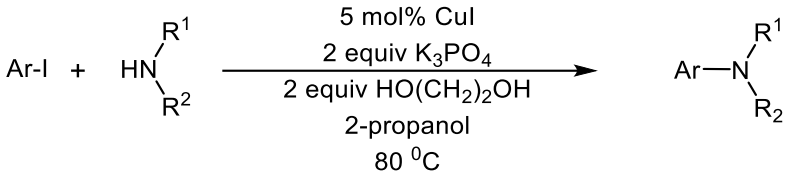
[102] Rattan K. Gujadhur, Craig G. Bates, and D. Venkataraman, "Formation of Aryl−Nitrogen, Aryl−Oxygen, and Aryl−Carbon Bonds Using Well-Defined Copper(I)-Based Catalysts," *Organic Letters* 3, no. 26 (December 1, 2001): 4315–17, doi:10.1021/ol0170105.

[103] Fuk Yee Kwong, Artis Klapars, and Stephen L. Buchwald, "Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere," *Organic Letters* 4, no. 4 (February 21, 2002): 581–84.



208 **209** **210**

Scheme 70

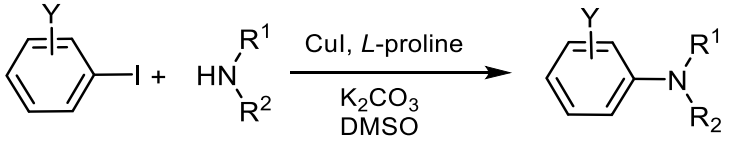


211 **212** **213**

Scheme 71

Control experiments revealed that no reaction was observed in the absence of ethylene glycol. Moreover, the yield of the reaction increased as the solvent 2-propanol was used as compared to the reaction performed in ethylene glycol.[104]

On the other hand, Ma *et al*., in 2003 demonstrated Ullmann-type aryl amination of aryl iodides in DMSO at 40-90 °C by using the amino acid *L*-proline as a ligand to give the corresponding *N*-arylamines or *N,N*-diarylamines in good to excellent yields.[105]



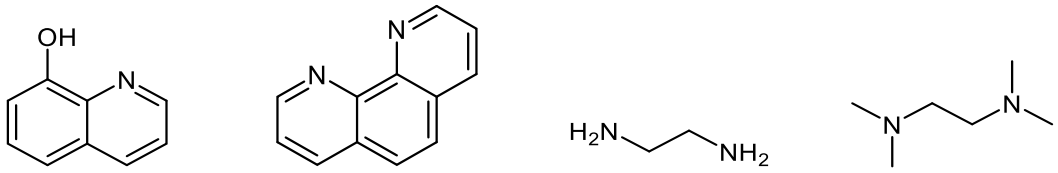
214 **212** **215**

Scheme 72

[104] Ibid.

[105] Dawei Ma, Qian Cai, and Hui Zhang, "Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides," *Organic Letters* 5, no. 14 (July 2003): 2453–55, doi:10.1021/ol0346584.

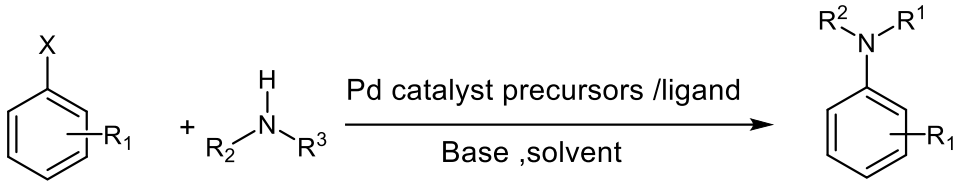
Some other ligands which has been in use for catalyzing of this kind of reaction are 8-hydroxyquinoline **216**, 1,10 phenanthroline **217** ethylenediamine **218** and TMEDA **219**.[106]



216 **217** **218** **219**

5.1.3 Buchwald–Hartwig cross coupling (Buchwald–Hartwig amination)

Buchwald–Hartwig cross coupling is a chemical reaction used for the synthesis of carbon-nitrogen bonds *via* the palladium-catalyzed cross-coupling of amines **221** with aryl halides **220** (Scheme 73).[107]



220 **221** **222**

Scheme 73

5.1.3.1 Mechanism

The reaction mechanism for this reaction has been demonstrated to proceed through steps includes oxidative addition of the aryl halide to a Pd(0) species; addition of

[106] Ashutosh A. Kelkar, Nandkumar M. Patil, and Raghunath V. Chaudhari, "Copper-Catalyzed Amination of Aryl Halides: Single-Step Synthesis of Triarylamines," *Tetrahedron Letters* 43, no. 40 (September 30, 2002): 7143–46, doi:10.1016/S0040-4039(02)01708-2; Lingkai Kong et al., "Copper-Catalyzed Synthesis of Substituted Quinolines via *C–N* Coupling/Condensation from *Ortho* -Acylanilines and Alkenyl Iodides," *The Journal of Organic Chemistry* 80, no. 2 (January 16, 2015): 1275–78, doi:10.1021/jo502630t; Klaus Kunz, Ulrich Scholz, and Dirk Ganzer, "Renaissance of Ullmann and Goldberg Reactions - Progress in Copper Catalyzed *C-N*-, *C-O*- and *C-S*-Coupling," *Synlett*, no. 15 (2003): 2428–39, doi:10.1055/s-2003-42473.

[107] Anil S. Guram, Roger A. Rennels, and Stephen L. Buchwald, "A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines," *Angewandte Chemie International Edition in English* 34, no. 12 (1995): 1348–1350; Janis Louie and John F. Hartwig, "Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents," *Tetrahedron Letters* 36, no. 21 (1995): 3609–3612.

the amine to the oxidative addition complex, deprotonation followed by reductive elimination (Scheme 74).[108]

5.1.3.1.1 Oxidative addition step

Oxidative addition products [$PdArXL_n$] exhibit anticipated catalytic activity [109] therefore; it has been received substantial attention in the literature in a trail to maximize the rate of the oxidative addition. The rate of oxidative addition depends on the electronic and steric properties of the catalyst and substrate; the more electron-rich and sterically unhindered the catalyst, the higher the rate of the oxidative addition.[110]

5.1.3.1.2 Amine coordination step

The rate of amine coordination depends on the catalyst and the substrate properties. When the amine substrate is more basic and/or is sterically unhindered, the rate of amine binding is higher. The rate of deprotonation of the bound amine is determined by the acidity of the amine, which increases on coordination to the metal.[111]

[108] David S. Surry and Stephen L. Buchwald, "Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide," *Chemical Science* 2, no. 1 (December 6, 2010): 27–50, doi:10.1039/C0SC00331J.

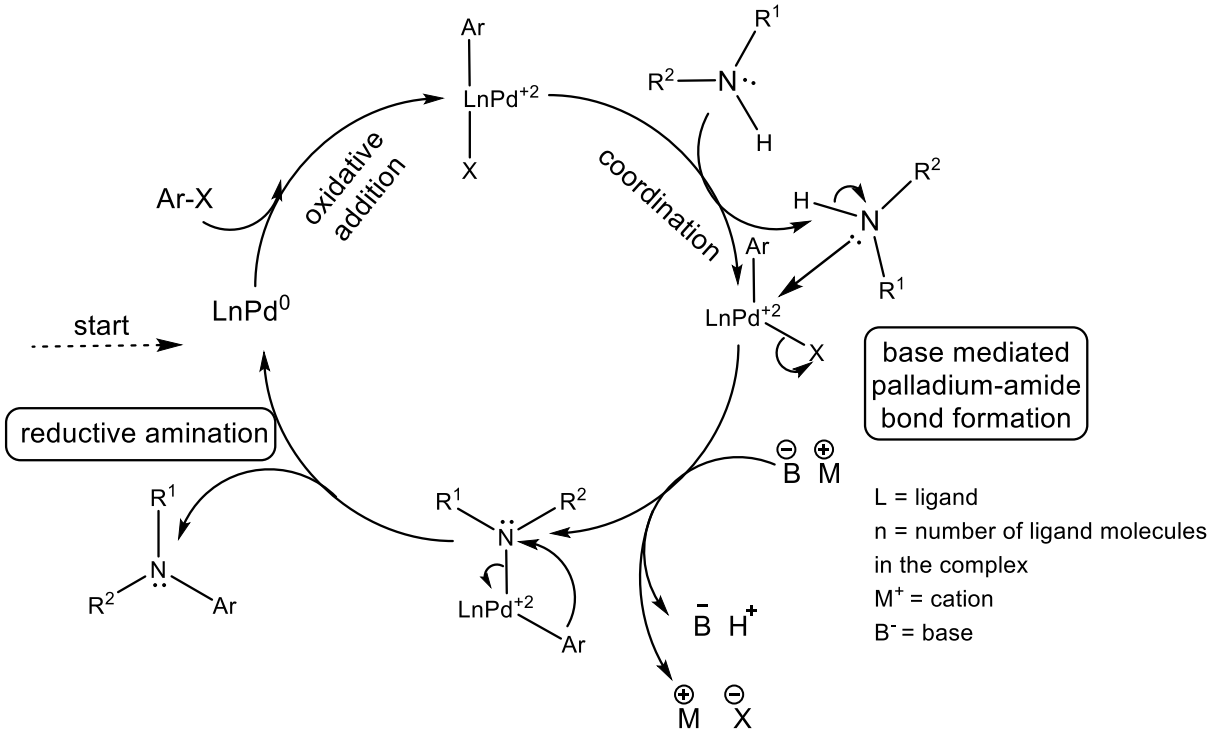
[109] Pamela G. Alsabeh et al., "An Examination of the Palladium/Mor-DalPhos Catalyst System in the Context of Selective Ammonia Monoarylation at Room Temperature," *Chemistry (Weinheim an Der Bergstrasse, Germany)* 19, no. 6 (February 4, 2013): 2131–41, doi:10.1002/chem.201203640; Bennett J. Tardiff and Mark Stradiotto, "Buchwald–Hartwig Amination of (Hetero)aryl Chlorides by Employing Mor-DalPhos under Aqueous and Solvent-Free Conditions," *European Journal of Organic Chemistry* 2012, no. 21 (July 1, 2012): 3972–77, doi:10.1002/ejoc.201200510; Rylan J. Lundgren et al., "A P,*N*-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions," *Angewandte Chemie International Edition* 49, no. 24 (June 1, 2010): 4071–74, doi:10.1002/anie.201000526.

[110] Fabiola Barrios-Landeros, Brad P. Carrow, and John F. Hartwig, "Effect of Ligand Steric Properties and Halide Identity on the Mechanism for Oxidative Addition of Haloarenes to Trialkylphosphine Pd(0) Complexes," *Journal of the American Chemical Society* 131, no. 23 (June 17, 2009): 8141–54, doi:10.1021/ja900798s; Giang D. Vo and John F. Hartwig, "Palladium-Catalyzed Coupling of Ammonia with Aryl Chlorides, Bromides, Iodides, and Sulfonates: A General Method for the Preparation of Primary Arylamines," *Journal of the American Chemical Society* 131, no. 31 (August 12, 2009): 11049–61, doi:10.1021/ja903049z; Isabel C.F.R Ferreira, Maria-João R.P Queiroz, and Gilbert Kirsch, "Synthesis of Diarylamines in the Benzo[*b*]thiophene Series Bearing Electron Donating or Withdrawing Groups by Buchwald–Hartwig *C–N* Coupling," *Tetrahedron* 59, no. 7 (February 2003): 975–81, doi:10.1016/S0040-4020(02)01656-3; Luis M. Alcazar-Roman and John F. Hartwig, "Mechanistic Studies on Oxidative Addition of Aryl Halides and Triflates to $Pd(BINAP)_2$ and Structural Characterization of the Product from Aryl Triflate Addition in the Presence of Amine," *Organometallics* 21, no. 3 (February 2002): 491–502, doi:10.1021/om0108088.

[111] Agathe Begouin et al., "Synthesis of Diarylamines in the Thiophene Series by Buchwald-Hartwig Coupling-," *Synthesis*, no. 14 (2005): 2373–78, doi:10.1055/s-2005-870014; Brett P. Fors et al., "A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides," *Journal of the American Chemical Society* 130, no. 41 (October 15, 2008): 13552–54, doi:10.1021/ja8055358; Brett P. Fors, Nicole R. Davis, and Stephen L. Buchwald, "An Efficient Process for Pd-Catalyzed *C-N* Cross-Coupling Reactions of Aryl Iodides: Insight into Controlling Factors," *Journal of the American Chemical Society* 131, no. 16 (April 29, 2009): 5766–68, doi:10.1021/ja901414u.

5.1.3.1.3 Reductive elimination step

Reductive elimination is a function of the metal/ligand properties. Since reductive elimination causes the metal to be more electron-rich and reduces the steric strain, bulkier and electron poor ligands will increase the rate of reductive elimination.[112]



Scheme 74: Mechanism of Buchwald–Hartwig cross coupling

In general, research into the Buchwald-Hartwig reaction has involved investigations of four key variables, palladium catalyst precursors, ligands, bases and solvents (Scheme 74). Other factors such as temperature, order of addition, precursor loading, and ligand to precursor ratio and even the rate of stirring, affect reaction rates and/or product distributions.

[112] Makoto Yamashita, Jose V. Cuevas Vicario, and John F. Hartwig, "Trans Influence on the Rate of Reductive Elimination. Reductive Elimination of Amines from Isomeric Arylpalladium Amides with Unsymmetrical Coordination Spheres," *Journal of the American Chemical Society* 125, no. 52 (December 31, 2003): 16347–60, doi:10.1021/ja037425g.

The nature of the halide also affects the rate of oxidative addition (I > Br >Cl> F) because the carbon-halogen bonds are broken during the oxidative addition step.[113]

5.1.3.2 Ligand

Buchwald-Hartwig coupling is mostly processed in presence of ligand. The type of ligand and the molar ratios to the substrate and the palladium source are key determining for accomplishment of the reaction.[114] Tri(*o*-tolyl)phosphine *p*(*o*-tolyl)$_3$ **223** and the chelating bisphosphines BINAP **224** are the earliest ligand in use since the development of the approach.[115] XPhos **225** is one of most stable biphenyl based ligand has been developed[116] XanthPhos **226**[117] is another example of very wide applicable ligand which

[113] Barrios-Landeros, Carrow, and Hartwig, "Effect of Ligand Steric Properties and Halide Identity on the Mechanism for Oxidative Addition of Haloarenes to Trialkylphosphine Pd(0) Complexes"; Vo and Hartwig, "Palladium-Catalyzed Coupling of Ammonia with Aryl Chlorides, Bromides, Iodides, and Sulfonates."

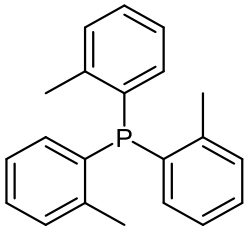
[114] Björn Schlummer and Ulrich Scholz, "Palladium-Catalyzed *C-N* and *C-O* Coupling–a Practical Guide from an Industrial Vantage Point†," *Advanced Synthesis & Catalysis* 346, no. 13–15 (December 1, 2004): 1599–1626, doi:10.1002/adsc.200404216.

[115] Guram, Rennels, and Buchwald, "A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines"; Louie and Hartwig, "Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents"; Seble Wagaw and Stephen L. Buchwald, "The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon-Nitrogen Bond Formation," *The Journal of Organic Chemistry* 61, no. 21 (1996): 7240–7241; John P. Wolfe, Seble Wagaw, and Stephen L. Buchwald, "An Improved Catalyst System for Aromatic Carbon-Nitrogen Bond Formation: The Possible Involvement of Bis (Phosphine) Palladium Complexes as Key Intermediates," *Journal of the American Chemical Society* 118, no. 30 (1996): 7215–7216; Anil S. Guram and Stephen L. Buchwald, "Palladium-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes," *Journal of the American Chemical Society* 116, no. 17 (1994): 7901–7902.

[116] Xiaohua Huang et al., "Expanding Pd-Catalyzed C−N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions," *Journal of the American Chemical Society* 125, no. 22 (June 1, 2003): 6653–55, doi:10.1021/ja035483w; Eric R. Strieter, Donna G. Blackmond, and Stephen L. Buchwald, "Insights into the Origin of High Activity and Stability of Catalysts Derived from Bulky, Electron-Rich Monophosphinobiaryl Ligands in the Pd-Catalyzed C−N Bond Formation," *Journal of the American Chemical Society* 125, no. 46 (November 1, 2003): 13978–80, doi:10.1021/ja037932y.

[117] Yannick Guari et al., "Palladium-Catalyzed Amination of Aryl Bromides and Aryl Triflates Using Diphosphane Ligands: A Kinetic Study," *Chemistry – A European Journal* 7, no. 2 (January 19, 2001): 475–82, doi:10.1002/1521-3765(20010119)7:2<475::AID-CHEM475>3.0.CO;2-6.

has showed high catalytic in different *C-N* reaction classes.[118] The high cost of the ligand is a crucial determining factor in production of large scale of the coupled products.[119]



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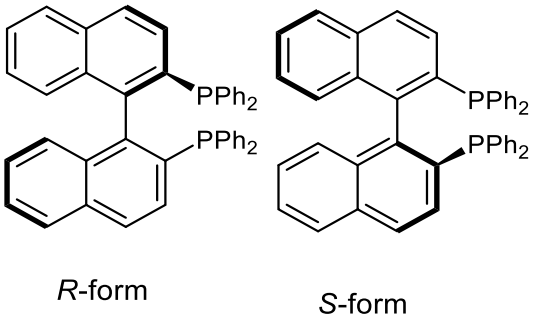
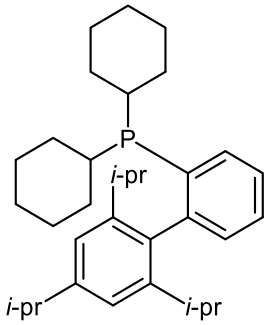
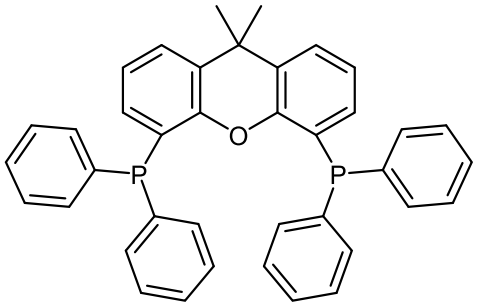


R-form *S*-form

224



225



226

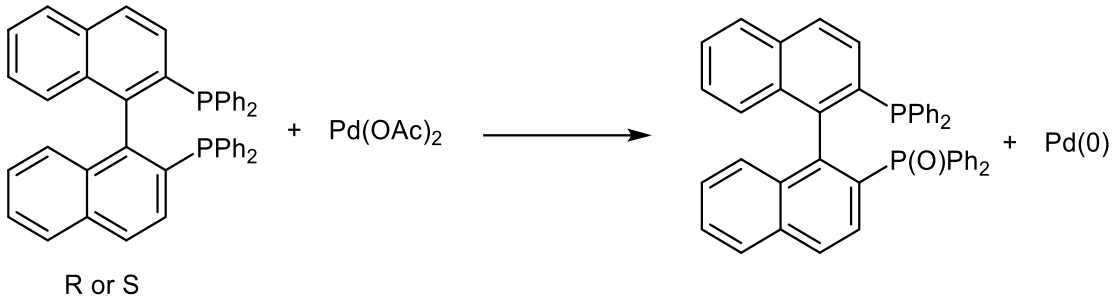
5.1.3.3 Palladium precursors

$Pd(OAc)_2$ and $Pd_2(dba)_3$ (dba: PhCH=CHCOCH=CHPh) are the common and the primary precursors which have been used for Buchwald-Hartwig reactions and they are

[118] Galina A Artamkina, Alexey G Sergeev, and Irina P Beletskaya, "Palladium-Catalyzed Reaction of Aryl Halides with Ureas," *Tetrahedron Letters* 42, no. 26 (June 25, 2001): 4381–84, doi:10.1016/S0040-4039(01)00716-X; Sandro Cacchi et al., "3-Aryl-2-Oxazolidinones through the Palladium-Catalyzed N-Arylation of 2-Oxazolidinones," *Organic Letters* 3, no. 16 (August 1, 2001): 2539–41, doi:10.1021/ol016208m; Seble Wagaw, Bryant H. Yang, and Stephen L. Buchwald, "A Palladium-Catalyzed Method for the Preparation of Indoles via the Fischer Indole Synthesis," *Journal of the American Chemical Society* 121, no. 44 (November 1, 1999): 10251–63, doi:10.1021/ja992077x; Bryant H. Yang and Stephen L. Buchwald, "The Development of Efficient Protocols for the Palladium-Catalyzed Cyclization Reactions of Secondary Amides and Carbamates," *Organic Letters* 1, no. 1 (July 1, 1999): 35–38, doi:10.1021/ol9905351; Jingjun Yin and Stephen L. Buchwald, "Palladium-Catalyzed Intermolecular Coupling of Aryl Halides and Amides," *Organic Letters* 2, no. 8 (April 1, 2000): 1101–4, doi:10.1021/ol005654r; Jingjun Yin and Stephen L. Buchwald, "Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery That Xantphos Can Be Trans-Chelating in a Palladium Complex," *Journal of the American Chemical Society* 124, no. 21 (May 1, 2002): 6043–48, doi:10.1021/ja012610k; Agathe Begouin et al., "Palladium-Catalyzed Buchwald–Hartwig Coupling of Deactivated Aminothiophenes with Substituted Halopyridines," *European Journal of Organic Chemistry* 2007, no. 10 (April 1, 2007): 1678–82, doi:10.1002/ejoc.200600951.

[119] Schlummer and Scholz, "Palladium-Catalyzed *C-N* and *C-O* Coupling–a Practical Guide from an Industrial Vantage Point†."

still being used. The palladium catalyst must be in the (0) oxidation state before the catalytic cycle initiates, and therefore the palladium (II) in $Pd(OAc)_2$ must be reduced prior to catalysis initiation [120]. $Pd(OAc)_2$ interacts *in situ* with BINAP to generate BINAP(O) and Pd(0) (Scheme 75).[121]



Scheme 75

5.1.3.4 Bases

Choosing a suitable, sufficiently strong base is another key factor in palladium-catalyzed amination reactions. *t*BuONa was the first base used[122] and it has been extensively used with dialkyl biaryl phosphine ligand systems by Buchwald and co-workers. *t*BuOK exhibits the same efficiency in some of these reactions[123] but both of these bases have some limitations because the functional group tolerance for substrates is limited. [124] Hydroxide bases KOH, NaOH have also been used recently because they are inexpensive, but they generally give lower reaction rates than alkoxides do.[125] Weak

[120] Christian Amatore et al., "Evidence for the Ligation of Palladium(0) Complexes by Acetate Ions: Consequences on the Mechanism of Their Oxidative Addition with Phenyl Iodide and PhPd(OAc)(PPh3)2 as Intermediate in the Heck Reaction," *Organometallics* 14, no. 12 (December 1, 1995): 5605–14, doi:10.1021/om00012a029; Christian Amatore, Anny Jutand, and Fouad Khalil, "Neutral palladium(0) Complexes from Pd(OAc)2 and Tri-2-Furylphosphine and Their Reactivity in Oxidative Addition of Phenyl Iodide," *Arkivoc* 2006, no. 4 (March 2, 2006): 38, doi:10.3998/ark.5550190.0007.405; Christian Amatore, Anny Jutand, and Audrey Thuilliez, "Formation of Palladium(0) Complexes from Pd(OAc)2 and a Bidentate Phosphine Ligand (Dppp) and Their Reactivity in Oxidative Addition," *Organometallics* 20, no. 15 (July 1, 2001): 3241–49, doi:10.1021/om0101137.

[121] William J. Marshall and Vladimir V. Grushin, "Palladium(II) and Palladium(0) Complexes of BINAP(O) (2-(Diphenylphosphino)-2'-(Diphenylphosphinyl)-1,1'-Binaphthyl)," *Organometallics* 22, no. 3 (February 1, 2003): 555–62, doi:10.1021/om020838q.

[122] Guram, Rennels, and Buchwald, "A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines."

[123] Johanne Renaud et al., "Selective Estrogen Receptor Modulators with Conformationally Restricted Side Chains. Synthesis and Structure-Activity Relationship of ERalpha-Selective Tetrahydroisoquinoline Ligands," *Journal of Medicinal Chemistry* 48, no. 2 (January 27, 2005): 364–79, doi:10.1021/jm040858p.

[124] Surry and Buchwald, "Dialkylbiaryl Phosphines in Pd-Catalyzed Amination."

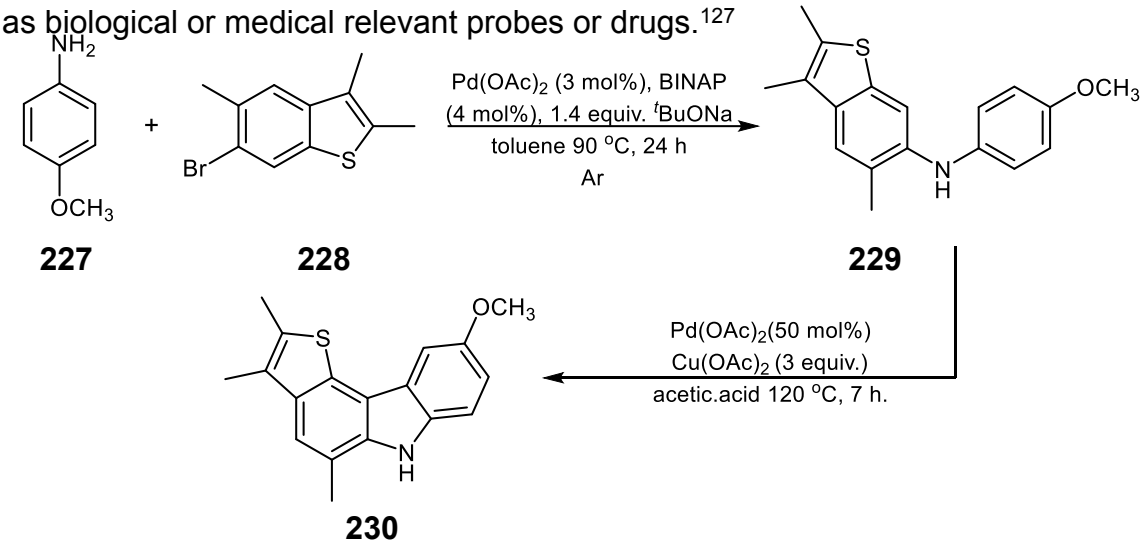
[125] Huang et al., "Expanding Pd-Catalyzed C−N Bond-Forming Processes"; Debabrata Maiti et al., "Palladium-Catalyzed Coupling of Functionalized Primary and Secondary Amines with Aryl and Heteroaryl Halides: Two Ligands Suffice in Most Cases," *Chemical Science (Royal Society of Chemistry: 2010)* 2, no. 1 (January 1, 2011): 57–68, doi:10.1039/C0SC00330A.

bases such as Cs_2CO_3, K_3PO_4 and K_2CO_3 have been investigated in efforts to increase the functional group tolerance. [126]

5.1.3.5 Examples of Buchwald–Hartwig coupling of some thiophene containing structures

It have been reported before novel synthetic routes to thienocarbazole based on the coupling of 6-bromo-2,3,5-trimethylthiophene with 4-methoxyaniline under Buchwald-Hartwing condition [$Pd(AcO)_2$ (3 mol%), BINAP (4 mol%) in toluene and in the presence of ^{t}BuOK as a base], then followed by intramolecular cyclization using [$Pd(AcO)_2$ (50mol%), $Cu(AcO)_2$ (3 equiv) in acetic acid] (

Scheme **76**). The target compound could act as DNA-binding agent which may be used as biological or medical relevant probes or drugs.[127]



227 **228** **229** **230**

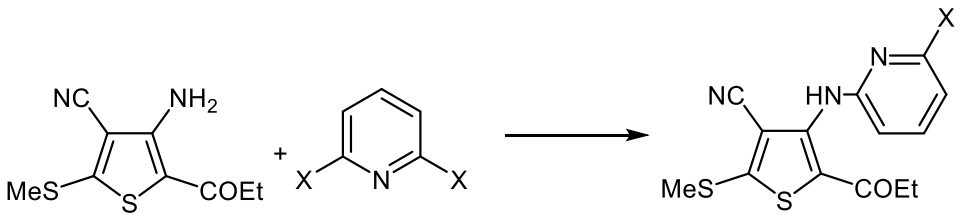
Scheme 76

[126] Maria-João R. P. Queiroz et al., "Synthesis and Antioxidant Activity Evaluation of New 7-Aryl or 7-Heteroarylamino-2,3-Dimethylbenzo[*b*]thiophenes Obtained by Buchwald-Hartwig *C-N* Cross-Coupling," *Bioorganic & Medicinal Chemistry* 15, no. 4 (February 15, 2007): 1788–94, doi:10.1016/j.bmc.2006.11.035; Maria-João R.P. Queiroz et al., "Synthesis and Antioxidant Activity Evaluation of New 7-Aryl or 7-Heteroarylamino-2,3-Dimethylbenzo[*b*]thiophenes Obtained by Buchwald–Hartwig C–N Cross-Coupling," *Bioorganic & Medicinal Chemistry* 15, no. 4 (February 2007): 1788–94, doi:10.1016/j.bmc.2006.11.035; David Montoir et al., "Efficient One-Pot Synthesis of 3,7-Disubstituted 1,6-Naphthyridin-2(1H)-Ones through Regioselective Palladium-Catalyzed Cross-Coupling and SNAr Reactions," *Tetrahedron* 71, no. 21 (May 27, 2015): 3303–13, doi:10.1016/j.tet.2015.03.110; Ferreira, Queiroz, and Kirsch, "Synthesis of Diarylamines in the Benzo[*b*]thiophene Series Bearing Electron Donating or Withdrawing Groups by Buchwald–Hartwig *C–N* Coupling"; Asish R. Das, Arunima Medda, and Raghunath Singha, "Synthesis of Biologically Potent New 3-(Heteroaryl)aminocoumarin Derivatives via Buchwald–Hartwig *C–N* Coupling," *Tetrahedron Letters* 51, no. 7 (February 17, 2010): 1099–1102, doi:10.1016/j.tetlet.2009.12.089.

[127] Isabel C. F. R Ferreira, Maria-João R. P Queiroz, and Gilbert Kirsch, "Novel Synthetic Routes to Thienocarbazoles via Palladium or Copper Catalyzed Amination or Amidation of Arylhalides and Intramolecular Cyclization," *Tetrahedron* 58, no. 39 (September 23, 2002): 7943–49, doi:10.1016/S0040-4020(02)00904-3.

Buchwald–Hartwig coupling of several deactivated aminothiophene carboxylates **231** with 2,6-dihalopyridines **232** in dry dioxane under argon atmosphere and $Pd(OAc)_2$(10 mol%), Xantphos (10 mol%), and Cs_2CO_3 (2.3equiv.) led to the formation of diaminated product **237** with proportions increases with the reactivity of the halopyridines (iodo>bromo>chloro) (Scheme 77), (Scheme 78).[128]

Several diarylamines in the benzo[*b*]thiophene series were prepared in good to high yields by palladium-catalysed amination of ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate **239** with anilines and 5-aminoindole in the presence of $Pd(OAc)_2$, BINAP and Cs_2CO_3 in toluene. The presence of the ester group at the 2-position of the benzo[*b*]thiophene moiety increases the yields and lowers the heating times relative to the reactions performed with 3-bromobenzo[*b*]thiophene (Scheme 79). Selectivity with low MICs was observed against *Bacillus Cereus*, and good results were also obtained against *Candida albicans.*[129]

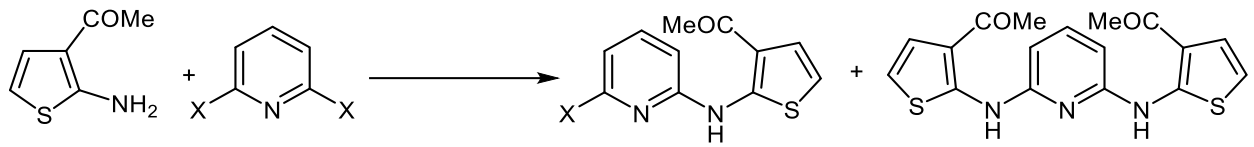


231 **232** **233**

Scheme 77

[128] Begouin et al., "Palladium-Catalyzed Buchwald–Hartwig Coupling of Deactivated Aminothiophenes with Substituted Halopyridines."

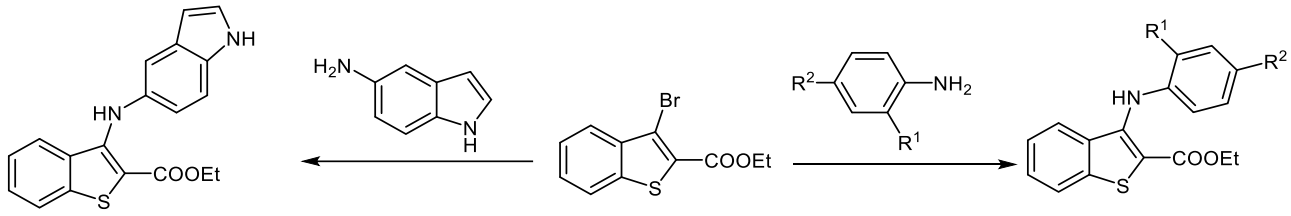
[129] Maria-João R. P. Queiroz et al., "Palladium-Catalysed Amination of Electron-Deficient or Relatively Electron-Rich Benzo[*b*]thienyl Bromides − Preliminary Studies of Antimicrobial Activity and SARs," *European Journal of Organic Chemistry* 2004, no. 17 (September 1, 2004): 3679–85, doi:10.1002/ejoc.200400218.



X=Br 73% 22%
X=I 28% 51%

234 **235** **236** **237**

Scheme 78



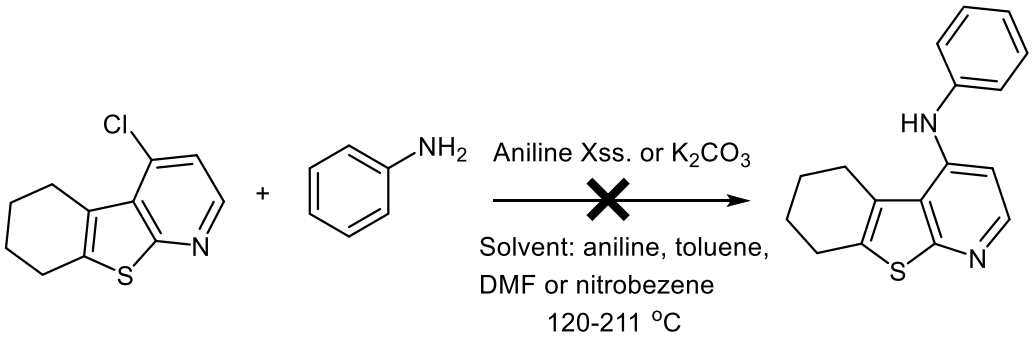
238 **239** **240**

Scheme 79

5.2 Results and discussion

5.2.1 Nucleophilic substitution

To explore the reactivity of the chlorine atom, thienopyridines were exposed to nucleophilic substitution using aniline as a nucleophile. The chlorine atom could not been replaced.



115 **194** **241**

Scheme 80

The reaction was tried under different conditions, either in excess of aniline or in the presence of base like K_2CO_3, and in different temperatures (from 120 °C to reflux in

nitrobenzene), different reaction vehicles were used (aniline, toluene, DMF or nitrobenzene). From all these trials no results were obtained.

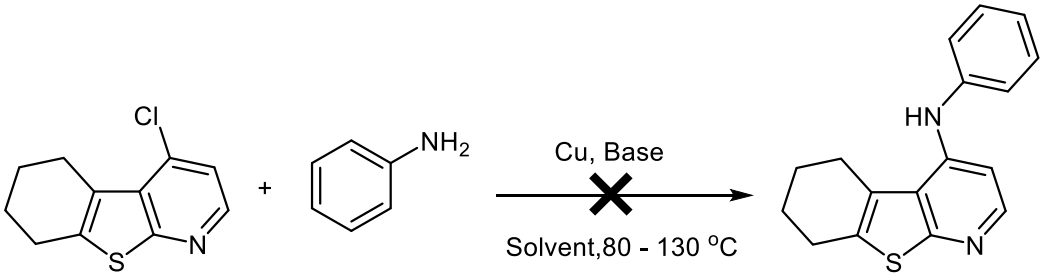
5.2.2 Ullmmann reaction

5.2.2.1 Ligand free trials

Classical Ullmann synthesis[130] was tried by using copper powder or copper oxide (II) and K_2CO_3 in presence of toluene, DMF or nitrobenzene as solvent. Open air or inert gas environment was applied and no product was noticed.

5.2.2.2 Ullmann synthesis in presence of ligand

Various reported combination[131] of ligands, copper salts, solvents, bases and temperature was matched in order to identify the optimum reaction conditions. All the trial are summarized in the following table, and as it is shown below, all of them were utterly failure (Table 6).



115 **194** **241**

Scheme 81

Table 6 Ullmann coupling trials

Trial	copper source	Solvent	atm	ligand	base	temp	time	yield
1	CuI 5 mol%	*i*-propanol	air	Ethylene glycol (2 eq)	K_3PO_4 (2 eq.)	80 °C	24 h	0%
2	CuI 3.5 mol%	Toluene	air	Pyridine 3.5 mol%	*t*-BuoNa (3 eq.)	110 °C	24 h	0%

[130] Ullmann, "Ueber Eine Neue Bildungsweise von Diphenylaminderivaten."

[131] Gujadhur, Bates, and Venkataraman, "Formation of Aryl−Nitrogen, Aryl−Oxygen, and Aryl−Carbon Bonds Using Well-Defined Copper(I)-Based Catalysts"; Kwong, Klapars, and Buchwald, "Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides"; Ma, Cai, and Zhang, "Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides"; Kelkar, Patil, and Chaudhari, "Copper-Catalyzed Amination of Aryl Halides"; Kong et al., "Copper-Catalyzed Synthesis of Substituted Quinolines via *C–N* Coupling/Condensation from *Ortho* -Acylanilines and Alkenyl Iodides"; Kunz, Scholz, and Ganzer, "Renaissance of Ullmann and Goldberg Reactions - Progress in Copper Catalyzed *C-N*-, *C-O*- and *C-S*-Coupling."

3	CuI 3.5 mol%	Toluene	air	8-hydroxyquinoline 3.5 mol%	*t*-BuoNa (3 eq.)	110 °C	24 h	0%
4	CuI 3.5 mol%	toluene	Ar	1,10-Phenanthroline 3.5 mol%	*t*-BuoNa (3 eq.)	110 °C	24 h	0%
5	$Cu(phen)(PPh_3)Br$ 10 mol%	toluene	Ar	$Cu(phen)(PPh_3)Br$ 3.5 mol%	Cs_2CO_3 (2.3 eq.)	110 °C	24 h	0%
6	CuO 20 mol%	DMF	Ar	*L*-proline 20 mol%	K_3CO_3 (2 eq.)	130 °C	24 h	0%
7	CuO 20 mol%	DMF	Ar	Ethylene diamine 20 mol%	K_3CO_3 (2 eq.)	130 °C	24 h	0%

Noteworthy that, ligand in trial five ($Cu(phen)(PPh_3)Br$) was prepared by reported procedure[132] through reacting of PPh_3 with $CuBr_2$ and 1,10-Phenanthroline in two steps.

5.2.3 Buchwald-Hartwig coupling

The coupled products were only accessible through Buchwald–Hartwig cross-coupling, which was mediated by palladium salt and suitable ligand in the presence of base and an inert gas atmosphere.[133] After several hours of heating in toluene, the starting material was consumed to different extents according to nature of both reactants. The products were separated by using flash column chromatography. The yields were variable according to the substituents on the benzene ring of aniline derivatives, and the scaffold of thiophene partner.

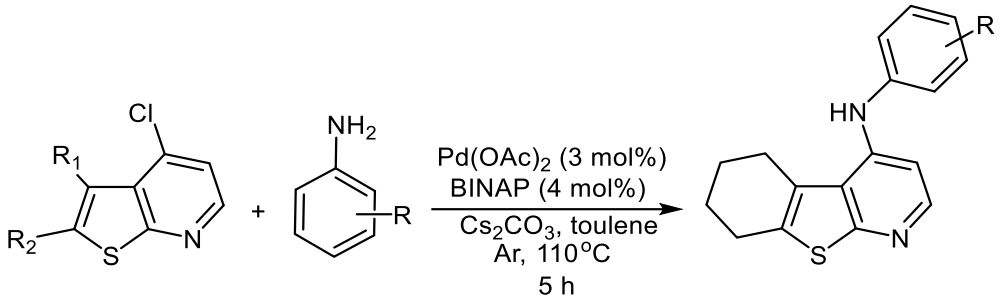
The reported condition by *Queiroz et al*[134] appeared to be the most suitable one, the yield for reaction between compound **115** and aniline **194** was obtainable in quantitative amount after 5 hours. The results from other substrates were quite variable from good yield to null. As which could be anticipated, presence of electron withdrawing group in the aniline derivative resulted in decreasing the nucleophilicity of the amine, hence diminishing the reactivity and the yield (Table 7).

[132] Gujadhur, Bates, and Venkataraman, "Formation of Aryl−Nitrogen, Aryl−Oxygen, and Aryl−Carbon Bonds Using Well-Defined Copper(I)-Based Catalysts."

[133] Queiroz et al., "Palladium-Catalysed Amination of Electron-Deficient or Relatively Electron-Rich Benzo[*b*]thienyl Bromides − Preliminary Studies of Antimicrobial Activity and SARs."

[134] Ibid.

The reaction was catalyzed by palladium acetate and 2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl (BINAP) as ligand in the presence of cesium carbonate and an inert gas atmosphere (Scheme 82).

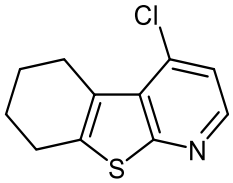
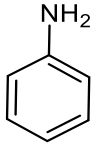
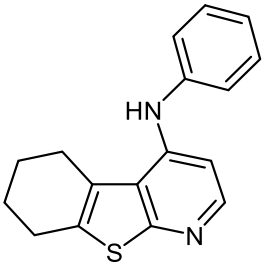


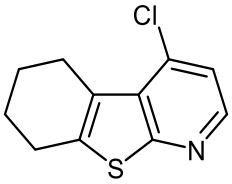
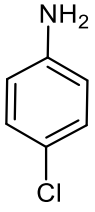
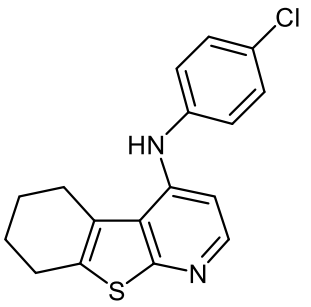
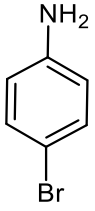
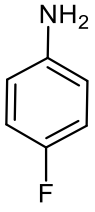
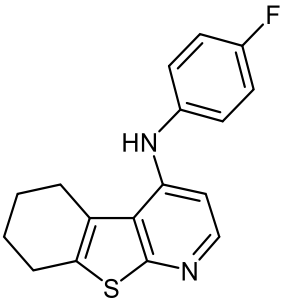
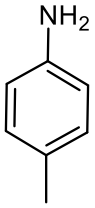
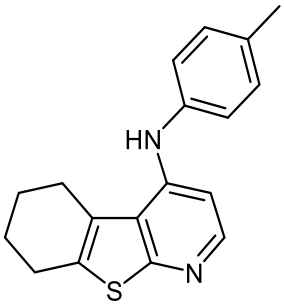
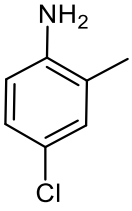
113 **242** **243**

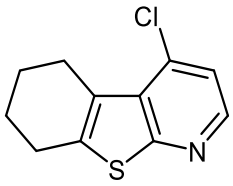
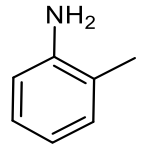
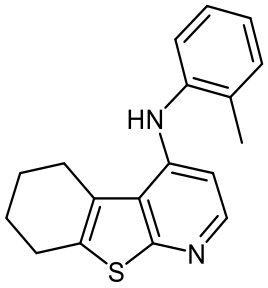
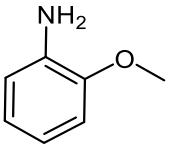
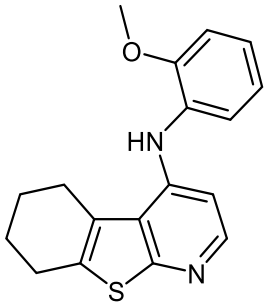
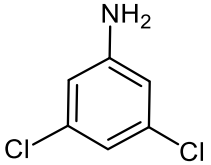
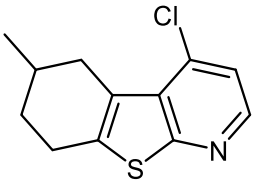
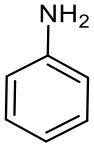
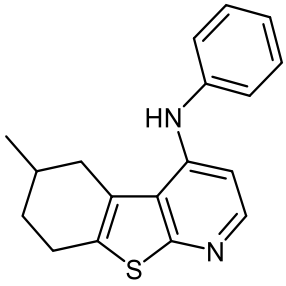
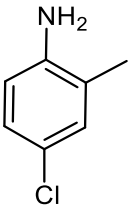
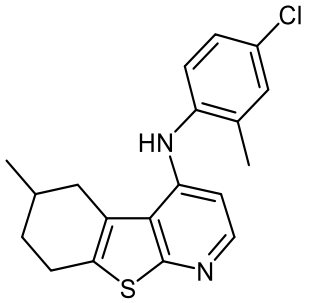
Scheme 82

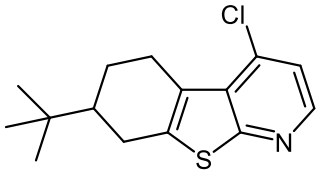
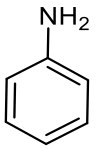
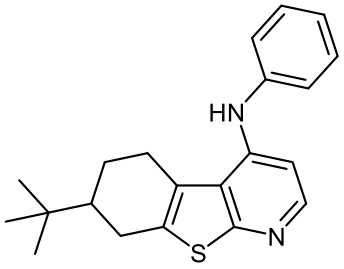
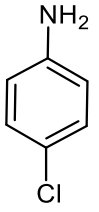
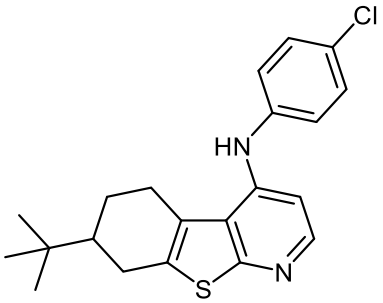
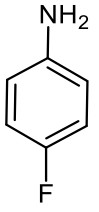
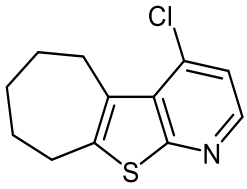
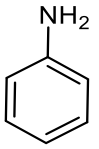
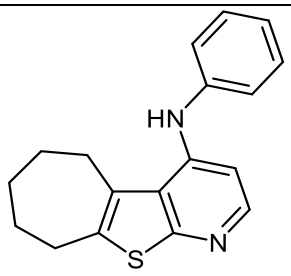
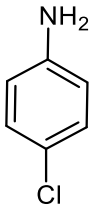
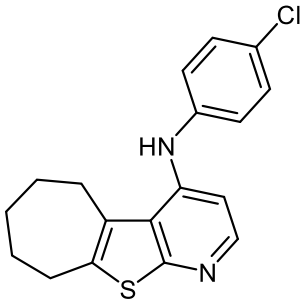
Some trials were done to find alternative combination of catalyst, ligand and solvent but they were not profitable. Using $Pd(PPh_3)_4$ instead of BINAP, replacement toluene by dioxane or changing the base to *t*-BuoK were not useful. For these substrates which gave incomplete reaction, elongation of the reaction time more than 5 hours did not help in consumption of the residual amount of the reactants.

Table 7 Products of coupling between 4-chlorothieno[2,3-*b*]pyridine derivatives and aromatic amines.

Thiophene derivatives	Aniline derivatives	Product	Yield
 **115**	 **194**	 **241**	99%

 **115**	 **244**	 **245**	57%
	 **246**	No product	
	 **247**	 **248**	60%
	 **249**	 **250**	83%
	 **251**	No product	

 **115**	 **252**	 **253**	54%
	 **254**	 **255**	54%
	 **256**	No product	
 **116**	 **194**	 **257**	81%
	 **251**	 **258**	28%

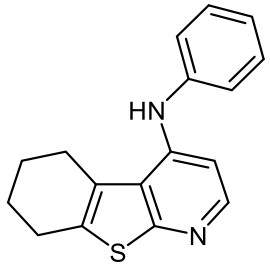
 **118**	 **194**	 **259**	66%
	 **244**	 **260**	75%
	 **247**	No product	
 **119**	 **194**	 **261**	56%
	 **244**	 **262**	36%

5.3 Experimental part

N-phenylthieno[2,3-*b*]pyridin-4-amine, general procedure

In a three-necked round-bottom flask fitted with a condenser, septum, and thermometer, 4-chlorothieno[2,3-*b*]pyridine derivatives (0.54 mmol) was dissolved in anhydrous toluene (5 mL), and Cs_2CO_3 (1.2 mmol), $Pd(OAc)_2$ (0.016 mmol) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.022 mmol) were added. Argon gas was applied and the reaction mixture was heated to 70–80 °C. Aniline derivative (0.54 mmol) was dissolved in anhydrous toluene (3 mL) and added dropwise to the reaction mixture by using a syringe through the septum under argon. Upon complete addition, the temperature was raised to 110 °C and the progress of the reaction was followed by TLC until consumption of the reactants was complete (ca. 5 h). The reaction mixture was poured over ice and water, and extracted with EtOAc. The final pure product was obtained after silica gel column chromatography (cyclohexane – EtOAc, 7:3) for compound **241** and (cyclohexane – EtOAc, 9:1) for the rest and recrystallization from suitable solvent if it is needed.

N-Phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (241)



Yield: 149 mg (99%); yellow solid; mp 102–105 °C (cyclohexane); *Rf* = 0.50 (EtOAc–cyclohexane, 3:7).

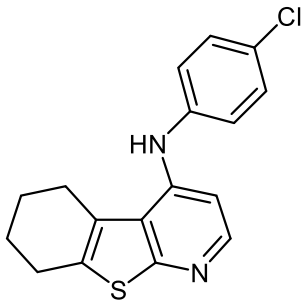
1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 5.5 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.15 (d, *J* = 8.4, 2 H), 7.08 (t, *J* = 8.4, 1 H), 6.77 (d, *J* = 5.5 Hz, 1 H), 6.55 (s, 1 H), 3.05–3.02 (m, 2 H), 2.79–2.77 (m, 2 H), 2.00–1.66 (m, 4 H).

13C NMR (100 MHz, $CDCl_3$): δ = 162.0, 147.1, 146.2, 139.8, 134.4, 129.7, 125.8, 124.3, 122.2, 121.2, 103.6, 27.1, 25.8, 22.9, 22.5.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{16}N_2S + H]^+$: 281.1112; found: 281.1121.

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.57; H, 5.85; N, 9.85; S, 11.59.

_N_-(4-chlorophenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (245)



Yield: 57%; yellow solid; mp 152-154 °C.

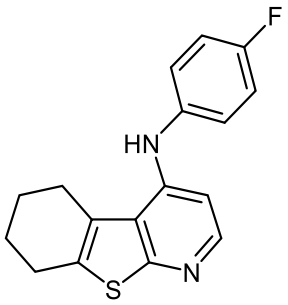
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 4.4 Hz, 1 H), 7.27 (d, *J* = 8.4 2 H), 7.09 (d, *J* = 8.4, 2 H), 6.72 (d, *J* = 4.4 Hz, 1 H), 6.50 (s, 1 H), 3.01–3.00 (m, 2 H), 2.79–2.77 (m, 2 H), 1.90–1.82 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 146.7, 146.0, 138.5, 134.9, 129.8, 129.4, 125.7, 123.4, 121.4, 103.8, 27.04, 26.9, 25.8, 22.8, 22.4.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{15}ClN_2S + H]^+$: 315.0717; found: 315.0693.

Anal. Calcd for $C_{17}H_{15}ClN_2S$: C, 64.86; H, 4.80; N, 8.90; S, 10.18. Found: C, 64.58; H, 5.04; N, 9.15; S, 10.42.

_N_-(4-fluorophenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (248)



Yield: 60%; yellow solid; mp 138-140 °C

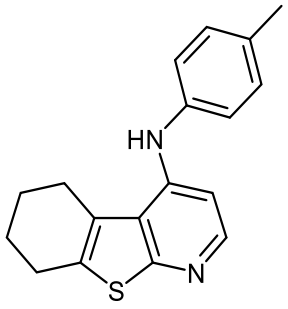
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 5.9 Hz, 1 H), 7.27 – 7.24 (m, 2 H), 7.15 (t, *J* = 8.5 Hz, 2 H), 6.82 (s, 1 H), 6.63 (d, *J* = 5.9 Hz, 1 H), 3.17 – 3.13 (m, 2 H), 2.90 – 2.87 (m, 2 H), 2.05 – 1.88 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.3, 158.8, 148.0, 145.8, 135.5, 134.5, 125.8, 125.4, 125.3, 116.6, 116.4, 103.0, 27.0, 25.8, 22.8, 22.4.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{15}FN_2S + H]^+$: 299.1013; found: 299.1039.

Anal. Calcd for $C_{17}H_{15}FN_2S$: C, 68.43; H, 5.07; N, 9.39; S, 10.74. Found: C, 68.51; H, 5.26; N, 9.27; S, 10.26.

_N_-(_p_-tolyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-_b_]pyridin-4-amine (250)



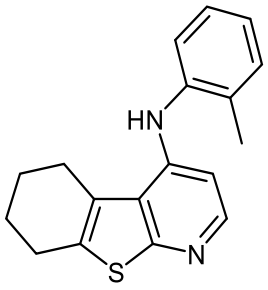
Yield: 83%; yellow solid; mp 106-108 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 5.6 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 6.65 (d, *J* = 5.6 Hz, 1 H), 6.54 (s, 1 H), 3.06 – 3.03 (m, 2 H), 2.80 – 2.76 (m, 2 H), 2.30 (s, 3 H), 1.89 – 1.82 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.5, 147.9, 145.9, 136.9, 134.6, 134.1, 130.2, 125.9, 123.2, 120.8, 103.0, 29.7, 27.1, 22.8, 22.5, 20.90.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{18}N_2S + H]^+$: 295.1269; found: 295.1280.

_N_-(_o_-tolyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-_b_]pyridin-4-amine (253)



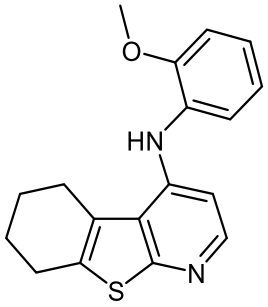
Yield: 54%; yellow solid; mp 185 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 5.7 Hz, 1 H), 7.33 (dd, *J* = 11.3, 5.1 Hz, 2 H), 7.31 – 7.26 (m, 1 H), 7.21 (t, *J* = 7.1 Hz, 1 H), 6.57 (s, 1 H), 6.45 (d, *J* = 5.6 Hz, 1 H), 3.17 – 3.14(m, 2H), 2.91 – 2.88 (m, 2 H), 2.29 (s, 3 H), 2.03 – 1.91 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6, 148.0, 146.2, 137.8, 134.1, 132.8, 131.3, 127.1, 125.8, 125.7, 124.7, 120.5, 102.9, 27.2, 25.8, 22.9, 22.5, 18.0.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{18}N_2S + H]^+$: 295.1263; found: 295.1250.

_N_-(2-methoxyphenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (255)



Yield: 54%; brown solid; mp 136-138 °C

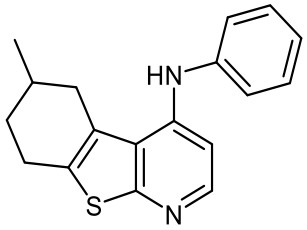
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 4.8 Hz, 1 H), 7.47 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.27 – 7.08 (m, 2 H), 7.02 (t, *J* = 8.5 Hz, 3 H), 3.93 (s, 3 H), 3.17 – 3.14 (m, 2 H), 2.91 – 2.88 (m, 2 H), 2.33 – 1.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.2, 150.4, 146.7, 145.6, 134.4, 129.2, 126.2, 123.6, 120.8, 120.0, 111.2, 103.7, 55.9, 26.9, 25.8, 22.9, 22.4.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{18}N_2OS + H]^+$: 311.1213; found: 311.1243.

Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.85; N, 9.02; S, 10.33. Found: C, 69.39; H, 6.02; N, 8.73; S, 9.70.

6-Methyl-*N*-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (257)



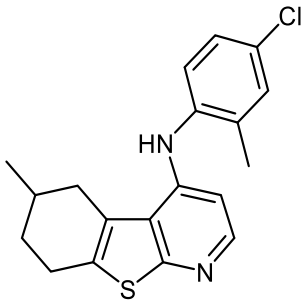
Yield: 81%; yellow solid; mp 138-140 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 5.3 Hz, 1 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 6.76 (d, *J* = 5.3 Hz, 1 H), 6.55 (s, 1 H), 3.16 (m, 1 H), 2.81 (d, *J* = 4.4 Hz, 11H), 2.61 – 2.48 (m, 5H), 1.92 (d, *J* = 11.7 Hz, 6H), 1.54 – 1.41 (m, 7H), 1.08 (d, *J* = 6.6 Hz, 26H), 0.56 – 0.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 148.7, 146.2, 138.7, 135.1, 129.9, 127.4, 125.8, 123.8, 121.1, 103.0, 35.3, 29.7, 29.1, 25.5, 21.6.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{18}N_2S + H]^+$: 295.1263; found: 295.1280.

***N*-(4-chloro-2-methylphenyl)-6-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (258)**



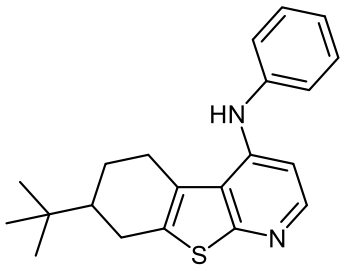
Yield: 28%; yellow solid; mp 138 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (s, 1 H), 7.25 (s, 1 H), 7.17 (s, 2 H), 6.46 (s, 1 H), 6.29 (s, 1 H), 3.18 – 3.11 (m, 1 H), 2.86 – 2.82 (m, 2 H), 2.60 – 2.54 (m, 1 H), 2.18 (s, 3 H), 1.98 – 1.90 (m, 2 H), 1.54 – 1.45 (m, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 148.8, 146.1, 138.9, 135.5, 130.1, 127.6, 126.0, 123.9, 121.4, 103.0, 35.3, 29.7, 29.1, 25.5, 21.6. 19.3

HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{19}ClN_2S + H]^+$: 343.1030; found: 343.1013.

7-(*tert*-butyl)-*N*-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (259)



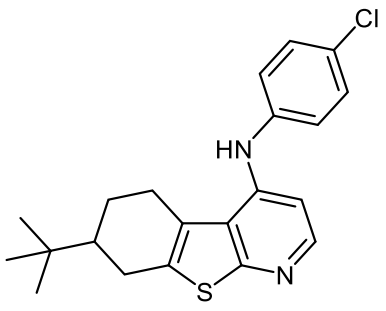
Yield: 66%; yellow solid; mp 92 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 5.3 Hz, 1 H), 7.42 (t, *J* = 7.9 Hz, 2 H), 7.26 (d, *J* = 7.6 Hz, 2 H), 7.18 (dd, *J* = 14.0, 6.5 Hz, 1 H), 6.86 (d, *J* = 5.3 Hz, 1 H), 6.70 (s, 1 H), 3.32 – 3.28 (m, 1 H), 3.08 – 3.00 (m, 1 H), 2.97 – 2.83 (m, 1 H), 2.71 – 2.57 (m, 1 H), 2.24 – 2.10 (m, 1 H), 1.67 – 1.56 (m, 1 H), 1.55 – 1.48 (m, 1 H), 1.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6, 147.1, 145.7, 139.7, 135.2, 129.7, 125.8, 124.5, 122.2, 121.0, 103.6, 44.4, 32.4, 29.7, 27.4, 27.2, 24.5.

HRMS (ESI): *m*/*z* calcd for $[C_{21}H_{24}N_2S + H]^+$: 337.1733; found: 337.1766.

7-(*tert*-butyl)-*N*-(4-chlorophenyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (260)



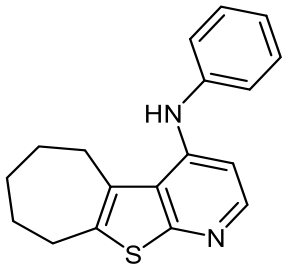
Yield: 75%; yellow solid; mp 80-83 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 4.5 Hz, 1 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 7.16 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 4.5 Hz, 1 H), 6.59 (s, 1 H), 3.28 – 3.23 (m, 1 H), 3.06 – 2.94 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.72 – 2.55 (m, 2H), 2.17 – 2.13 (m, 1 H), 1.65 – 1.54 (m, 1 H), 1.54 – 1.46 (m, 1 H), 0.99 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.2, 146.5, 146.1, 138.6, 135.5, 129.7, 129.2, 125.7, 123.2, 121.2, 103.9, 44.4, 32.4, 28.1, 27.4, 27.2, 24.4.

HRMS (ESI): *m*/*z* calcd for $[C_{21}H_{23}ClN_2S + H]^+$: 371.1343; found: 371.1361.

_N_-phenyl-6,7,8,9-tetrahydro-5_H_-cyclohepta[4,5]thieno[2,3-_b_]pyridin-4-amine (261)



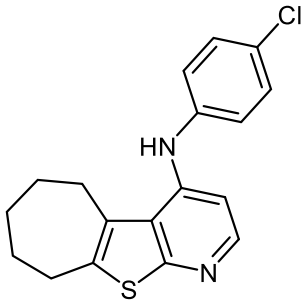
Yield: 56%; yellow solid; mp 160 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 5.0 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 2 H), 7.22 – 7.10 (m, 3 H), 6.92 (d, *J* = 5.3 Hz, 1 H), 6.41 (s, 1 H), 3.24 – 3.15 (m, 2 H), 2.97 – 2.87 (m, 2 H), 1.97 – 1.74 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.1, 146.7, 145.8, 140.7, 138.9, 131.3, 129.7, 123.7, 123.4, 121.3, 105.8, 30.9, 29.9, 29.4, 27.1, 26.6.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{18}N_2S + H]^+$: 295.1263; found: 295.12911.

_N_-(4-chlorophenyl)-6,7,8,9-tetrahydro-5_H_-cyclohepta[4,5]thieno[2,3-_b_]pyridin-4-amine (262)



Yield: 36%; yellow solid; mp 190-192 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 5.5 Hz, 1 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 6.84 (d, *J* = 5.5 Hz, 1 H), 6.58 (s, 1 H), 3.24 – 3.12 (m, 2 H), 2.97 – 2.87 (m, 2 H), 1.98 – 1.76 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.2, 146.9, 144.7, 140.0, 139.2, 131.4, 129.8, 129.0, 123.7, 122.6, 106.0, 30.8, 29.9, 29.4, 27.0, 26.6.

HRMS (ESI): *m*/*z* calcd for $[C_{18}H_{17}ClN_2S + H]^+$: 329.0874; found: 329.0890.

Conclusion and Perspective

onclusions et perspectives

Durant ces travaux, presque 80 nouveaux composés à noyau thiophénique ont été préparés. Les produits de départ -3-acétyl-2-aminothiophènes-ont été synthétisés par une classique réaction de Gewald utilisant la cyanoacétone, réaction non décrite précédemment. Lorsque ces composés sont étudiés dans les conditions de Vilsmeier-Haack-Arnold, ils présentent des comportements différents dans la cyclisation en thiénopyridines apparemment dues au remplacement du noyau benzénique d'o-aminoacétophénones par le thiophène. Alors que la protection de l'amine par acétylation fait que le thiophène se comporte comme l'o-amino acétophénone, permettant l'accès au composé chloro-formylé, en contrôlant les conditions de réaction on peut également accéder au dérivé uniquement chloré.

D'autre part l'autre voie pour construire les thiéno[2,3-*b*]pyridines, la réaction de Friedländer, a été étudiée et a permis de préparer d'autres thiénopyridinres.

Le couplage *C-N* utilisant le palladium comme catalyseur (Buchwald-Hartwig) a été appliquée aux 4-chloro- thiéno[2,3-*b*]pyridines, produits de la réaction de Vilsmeier-Haack-Arnold, a conduit à la formation des *N*-phenylthiéno[2,3-*b*]pyridin-4-amines.

Ce travail a donc été utilisé pour permettre la préparation de nouveaux dérivés thiophéniques ainsi que de dérivés condensés. Différents réactifs ont été utilisés qui ont permis l'accès à des composés divers à partir de la cyanoacétone de départ.

Plusieurs médicaments ont le noyau thiophénique dans leur structure, par exemple la Ticlopidine® et le Clopidogre®l contre l'agrégation plaquettaire par inhibition du récepteur P_2Y_{12}, le Raloxifène®, modulateur du récepteur oestrogénique et l'Olanzapine® comme anti-psychotique.

Nombreuses autres activités biologiques sont décrites dans la littérature : traitement de l'anxiété et de la dépression, bactéricide, anti-leishmania et antipaludique, contre les maladies auto-immunes. Pour cela, une étude biologique des produits préparés pourrait être considérée. Une seconde option serait d'utiliser les produits préparés pendant la

thèse comme structure de base et par modifications structurales tenter de préparer des composés biologiquement actifs.

Conclusion and Perspective

During this PhD nearly 80 novel thiophene based structure have been delivered. The starting material (3-acetyl-2-amino-thiophenes) in this work was prepared using simple classical Gewald's synthesis starting from cyanocacetone which was not reported before.

When the new prepared thiophenes were studied under Vilsmeier-Haack-Arnold condition, they displayed different cyclization behaviour for the formation of the thienopyridines as a consequence of replacement of benzene ring from *o*-aminoacetophenones by the thiophene ring.

While the protection of amino group by acetylation made the thiophene behave like *o*-aminoacetophenone allowing access to interesting chloro-formyl derivatives, the formyl-free products still could be producible by controlling the reaction conditions. On other hand, another way for building thieno[2,3-*b*]pyridine, the Friedländer reaction, has been achieved and allows to prepare different thienopyridines .

C-*N* coupling using palladium as catalyst (Buchwald-Hartwig) was also applicable on 4-chlorothieno[2,3-*b*]pyridines, the products of Vilsmeier-Haack-Arnold reaction. *N*-phenylthieno[2,3-*b*]pyridin-4-amines were produced in this way.

This project has be used as a guide for planning synthesis of more thiophene derivatives and thiophene condensed scaffolds. Wide variety of different reagents have been involved in the different synthetic pathway from the starting cyanoacetone.

Many drugs have thiophene in their core structure, e.g. Ticlopidine®, Clopidogrel® which are a group of drugs acting as antiplatelet aggregation by inhibition of P_2Y_{12} receptor, additionally Raloxifene® (estrogen receptor modulator) and Olanzapine® as antipsychotic drug. Many other biological activities are reported in the literatures like treatment of anxiety, depression, bacterial infection, inflammation, leishmania, malaria and autoimmune diseases. Therefore the biological study of the synthetized products should to be considered.

Using the compounds which were produced during the PhD as lead structure for producing biologically active materials is also another option.

Annex

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Synthesis A. B. Abdelwahab et al. Paper

Synthesis of Novel 3-Acetyl-2-aminothiophenes and Investigation of their Behaviour in the Reaction with Vilsmeier–Haack Reagent

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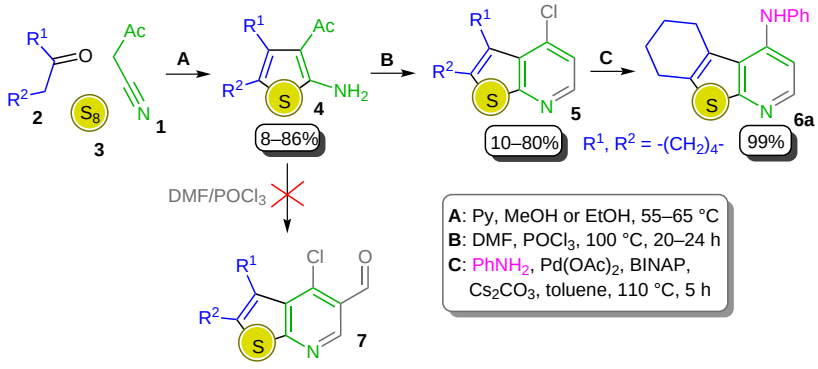

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Abstract Through an investigation into the behaviour of 3-acetyl-2-aminothiophene in the reaction with Vilsmeier–Haack reagent, an efficient method for the synthesis of 4-chlorothieno[2,3-*b*]pyridine derivatives has been established. Gewald's classical synthesis starting from cyanoacetone, ketones and elemental sulphur has been applied to produce the starting materials.

Key words Vilsmeier–Haack, Gewald's reaction, thieno[2,3-*b*]pyridine, Buchwald–Hartwig, cross coupling

Significant interest in the thieno[2,3-*b*]pyridine nucleus has arisen during the last three decades. Many researchers have reported the use of compounds based on this scaffold as a possible treatment of anxiety and depression,[1] bacterial infection,[2] inflammation,[3] leishmaniasis,[4] malaria[5] and autoimmune diseases.[6]

Vilsmeier–Haack reaction is very practical method for versatile synthetic purposes. [7] The Vilsmeier–Haack reagent ($POCl_3$/DMF) has been widely used in formylation, chlorination and cyclisation processes.[8] The preparation of 3-formylquinoline through such reactions in one step starting from *o*-aminoacetophenone, inspired by the synthesis of 3-formylchromone from *o*-hydroxyacetophenone, was reported.[9]

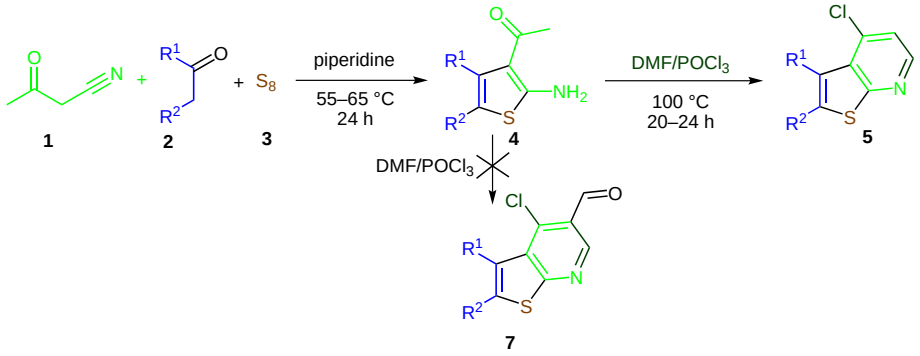
The impact of replacement of a benzene ring with thiophene in the aforementioned cyclisation has not been investigated before. To study this reaction, we decided to construct 3-acetyl-2-amino thiophene, which could be used as a starting material for this purpose.

In our research group, we have long experience of synthesising the thiophene nucleus by diverse synthetic pathways including Gewald's reaction.[10] Gewald's reaction is a one-pot reaction in which a carbonyl compound containing a methylene group in the α-position reacts with elemental sulfur and activated nitriles to produce 2-aminothiophene.[11] This reaction has been widely applied since it was discovered to result in many derivatives including different electron-withdrawing groups in the 3-position (e.g., CN, COOR, $CONH_2$ and COPh).[12] In 2006, Eller et al. introduced the first derivative having an acetyl group in the 3-position by following a two-component pathway involving cyanoacetone and 1,4-dithiane (the source of sulfur at the same time).[13]

Herein, a typical three-component Gewald reaction was applied in which the cyanoacetone, carbonyl compound, and elemental sulfur reacted to produce 3-acetyl-2-aminothiophene derivatives (Scheme 1). Different amines (morpholine, triethyl amine and piperidine) were tried as basic catalyst in either ethanol or methanol. From our experiments, we can arrange the bases in decreasing order according to their efficiency: piperidine > triethylamine > morpholine.

It was found that alicyclic ketones gave better results than straight-chain aliphatic ketones; the reactivity in this case depended on the type and the place of substituents in relation to the carbonyl group and the α-methylene. The yields appeared to be low to moderate, with 4-*tert*-butyl cyclohexanone and saturated heterocyclic ketones giving increased yield (**4e**, **4j** and **4k** gave 86, 72 and 65% respectively) (Table 1).

The Vilsmeier–Haack–Arnold reaction was applied for the second step to achieve the cyclisation. The influence of the thiophene nucleus on the reaction is clear. Several trials were applied to achieve the cyclisation. By working in the reported conditions of 60 °C for five hours,[9c] an unknown product was separated as a major component. Increasing the time of the reaction did not help. When the temperature was elevated to 100 °C for five hours, a mixture of the desired compound and an unknown by-product were ob-



Scheme 1 General method for the synthesis of 3-acetyl-2-amino-thiophene and 4-chlorothieno[2,3-*b*]pyridine

tained; increasing the time of the reaction did not lead to the production of the desired compounds exclusively. The number of equivalents of the Vilsmeier–Haack reagent was found to have great influence upon the completion of the reaction. The mode of addition was also found to govern both the type of product formed and the yield. Addition of the reagent over seven hours then stirring the reaction mixture overnight appeared to be the best reaction conditions. In contrast to previous reports on the synthesis of 3-formylquinoline and 3-formylchromone, the product was free from a formyl group (Scheme 1).[9]

The replacement of the benzene ring with a thiophene ring is likely to have an impact on the final products, and may prevent further attack of the Vilsmeier–Haack reactant.

All the reactants gave yields from low to moderate, with the exception of **4j** and **4k**, which gave undefined mixtures on TLC, without any major component. Attempts to separate pure compounds from these mixtures by using flash chromatography failed (Table 1).

Table 1 Gewald and Vilsmeier–Haack Reactions

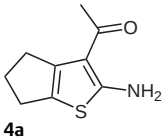
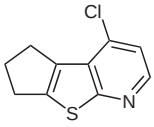
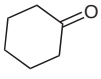
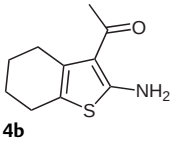
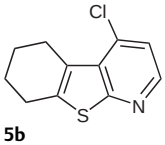
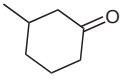
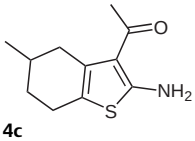
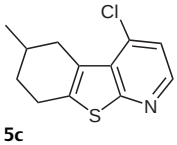
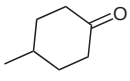
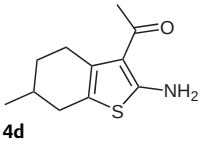
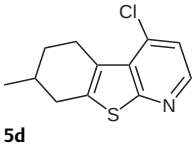
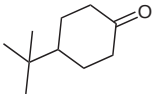
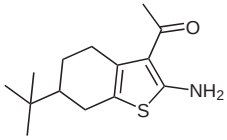
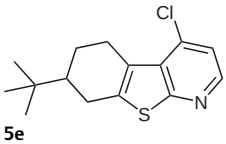
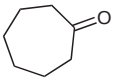
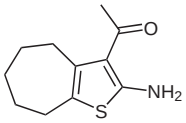
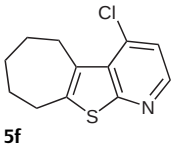
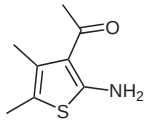
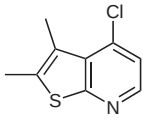
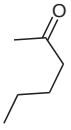
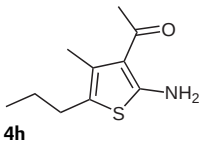
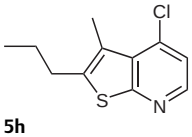
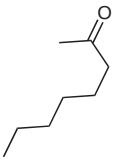
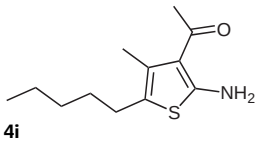
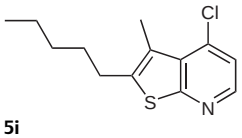
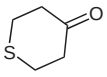
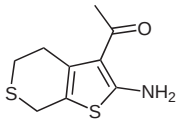
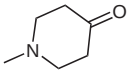
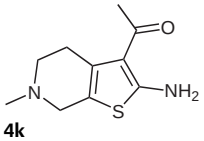
Ketone	Thiophene	Yield (%)	Thieno[2,3-*b*]pyridine	Yield (%)
	 **4a**	61	 **5a**	30
	 **4b**	58	 **5b**	43
	 **4c**	30	 **5c**	36
	 **4d**	28	 **5d**	36

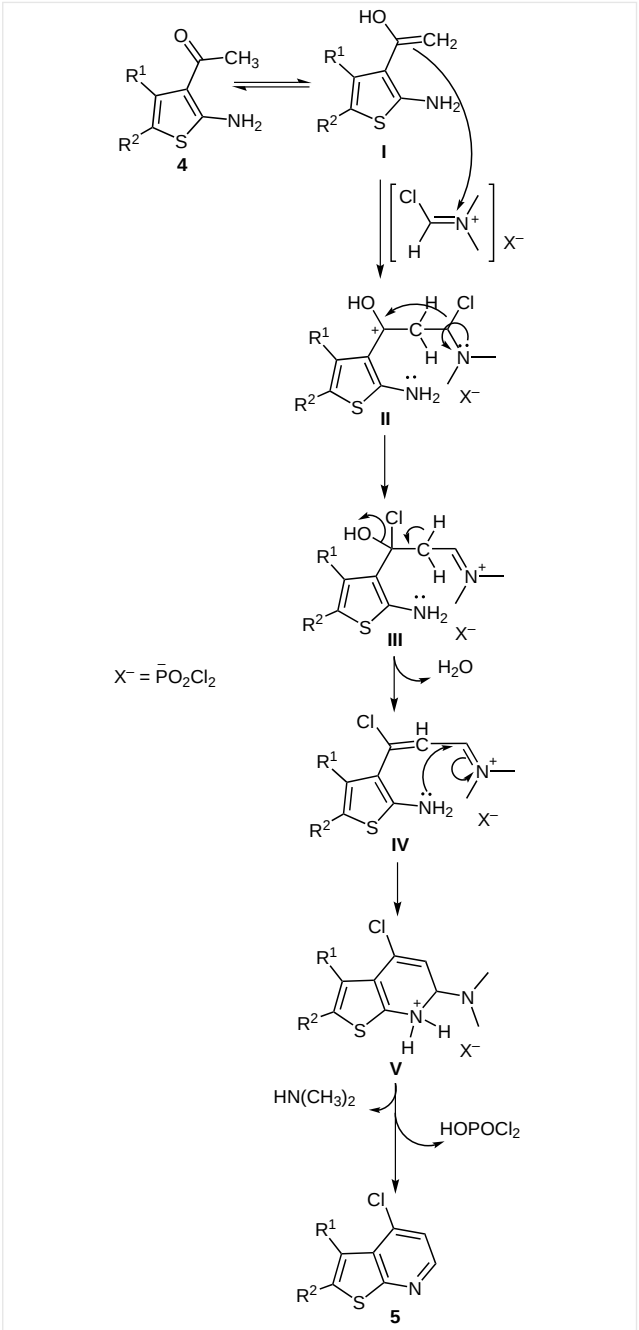
Table 1 (continued)

Ketone	Thiophene	Yield (%)	Thieno[2,3-*b*]pyridine	Yield (%)
	 **4e**	86	 **5e**	80
	 **4f**	32	 **5f**	53
	 **4g**	36	 **5g**	10
	 **4h**	30	 **5h**	25
	 **4i**	8	 **5i**	36
	 **4j**	72		
	 **4k**	66		

The mechanism of cyclisation is postulated to involve attack of the Vilsmeier–Haack reagent. In this mode, the enol form (**I**) is attacked by the reagent to form intermediate (**II**), which gives, after losing water, the iminium salt (intermediate **IV**). The latter intermediate is cyclised to the final product **5** (Scheme 2).

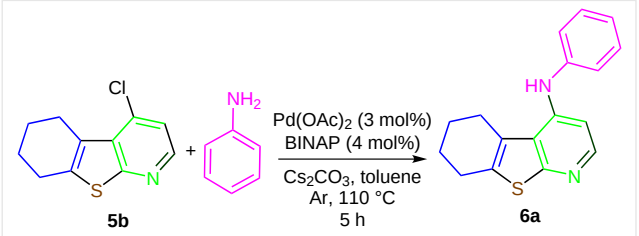
Increasing the number of equivalents of reagent, the time of reaction, or the temperature did not result in the production of formylated derivatives. The inductive effect of the thiophene ring may stabilise the electron within the system, which could decrease the nucleophilicity of the pyridine ring.

To explore the reactivity of the chlorine atom, thienopyridines were exposed to nucleophilic substitution using aniline as a nucleophile either in excess or in the presence of base. The chlorine atom could not been replaced, and application of Ullmann coupling conditions[14] did not help in performing the reaction. The product **6a** was only accessible through Buchwald–Hartwig cross-coupling,[15] which was mediated by palladium acetate and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as ligand[16] in the presence of caesium carbonate and an inert gas atmosphere. After five hours, the starting material was completely consumed



Scheme 2 Possible mechanism of cyclisation of 3-acetyl-2aminothiophene through Vilsmeier–Haack–Arnold procedures

and the product was separated by using flash column chromatography. The product was obtained in very high yield (99%; Scheme 3).



Scheme 3 Buchwald–Hartwig synthesis of *N*-phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (**6b**)

In conclusion, we report here the first synthesis of 3-acetyl-2-aminothiophene by using the three-component Gewald reaction. The compounds exhibit a different mode of cyclisation in the reaction with Vilsmeier–Haack reagent than that reported for the reaction with *o*-aminoacetophenone,[9c] which could be ascribed to the influence of the thiophene nucleus. This simple, two-step reaction allows the construction of some novel 4-chlorothieno[2,3-*b*]pyridine derivatives from very simple building units. Compound **5b** reacted further with aniline by palladium-catalysed C–N cross-coupling to give the coupled product in high yield.

All solvents and reagents were purchased from commercial sources unless otherwise noted. Melting points were determined with a Büchi 530 digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using Me_4Si as the internal standard. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High-resolution mass spectra were measured with a Micro-Tof-Q98 instrument in ESI mode. Column chromatography was performed using silica gel (60M, 0.04–0.063 mm). Thin-layer chromatography (TLC) was performed using silica gel plates (POLYGRAM SIL G/UV254, 0.20 mm), which were visualised under UV light.

Cyanoacetone (1)

(*E*,*Z*)-3-Aminocrotonitrile (10 g, 0.12 mol) was dissolved in 6N HCl (28.5 mL), and the solution was stirred and heated to 80 °C for 3 h. The reaction mixture was cooled, extracted several times with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under vacuo.

Yield: 5 g (53%); colourless liquid.[17]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 2 H), 2.28 (s, 3 H).

3-Acetyl-2-aminothiophene Derivatives; General Procedure

Carbonyl compound (0.025 mol) was added to freshly prepared cyanoacetone (0.03 mol) in either MeOH or EtOH (40 mL). Sublimed sulfur S_8 (0.03 mol) and piperidine (0.03 mol) were added and the mixture was stirred and heated to 55–65 °C for 24 h. Ice was then added and the formed precipitate was filtered under vacuum and washed with water. The obtained solid was crystallised from a suitable solvent, with the exception of **4g** and **4j**, which were collected directly without further purification.

1-(2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-yl)ethanone (4a)

Yield: 2.7 g (61%); brown solid; mp 230 °C (toluene).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 2 H), 2.92–2.87 (m, 2 H), 2.78–2.72 (m, 2 H), 2.44–2.38 (m, 2 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 168.6, 141.0, 121.3, 112.2, 31.74, 29.1, 28.7, 27.3.

HRMS (ESI): *m*/*z* calcd for $[C_9H_{11}NOS + Na]^+$: 204.0454; found: 204.0464.

Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 60.14; H, 6.10, N, 7.48; S, 17.25.

1-(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (4b)

Yield: 2.8 g (58%); brown solid; mp 114–117 °C (toluene).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 2 H), 2.74–2.67 (m, 2 H), 2.58–2.52 (m, 2 H), 2.42 (s, 3 H), 1.86–1.79 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.1, 163.9, 130.6, 117.6, 115.8, 30.7, 28.1, 24.7, 23.1, 22.9.

HRMS (ESI): *m*/*z* calcd for $[C_{10}H_{13}NOS + Na]^+$: 218.0610; found: 218.0602.

Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.17; O, 8.19; S, 16.42. Found: C, 61.85; H, 6.65, N, 6.86; S, 16.18.

1-(2-Amino-5-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (4c)

Yield: 1.5 g (28%); greenish solid; mp 180–182 °C (abs. EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 2 H), 2.83 (dd, *J* = 15.6, 4.5 Hz, 1 H), 2.60–2.53 (m, 2 H), 2.42 (s, 3 H), 2.30–2.15 (m, 1 H), 2.01–1.76 (m, 2 H), 1.51–1.36 (m, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 164.3, 130.6, 117.3, 115.7, 36.6, 31.0, 30.6, 29.3, 24.5, 22.1.

HRMS (ESI): *m*/*z* calcd for $[C_{11}H_{15}NOS - H + Na]^+$: 231.0694; found: 231.0699.

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.84; H, 7.12; N, 6.53; S, 15.12.

1-(2-Amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (4d)

Yield: 1.5 g (28%); greenish solid; mp 127 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, 2 H), 2.85–2.76 (m, 1 H), 2.72–2.61 (m, 1 H), 2.61–2.54 (m, 1 H), 2.41 (s, 3 H), 2.21–2.12 (m, 1 H), 1.95–1.86 (m, 2 H), 1.47–1.35 (m, 1 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 164.2, 130.2, 117.2, 115.6, 32.9, 31.3, 30.6, 29.2, 27.8, 21.4.

HRMS (ESI): *m*/*z* calcd for $[C_9H_{16}OS - H + Na]^+$: 232.0767; found: 232.0801.

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.61; H, 7.19; N, 6.88; S, 15.75.

1-{2-Amino-6-(*tert*-butyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl}ethanone (4e)

Yield: 5.4 g (86%); beige-brown solid; mp 155–158 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 2.88 (ddt, *J* = 15.9, 4.7, 1.8 Hz, 1 H), 2.66–2.49 (m, 2 H), 2.40 (s, 3 H), 2.37–2.28 (m, 1 H), 2.07–2.00 (m, 1 H), 1.56–1.46 (m, 1 H), 1.40–1.28 (m, 1 H), 0.94 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 164.2, 130.6, 118.3, 115.5, 32.4, 30.5, 29.2, 27.2, 26.3, 24.7

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{21}NOS + Na]^+$: 274.1207; found: 274.1236.

Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57; S, 12.76. Found: C, 66.41; H, 8.42; N, 5.55; S, 13.03.

1-(2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-yl)ethanone (4f)

Yield: 1.7 g (32%); brown solid; mp 129–130 °C (toluene).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (s, 2 H), 2.87–2.79 (m, 2 H), 2.61–2.59 (m, 2 H), 2.43 (s, 1 H), 1.89–1.83 (m, 2 H), 1.75–1.64 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 161.4, 136.1, 121.1, 118.5, 31.7, 31.0, 29.8, 28.4, 27.6, 26.6.

HRMS (ESI): *m*/*z* calcd for $[C_{11}H_{15}NOS + Na]^+$: 232.0767; found: 232.0778.

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; O, 7.64; S, 15.32. Found: C, 62.99; H, 7.13; N, 7.11; S, 15.08.

1-(2-Amino-4,5-dimethylthiophen-3-yl)ethanone (4g)

Yield: 1.5 g (36%); brown solid; mp 154–157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (s, 2 H), 2.46 (s, 3 H), 2.23 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 163.1, 128.4, 117.0, 113.8, 30.6, 15.8, 12.6.

HRMS (ESI): *m*/*z* calcd for $[C_8H_{11}NOS + H]^+$: 170.634; found: 170.0633; calcd for $[C_8H_{11}NOS + Na]^+$: 192.0454; found: 192.0456.

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28; S, 18.95. Found: C, 56.65; H, 6.41; N, 9.07; S, 19.07.

1-(2-Amino-4-methyl-5-propylthiophen-3-yl)ethanone (4h)

Yield: 4.9 g (30%); brown solid; mp 113–115 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (t, *J* = 7.6 MHz, 2 H), 2.47 (s, 3 H), 2.24 (s, 3 H), 1.57 (m, 2 H), 0.96 (t, *J* = 7.2, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 163.3, 128.0, 120.0, 13.6, 117.0, 30.6, 29.2, 24.4, 15.86.

HRMS (ESI): *m*/*z* calcd for $[C_{10}H_{15}NOS + Na]^+$: 220.0767; found: 220.0781.

Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.55; H, 7.58; N, 7.20; S, 16.70.

1-(2-Amino-4-methyl-5-pentylthiophen-3-yl)ethanone (4i)

Yield: 0.45 g (8%); greenish solid; mp 112–113 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59–2.53 (m, 2 H), 2.46 (s, 3 H), 2.24 (s, 3 H), 1.58–1.51 (m, 2 H), 1.39–1.28 (m, 4 H), 0.92 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 163.4, 127.9, 120.3, 117.04, 31.3, 30.9, 27.3, 22.5, 15.8, 14.02.

HRMS (ESI): *m*/*z* calcd for $[C_{12}H_{19}NOS - H + Na]^+$: 247.0993; found: 247.1001.

Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22; S, 14.23. Found: C, 64.01; H, 8.34; N, 6.17; S, 14.35.

1-(2-Amino-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-yl)ethanone (4j)

Yield: 3.8 g (72%); brownish solid; mp 167–170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 2 H), 3.62 (t, *J* = 1.6 Hz, 2 H), 3.02 (ddd, *J* = 5.8, 4.6, 1.2 Hz, 2 H), 2.93 (t, *J* = 5.5 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 163.1, 130.5, 116.2, 113.6, 31.0, 29.8, 26.1, 25.4.

HRMS (ESI): *m*/*z* calcd for $[C_9H_{11}NOS_2 + H]^+$: 214.0355; found: 214.0353.

Anal. Calcd for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20; N, 6.57; S, 30.06. Found: C, 50.35; H, 5.16; N, 6.75; S, 29.44.

1-(2-Amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)ethanone (4k)

Yield: 3.5 g (66%); black solid; mp 149–151 °C (CH_2Cl_2–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19 (s, 2 H), 3.24 (s, 2 H), 2.73 (t, *J* = 5.7 Hz, 2 H), 2.57 (t, *J* = 5.7 Hz, 2 H), 2.31 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.2, 164.6, 113.3, 128.5, 113.3, 113.2, 53.0, 52.0, 45.1, 30.1, 27.7.

HRMS (ESI): *m*/*z* calcd for $[C_{10}H_{14}N_2OS + H]^+$: 211.0900; found: 211.0891.

Anal. Calcd for $C_{10}H_{14}N_2OS·H_2O$: C, 52.54; H, 7.06; N, 12.25; S, 14.02. Found: C, 52.48; H, 7.01; N, 12.62; S, 14.04.

4-Chlorothieno[2,3-*b*]pyridine Derivatives; General Procedure

For preparation of the Vilsmeier reagent, $POCl_3$ (2.5 mL) was dropped into DMF (10 mL) at 0 °C over 15 min with stirring. The starting materials (2.5 mmol) was dissolved in a minimum amount of DMF and the Vilsmeier reagent was added dropwise over 7 hours to the stirred solution at 100 °C. The reaction mixture was stirred at 100 °C. The progress of the reaction was monitored by TLC until the consumption of the starting material was complete (ca. 20–24 h), then the reaction mixture was treated with ice and water, neutralised with ammonium acetate and extracted with EtOAc several times. The product was obtained in pure form after purification by silica gel column chromatography (EtOAc–cyclohexane, 1:9) followed by recrystallisation (MeOH–H_2O, 1:1).

4-Chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (5a)

Yield: 156 mg (30%); white solid; mp 123 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 5.1 Hz, 1 H), 7.17 (d, *J* = 5.1 Hz, 1 H), 3.17–3.07 (m, 2 H), 3.03–2.92 (m, 2 H), 2.47–2.37 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 145.0, 144.0, 137.1, 136.7, 128.2, 120.0, 30.1, 29.9, 27.3.

HRMS (ESI): *m*/*z* calcd for $[C_{10}H_8ClNS + H]^+$: 210.0144; found: 210.0142.

Anal. Calcd for $C_{10}H_8ClNS·H_2O$: C, 55.55; H, 4.06; N, 6.47; S′ 14.88. Found: C, 55.20; H, 4.03; N, 6.28; H, 14.66.

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (5b)

Yield: 240 mg (43%); white solid; mp 67 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 3.16 (dd, *J* = 5.8, 2.7 Hz, 2 H), 2.89 (t, *J* = 4.2 Hz, 2 H), 1.98–1.85 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 144.8, 139.1, 137.9, 130.6, 127.8, 120.8, 26.7, 26.1, 22.5.

HRMS (ESI): *m*/*z* calcd for $[C_{11}H_{10}ClNS + Na]^+$: 246.0115; found: 246.0133.

Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; N, 6.26; S, 14.33. Found: C, 59.70; H, 4.58; N, 6.48; S, 14.08.

4-Chloro-6-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (5c)

Yield: 213 mg (36%); white solid; mp 112–115 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 3.40 (dd, *J* = 17.4, 5.6 Hz, 1 H), 2.97–2.89 (m, 2 H), 2.64–2.56 (m, 1 H), 2.03–1.92 (m, 2 H), 1.60–1.48 (m, 1 H), 1.17 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 145.1, 138.6, 137.6, 130.3, 127.8, 120.7, 35.0, 30.6, 28.9, 25.9, 21.7.

HRMS (ESI): *m*/*z* calcd for $[C_{12}H_{13}ClNS]^+$: 238.0452; found: 238.0456.

Anal. Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 60.44; H, 5.11; N, 5.82; S, 13.03.

4-Chloro-7-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (5d)

Yield: 213 mg (36%); white solid; mp 54–56 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 5.1 Hz, 1 H), 7.22 (d, *J* = 5.1 Hz, 1 H), 3.38–3.29 (m, 1 H), 3.08–2.90 (m, 2 H), 2.56–2.46 (m, 1 H), 2.07–1.96 (m, 2 H), 1.57–1.47 (m, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 145.2, 138.5, 137.6, 130.2, 127.4, 120.7, 35.1, 30.7, 28.8, 26.5, 21.3.

HRMS (ESI): *m*/*z* calcd for $[C_{12}H_{12}ClNS + H]^+$: 238.0452; found: 238.0463.

Anal. Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 60.89; H, 5.13; N, 6.02; S, 13.07.

7-(*tert*-Butyl)-4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine (5e)

Yield: 558 mg (80%); white solid; mp 75–77 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 4.8 Hz, 1 H), 7.23 (d, *J* = 4.8 Hz, 1 H), 3.50–3.40 (m, 1 H), 2.97–2.89 (m, 2 H), 2.70–2.60 (m, 1 H), 2.19–2.12 (m, 1 H), 1.66–1.60 (m, 1 H), 1.49–1.34 (m, 1 H), 1.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 145.2, 140.0, 137.5, 130.2, 127.8, 120.7, 44.5, 32.4, 27.8, 27.7, 27.2, 24.2.

HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{18}ClNS + H]^+$: 280.0921; found: 280.0929.

Anal. Calcd for $C_{15}H_{18}ClNS$: C, 64.38; H, 6.48; N, 5.01; S, 11.46. Found: C, 63.93; H, 6.55; N, 5.06; S, 10.96.

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*b*]pyridine (5f)

Yield: 313 mg (53%); white solid; mp 60–63 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 5.0 Hz, 1 H), 7.25 (d, *J* = 5.0 Hz, 1 H), 3.45–3.38 (m, 2 H), 3.00–2.94 (m, 2 H), 1.99–1.91 (m, 2 H), 1.82–1.72 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 144.9, 143.4, 137.4, 133.1, 130.3, 121.4, 32.0, 30.1, 28.3, 27.1, 26.60.

HRMS (ESI): *m*/*z* calcd for $[C_{12}H_{12}ClNS + H]^+$: 238.0452; found: 238.0458.

Anal. Calcd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09; N, 5.89; S, 13.49. Found: C, 61.01; H, 5.38; N, 6.06; S, 13.48.

4-Chloro-2,3-dimethylthieno[2,3-*b*]pyridine (5g)

Yield: 49 mg (10%); white solid; mp 69–72 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (d, *J* = 5.1 Hz, 1 H), 7.48 (d, *J* = 5.1 Hz, 1 H), 3.33 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.8, 145.8, 136.7, 135.6, 129.8, 125.3, 121.2, 14.3, 13.7.

HRMS (ESI): *m*/*z* calcd for $[C_9H_8ClNS + H]^+$: 198.0139; found: 198.0141.

Anal. Calcd for $C_9H_8ClNS{\cdot}H_2O$: C, 53.04; H, 4.20; N, 6.87; S, 15.70. Found: C, 53.34; H, 3.94; N, 7.00; S, 15.31.

4-Chloro-3-methyl-2-propylthieno[2,3-*b*]pyridine (5h)

Yield: 141 mg (25%); white solid; mp 36–38 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 5.1 Hz, 1 H), 7.24 (d, *J* = 5.1 Hz, 1 H), 2.86 (t, *J* = 7.6 Hz, 2 H), 2.60 (s, 3 H), 1.80–1.76 (m, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 145.2, 141.4, 137.9, 130.9, 125.3, 121.0, 30.4, 24.2, 14.7, 13.8.

HRMS (ESI): *m*/*z* calcd for $[C_{11}H_{12}ClNS + H]^+$: 226.0452; found: 226.0456.

Anal. Calcd for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 6.20; S, 14.20. Found: C, 58.70; H, 5.48; N, 6.38; S, 13.87.

4-Chloro-3-methyl-2-pentylthieno[2,3-*b*]pyridine (5i)

Yield: 228 mg (36%); white solid; mp 36–38 °C (MeOH–H_2O); R_f = 0.48 (EtOAc–cyclohexane, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (d, *J* = 5.1 Hz, 1 H), 7.47 (d, *J* = 5.1 Hz, 1 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 2.53 (s, 3 H), 1.63 (t, *J* = 8 Hz, 2 H), 1.37–1.30 (m, 4 H), 0.90–0.85 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 145.2, 141.7, 137.8, 130.9, 125.1, 121.0, 31.4, 30.6, 28.4, 22.4, 14.7, 14.0.

HRMS (ESI): *m*/*z* calcd for $[C_{13}H_{16}ClNS + H]^+$: 254.0765; found: 254.0770.

Anal. Calcd for $C_{13}H_{16}ClNS$: C, 61.52; H, 6.35; N, 5.52; S, 12.63. Found: C, 61.82; H, 6.45; N, 5.60; S, 12.18.

***N*-Phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (6a)**

In a three-necked round-bottom flask fitted with a condenser, septum, and thermometer, **5b** (120 mg, 0.54 mmol) was dissolved in anhydrous toluene (5 mL), and Cs_2CO_3 (400 mg, 0.12 mmol), $Pd(OAc)_2$ (4 mg, 0.054 mmol) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (13 mg, 0.022 mmol) were added. Argon gas was applied and the reaction mixture was heated to 70–80 °C. Aniline (50 mg, 0.54 mmol) was dissolved in anhydrous toluene (3 mL) and added dropwise to the reaction mixture by using a syringe through the septum under argon. Upon complete addition, the temperature was raised to 110 °C and the progress of the reaction was followed by TLC until consumption of the reactants was complete (ca. 5 h). The reaction mixture was poured over ice and water, and extracted with EtOAc. The final pure product was obtained after silica gel column chromatography (cyclohexane–EtOAc, 7:3) and recrystallisation (cyclohexane).

***N*-Phenyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridin-4-amine (6a)**

Yield: 149 mg (99%); yellow solid; mp 102–105 °C (cyclohexane); R_f = 0.50 (EtOAc–cyclohexane, 3:7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 5.5 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.15 (d, *J* = 8.4, 2 H), 7.08 (t, *J* = 8.4, 1 H), 6.77 (d, *J* = 5.5 Hz, 1 H), 6.55 (s, 1 H), 3.05–3.02 (m, 2 H), 2.79–2.77 (m, 2 H), 2.00–1.66 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 147.1, 146.2, 139.8, 134.4, 129.7, 125.8, 124.3, 122.2, 121.2, 103.6, 27.1, 25.8, 22.9, 22.5.

HRMS (ESI): *m*/*z* calcd for $[C_{17}H_{16}N_2S + H]^+$: 281.1112; found: 281.1121.

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.57; H, 5.85; N, 9.85; S, 11.59.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561459.

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Synthesis and Molecular modeling of some new chalcones derived from coumarine as CDC25 phosphatases inhibitors

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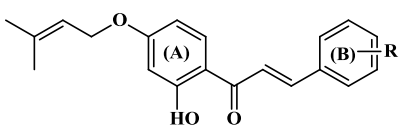
Abstract: New chalcones derived from coumarines were synthesized and tested as CDC25 phosphatase inhibitors. Molecular modeling of these new compounds was also presented in aim to study the mode of compounds orientation within CDC25 A and B. The reversibility of compounds 3, 4 and 5 was confirmed by application of MALDI–TOFMS technique**.**

Keywords: Chalcones, Coumarines, CDC25 phosphatase, MALDI-TOFMS, Molecular Modeling.

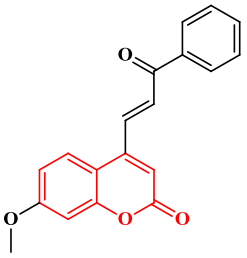
Introduction

CDC25 (Cell Division Cycle) is dual specificity phosphatase that play critical role in the division of eukaryotic cells. Up to date, three CDC25 isoforms were identified: A, B and C [1–4]. They dephosphorylate CDK/cyclin protein complexes which are key regulator of cell division. Noteworthy,CDC25B is needed for checkpoint recovery to repair DNA before mitosis [3,5].
CDC25A and CDC25B are overexpressed in many different human cancers: (e.g.: breast cancer: 70% and 57%, colorectal cancer: 47-53% esophageal cancer: 46-66% and 48-79% respectively) [1]. Consequently, they appear as potential target in cancer therapy. Wide range of different scaffolds has been reported as CDC25 phosphatase inhibitors including quinoids, dysidiolide and large collection of miscellaneous structures [6,7]. Chalcones have numerous biological activities containing antihypertensive, antifungal, anticonvulsant, antiviral, antioxidant, anti-inflammatory, antimalarial, anti-HIV, antiprotozoal, antimicrobial, antifilarial, [8,9] they also proved their antitumor activities through their action against many molecular targets [10]. The substituted chalcones in position 4 of ring (B) was even reported as CDC25 inhibitors with considerable activity (**Figure 1**)[11].Coumarines are well known as anticancer [12] active compounds with many different mechanisms like kinase inhibitors, apoptosis induction, angiogenetic inhibition, HSP90 inhibitors, telomerase inhibitor and antimitotic. [13] Some coumarines have anticoagulant and cardiovascular properties (dicoumarol and warfarin) others have antibiotic activities as novobiocin and clorobiocin which are naturally occurring. [14] Geiparvarin is another example of coumarine with dual activities: MAO-B inhibitory and antitumor.[15] Coumarine has been combined with different pharmacophores, and showed antioxidant, anti-inflammatory, anticancer, and antimicrobial activities. [16] Some of them, hybridized with quinones [17,18] or dimerized thanks to a disulfide bond of various lengths **(Figure 1)** [19]are particularly active.

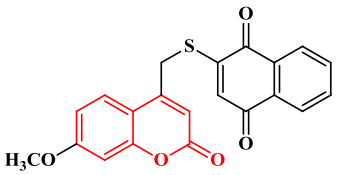


I:R=4-Cl
II:R=4-
III:R=3,4[$CH_2CH=CCH_3$]

inhibitor activity (CDC25)>97,5%



IC_{50}(CDC25B)= 16,1 %



SV37: Inhibitor of CDC25s

Figure 1. Examples of substituted and coumarines based chalcones inhibitors of CDC25s

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Synergistically, coumarine and chalcones combined structure appeared as promising anticancer molecules. They showed their abilities against number of human cancer cell lines, [20] therefore, series of novel chalcones derived from coumarine were synthesized by aldol condensation. The obtained compounds were investigated by docking simulation and then evaluated *in vitro* on CDC25A and B enzymes.

Results and Discussion

Chemistry

All compounds were synthesized by well-known base-catalyzed aldol condensation [21] between 3-acetyl coumarines and cinnamaldehyde. Previously, in our laboratory, substituted 3-acetyl coumarines were prepared starting from salicylaldehyde [22] and ethylacetoacetate [23,24]. Commercially available cinnamaldehyde and other synthesized derivatives were introduced as condensed partner. In addition cinnamaldehydes compounds were synthesized with two different methods:

Method A consisted of the reduction of cinnamic acid using $LiAlH(OtBu)_4$ [25] **Method B** was done by Wittig reaction [26] between a benzaldehyde and an acetal [27]. All prepared compounds were purified by column chromatography (cyclohexane: ethyl acetate 9:1).

Biological evaluation

Fluorimetric analysis

Compounds **1** to **8** were evaluated *in-vitro* against recombinant human CDC25 phosphatases by fluorimitric method. (**Table 1**)

Table 1. Inhibitory activity of product **1**-**8** with CDC25A and B (concentration of compounds 20 µM)

compounds	CDC25A	CDC25B
DMSO	0±3.81	0±1 .25
1	24.02±3.98	30.42±2.66
2	16.59±5.59	28.32±3.95
3	28.65±3.23	18.39±1.29
4	35.95±1.29	16.42±1.13
5	40.64±0.92	54.94±1.13
6	32.72±3.97	34.63±2.31
7	28.56±2.38	32.89±1.09
8	7.34±1.77	28.94±3.43
Naphtoquinone	99.68±4.52	99.41±3.12

The electrophilic substitution: Cl and Br on position 6 of the coumarine part led to inhibit CDC25A in higher extent than methoxy substituted analogue. The order of activity of these compounds was **4**>**3**>**2**. This order was inversed in the case of CDC25B. Introduction of methoxy group on the phenyl moiety increased the activity of compound **4** toward CDC25B but it diminished with CDC25A (from 35.95% to 7.34%). Furthermore, comparing the activities of compounds **1**, **6** and **7**; it showed that the methoxy group substitution on the phenyl ring increased the activity against both isoforms. The substitution on position 7 of coumarine with N, N-diethylamino group (compound **5**) increased the inhibitory activity on CDC25A: 40.64±0.92% and CDC25B: 54.94±1.13%). This compound was finally the most potent candidate among all tested structures (Table 1).

MALDI-TOFMS

Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI–TOFMS) was applied to check if the synthesized structures may be a candidate to CDC25 inhibition. In case of inhibition, the applied procedure is also able to inform about its reversibility or irreversibility. [28]

Compounds with the highest values in biological analysis as inhibitor (**3**, **4** and **5**) gave a positive results in MALDI-TOFMS Their protonated molecular ion directly appeared in the mass spectrum meaning that they behaves as reversible inhibitors as described by *Sibille et al*. [29] and *Bana et al*. [17].

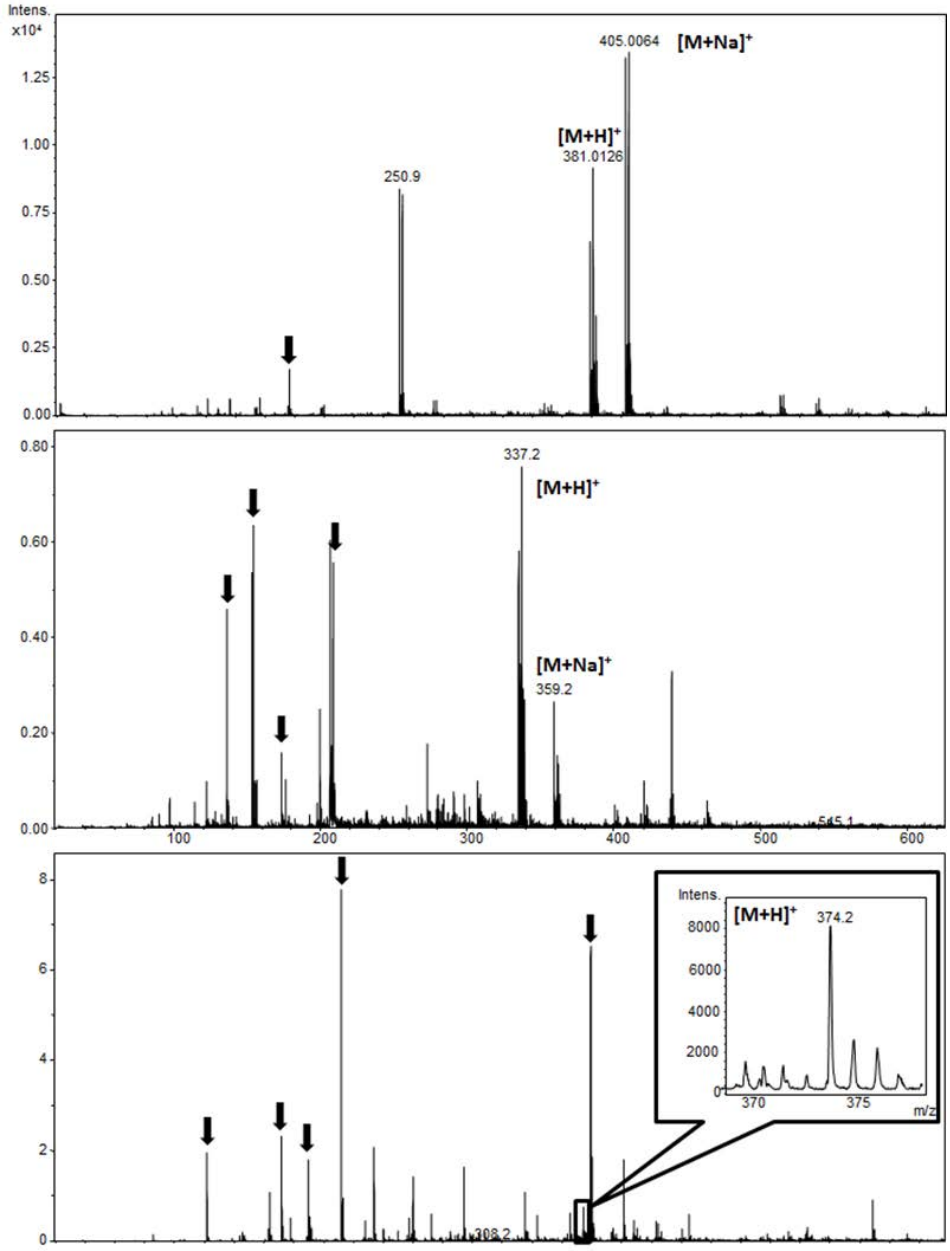


Figure 2. MALDI–TOF mass spectra (reflectron mode) of compounds **3**, **4** and **5** from up chart to down (DHB matrix for compound 3 and HCCA matrix for compounds **4** and **5**, C = 2×10^{-4} M) and CDC25A incubated with them. The ion m/z=381.01, m/z=337.2 and m/z=374.2 corresponding to $[M+H^+]$ of 3, 4 and 5 respectively.

Molecular modelling

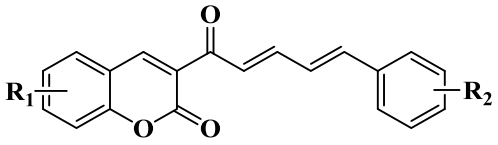
The molecular surface scanning of CDC25B reveals that its 3D structure exhibits a large groove just close to active cysteine [30]. Thus, this site called swimming pool also appears as an interesting target for inhibiting CDC25 by the binding of small molecules. [31]

Hence, the binding inside this catalytic site cannot only be taken into account as a dependable mode of inhibition. We suggested designing of chalcones derived from coumarine and investigating the designed products by docking simulation to test the mode of orientation of each moiety in relation to active and inhibitory sites. Possibility of formyl pyranone ring to surrogate the phosphate group of the native substrate was presumed [6].

The surface structure of the CDC25B catalytic domain (1QB0) [32], indicated that the distance between the shallow active site and the large groove is ~ 7.3 Å. This distance must correspond to the linker length between the position 3 of the coumarine and the position 1 of the ring (B) of the chalcone-like moiety for inhibitor in 3D model.

Using CDC25B as key model, we found that conjugating ketone-diene chain (n=2) provided a better linker length than a single double bond (n=1) for our approach. Coumarine was one of the counterparts of choice while the other was substituted aromatic ring, and they were intended to be hybridized.

Table 2. Synthesized derivatives and their molecular modeling interaction scores with CDC25 phosphatase A and B indicating hydrogen bonds (number and length) and energy.



Compounds	R1	R2	CDC25A Energy (Kcal/mol)	HB no°	Length (A°)	CDC25B Energy (Kcal/mol)	HB no°	Length (A°)
1	H	H	-4.5	3	2.4; 2.6	-6.9	1	2.8
2	6-OMe	H	-5,6	1	2	-7.3	1	2.6
3	6-Br	H	-5,4	2	2; 2.5	-6.5	1	2.7
4	6-Cl	H	-5,6	2	2.5; 2.6	-7.5	1	2.7
5	7-N(C_2H_5)$_2$	H	-3.9	2	2.7	-7.7	2	2.5; 2.6
6	H	2,4-OMe	-6.2	1	2.9	-7.6	2	2; 2.7
7	H	2,5-OMe	-6.1	2	2.6; 2.9	-7.8	2	2.3; 2.7
8	6-Cl	2,4-OMe	-5,9	2	2.7; 2.9	-7.4	1	2.2

The docking study was achieved using AUTODOCK Vina [33]. We assumed that the coumarine compound is able to bind the cysteine of the catalytic site of CDC25B. Our docking study showed that, for the half of the structures tested, the coumarine part rather fitted inside the swimming pool of CDC25B, while the chalcone part entered the active site. This is observed for compounds **1**, **4**, **5** (**Figure 3**) and **6** blocked whereas it is the contrary for compounds **2**, **3**, **7** and **8**.

The docking with CDC25A was more challenging as the catalytic cysteine is located inside very shallow groove, with a very small cavity appearing unsuitable for fitting neither coumarine nor phenyl moiety of the compounds series. The docking results showed that the most of molecular poses are oriented in a way that the coumarine was toward the catalytic cysteine (cys430) which complying with phosphates group simulation assumption (**1**, **2**, **3** (**Figure 4**), **4**, **5**, **6**). (**Table 1**).

This orientations similar to phosphate cradling model of the native substrate [34]. Compounds **7** and **8** had their binding mode in the opposite direction.

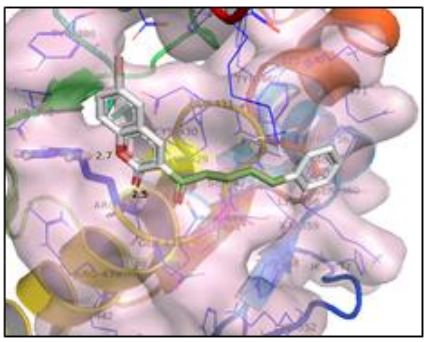


Figure 3. Compound **5** docking orientation with CDC25B interacting by two hydrogen bonds with Tyr428 and Arg544

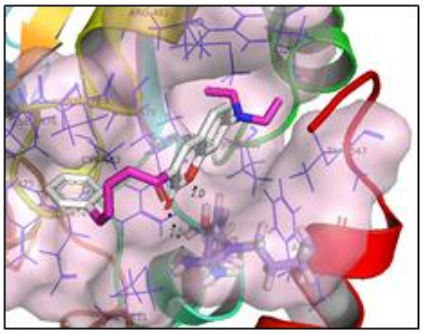


Figure 4. Docking of compound **3** with CDC25A forming two Hydrogen bonds with Arg436

Docking could not give the explanation of the inhibitory activity [29,35–47], so it was necessary to synthesize these molecules and evaluated their biological activities with CDC25A and B then verification of their reversibility.

The CDC25s have two interesting sites: the active site and the swimming pool which can play an important role, so it would be efficient if both of them are tested in same time.

It has been suggested that the hybrid structure may be more efficient at inhibiting CDC25s. Indeed, the first moiety of the inhibitor could fit the binding pocket (i.e. the swimming pool) while the other part could bind to the active cysteine [48].

Conclusion

The antitumor characteristics of both coumarine and chalcones inspired our approach to design hybrid structures could block both grooves of the protein

(active and inhibitory) highlighting the lack of toxicity in the same time.

Several chalcones derived from coumarine were synthesized, the binding modes of them were tested by molecular modelling simulation, the probability of phosphate surrogating by coumarine ring has been shown by certain derivatives. Biological evaluation revealed some activity of the compounds. *N, N*-diethylamino substitution on position 7 of coumarine (compound **5**) increasing the inhibitory activity on both isoforms of CDC25. The derivatives proved to perform reversible inhibition by MALDI-TOF analysis (compounds **3**, **4** and **5**). The designed scaffold could be considered as a basis of further lead optimization in order to obtain better inhibition.

Experimental Section

Chemistry

All solvents were used as purchased unless otherwise noted.

Melting points were determined on a Buchi 530 digital melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, using Me_4Si as the internal standard. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). High resolution mass spectra were measured using a MicroTof-Q98 instrument in ESI mode. Column chromatography was performed using silica gel (60M, 0.04-0.063 mm). Thin layer chromatography (TLC) was performed using silica gel plates (POLYGRAM SIL G/UV_{254}, 0,20mm). For the visualization, TLC plates were placed under UV light.

General procedure for synthesis of compounds 1 to 8

In round bottom flask, 1.1 mmole of cinnamaldehydes and 1 mmole of substituted 3-acetyl coumarine were mixed in ethanol, and stirred under reflux till dissolving of coumarine derivatives. Afterward, 5% mole of piperidine was added and the reaction retained under reflux for 24 h. When the reaction completed, the solution allowed to be cooled, and the product started to precipitate. The obtained solid was filtered and recrystallized using ethanol.

3-(1-Oxo-5-phenyl-2Z, 4Z-pentadien-1-yl)-2H-1-benzopyran-2-one (1)

Yellow powder; Yield: 52%; Mp: 184°C. [49]

^{1}H NMR (400 MHz, $CDCl_3$):δ(ppm)=7.07 (d, 1H, *J*=6Hz); 7.08 (d, 1H, *J*=8Hz); 7.35- 7.42 (m, 5H); 7.68-7.70 (d, 1H, *J*=8Hz); 7.67-7.69(dd, 1H, *J*=8Hz, *J*=1.6Hz);7.52-7.54(dd, 1H, *J*=8.4Hz; *J*=1.6 Hz);7.51-7.34(d,1H, *J*=9.6Hz); 7.49-7.52 (d, 1H, *J*=10Hz); 7.72 (d,1H, *J*=2.4Hz); 8.60 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=116.7, 118.6, 124.9, 125.39, 127.3, 127.4, 128.9, 129.3, 130, 134.1, 136.1, 142.7, 145.2, 147.8, 155.2, 186.3.

HRMS (ESI): m/z [M+Na]$^{+}$ calculated for $C_{20}H_{14}O_2$: 302,32; found : 325,085

6-Methoxy- 3-(1-oxo-5-phenyl-2E,4E-pentadien-1-yl)-2H-1-benzopyran-2-one (2)

Yellow powder; Yield: 24%; Mp: 190°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)= 3.89 (s, 3H, OCH_3); 7.07 (s, 1H); 7.09 (dd, 2H, *J*=5.6Hz and *J*=2.5Hz) ; 7.24 (d, 1H, *J*=6Hz) ; 7.32-7.35 (d, 1H, *J*=14.4Hz) ; 7.33-7.38(dd, 1H, *J*=18Hz); 7.36-7.40 (d, 1H, *J*=14.4Hz) ;7.50 (d, 1H, *J*=6.8Hz); 7.53 (dd,2H, *J*=8Hz); 7.60 (t,1H); 7.68 (dd, 1H, J=18Hz); 8.50 (s,1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)= 55.9, 111.0, 117.8, 118.9, 122.6, 125.5, 127.3, 127.4, 127.5, 128.9, 129.3, 136.1, 142.7, 145.1, 147.7, 149.9, 156.4, 159.4, 186.4.

HRMS (ESI): m/z [M+Na]$^{+}$ calculated for $C_{21}H_{16}O_4$: 332.35; found 355.095

6-Bromo-3-(1-oxo-5-phenyl-2E,4E-pentadien-1-yl)-2H-1-benzopyran-2-one (3)

Yellow-orange powder; Yield: 54%; Mp: 237°C. [50]

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)= 7.08 (d, 1H, *J*=6Hz) ; 7.30 (d ,1H, *J*=16Hz) ; 7.38 (m, 3H) ; 7.46 (d, H, *J*=16Hz) ; 7.53 (d, 2H, *J*=9.2Hz); 7.68 (dd, 1H, *J*=16.8Hz); 7.71 (dd,1H,*J*=16.8Hz); 7.73 (dd, 1H, *J*=2.4 Hz and *J*=8Hz); 7.81 (d, 1H, *J*=2.4Hz); 8.48 (s,1H); 8.47 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)=117.5, 118.4, 119.7, 125.5, 127.5, 128.9, 132.2, 137, 145.9, 154.1, 158.5, 194.9.

HRMS (ESI): m/z [M+Na]$^{+}$ calculated for $C_{20}H_{13}BrO_3$: 380,9; found: 402,994

6-Chloro-3-(1-oxo-5-phenyl-2E,4E-pentadien-1-yl)-2H-1-benzopyran-2-one (4)

Yellow-orange powder; Yield: 70%; Mp: 244°C [50]

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm)= 7.08 (d, 2H, *J*=6Hz) ; 7.34 (d, 1H, 14Hz) ; 7.36 (d, 1H, *J*=8.8Hz) ; 7.41 (m,2H); 7.46 (d, H, *J*=14.4Hz); 7.53 (d,1H, J=6.8Hz); 7.61(dd, 1H, J=14Hz); 7.55 (d, 1H, J=1.2Hz); 7.7 (dd, 1H, J=14Hz); 8.50 (s,1H); 8.47(s,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm)= 118.1 ; 119.2 ; 125.5 ; 127.1 ; 127.2 ; 127.5 ; 128.9 ; 129.1 ; 129.5 ; 130.3 ; 133.9 ; 134.2 ; 143.1 ; 145.6 ; 146 ; 158.6 ; 195.

HRMS (ESI): m/z [M+Na]$^{+}$ calculated for $C_{20}H_{13}ClO_3$: 336,06; found: 359,045

7-N,N-diethylamino-3-(1-oxo-5-phenyl-2Z,4Z-pentadien-1-yl)-2H-1-benzopyran-2-one (5)

Orange powder; Yield: 33% ; Mp: 166°C [51]

^{1}H RMN (400 MHz, $CDCl_3$) : δ(ppm)=1.17 (t,6H); 3.38 (q,4H); 6.40 (d, 1H, J=1.6Hz); 6.54 (dd, 1H, J=2.5Hz and 9.2Hz); 6.98 (d,1H, *J*= 10Hz) ; 7.08 (dd,1H, *J*= 10Hz and 10.8Hz) ; 7.23 (d,1H) ; 7.31 (m,5 H); 7.33 (d, H,J=9.2Hz); 7.57 (d ,1H, *J*= 9.6Hz) ; 7.60 (dd,1H ,*J*= 9.6Hz) ;8.45 (s:1H) ; ^{13}C RMN (100 MHz, $CDCl_3$) : δ(ppm)= 12.5 ; 30.6 ; 96.7 ; 108.7 ; 109.8 ; 116.8 ; 127.3 ; 127.8 ; 128.8 ;

131.8 ; 136.4 ; 141.2 ; 143.5 ; 148.6 ; 153.0 ; 158.6 ; 160.9 ; 186.4.
HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{24}H_{23}NO_3$: 373,17; found: 396,158

3-[1-Oxo-5-(2,4-diméthoxyphenyl)-2E,4E-pentadien-1-yl]-2H-1-benzopyran-2-one (6)
Red Powder; Yield: 31%; Mp: 195°C

^{1}H NMR (400 MHz, $CDCl_3$) : δ(ppm)= 3.88 (s ,3H); 3.92 (s,3H); 6.54-6.56 (2d, 2H, *J*=2.4Hz and *J*=8Hz), 6.48 (d,1H, *J*=2Hz), 7.34-7.43 (m,3H), 7.63 (s,1H), 7.66- 7.69 (dd,2H, *J*=18Hz), 7.89 (d,1H, *J*=16Hz), 8.17 (d ,1H, *J*=16Hz), 8.56 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm)= 55.5, 98.4, 105.6, 116.6, 117.2, 118.7, 122, 124.8, 126.1, 129.8, 131.1, 133.8, 140.7, 147.3, 155.1, 159.3, 160.7, 163.5, 186.8.
HRMS (ESI): m/z [M+Na]$^+$ calculated for $C_{22}H_{18}O_5$: 362.12; found 385.015

3-[1-Oxo-5-(2,5-diméthoxyphenyl)-2E,4E-pentadien-1-yl]-2H-1-benzopyran-2-one (7)
Yellow powder; Yield: 36%; Mp: 132°C.

^{1}H RMN (400 MHz, $CDCl_3$): δ(ppm)= 3.75 (s,3H, OMe), 3.81 (s,3H, OMe), 6.48 (d,1H, *J*=8Hz); 6.79(d,1H, *J*=8.8Hz); 6.88 (dd,1H, J_1=6Hz, J_2=2.4Hz), 7.14 (d,1H, *J*=3.2Hz), 7.36 (dd,1H, *J*=14.4Hz); 7.38(dd,1H, *J*=14.4Hz); 7.58 (m,2H); 7.86 (d,1H, *J*=16Hz), 8.10 (d, 1H, *J*=16Hz); 8.17(d,1H,J=7.2Hz); 8.48 (s,1H). ^{13}C RMN (100 MHz, $CDCl_3$): δ (ppm)= 55.9, 56.2, 112.6, 113.4, 116.7, 118.2, 118.6, 124.4, 124.6, 124.9, 125.7, 129.9, 134.0, 140, 147.7, 153.6, 153.7, 155.2, 159.3.
HRMS (ESI): m/z [M+Na]$^+$ calculated for $C_{22}H_{18}O_5$: 362.12; found 385.015

6-Chloro-3-[1-oxo-5-(2,4-diméthoxyphenyl)-2E,4E-pentadien-1-yl]-2H-1-benzopyran-2-one (8)
Colorless solid, Yield: 20%; Mp: 80°C

^{1}H RMN (400 MHz, $CDCl_3$) : δ(ppm)= 3.77 (s,3H); 3.88 (s ,3H), 6.34(s1H); 6.38(dd,2H, *J*=8Hz); 6.4(dd,1H, *J*=16Hz); 6.7(d,1H,J=15.5Hz); 7.36(d,1H, *J*=16Hz);7.43 (dd, 2H, J=8.4Hz); 7.57 (dd,1H, *J*=15.5Hz) ; 7.24 (d, H) ; 7.99 (s,1H) ; 8.47 (s,1H); ^{13}C RMN (100 MHz, $CDCl_3$) : δ(ppm)= 55.4, 60.1, 98.5, 105.2, 116.2, 116.7, 130.4, 139.9, 145, 153, 159.8, 162.6, 167.9, 182.49, 199.13.
HRMS (ESI): m/z [M+Na]$^+$ calculated for $C_{22}H_{17}ClO_5$: 396.08; found 418.9755

Docking simulation

3D structures of all compounds were designed and the best conformer picked by VEGA ZZ 2.3.1 software [52]. It was also used for adjusting the force field of the molecule as AMBER, and atomic charge which applied as Gasteiger, products was energetically minimized using MOPAC and finally introduced as PDB format.

CDC25B (1QB0) and CDC25A (1C25) [53] phosphatase catalytic domain was obtained from the Protein Data Bank. AutoDock Tools was employed to remove unwanted elements and water. It transformed to PDBQT file format, to make them ready for docking which was processed using AUTODOCK Vina. Docking parameters was adjusted as the following
CDC25B: Grid box centered in X= 18.3, Y= 4.6, Z= 16.3, Volume = 23*23*23 Å
CDC25A: Grid box center: X= 11.6, Y= 40.2, Z= 69.3, Volume = 16*16*18 Å
Pymol software [54] was used for visualization and determination of the interaction of compounds with enzyme.

Biological evaluation

Recombinant human CDC25 phosphatases were prepared by previously described method [19]. Assay took place in 96-well plates; buffer solution was adjusted in the following quantities: 50 mM Tris–HCl, 50 mM NaCl, 1 mM EDTA, and 0.1% Bovine Serum Albumine, pH 8.1. Incubation period of substrate 3-*O*-methylfluorescein phosphate with enzyme was 2 h in 30^{0}C. Enzyme was exposed to the inhibitors for 20 min and the residual activity of the enzyme has been determined by fluorimetric method.

MALDI/TOFMS

All compounds were dissolved in ethanol at a concentration of 10^{-2} M. The solution were then further diluted to 2.10^{-3} M with ultrapure water. Phosphatases CDC25A was solubilized in Tris A buffer (50 mM Tris, 50 mM NaCl, 1 mM EDTA and 1 mM dithiothreitol [DTT], pH 8.0) at a concentration of 8.10^{-5}M. One hundred and fifty µl of CDC25A was incubated with 40 µl of compounds for 1 h. Solution was ultracentrifugated on Microcon filter unit with a mass cutoff of 30 kDa (Millipore). The unbound material was eliminated by centrifugation during 10 min at 12,000 rpm and washed three times by 100 µL of ultrapure water. The retentate was then dissolved in 20 µL of ultrapure water. Two µl of the retentate was spotted on the MALDI plate (2 spot for sample in two line) , evaporated to dryness at room temperature. Then one µl of saturated solution of DHB (dihydroxybenzoic acid) was deposited for one of spot and HCCA (α-hydroxycyanocinnamic acid) was deposited for the second spot of each sample on the plate to evaluate the response of each compound with both of matrix, and conserved the spectrum which had the intense response.

The presence of the protonated molecular ion in the MS spectrum is corresponding to a reversible inhibitor activity.

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Review

Natural and Synthetic Coumarins with Effects on Inflammation

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Abstract: In this review, we will present the different aspects of coumarins and derivatives, from natural origins or synthetically prepared, and their action on inflammation. Coumarins and also furo- and pyranocoumarins are found in many different plants. These compounds are very often investigated for antioxidant properties. Other biological properties are also possible and anti-inflammation activity is one of these. As coumarins are also available quite easily via synthesis, natural ones can be prepared this way but derivatives with special substituents are also feasible. A review on the same topic appeared in 2004 and our contribution will take into account everything published since then.

Keywords: coumarins; furocoumarins; pyranocoumarins; inflammation

1. Introduction

Inflammation is a general and essential response to any aggression and may be shown by a localized response or by a more generalized one. Inflammation is thought to be at the start of different diseases including obesity, cancer and neurodegenerative illness. The biosynthetic cascade of arachidonic acid leading to the formation of prostaglandins (PG), leukotrienes (LT), hydroxyeicosatetraenoic acids (HETE) have been shown to be involved in the inflammation as well as other processes. Blocking the cascade is a possible way to fight inflammation. Inflammation is the process by which leucocytes and material derived from the serum are directed to the site of tissue injury. Coumarins are widespread natural chemicals [1]. Many of these compounds have a pharmacological use [2]. In this review we will investigate coumarins and derivatives with anti-inflammatory activity. We will present this study in terms of the chemical structure: simple coumarins, furo- and pyrano-coumarins.

In the first part, naturally occurring coumarins will be presented. The second part will be devoted to synthetic coumarins.

2. Naturally Occurring Coumarins

2.1. Simple Coumarins

Figure 1 shows the plant derived coumarins described in the literature with anti-inflammatory activities.

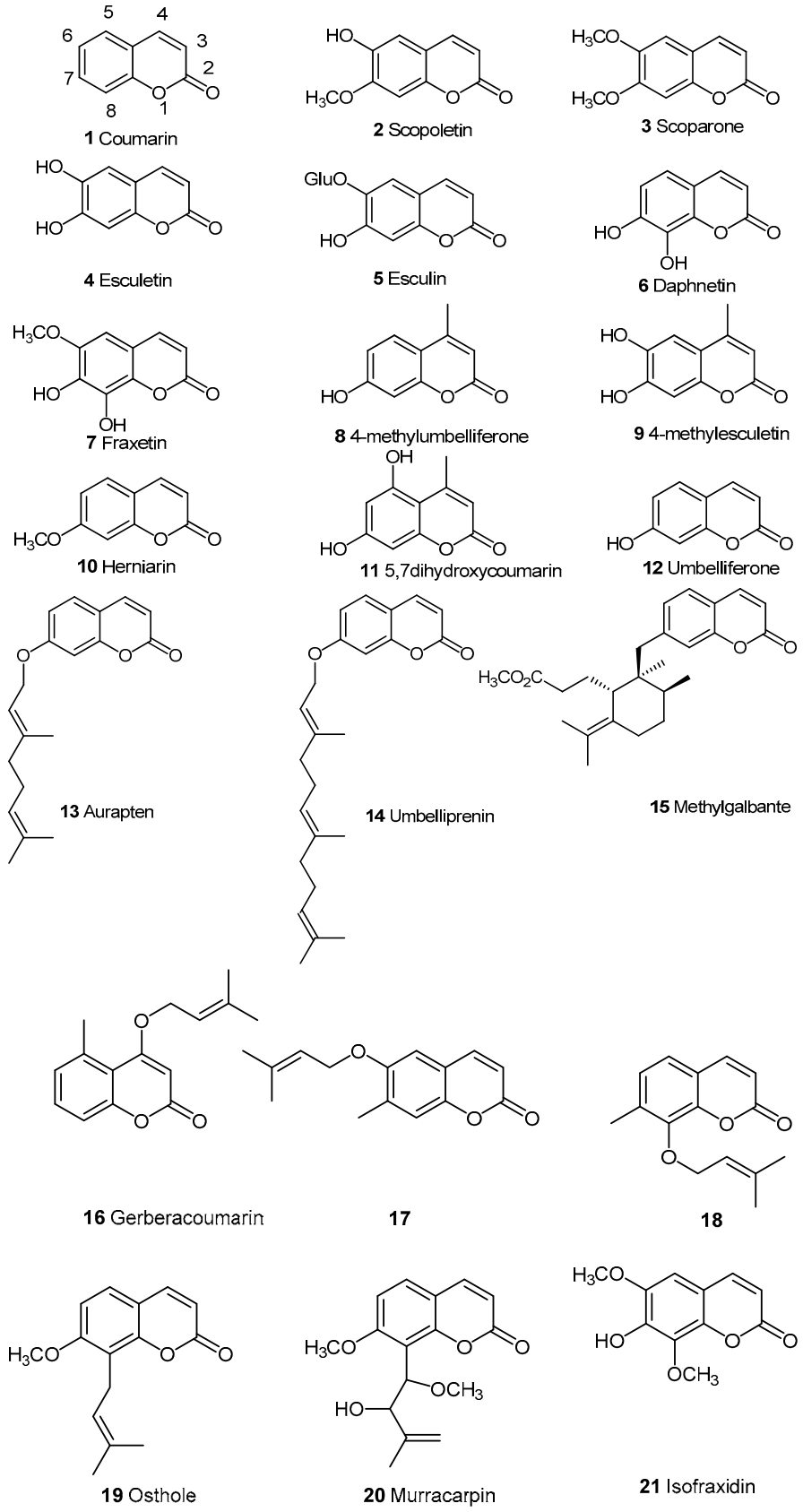

Figure 1. Natural coumarins.

Coumarin **1** itself was used for the treatment of edema [3]. A general study on **2**, **3**, **5**, **6**, **7**, **8** has been run on TNBS (trinitrobenzenesulfonic acid) induced colitis [4]. The study showed that these coumarins are potential agents for treating the inflammation. The effect seems directly related to the

Coumarin **1** itself was used for the treatment of edema [3]. A general study on **2**, **3**, **5**, **6**, **7**, **8** has been run on TNBS (trinitrobenzenesulfonic acid) induced colitis [4]. The study showed that these coumarins are potential agents for treating the inflammation. The effect seems directly related to the antioxidant properties of the coumarins, in particular for daphnetin **6**, esculin **5** and scoparone **3**. Food containing coumarins could be a possible strategy to prevent Inflammation Bowel Diseases (IBD). Natural products like esculetin **4**, fraxetin **7**, daphnetin **6** and other related coumarin derivatives are recognized as inhibitors not only of the lipoxygenase and cycloxygenase enzymic systems, but also of the neutrophil-dependent superoxide anion generation [5].The study on the ethanolic extract of Artemisia capillaris Thunberg (Compositaea) used in traditional Chinese medicine for amelioration of skin inflammation showed inhibition activity on 5-lipooxygenase [6]. In particular, esculetin 4 had the property along with other compounds [6]. Experiments run on inflammation in animal models (xylene induced ear edema, carrageanan induced paw edema and carrageanan induced mouse pleuresy) [7] have shown that esculin **5**, a glycoside of esculetin, attenuated the phenomena. In-vitro pro-inflammatory cytokines levels of TNF-α and IL-6 were reduced by esculin. It was also found that esculin significantly inhibited LPS (lipopolysaccharide) induced activation of MAPK pathway in peritoneal macrophages. Esculin could be a promising agent for treating inflammatory diseases in humans. Another study on rat peritoneal leukocytes using 16 different coumarins [8] has pointed out the effect on LTB_4 and TXB_2 generated by calimycin (A23187). Fraxetin **7**, esculetin **4**, daphnetin **6**, 4-methylesculetin **9** were the most active on LTB_4 and herniarin **10**, 4-methyl-5,7 dihydroxycoumarin **11** and daphnetin **6** on TXB_2 with IC_{50} ranging from 1–75 μM. Daphnetin **6** appears often as an effective compound. The compound extracted from Daphnea odora was tested in collagen induced arthritis in rats [9]. The therapeutic effect was determined by the balance of Tregs and Th-17. The levels of these lymphocytes were evaluated by ELISA and those related receptors. by immunochemistry. Administration of daphnetin for 21 days highly alleviated the severity of arthritis by modulating the balance. In continuation looking at the power of daphnetin, some finding suggest that it might have a neuroprotective effect in stressed mice [10]. The role of daphnetin in microglial inflammatory response was explored. The study showed that all the pro-inflammatory mediators (IL-1B, TNFα induced by LPS) were strongly depressed in a dose dependent manner in BV_2 microglia and it inhibited the LPS-induced iNOS and COX-2, even NO formation by microglia. In general daphnetin inhibits microglial activation and proinflammatory responses by modulating a series of intracellular pathways (IKK/κB,MAPKs and Pt.3K/Akt).

Umbelliferone **12** has not been found to have anti-inflammatory properties but some of its derivatives did. Among these, aurapten **13** and umbelliprenin **14** were the most studied. These compounds are found especially in the Ferula species. Aurapten **13** from Ferula szowitsiana showed cancer chemopreventive properties suggested by anti-inflammatory activity of the compound [11]. A mini-review on the biological activity of umbelliprenin from Artemisia species has appeared [12] linking the activity to iNOS inhibition. A paper [13] describing an extract from Ferula szowitsiana describes the activity of 6 terpenoïd coumarins isolated (methyl galbanate, galbanic acid, farnesiferol A, badrakemone, umbelliprenin and aurapten). In this case methylgalbanate **15** was the best inhibitor of nitric oxide production; it was better than umbelliprenin isolated from the same species.

Three naturally occurring O-prenyl coumarins; 4-isopentenyloxy-5-methyl-coumarin **16**, 6-isopentenyloxy, -7-methoxy-coumarin **17**, 8-isopentenyloxy-7-methoxy-coumarin **18**; from respectively Gerbera crocera and Gerbera serrata (Asteraceae), Haplophyllum pedicellatum (Rutaceae) and divers Artemisia species were prepared by synthesis [14]. They have been studied as dual anti-bacterial and anti-inflammatory compounds for controlling peritoneal diseases. U937-3xκB-LUC cell line was used to evaluate the ability to inhibit the activation of NF-κB signaling pathway induced by LPS. Compounds **17** and **18** were effective in the inhibition but not **16**. In fact, these two compounds also had anti-bacterial activity and were examples of dual action.

Osthole **19**, 8-prenyl-7-methoxy-coumarinapplied in clinical practice in Traditional Chinese Medicine is found in different plants (Angelica, Archangelica, Citrus, Clausena) and in high content

in the mature fruit of Cnidium monnieri. The anti-inflammatory properties are described in a recent review ([15] and ref cited therein). Osthole has also been described as decreasing ocular inflammation [16].

Murracarpin **20**, structurally close to osthole and isolated from Murraya exotica showed strong anti-inflammatory and analgesic effect [17].

Ethylacetate extract of Canadian marple syrup contains many phenolics related compounds including coumarins. Fifteen pure compounds available were tested in LPS stimulated RAW264.7 murine macrophage and the decrease of nitric oxide and PGE_2 measured. Unfortunately, the coumarinic isofraxidin **21** was not active [18]. All the biological results of simple coumarins are summarized in (Table 1).

Table 1. Some anti-inflammatory activities of Simple coumarins.

Cpd	CPE% [1]	IL-1β	IL-6	5-LOX	NF-κB	NO	TNF-α	Ref.
4				IC_{50}: 6.6 [2]				[5]
5			<200 ng/mL (20 mg/kg) [3,**]				<400 ng/mL (20 mg/kg) [3,**]	[7]
6		<3000 pg/mL (160 µg/mL, 24 h) [4,*]; <1000 pg/mL (160 µg/mL) [5,**]			Activity < 1 (160 µM) [4,*]	<20 µM (160 µM) [4,**]	<500 pg/mL (160 µg/mL, 24 h) [4,*]; <400 pg/mL (160 µg/mL) [5,**]	[10]
14	39% (0.01 mmol/kg)			IC_{50}: 72.5 nm				[12]
15						<10 µM (10 µM) [6,*]		[13]
16					>80% (50 µg/mL) [1]			[14]
17					<10% (50 µg/mL) [1]			[14]
18					<5% (50 µg/mL) [7]			[14]
21					0% [6]	0% [6]	0% [6]	[18]

[1] Carageenin paw edema in rat; [2] Arachidonic acid induced ear edema in mice; [3] LPS-stimulated mouse peritoneal macrophage; [4] LPS-stimulated BV2 microglia; [5] Aβ-stimulated BV2 microglia; [6] LPS-stimulated macrophage RAW264.7; [7] LPS-stimulated U937-3xxKB-LUC human monocytic cell line; kg is referring to the mice weight; % is referring to percentage of inhibition. * $p < 0.05$ versus negative control. ** $p < 0.01$ versus negative control.)

2.2. Condensed Coumarins

The most condensed coumarins isolated from natural sources are furo- and pyranocoumarins. A review in 2006 [19] reports the biological activities of prenyloxy-furocoumarins and the in-vivo remarkable anti-inflammatory effect. We will review the publications appearing since then.

2.2.1. Furocoumarins

Among furocoumarins (Figure 2), imperatorin 22 has been the most investigated. The substance is found in *Angelica dahurica, Glhenia littoralis, Cnidium monnieri and Peucedanum praeruptorum* as well as in other *Apiaceae* and *Umbellifereae* species. These plants are used in traditional Chinese and Korean Medicine. as antipyretic and analgesic. Most assays that investigated the behavior against inflammation were run on LPS activated RAW264.7 cells [20–26] and carrageanan induced mouse paw edema [21]. In general, inhibition of NOS as well as COX-2 were found to be the cause. Imperatorin has also proved to be efficient on allergic rhinitis [27], acute lung injury induced by LPS in mouse [28], on sebum production in human sebocytes in vitro [29] and it has had an anti-allergic effect on Th-2 mediated allergic asthma [30]. It has been stated that phellopterin 23 presents the same features as imperatorin concerning this activity [20]. Dimeric furocoumarins from the roots of *Angelica dahurica* had the same activity [31].

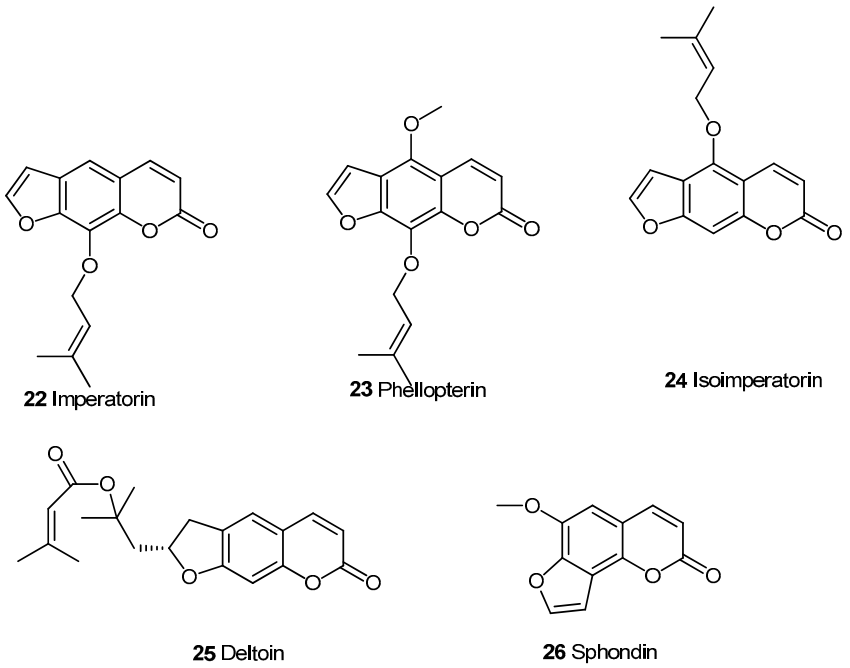

Figure 2. Naturally occurring furocoumarins.
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An isomer of imperatorin, isoimperatorin **24**, from the roots of *Angelica dahurica* [32] or *Cimicifugae* rhizome [33] was found to inhibit COX-dependent phases or TNF-α induced expression indicating its anti-inflammatory properties.
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Various furocoumarins extracted from Chinese herbs were tested for iNOS 5 inhibition [34,35]. Among the different furocoumarins: imperatorin **22**, deltoin **25** and sphondin **26** gave the best results. As sphondin is also available in different *Heracleum* species it may provide a basis for the use of plant extracts against inflammation. For example, sphondin extracted from *Heracleum lacinatum* inhibits IL-1β induced PGE_2 release in A549 cells [36]. This inhibition is mediated by suppressing of COX-2 expression and maybe at least in part through suppression of NF-κB activity. It is worth noting that the extract of fruits from *Heracleum crenatifolium* contains different furocoumarins and has anticonvulsivant activity in male albino mice [37]. A review on *Heracleum persicum* details the pharmacology of the furocoumarins in it [38].The biological results of furocoumarins are summarized in (Table 2).
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2.2.2. Pyranocoumarins
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Pyranocoumarins (Figure 3) have less been tested for this activity. The first compound of this class extracted was seselin **27** from *Sigmathamnus trifoliatus* able to inhibit inflammatory hyperalgesia and having also antinociceptive effect [39]. Obtained from *Seseli resinosum*, calipteryxin **28** and a dihydroseselin derivative were associated in the inhibition of inflammatory enzymes (iNOS and COX-2) and cytokines (TNF-α and IL-6) via NF-κB, MAPK and Akt pathways [40]. (+)-Praeruptorin **29** from the roots of *Peucedanum praerupotorum* reduced NO production and release of IL-1β, IL-6 and TNF-α induced by LPS-stimulated macrophage [41,42]. Other derivatives anomalin **30** and corymbocoumarin **31** were obtained respectively from *Saposhnikovia divaricata* and *Seseli gummniferum* have been used in LPS-stimulated RAW264.7 macrophages [43]. Anomalin dose-dependently inhibited iNOS, COX-2 mRNA and protein expression. Concerning corymbocoumarin, it exerts its effect by suppressing NF-κB activation and inducing HO-1 expression [44]. The biological results of this kind of coumarins are summarized below in (Table 3).
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Table 2. Some anti-inflammatory activities of furocoumarins.

Cpd	COX-2	IL-1β	IL-6	IL-10	NF-κB	NO	iNO	PGE_2	TNF-α	Ref.
22	<40% (10 μg/mL) [3,***]	<20 pg/mL (10 μg/mL) [1,*]; <300 pg/mL (30 mg/kg) [2,*]	<600 pg/mL (30 mg/kg) [2,*]	<600 pg/mL (15 mg/kg) [2,**]		<30 μM (10 μg/mL) [3,***]; <6 μM (10 mg/kg) [4]; IC_{50}: 52.3 ± 5.4 μM [3,***]	<40% (10 μg/mL) [3,***]; 83.3% (20 μg/mL) [3]	<400 pg/mL (10 μg/mL) [3,***]; <80 pg/mL (10 mg/kg) [4,***]	<40 μM (10 ng/mL) [3,***]; <300 ng/mL (10 mg/kg) [4]; <1500 pg/mL (30 mg/kg) [2,**]	[21,22,27,28,34]
23						IC_{50}: 38.3 ± 1.7 μM [3,***]				[22]
24	IC_{50}: 10.7 μM [5]					IC_{50}>20 μg/mL [3], 28.1% ± 39.7% (20 μg/mL) [3]				[32,35]
25						<20% (20 μg/mL) [3,****]	92.4% (20 μg/mL) [3]			[34]
26					<60% at 50 μM [6,*]	IC_{50}: 9.8 μg/mL [3]; 85.3% ± 8.7% (20 μg/mL) [3]	<5 μM (20 μg/mL) [3**]	<10 ng/mL (50 μM) [6,*]		[35,36]

[1] PMACI induced of HMC-1 cells; [2] LPS-induced of BALF (broncoalveolar lavage fluid); [3] LPS-stimulated macrophage RAW264.7'; [4] Carageenin paw edema in rat; [5] In bone marrow-derived mast cell (BMMC); [6] IL-1β induced of A549 cells; kg is referring to the mice weight; % is referring to percentage of inhibition; * $p < 0.05$ versus negative control; ** $p < 0.01$ versus negative control; *** $p < 0.001$ versus negative control; **** $p < 0.005$ versus negative control.

Table 3. Some anti-inflammatory activities of pyranocoumarins.

Cpd	COX-2	IL-1β	IL-6	NF-κB	NO	iNO	PGE_2	TNF-α	Ref.
28	<20% (30 μM) [1,***]	<40% (30 μM) [1,***]			<20 μM (30 μM) [1,***]; <40 μM (30 μM) [2,**]	<20% (30 μM) [1,***]		<40% (30 μM) [1,***]	[40]
29		<100 pg/mL (25 μg/mL) [1,**]	<100 pg/mL (100 μM) [1,**]		<15 μM (25 μg/mL) [1,**]			<10000 pg/mL (25 μg/mL) [1,*]	[41,42]
30	<60% (50 μM) [1,***]			<4000 RFU (50 μM) for NF-κB-dependent alkaline phosphate (SEAP) [1,***]		<60% (50 μM) [1,***]		<60% (50 μM) [1,***]	[43]
31				<8000 RFU (60 μg/mL) [1,**]	<20 μM (60 μM) [1,***]		<500 pg/mL (60 μM) [1,***]		[44]

[1] LPS-stimulated macrophage RAW264.7; [2] SNP induced macrophage RAW264.7; % is referring to percentage of inhibition; * $p < 0.05$ versus negative control; ** $p < 0.01$ versus negative control; *** $p < 0.001$ versus negative control.

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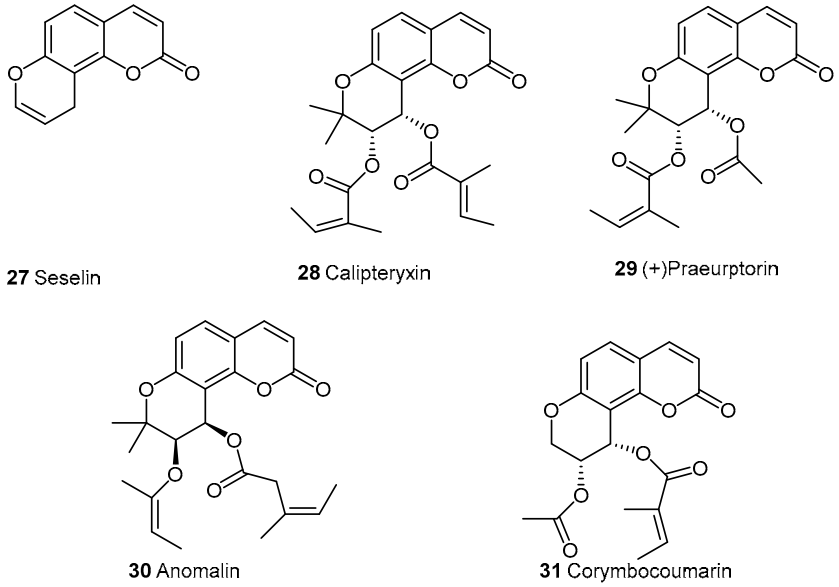

Figure 3. Naturally occurring pyranocoumarins.
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3. Synthetic Coumarins and Pyranocoumarins
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As functionalized coumarins can be easily prepared through synthesis, different compounds not naturally found have been prepared and tested (Figure 4). Starting from 6-chloro and 6-methoxy 4-bromomethyl-coumarin, paracetamol ethers **32**, **33**, **34** have been prepared (Figure 4).
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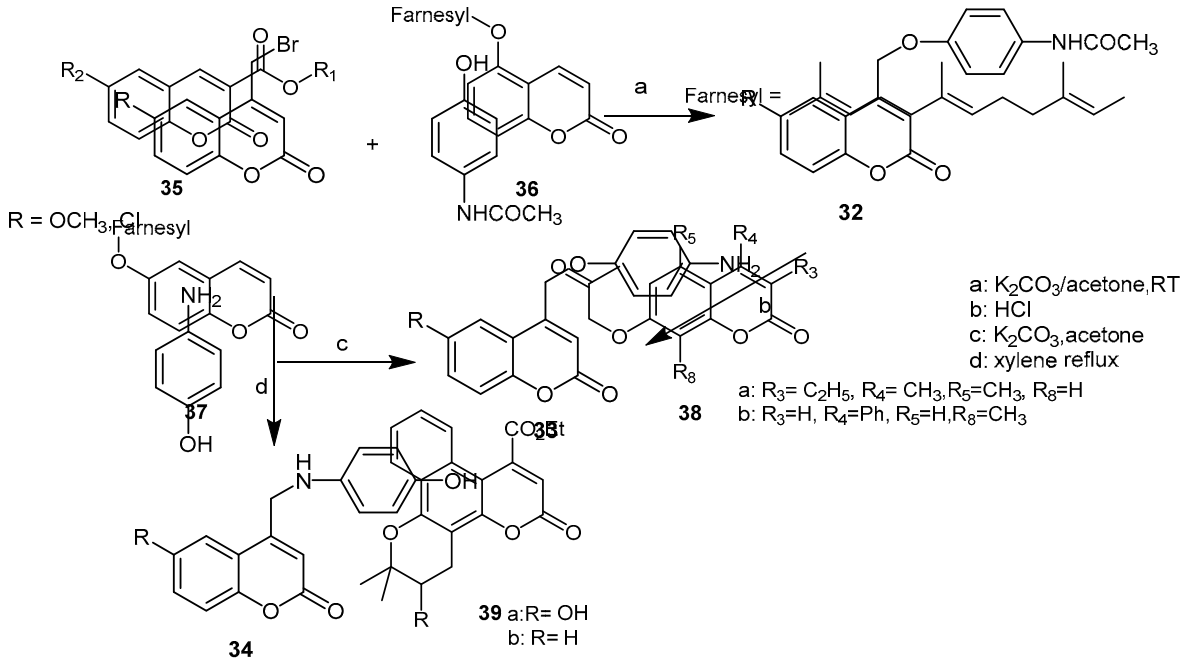

Figure 4. Synthetic coumarins and derivatives.
Figure 5. Synthetic coumarins and derivatives.
Figure 4. Synthesis of paracetamol modified coumarins.

Screening the activity using carrageenan induced edema in rats gave the best results for compounds **32** where R = Cl and OCH_3 was in position 6 [45]. A series of esters prepared from coumarin-3-carboxylic acids **35** obtained from the corresponding salicaldehydes, were tested in LPS-induced lung inflammation and elastase induced lung injury [46]. The data obtained showed that all coumarins had anti-inflammatory properties and that anti-elastase activity is essential to reducing lung inflammation *in-vivo*. For looking at 15-LPO inhibitors, a series of *O*-prenylated coumarins were synthesized (isopentyloxy, farnesyloxy, geranyloxy in 4, 5, 6, 7, and 8 position) [47]. 5-Farnesyloxycoumarin **36** showed the most potent activity against soybean lipoxygenase and 6-farnesyloxycoumarin **37** against human lipoxygenase. A great number of 7(2-oxoalkoxy)coumarins **38** have been prepared by condensation of hydroxycoumarins with α-chloroacetone [48] and the effects on expression of iNOS and COX-2 measured in comparison with

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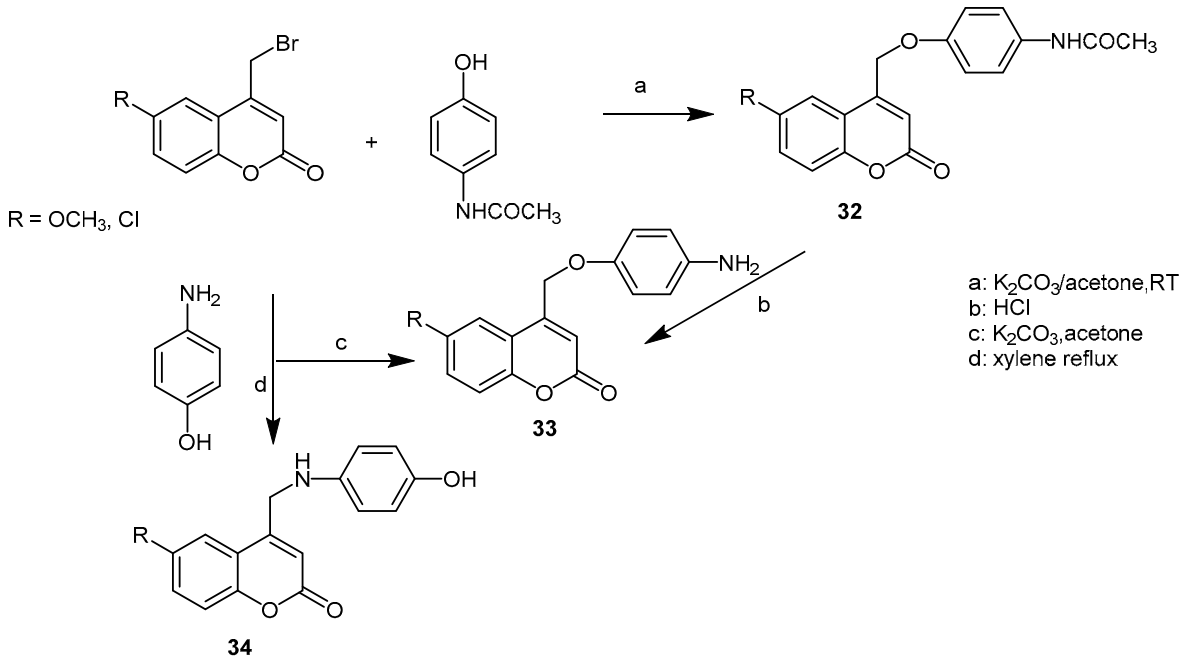

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A methodology to prepare coumarins from ortho-benzoquinones has been used for the synthesis of benzopyranocoumarins **39** [51–53] analogs to benzo[1]khellactone. All tested compounds [52], highly inhibited soybean lipoxygenase, competing with DMSO for $OH^{\bullet}$ and some induced protection against carrageenan induced rat paw edema. Another series [53] showed similar results for competition with DMSO for $OH^{\bullet}$, for O_2^- scavenging and lipoxygenase inhibition. The biological results of synthetic coumarins are summarized in (Table 4).

Table 4. Some anti-inflammatory activities of synthetic coumarins.

Cpd	COX-2	CPE% [3]	IL-6	LOX	NO	iNO	TNF-α	Ref.
32, R = 6-Cl		69 (3 h); 60 (6 h) *						[45]
35, R1 = 5-chloropyridin-3-yl; R2 = CH_3COOCH_2			<600 pg/mL (1 μM/kg) [1,*]				<1200 pg/mL (1 μM/kg) [1,*]	[46]
38a	−8 ± 17.4 (10 μM) [2]; 37 ± 15.2 (100 μM) [2]		IC50: 10 μM [2]; 33 ± 4.6 (10 μM) [2]; 89 ± 0.7 (100 μM) [2]		IC30: 30 μM [2]; 49 ± 2 (10 μM) [2]; 90 ± 1.6 (100 μM) [2]	58 ± 5.5 (10 μM) [2]; 99 ± 0.1 (100 μM) [2]		[48]
38b	29 ± 7.8 (10 μM) [2] ; 57 ± 1.6 (100 μM) [2]		IC50: 24 μM [2]; 47 ± 4.5 (10 μM) [2]; 90 ± 0.4 (100 μM) [2]		IC50: 21 μM [2]; 27 ± 3.6 (10 μM) [2]; 89 ± 0.4 (100 μM) [2]	47 ± 7.2 (10 μM) [2]; 97 ± 0.6 (100 μM) [2]		[48]
39a, R = OH		48.7 (0.1 mmol/kg, 3.5 h)		89.8% (1 mM)				[52]
39b, R = H		54 (0.1 mmol/kg, 3.5 h)		No (1 mM)				[52]

[1] LPS induced alveolar macrophage; [2] J774 macrophage stimulated by LPS; [3] Carageenin paw edema in rat; kg is referring to the mice weight; % is referring to percentage of inhibition.
* $p < 0.05$ versus negative control.

4. Conclusions

Coumarins and derivatives, even those that have been known for a long time, are still a source of interesting biological active compounds. As the synthesis of these compounds is quite easy, access to a greater amount of derivatives is possible. Since the compounds are sometimes present in edible foods, these may serve as anti-inflammatory supply and as fiber containing plants are considered prebiotics this may help even more to fight inflammation.

Conflicts of Interest: The authors declare no conflict of interest.

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Targeted synthesis of 4-chloro-3-formylthieno[2,3-*b*]pyridine and/or 4-chlorothieno[2,3-*b*]pyridine by reaction between *N*-protected 3-acetyl-2-aminothiophenes and Vilsmeier-Haack reagent

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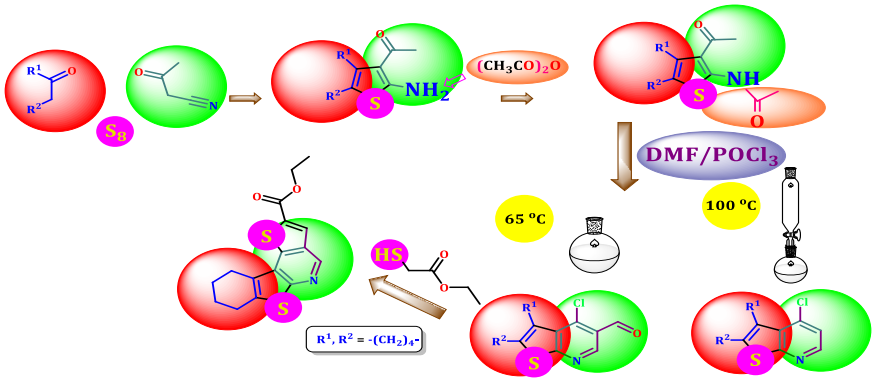

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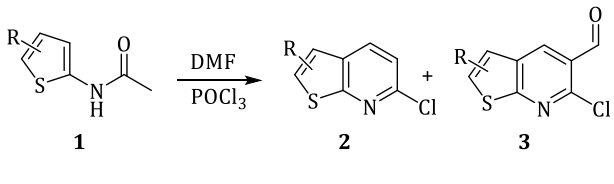
Abstract Formylated chlorothieno[2,3-*b*]pyridine derivatives were synthesized by reaction between *N*-protected 3-acetyl-2-aminothiophenes and Vilsmeier-Haack reagent under classical conditions. These products were not accessible without *N*-protection of the starting materials or by reaction between the reagent and 4-chlorothieno[2,3-*b*]pyridine under any condition. The conditions of the reaction could be altered to produce unformylated derivatives in better yield than reaction with unprotected aminothiophene.

Key words Thiphenes, Vilsmeier-Haak, thieno[2,3-*b*]pyridine, *N*-protection,

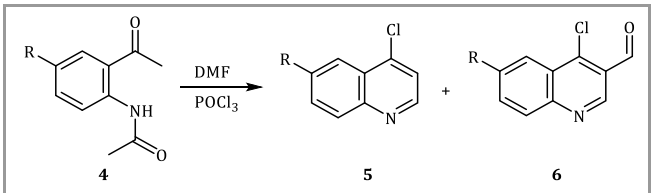
Vilsmeier-Haack reaction is very applicable method for versatile synthetic purposes.[1] Vilsmeier-Haack reagent ($POCl_3$/DMF) has been widely used in formylation, chloro-formylation of ketones and cyclization.[2] Preparation of 3-formylchromone from *o*-hydroxyacetophenone *via* such reaction through one step inspired synthesis of 3-formylquinoline from *o*-aminoacetophenone.[3]

Also, 2-acetamido-5 substituted thiophene **1** are reported to react with VH reagent under classical conditions (65 °C) to give mixture of compounds **2** and **3** (Scheme 1).[4] Adjusting the reaction condition allowed the authors to prepared **2** or **3**.[6] Noteworthy that the reaction condition in case of **3** was harsh (reflux in VH reagent for 1.5 - 4 hours).[4]



Scheme 1 Synthesis of 2-chlorothieno[2,3-*b*]pyridine and 2-chloro-3-formylthieno[2,3-*b*]pyridine.

Various derivatives of 4-chloroquinolines **5** and 4-chloro-3-formylquinoline **6** were prepared from *N*-(2-acetylphenyl)acetamide derivatives **4**. When the reaction temperature was 90 °C, **5** was obtained in low yield (0 – 14%) and **6** was major products (Scheme 2).[5]



Scheme 2 Synthesis of 4-chloroquinoline **5** and 4-chloroquinoline-3-carbaldehyde **6** starting from acetanilides **4**.

In a previous work we have already described the reaction of 3-acetyl-2-aminothiophenes **10** with VH reagent. Only 4-chlorothieno[2,3-*b*]pyridine **12** was obtained in low to moderate yield when reaction run at 100 °C for 24 hours (at 65 °C mixture of unknown compound as major and **12** as minor was obtained).[6]

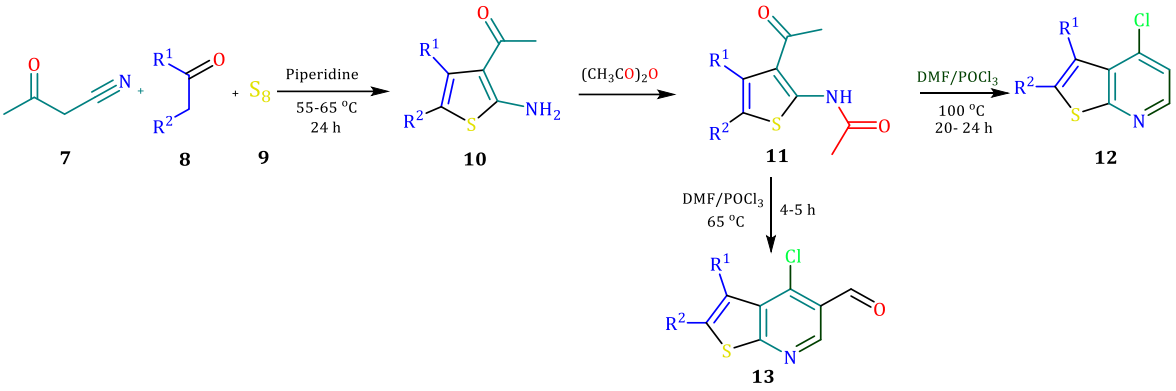
Formylation was not obtained when compound **12** was subjected to VH reagent at different heating condition (65 – 100 ^{0}C) which is expected from pyridine as an electron deficient nucleus.

To make approach toward comprehension of reaction mechanism, we decided to construct *N*-protected starting materials. This protection was intended to be done by electron withdrawing group, like acetyl or pivaloyl groups.

All thiophenes were synthesized by three components classical Gewald's synthesis which we reported.[6] *N*-acetylated aminothiophenes were simply prepared by a known procedure for most compounds.[7] This procedure was required addition of acetyl chloride to a dissolved thiophene in acetic anhydride

(**11h** and **11i**) or by using trimethylamine as another additive to catalyse the reaction (compound **11j**).

These *N*-acetylated products were treated by Vilsmeier-Haack reagent at 65 ^{0}C and 100 ^{0}C. At each temperature we used two equivalents of reagent (same equivalent of preparation of chlorothienopyridine[6] or double amount). Addition of the reagent was done at once or dropwise over nearly 7 hours. It was found that every alteration of VH reagent amount and mode of addition at different temperatures led to different yields and products.



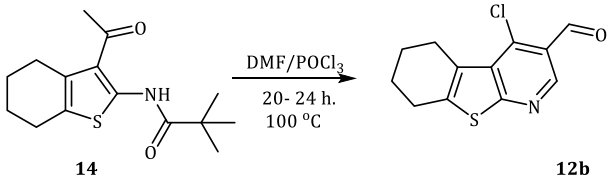
Scheme 3 General synthesis of formylated chlorothieno[2,3-*b*]pyridine and formyl-free chlorothieno[2,3-*b*]pyridine from *N*-acetyl-3-amino-2-acetylthiophenes

At 65 °C; when same previously used reagent equivalent was applied, chlorothienopyridine **12** was the major product in low yield, while formylated product **13** was traces. When this amount was doubled and added at once, yield of formylated product **13** raised to be around 94% - 32%) while formyl-free compounds **12** were 25% to 0% in 4-5 hours. Dropping the reagent over long period of time resulted in excessive decrease in the yield of both products, the reagent amount made no difference.

At 100 °C the reagent was dropped over long period of time (5-7 hours) and the reaction left under stirring for 20-24 hours.[6] Maximum yield of chlorothienopyridines was obtained. When the same amount of the reagent was added at once, yields of both folmylated and formyl-free compounds were dramatically decreased, but the formylated product was in greater amount.

Noteworthy that performing the reaction at room temperature resulted in synthesizing chloroformylthienopyridine **12** as major product. The reaction time needed to be beyond 72 hours in order to obtain maximum productivity, using the same reagent equivalent which we described.[8]

Pivaloyl derivative **14** was exposed to the same reaction condition of synthesis of chlrothienopyridine[6] and formylated product **12b** was the only output of this reaction (yield, 42%), the same protected analogue gave no reaction at room temperature and 19% yield only at 65 °C using doubled amount of reagent (Scheme 4).



Scheme 4 Exclusive synthesis of formylated cholorothienopyridine under the condition of synthesis formul-free chlorothienopyridine

Differently from reported before,[4] acetyl group was not involved in cyclization. It is suggested to play role by its electron withdrawing capability, which may result in stabilizing the double bond in intermediate **IV** (Scheme 5) making it more prone to another iminum ion attack. In contrary to the reaction of acetanilide,[5] in which *N*-acetylation allowed synthesizing the 4-chloroquinoline **5** in low yield or had no influence.

Using higher amount of the reagent, may result in rapid reaction and cyclization so acetyl group leaves the reactant after accomplishment of another nucleophilic attack (intermediate **VII**) (Scheme 5). Additionally, acetyl group protection is stable toward deacetylation at 65 °C.

In contrast, lower quantity of the reagent added dropwise and higher temperature (100 °C) gives chance to departure of the acetyl group in the acidic media. This made the amino group free at the early stage of the reaction and pyridine seems like not susceptible to the excessive iminium ion.

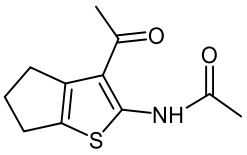
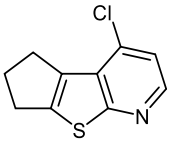
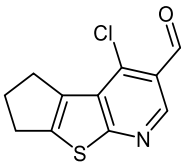
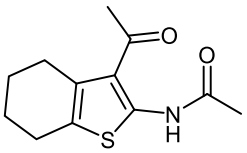
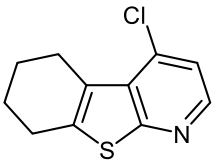
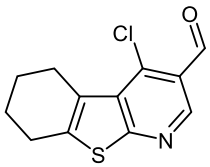
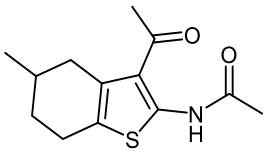
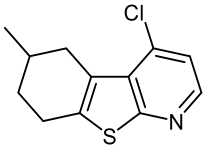
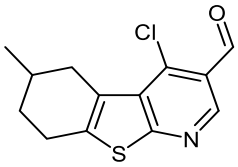
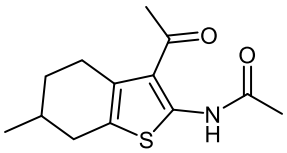
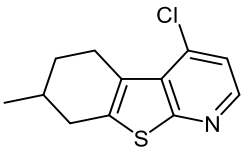
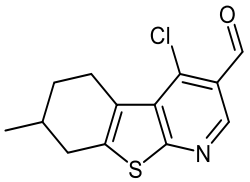
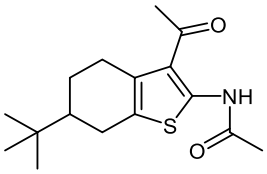
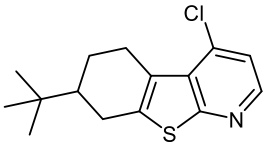
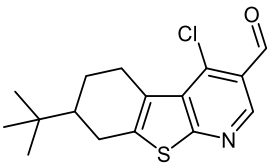
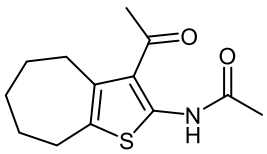
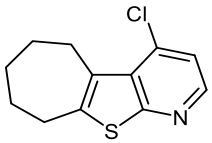
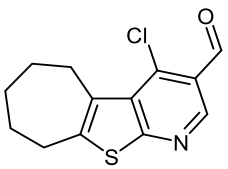
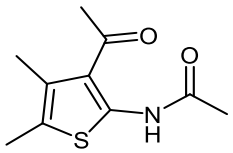
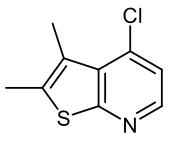
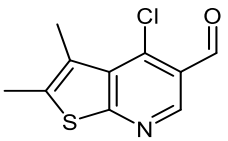
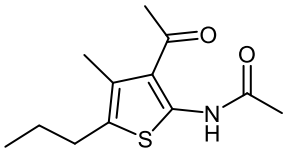
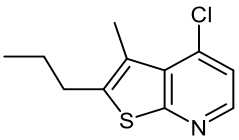
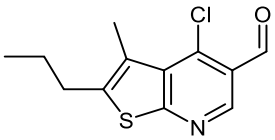
By the way, pivaloyl group is more stable than acetyl group. Working under higher temperature (100 ^{0}C), and with the normal reagent quantity,[6] gave only the formylated product, that may emphasize our suggestion.

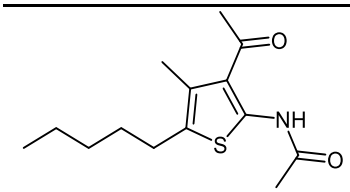
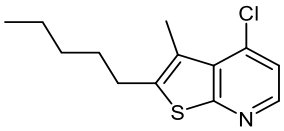
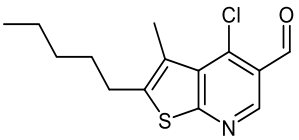
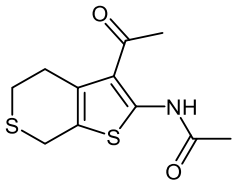
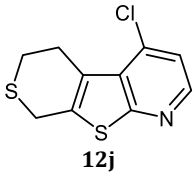
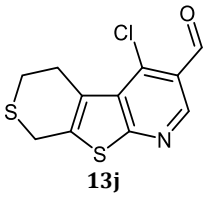
N-protection provides us more knowledge about the mechanisms of cyclization and chlorination of 3-acetyl-2-aminothiophene. These two processes more reasonable to happen by two attacks of iminium ion rather than one. In case of our previous proposal; that cyclization and chlorination take places by only one nucleophilic attack,[6] *N*-acetylation is supposed to produce merely chlrothienopyridine rather than 3-formyl derivatives.

The mechanism of reaction is postulated to occur by two possible routes. First mode of cyclization in which the acetyl group leaves just prior to the chlorination (intermediate **IV**). One HCl molecule help in liberation of acetyl group as acetyl chloride. The second pathway is assumed to happen at lower temperature, in which the acetyl group departure is retarded to allow the non-resonating double bond of pyridine ring (intermediate **VII**) to attack another iminium ion. The chlorination occurs afterward by third molecule of VH reagent

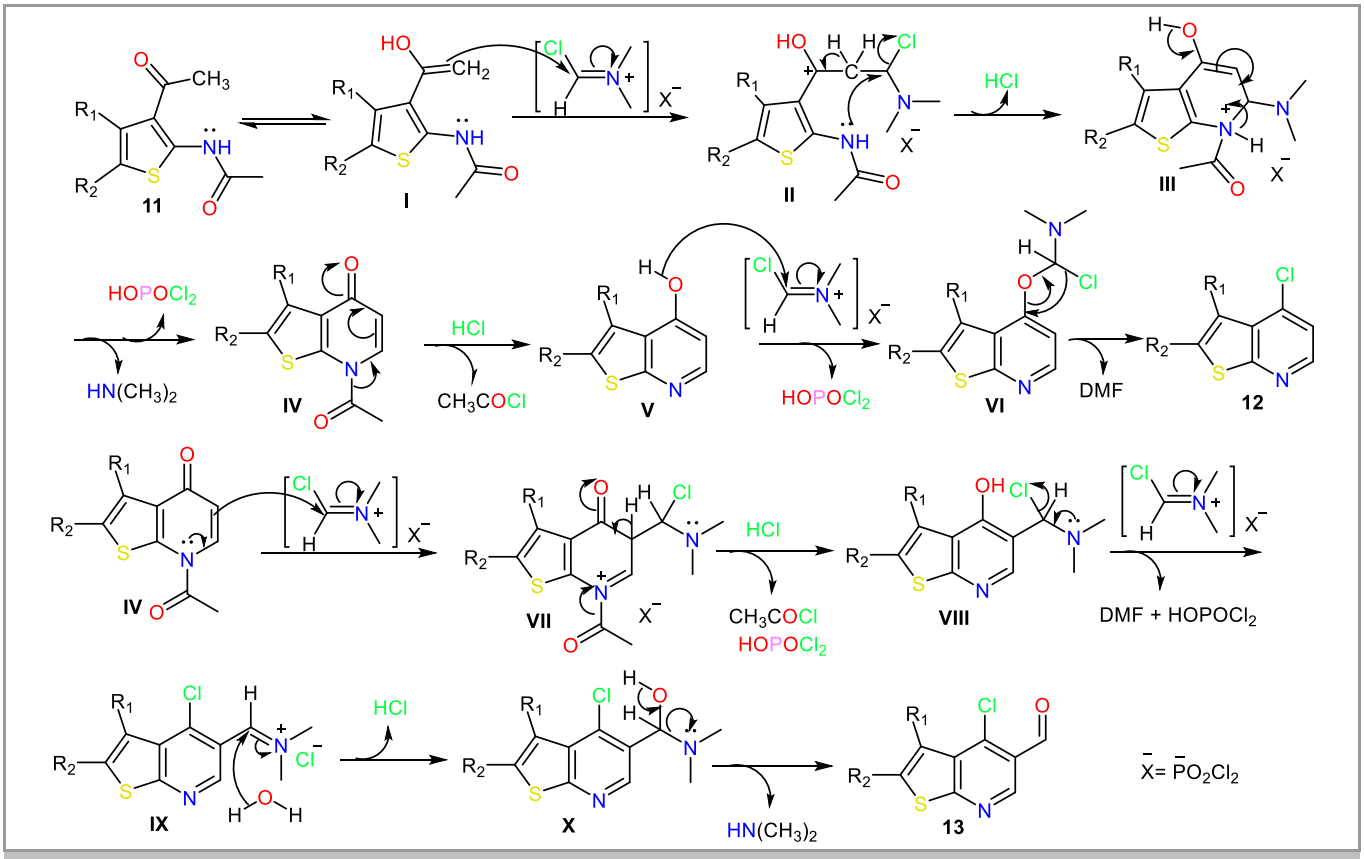
(intermediate **VIII, IX)**. This last intermediate transformed to the final product **13** by water treatment at the end of the reaction (Scheme 6). To explore the reactivity of the obtained products we applied the method described by Hauptmann, s. *et al.*8 for compound **13b**. It exhibited high reactivity and the reaction was complete within 30 minutes at 70°C (Scheme 5).

Table 1 products and yields of VH reaction with *N*-protected 3-acetyl-2-aminothiophenes at 65 °C and 100 °C

N-protected 3-acetyl-2-aminothiophenes	Thieno[2,3-*b*]pyridine	Yield 65 °C	Yield 100 °C	4-Chloro-3-formylthieno[2,3-*b*]pyridine	Yield 65 °C	Yield 100 °C
 **11a**	 **12a**	-	21%	 **13a**	94%	9%
 **11b**	 **12b**	25%	58%	 **13b**	60%	-
 **11c**	 **12c**	-	48%	 **13c**	86%	30%
 **11d**	 **12d**	11%	54%	 **13d**	65%	9%
 **11e**	 **12e**	23%	30%	 **13e**	32%	22%
 **11f**	 **12f**	14%	70%	 **13f**	53%	traces
 **11g**	 **12g**	-	55%	 **13g**	63%	traces
 **11h**	 **12h**	10%	85%	 **13h**	77%	-

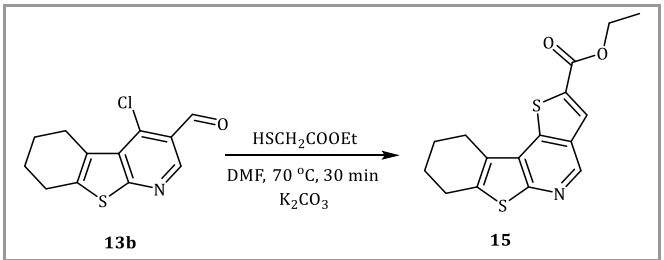
 **11i**	 **12i**	15%	36%	 **13i**	62%	19%
 **11j**	 **12j**	23%	11%	 **13j**	43%	-

In conclusion, we reported here new synthetic pathway of both 4-chlorothieno[2,3-*b*]pyridine and 4-chloro-3-formylthieno[2,3-*b*]pyridine by application of *N*-protection. This acylation helped increasing the yield of unformylated products and introduction of mild synthesis of novel 4-chloro-3-formylthieno[2,3-*b*]pyridine.



Scheme 5 Proposed mechanism for synthesis of formylated chlorothieno[2,3-*b*]pyridine and formyl-free chlorothieno[2,3-*b*]pyridine from *N*-acetyl-3-amino-2-acetylthiophenes

Directing the reaction toward one of the two products could be considered as controllable by modification the conditions of the reaction; temperature, mode of addition (which was found very crucial) and amount of the reagent. Differently from what reported before for the synthesis of chloroquinoline, our product appeared to behave completely in opposite way. Chloroquinoline is formed as traces when acetamido acetophenone was used while chlorothieno[2,3-*b*]pyridin was formed by using of 3-acetyl-2-aminothiophene.[6] Protection of the amino group of the last, made the production of formylated product reachable which is the normal result of this procedure with *o*-aminoacetopenone and *o*-hydroxyacetophenone.



Scheme 6 Synthesis of compound **15** as an example proved the reactivity of novel formylated chlorothienopyridines.

The experimental section has no title; please leave this line here.

All solvents and reagents were purchased from commercial sources unless otherwise noted. Melting points were determined with a Büchi 530 digital melting point apparatus and are uncorrected. 1H and 13C NMR spectra were recorded at 400 and 100 MHz, respectively, using Me4Si as the internal standard. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High-resolution mass spectra were measured with a Micro-Tof-Q98 instrument in ESI mode. Column chromatography was performed using silica gel (60M, 0.04–0.063 mm). Thin-layer chromatography (TLC) was performed using silica gel plates (POLYGRAM SILG/UV254, 0.20 mm), which were visualised under UV light.

All thiophenes were prepared by the Gewald's synthesis which we reported, the procedure, experimental data and supporting information of compounds **12a-12i** are available on the published article. [6]

***N*-(3-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)pivalamide (14)**

Pivaloyl chloride (0.92 g, 7.7 mmol) was added to 10 ml of dichloromethane in which 1-(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)ethanone (1g, 5.1 mmol) was previously dissolved, triethyl amine (0.78 g, 7.7 mmol) was added and the solution was stirred at room temperature for 3 hours, afterward the solution was dried under vacuum to evaporate the solvent and the residue was dissolved in acetone and the precipitation was provoked by addition of ice and water. The solution was left for 30 minutes for allowing maximum precipitation, the solid was collected by filtration under vacuum and washed by water, the solid was of sufficient purity to be used without further purification (yield: 1.16 g; 81%)

Yield: 1.16 g (81%); grey solid; mp 112-116 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.79 (s, 1 H), 2.85 – 2.70 (m, 2 H), 2.71 – 2.66 (m, 2 H), 2.54 (s, 3 H), 1.89 – 1.80 (m, 4 H), 1.35 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 176.8, 149.8, 129.4, 127.1, 120.9, 39.3, 31.3, 27.5, 27.3, 24.5, 23.1, 22.7.

HRMS (ESI): *m/z* calcd for $[C_{15}H_{21}NO_2S + Na]^+$: 302.1185; found: 302.1202.

Anal Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.47. Found: C, 64.92; H, 7.48; N, 4.93; S, 11.46.

***N*-(3-acetylthiophen-2-yl)acetamide derivatives (11a-11g), general procedure [9]**

1 g of 3-acetyl-2-aminothiophene derivatives was dissolved in 3 ml of acetic anhydride, the mixture was refluxed gently for 10-15 minutes, and quenched with water/ice, and then the solution was boiled gently, to breakdown the leftover acetic anhydride, the formed solid was filtered under vacuum and washed with water, dried and recrystallized in appropriate solvent if it needed.

***N*-(3-acetyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)acetamide (11a)**

Yield: 1.03 g (84%); green solid; mp 117-119 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.01 (s, 1 H), 2.96 – 2.85 (m, 2 H), 2.82 – 2.63 (m, 2 H), 2.42 – 2.33 (m, 5 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.1, 167.7, 153.0, 140.0, 133.0, 116.8, 31.4, 29.8, 28.6, 28.0, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{13}NO_2S + Na]^+$: 246.0565; found: 246.0567.

Anal Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; O, 14.33; S, 14.36. Found: C, 58.87; H, 5.88; N, 6.03; S, 14.47.

***N*-(3-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (11b)**

Yield: 1.17 g (96%); brown solid; mp 100-103 °C; (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.36 (s, 1 H), 2.83 – 2.76 (m, 2 H), 2.71 – 2.65 (m, 2 H), 2.52 (s, 3 H), 2.28 (s, 3 H), 1.89 – 1.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 167.8, 148.9, 129.3, 127.2, 120.8, 31.4, 27.5, 24.5, 23.8, 23.1, 22.6.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{15}NO_2S + H]^+$: 238.0896; found: 238.0921.

Anal Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.72; H, 6.34; N, 5.96; S, 13.48.

***N*-(3-acetyl-5-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (11c)**

Yield: 1 g (83%); brown solid; mp 148 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.35 (s, 1H), 2.95 – 2.89 (m, 1 H), 2.76 – 2.66 (m, 2 H), 2.53 (s, 3 H), 2.27 (s, 3 H), 2.05 – 1.85 (m, 3 H), 1.56 – 1.37 (m, 1 H), 1.13 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 169.2, 150.6, 130.8, 128.3, 122.1, 37.4, 32.9, 32.2, 30.8, 25.7, 25.2, 23.2.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + Na]^+$: 274.0872; found: 274.0882.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; O, 12.73; S, 12.76. Found: C, 62.40; H, 6.76; N, 5.59; S, 12.68

***N*-(3-acetyl-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (11d)**

Yield: 1.19 g (99%); beige-brown solid; mp 120-122 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.36 (s, 1 H), 2.94 – 2.85 (m, 1 H), 2.80 – 2.68 (m, 2 H), 2.52 (s, 3 H), 2.35 – 2.21 (m, 4 H), 2.02 – 1.86 (m, 2 H), 1.55 – 1.37 (m, 1 H), 1.10 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.8, 167.8, 149.1, 129.0, 126.9, 120.6, 32.6, 31.4, 31.3, 28.9, 27.3, 23.8, 21.3.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + Na]^+$: 274.0872; found: 274.0890.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.03; H, 6.82; N, 5.53; S, 12.70.

***N*-(3-acetyl-6-(*tert*-butyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide (11e)**

Yield: 1.17 (82%); beige-brown solid; mp 141-143 °C (cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.26 (s, 1 H), 2.96 – 2.83 (m, 1 H), 2.72 – 2.49 (m, 2 H), 2.43 (s, 3 H), 2.39 – 2.30 (m, 1 H), 2.19 (s, 3 H), 2.08 – 1.88 (m, 1 H), 1.53 – 1.32 (m, 1 H), 1.32 – 1.03 (m, 1 H), 0.88 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 167.8, 149.5, 127.5, 124.1, 120.1, 53.2, 52.3, 45.23, 31.1, 29.7, 27.7, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{16}H_{23}NO_2S + Na]^+$: 316.1342; found: 316.1338.

Anal Calcd for C, 65.49; H, 7.90; N, 4.77; S, 10.93. Found: C, 65.51; H, 7.92; N, 5.26; S, 10.95.

***N*-(3-acetyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-2-yl)acetamide (11f)**

Yield: 1 g (83%); beige-brown solid; mp 75-78 °C (EtOH 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.90 (s, 1 H), 2.93 – 2.90 (m, 2 H), 2.76 – 2.73 (m, 2 H), 2.53 (s, 3 H), 2.25 (s, 3 H), 1.92 – 1.86 (m, 2 H), 1.75 – 1.64 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.5, 167.6, 145.7, 135.0, 131.4, 123.1, 31.9, 31.6, 29.3, 28.4, 27.6, 26.7, 23.71.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + H]^+$: 252.1058; found: 252.1049.

Anal Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.56; H, 6.70; N, 5.45; S, 12.65.

***N*-(3-acetyl-4,5-dimethylthiophen-2-yl)acetamide (11g)**

Yield: 1 g (81%); brown solid; mp 115-119 °C (EtOH 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.29 (s, 1 H), 2.55 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 167.7, 147.9, 127.3, 123.8, 121.9, 31.3, 23.8, 15.3, 12.5 (s).

HRMS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_2S + H]^+$: 234.0565; found: 234.0572.

Anal Calcd for C, 56.85; H, 6.20; N, 6.63; O, 15.14; S, 15.17. Found: C, 56.85; H, 6.16; N, 6.98; S, 15.14.

_N_-(3-acetylthiophen-2-yl)acetamide derivatives (11h,11i), general procedure

Corresponding thiophene (5.1 mmol) and acetyl chloride (0.4 g, 5.1 mmol) was dissolved and stirred in excess of acetic anhydride at 35 °C. After 30 minutes the solution was treated with water and ice and heated to decompose the acetic anhydride and then extracted with ethyl acetate. It was subsequently exposed to flash column purification (EtOAc–cyclohexane, 1:3) for maximum purity.

_N_-(3-acetyl-4-methyl-5-propylthiophen-2-yl)acetamide (11h)

Yield: 1 g (82%); brown solid; mp 58-60 °C; R_f = 0.54 (EtOAc–cyclohexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.28 (s, 1 H), 2.67 – 2.63 (m, 2 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 1.70 – 1.59 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.2, 167.7, 148.3, 129.7, 127.0, 122.0, 31.4, 29.3, 24.4, 23.8, 15.3, 13.7.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{17}NO_2S + Na]^+$: 262.0872; found: 262.0909.

Anal Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.02; H, 7.10; N, 5.80; S, 13.12.

_N_-(3-acetyl-4-methyl-5-pentylthiophen-2-yl)acetamide (11i)

Yield; 1.32 g (97%); brown solid; mp 40 °C; R_f = 0.53 (EtOAc–cyclohexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.31 (s, 1 H), 2.66 (t, *J* = 7.7 Hz, 2 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H), 1.66 – 1.54 (m, 2 H), 1.38 – 1.29 (m, 4 H), 0.96 – 0.85 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 167.7, 148.2, 130.0, 126.8, 122.0, 31.4, 31.3, 30.9, 27.3, 23.8, 22.4, 15.3, 14.0.

HRMS (ESI): *m/z* calcd for $[C_{14}H_{21}NO_2S + H]^+$: 268.1366; found: 268.1369.

Anal Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.75; H, 7.89; N, 5.41; S, 12.08.

_N_-(3-acetyl-4,7-dihydro-5_H_-thieno[2,3-_c_]thiopyran-2-yl)acetamide (11j)

1-(2-Amino-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-yl)ethanone (1g, 4.6 mmol) dissolved in 10 ml of dichloromethane, 3 ml of acetic anhydride, acetyl chloride (1.08 g, 13.8 mmol) and triethyl amine (1.4 g, 13.8 mmol) were added and the reaction mixture was gently refluxed for 30 hours, the solvent was evaporated and residue dissolved in acetone and treated by ice and water. The reaction mixture was boiled for decomposing the acetic anhydride and the formed precipitate was filtered under vacuum and washed with water and crystallized from EtOH 96%.

Yield; 1 g (84%); brown solid; mp 132-135 °C (EtOH 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (s, 1 H), 3.76 (s, 2 H), 3.10 (t, *J* = 5.8 Hz, 2 H), 2.97 (t, *J* = 5.8 Hz, 2 H), 2.53 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.5, 167.9, 148.5, 129.1, 123.2, 121.3, 31.7, 29.2, 26.3, 25.4, 23.7.

HRMS (ESI): *m/z* calcd for $[C_{11}H_{13}NO_2S_2 + H]^+$: 256.0460; found: 256.0460.

Anal Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49; S, 25.11. Found: C, 51.94; H, 5.67; N, 5.17; S, 25.56.

4-chloro-5,8-dihydro-6H-thiopyrano[4',3':4,5]thieno[2,3-b]pyridine (12j)

Compounds **12j** was prepared from **11j** (0.3 g, 1.2 mmol) by same procedure reported before. [6]

Yield: 31 mg (11%); colorless solid; mp 154 °C R_f = 0.29 (EtOAc–cyclohexane, 1:9).

1H NMR (400 MHz, CDCl3) δ 8.34 (d, J = 5.0 Hz, 1 H), 7.26 (d, J = 5.0 Hz, 1 H), 3.93 (s, 2 H), 3.51 – 3.43 (m, 2 H), 3.03 (t, J = 5.2 Hz, 2 H).

13C NMR (100 MHz, CDCl3) δ = 161.1, 145.9, 138.1, 134.7, 130.4, 127.5, 121.2, 28.7, 26.6, 25.9.

HRMS (ESI): *m/z* calcd for $[C_{10}H_8ClNS_2 + H]^+$: 241.9859; found: 241.9864.

Anal Calcd for $C_{10}H_8ClNS_2$; C, 49.68; H, 3.34; N, 5.79; S, 26.52. Found: C, 49.99; H, 3.60; N, 5.52; S, 26.85

4-Chloro-3-formyl-thieno[2,3-*b*]pyridine, general procedure

Vilsmeier-Haack reagent was prepared by previously mentioned method, in this case the amount of the reagent was: 5 ml of $POCl_3$, and 20 mL of DMF for 2.5 mmol of the starting material. The reagent was added to the thiophene at one time, and stirred at 65 °C for 4-5 hours. At the end of the reaction, the solution was decomposed by mixture of ice and water and neutralized by sodium acetate. In case of formation of precipitate, filtration under vacuum was applied, the obtained solid was dissolved in ethyl acetate and washed 2-3 times with water, the residue was purified by silica gel column chromatography (EtOAc–cyclohexane, 1:9), and otherwise the solution was directly extracted by ethyl acetate, and purified by the same way.

4-Chloro-6,7-dihydro-5_H_-cyclopenta[4,5]thieno[2,3-_b_]pyridine-3-carbaldehyde (13a)

Yield: 560 mg (94%); White solid; mp 160 -163 °C (cyclohexane); R_f = 0.36 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 = (s, 1 H), 8.76 (s, 1 H), 3.21 – 3.13 (m, 2 H), 3.04 – 2.96 (m, 2 H), 2.50 – 2.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.7, 171.0, 146.0, 145.3, 140.4, 137.4, 128.1, 124.2, 30.1, 27.4.

HRMS (ESI): *m/z* calcd for $[C_{11}H_8ClNOS + H]^+$: 238.0088; found: 238.0122.

Anal Calcd for $C_{11}H_8ClNOS$: C, 55.58; H, 3.39; N, 5.89; S, 13.49. Found: C, 56.35; H, 3.44; N, 5.82; S, 13.10.

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13b)

Yield: 346 mg (60%); White solid; mp 162-165 °C (cyclohexane); ; R_f = 0.36 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.77 (s, 1 H), 3.15 – 3.12 (m, 2 H), 2.84 – 2.80 (m, 2 H), 1.95 – 1.78 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.1, 166.4, 145.7, 141.2, 140.7, 130.0, 128.8, 124.3, 26.9, 26.3, 22.4, 22.3.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{10}ClNOS + H]^+$: 252.0244; found: 252.0266.

Anal Calcd for $C_{12}H_{10}ClNOS$: C, 57.26; H, 4.00; N, 5.56; S, 12.74. Found: C, 57.89; H, 4.28; N, 5.30; S, 12.22.

4-Chloro-6-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13c)

Yield: 571 mg (86%); White solid; mp 148-152 °C (cyclohexane); ; R_f = 0.40 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.76 (s, 1 H), 3.41 – 3.31 (m, 1 H), 2.90 – 2.81 (m, 2 H), 2.61 – 2.54 (m, 1 H), 1.99 – 1.83 (m, 2 H), 1.53 – 1.43(m, 2 H), 1.10 (d, *J* = 6.5 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl3) δ = 189.0, 166.3, 145.4, 141.4, 140.6, 130.2, 128.9, 124.4, 35.2, 30.3, 28.9, 26.1, 21.6.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.0397.

Anal Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H, 4.55; N, 5.27; S, 12.06. Found: C, 58.82; H, 4.56; N, 5.11; S, 12.00.

4-Chloro-7-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13d)

Yield: 429 mg (65%); White solid; mp 148 -152 °C (cyclohexane) ; R_f = 0.36 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.55 (s, 1 H), 8.80 (s, 1 H), 3.34 – 3.30(m, 1 H), 3.08 – 2.91 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.55 – 2.34 (m, 1 H), 2.01 – 1.86 (m, 2 H), 1.51 – 1.41 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.1, 166.6, 145.7, 141.2, 140.3, 129.9, 128.5, 124.4, 34.2, 30.6, 28.6, 26.7, 21.2.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.04201.

Anal Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H, 4.55; N, 5.27; S, 12.06. Found: C, 58.59; H, 4.54; N, 5.12; S, 11.92.

7-(*tert*-Butyl)-4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13e)

Yield: 246 mg (32%); White solid; mp 190-192 °C (cyclohexane); ; R_f = 0.40 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.55 (s, 1 H), 8.77 (s, 1 H), 3.50 – 3.35 (m, 1 H), 2.96 – 2.80 (m, 2 H), 2.63 – 2.55 (m, 1 H), 2.18 – 2.01 (m, 1 H), 1.58 – 1.50 (m, 2 H), 1.41 – 1.31 (m, 1 H), 0.92 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0, 166.6, 145.6, 141.4, 141.1, 129.8, 128.8, 124.3, 44.4, 32.4, 28.0, 27.9, 27.2, 24.1.

HRMS (ESI): *m/z* calcd for $[C_{16}H_{18}ClNOS + H + CH_4O]^+$: 340.1133; found: 340.11691.

Anal Calcd for $C_{16}H_{18}ClNOS$: C, 62.43; H, 5.89; N, 4.55; S, 10.41. Found: C, 62.43; H, 5.90; N, 4.50; S, 10.35.

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13f)

Yield: 350 mg (53%); yellow solid; mp 120-122 °C (cyclohexane); ; R_f = 0.38 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.58 (s, 1 H), 8.75 (s, 1 H), 3.41 – 3.33 (m, 2 H), 2.94 – 2.86 (m, 2 H), 1.95 – 1.80 (m, 2 H), 1.76 – 1.67 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.3, 165.4, 145.3, 145.1, 141.3, 134.3, 129.9, 124.7, 31.7, 30.1, 28.4, 26.9, 26.4.

HRMS (ESI): *m/z* calcd for $[C_{13}H_{12}ClNOS + H]^+$: 266.0401; found: 266.0429.

Anal Calcd for $C_{13}H_{12}ClNOS$: 58.75; H, 4.55; N, 5.27; S, 12.06. Found: 58.62; H, 4.50; N, 5.15; S, 12.22.

4-Chloro-2,3-dimethylthieno[2,3-*b*]pyridine-5-carbaldehyde (13g)

Yield: 354 mg (63%); yellow solid; mp 216-218 °C (cyclohexane); ; R_f = 0.29 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.56 (s, 1 H), 8.77 (s, 1 H), 2.55 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0, 165.8, 145.7, 141.4, 137.3, 126.8, 14.8, 14.1.

HRMS (ESI): *m/z* calcd for $[C_{10}H_8ClNOS – CHO + H]^+$: 198.0139; found: 198.0165.

Anal Calcd for $C_{10}H_8ClNOS$: C, 53.22; H, 3.57; N, 6.21; S, 14.21. Found: C, 53.25; H, 3.60; N, 6.04; S, 14.17.

4-Chloro-3-methyl-2-propylthieno[2,3-*b*]pyridine-5-carbaldehyde (13h)

Yield: 487 mg (77%); White solid; mp 102-105 °C; ; R_f = 0.38 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.67 (s, 1 H), 8.88 (s, 1 H), 2.89 (t, *J* = 7.6 Hz, 2 H), 2.67 (s, 3 H), 1.85 – 1.69 (m, 4 H), 1.06 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.2, 166.1, 145.7, 143.2, 141.6, 130.5, 126.4, 124.4, 30.5 24.2, 15.0, 13.7.

HRMS (ESI): *m/z* calcd for $[C_{12}H_{12}ClNOS + H]^+$: 254.0401; found: 254.0419.

Anal Calcd for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.77; N, 5.52; S, 12.63. Found: C, 56.71; H, 4.79; N, 5.35; S, 12.48.

4-Chloro-3-methyl-2-pentylthieno[2,3-*b*]pyridine-5-carbaldehyde (13i)

Yield: 436 mg (62%); White solid; mp 65-67 °C (EtOH-H_2O); ; R_f = 0.42 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.65 (s, 1 H), 8.87 (s, 1 H), 2.89 (t, *J* = 7.6 Hz, 2 H), 2.64 (s, 3 H), 1.80 – 1.66 (m, 2 H), 1.45 – 1.35 (m, 4 H), 0.97 – 0.88 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 189.2, 166.1, 145.7, 143.5, 141.5, 130.5, 126.2, 124.5, 31.4, 30.5, 28.5, 22.4, 15.0, 13.92.

HRMS (ESI): *m/z* calcd for $[C_{14}H_{16}ClNOS + H]^+$: 282.0719; found: 282.0732

Anal Calcd for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; Cl, 12.58; N, 4.97; S, 11.38. Found: C, 59.97; H, 5.23; N, 5.25; S, 11.60.

4-Chloro-5,8-dihydro-6*H*-thiopyrano[4',3':4,5]thieno[2,3-*b*]pyridine-3-carbaldehyde (13j)

Yield: 289 mg (43%); yellow solid; mp 180 °C (cyclohexane); R_f = 0.29 (EtOAc–cyclohexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H), 8.81 (s, 1 H), 3.86 (s, 2 H), 3.46 (t, *J* = 5.9 Hz, 2 H), 2.97 (t, *J* = 5.9 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8, 165.35, 146.6, 141.6, 136.5, 130.0, 128.6, 124.6, 28.9, 26.7, 25.9.

HRMS (ESI): *m/z* calcd for $[C_{11}H_8ClNOS_2 + H]^+$: 269.9814; found: 269.9821.

Anal Calcd for $C_{11}H_8ClNOS_2$: C, 48.98; H, 2.99; Cl, 13.14; N, 5.19; O, 5.93; S, 23.77. Found: C, 49.00; H, 3.14; N, 5.92; S, 23.47.

Ethyl 7,8,9,10-tetrahydrobenzo[4,5]thieno[2,3-*b*]thieno[2,3-*d*]pyridine-2-carboxylate (15)

Compound **13b** (0.1 g, 0.4 mmol) was dissolved with ethyl thioglycolate (0.05 g, 0.4 mmol) in DMF (3 ml) and potassium carbonate (0.06 g, 0.4 mmol) was introduced. The solution was stirred for 30 minutes at 70°C. The reaction mixture was treated by ice and water. If precipitate was formed; it was filtered under vacuum, washed and dried, otherwise the solution was extracted by ethyl acetate and dried by Na_2SO_4 *anhyd* and concentrated under vacuum. The precipitate or the residue was recrystallized from ethanol.

Yield: 69 mg (55%); white solid; mp 168 °C (ethanol 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.97 (s, 1 H), 8.24 (s, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 3.07 – 3.03 (m, 2 H), 2.98 – 2.95 (m, 2 H), 2.08 – 1.95 (m, 4 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.3, 155.3, 142.8, 142.6, 138.5, 133.4, 132.6, 129.3, 127.6, 127.3, 61.9, 25.7, 25.3, 23.0, 22.4, 14.3.

HRMS (ESI): *m/z* calcd for $[C_{16}H_{15}NO_2S_2 + H]^+$: 318.0617; found: 318.0626.

Anal Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.54; H, 4.76; N, 4.41; S, 20.20. Found: C, 60.72; H, 4.72; N, 4.80; S, 20.13.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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