Transition-Metal-Free Synthesis of Aryl Thiocyanates, Aldehydes and Ketones, Azaheterocyclic carboxamides and Styrenyl Ethers

A Thesis
Submitted in Partial Fulfilment of the
Requirements of the Degree of
Doctor of Philosophy

By
Trimbak Baliram Mete
ID: 20123191

Research Supervisor
Dr. Ramakrishna G. Bhat
Associate Professor

Indian Institute of Science Education and Research, Pune

May 2018

Dedicated to My Family,

Friends and Teachers

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH (IISER), PUNE
(An Autonomous Institution, Ministry of Human Resource Development, Govt. of India)
Main Building, Dr. Homi Bhabha Road, Pashan, Pune, 411008, Maharashtra, India

Dr. Ramakrishna G. Bhat
Associate Professor
Department of Chemistry,
IISER Pune

CERTIFICATE

This is to certify that the work incorporated in this thesis entitled **"*Transition-Metal-Free Synthesis of Aryl Thiocyanates, Aldehydes and Ketones, Azaheterocyclic carboxamides and Styrenyl Ethers* "** submitted by **Trimbak Baliram Mete** carried out by candidate at Indian Institute of Science Education and Research (IISER), Pune, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

Date: 3rd May 2018, Pune

Dr. Ramakrishna G. Bhat
(Research supervisor)

rgb@iiserpune.ac.in • Ph: +91-20-25908092 • Fax: +91-20-25898022

DECLARATION

I hereby declare that the thesis entitled **“Transition-Metal-Free Synthesis of Aryl Thiocyanates, Aldehydes and Ketones, Azaheterocyclic carboxamides and Styrenyl Ethers”** submitted for Doctor of Philosophy in Chemistry at Indian Institute of Science Education and Research (IISER), Pune, has not been submitted by me to any other University or Institution. This work presented here was carried out at the, Indian Institute of Science Education and Research, Pune, India under the supervision of **Dr. Ramakrishna G Bhat**.

Trimbak Baliram Mete

ID- 20123191
(Senior Research Fellow)
Department of Chemistry,
IISER Pune-411008, India

Date: 3rd May 2018, Pune

Acknowledgements

This is the time to express my deepest gratitude and honest thanks to all the people who have guided, supported and helped me in various ways during the past five years. First of all I would like to express sincere appreciation to my thesis supervisor Dr. Ramakrishna G Bhat, for accepting me as a Ph.D. student and giving me an opportunity to work in his lab. Without his backing, I would not have been able to finish my Ph.D. Thanks to him for his all support, guidance, opportunities, advice and patience.

I thank our former Director, Prof. K. N. Ganesh and present Director, Prof. Jayant B. Udgaonkar for giving excellent research platform, financial support and facilities that I have been fortunate with during my research here in Indian Institute of Science Education and Research (IISER), Pune. I would like to acknowledge my RAC members Dr. Nitin Patil, Dr. Jeet Kalia , Dr. Ravindar Kontham for their valuable inputs during my RAC meetings. I would like to thank Chair chemistry Prof. Manickam Jayakannan for various departmental activities including Chemsymphoria. I would like to thank CSIR, India for the financial support during my Ph. D. I am also thankful to all the chemistry faculty members in IISER-Pune for their support. I also thank to all administrative staffs of our department.

In my daily work, I have been extremely fortunate and blessed with many cheerful and friendly colleagues: Dr. Prakash Sultane, Dr. Amar Mohite, Dr.Nayeem Ahmad, Dr.Chennakesavareddy, Rajesh, Balu, Tushar, Rameshwar, Manish, Amol, Prakash, Ankit, Debasish, Javed, and Vikas without them working would have become difficult. Herein, I would also like to thanks my other friends: Dr. Madhuri, Dr. Priya, , Dr. Nagesh, Dr. Kavita, Prabhakar, Balaji, Ashruba, Bapurao, Krishna, Shahaji, Datta, Rajkumar, Ravi, Nilesh, Sopan for their encouragement. I would also like to thank cricket team 'Alchemist' for keeping me happy and healthy. I would also like to acknowledge my M. Sc. teachers Dr. R A Mane, Dr. Bapu Shingate, Dr. Sathe, and B. Sc. teachers Mr. R. R. Jadhav, Mr. R. N. Bansode and Mr. V. G. Chaudhary for their support and encouragement. I would also like to thank Dr. Balasaheb Jadhav and Mr. Balasaheb Bhairat for their directions and support during my whole education process.

Finally, I would like to thank my family especially my father, my mother and my brother, my gratitude becomes speechless when I think of them. Thank you, thank you and thank you! Finally, I would like to thank the Almighty God who made all things possible in my life.

Thank you all

Trimbak Baliram Mete

CONTENTS

Chapter 1: Introduction to Transition-Metal-Free reactions

Chapter 2: Transition-Metal-Free Regioselective Thiocyanation of Phenols, Anilines and Heterocycles

Chapter 3: Oxidative Decarboxylation of Aryl Acetic Acids in Water: One-Pot Transition-Metal-Free Synthesis of Aldehydes and Ketones

Chapter 4: Transition-Metal-Free Synthesis of Primary to Tertiary Carboxamides: A Quick Access to Prodrug-Pyrazinecarboxamide

Chapter 5: Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones via Bamford-Stevens Reaction

******

ABBREVIATIONS

°C	degrees Celsius
°C	degrees centigrade
µ	micro
Å	angstrom
Ac	Acetyl
AcOH	Acetic acid
aq	aqueous
Ar	Aryl
atm	atmosphere
Bn	benzyl ($C_6H_5CH_2$)
BnCl	benzyl chloride
Boc	tert-butyldicarbonate
BQ	benzoquinone
bs	broad singlet
Bu	Butyl
calcd.	calculated
CAN	Cerium(IV)-ammonium nitrate
Cat.	catalytic
Cbz	benzyloxycarbonyl
CD_3OD	Duterated methanol
CDC	cross dehydrogenative coupling
$CDCl_3$	Duterated chloroform
CFL	compact fluorescent lamp
cm^{-1}	wavenumber(s)
conc.	concentrated

CT	Charge Transfer
d	doublet (NMR)
DalPhos	di(1-adamantyl)phosphino [P(1-Ad)2]
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	dichloromethane
dd	doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyanobezoquinone
DEPT	Distortionless Enhancement by Polarization Transfer
DMEDA	N,N'-dimethylethylendiamine
DMF	N,N’-dimethyl formamide
DMP	Dess–Martin periodinane
DMSO	Dimethylsulfoxide
DMSO-d$_6$	Duterated dimethyl sulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
DTBP	Di-tert-butyl peroxide
DTBQ	3,5-di-tert-butylquinone
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalents
ESI TOF	Electrospray ionisation time-of-flight
ESMS	electrospray mass spectrometry
ET	electron transfer
Et	Ethyl (CH$_3$CH$_2$)
EtOAc	ethyl acetate
eV	Electron volt

FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
GC	Gas Chromatography
h	hour(s)
HAS	Homolytic aromatic substitution
HCl	Hydrochloric acid
HFIP	Hexafluoroisopropanol
HRMS	High Resolution Mass Spectroscopy
HTIB	Hydroxy(tosyloxy)iodobenzene
Hz	Hertz
i-, iso-	Isomeric (branched alkyl chain)
^{i}Bu	isobutyl
IBX	2-Iodoxybenzoic acid
^{i}Pr	isopropyl
J	Spin coupling constant (in NMR spectroscopy)
L,	Ligand
LA,	Lewis acid
lit.	literature
m	meta
M	molar (mol L^{-1})
m	multiplet (in NMR)
M	Metal
m/z	mass to charge ratio
m-CPBA	m-chloroperbenzoic acid
Me	Methyl (CH_3)
MeCN	Acetonitrile
MeOH	Methanol

mg	milligram
min	minute(s)
mL	millilitres
mmol	millimoles
mol	mole(s); molecular (as in mol. weight)
mp	melting point
MS	Molecular Sieves
NBS	N-bromosuccinimide
NHPI	N-hydroxyphthalimide
nm	nanometer
NMF	N-methyl formamide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
o	ortho
p	para
Ph	Phenyl (C_6H_5)
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine(III)bis(trifluoroacetate
PPAR	peroxisome proliferator-activated receptor
ppm	parts per million
Pr	Propyl
PT	proton transfer
Py	pyridine
Pyr	pyridine
q	quartet (NMR)
quin.	quintet

r.t.	room temperature
R_f	retention factor (in chromatography)
s	singlet (NMR)
SET	Single electron transfer
t	triplet(NMR)
t-, tert-	Tertiary (branched alkyl chain)
TBAB	tetrabutyl ammonium bromide
TBAX	Tetrabutyl ammonium halide
TBDMS	tert-Butyldimetylsilyl
TBHP	tert-Butyl hydroperoxide
TBS	tert-Butyldimetylsilyl
^{t}Bu	tert-butyl
td	triplet of doublet
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulphonyl (triflyl)
Tf	triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOF	Turn-over frequency [s^{-1}] (number of moles of formed product per mole of catalyst per unit of time)
TS	transition state
Ts	tosyl
UV	ultraviolet
vis	visible
W	Watt

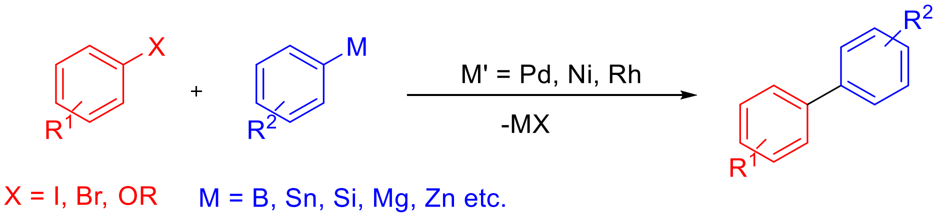
X	Heteroatom
δ	chemical shift in ppm downfield from trimethylsilane

SYNOPSIS

The thesis entitled "***Transition-Metal-Free Synthesis of Aryl Thiocyanates, Aldehydes and Ketones, Azaheterocyclic carboxamides and Styrenyl Ethers***" comprises of five chapters.

Chapter 1: *Introduction to Transition-Metal-Free reactions*

This chapter presents a brief introduction on the transition-metal-free reactions and use of some of the transition-metal-free reagents in variety of transformations. The transition-metal-catalyzed reactions have been studied extensively since the very beginning of the past century and they represent a great success in organic chemistry, along with the birth and growth of organometallic chemistry. Many coupling reactions utilize organoboron, organotin reagents, and the conventional organometallic reagents, including Grignard reagents, organolithium, organozinc, and organosilane reagents in presence of transition metal catalysts (Scheme 1.1).



Scheme 1.1 Traditional transition-metal-catalyzed reactions

Even though, traditional transition-metal-catalyzed reactions have become indispensible to some extent, yet they are facing some challenges and are still limited in applications due to some of the drawbacks of the catalytic systems and inherent properties of heavy metals. Some of the limitations of transition-metal-catalyzed reactions are that they are usually very expensive and require supporting ligands during the reactions and are toxic to some extents (though there are exceptions). They are usually sensitive to moisture and oxygen (O_2), co-catalysts and additives are also critical to promote the efficiency and selectivity of reactions.

In this regard, transition-metal-free coupling reactions are of great significance to provide a better understanding of how the reactions work with or without transition metals. This chapter also presents a classification of transition-metal-free reactions based on different reaction pathways. A detailed account on environmentally friendly persulfate reagent and its synthetic applications in transition-metal-free reactions have been described.

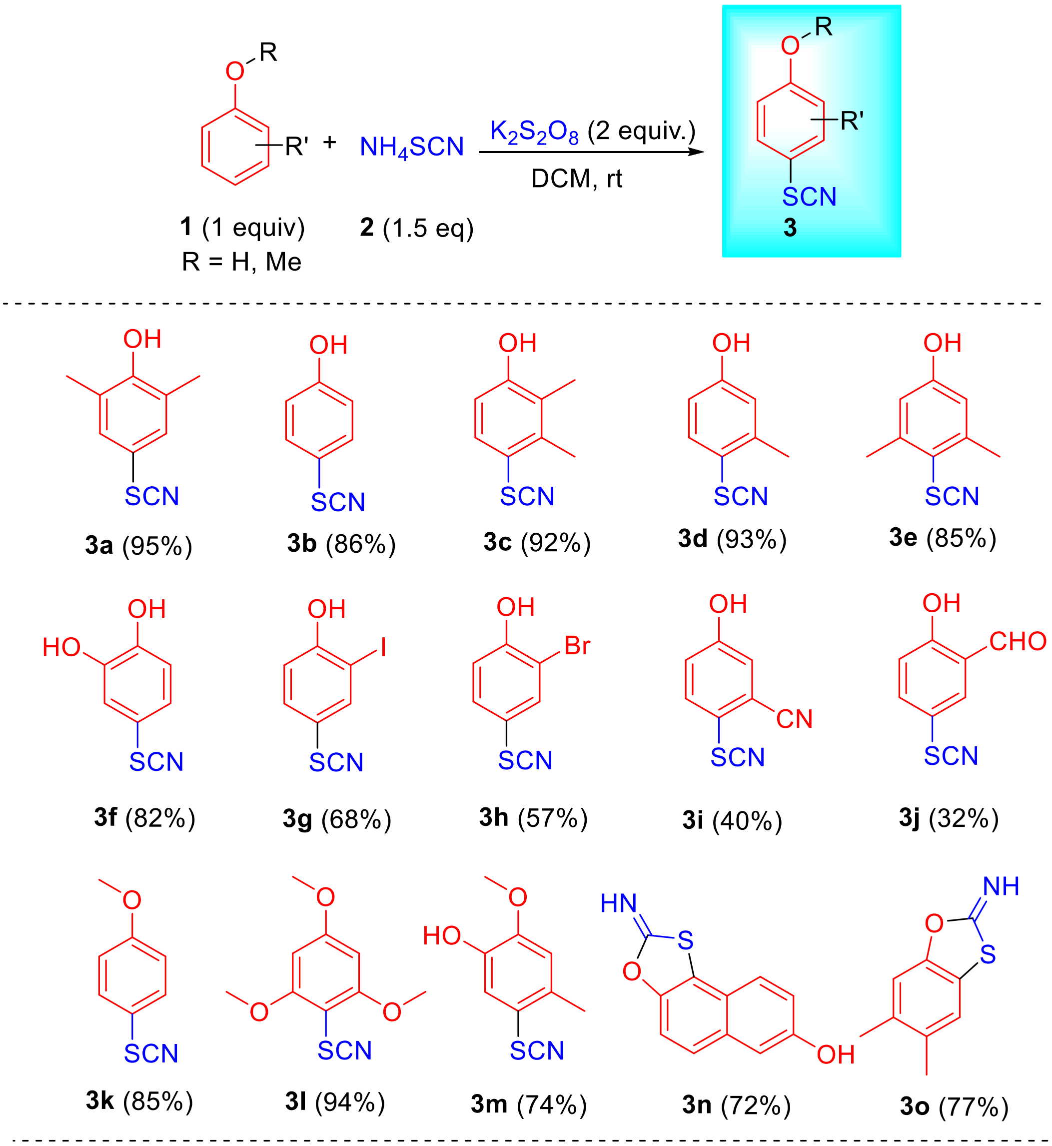
Chapter 2: *Transition-Metal-Free Regioselective Thiocyanation of Phenols, Anilines and Heterocycles*

This chapter describes a novel, practical and direct transition-metal-free regioselective thiocyanation of phenols, aromatic amines and heterocycles using potassium persulfate and inexpensive NH_4SCN under mild conditions. The chapter begins with a brief overview on the previous thiocynations protocols. At the outset of our investigation, we selected 2,6-dimethyl phenol **1a** and ammonium thiocyanate **2** as model substrates. In order to optimize the reaction conditions, different oxidants, solvents, and conditions were explored and we found that 2 equiv. of potassium persulfate ($K_2S_2O_8$) works well in DCM at room temperature within 4 h (Table 2.1).

To our delight, various substrates underwent a facile, direct and regioselective thiocyanation under optimized reaction conditions by affording the desired products in good to excellent yields. Various phenols and anisole derivatives with electron donating and withdrawing groups reacted efficiently under the optimized reaction conditions to afford the corresponding desired products (**3a-3m,** Table 2.1). Reactions of naphthalene derivative (**1n**) and 3,4-dimethyl phenol (**1o**) under the reaction conditions resulted in the corresponding stable oxathioimines (**3n**, **3o**).

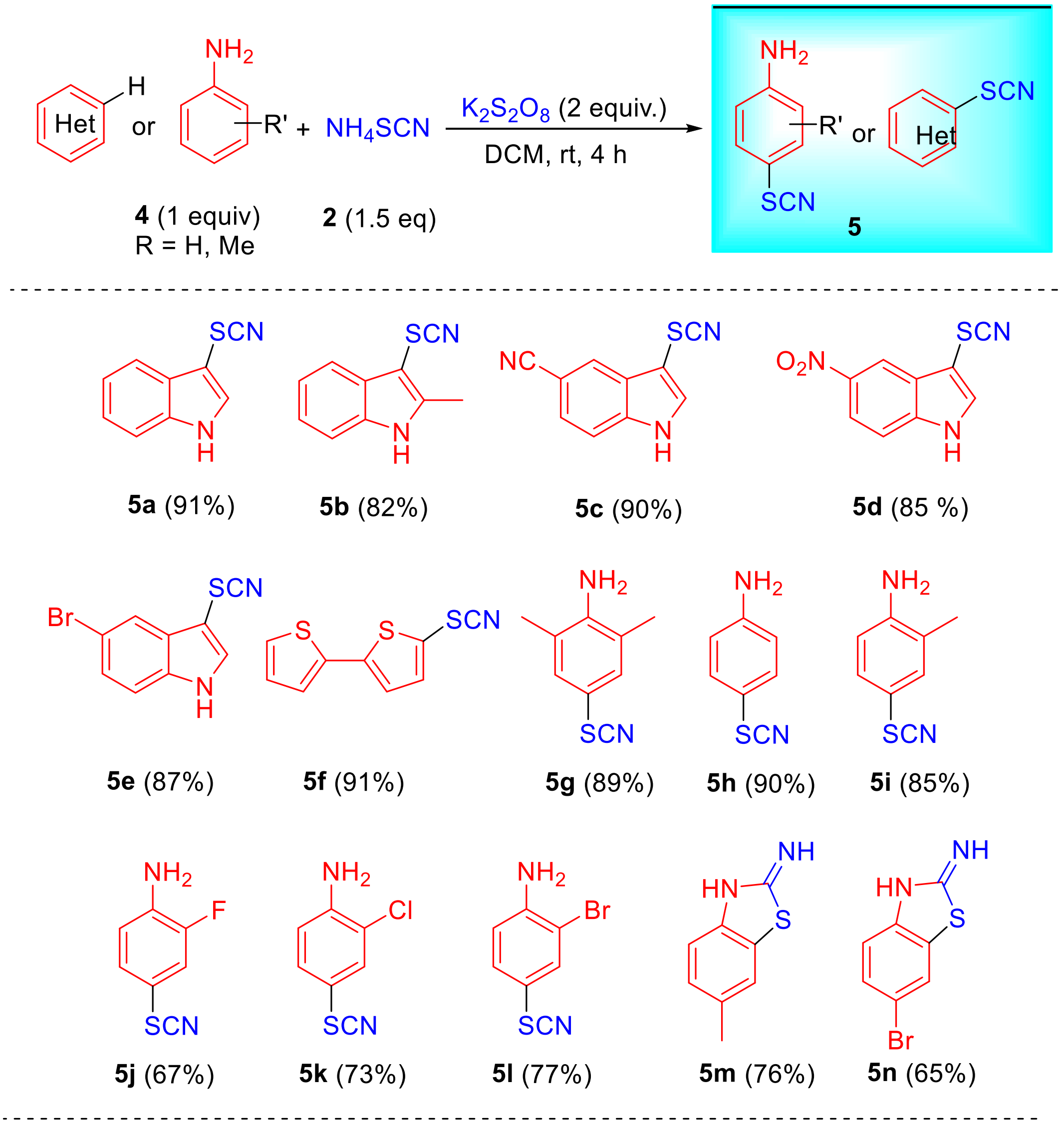
Encouraged by the initial success, we turned our attention towards the relatively more reactive anilines and heterocycles. Different indole derivatives (**4a-4e**) under the optimized reaction conditions underwent direct C-3 thiocyanation easily in excellent yields (**5a-5e**, Table 2.2). Notably, 2, 2'-bithiophene (**4f**) reacted with an ease to afford the C-2 mono thiocyanated product **5f** in excellent yield. Later, we explored the reactivity of various aniline derivatives. All the aniline derivatives under the optimized reaction conditions afforded the corresponding thiocyanted products (**5g-5l**) in good to excellent yields (Table 2.2). It is very important to note that direct thiocyanation was highly regioselective and occurred at *para* position. However, *para* substituted anilines resulted in the formation of the corresponding stable azathioimines (**5m, 5n**) via *ortho* thiocyanation.

Table 2.1: Direct regioselective thiocyanation of phenol derivatives[a,b]



[a]Reaction conditions: Substituted phenols and anisoles **1** (1 equiv.), NH_4SCN **2** (1.5 equiv), $K_2S_2O_8$ (2 equiv.), DCM, (2 mL), reaction time (4 h), [b]Isolated yield after column chromatography is given in parenthesis. rt (24 °C)

Table 2.2 Direct and regioselective thiocyanation of anilines and heterocycles[a,b]



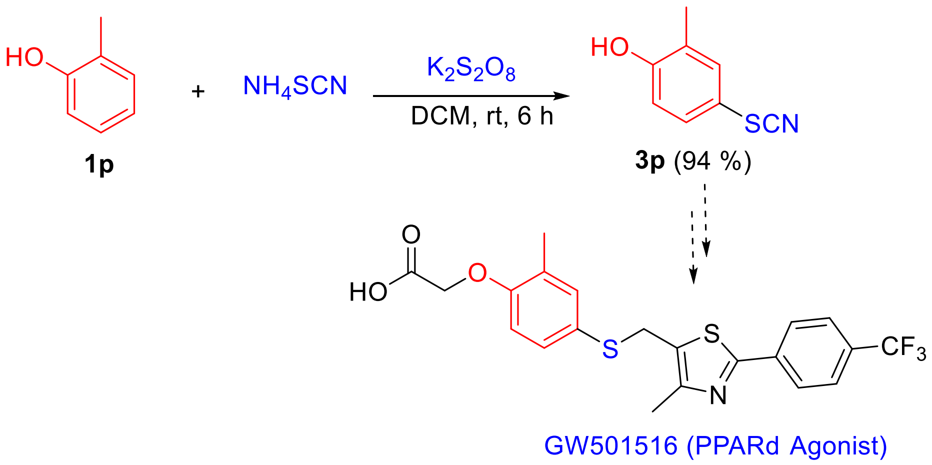
5a (91%) **5b** (82%) **5c** (90%) **5d** (85 %)

5e (87%) **5f** (91%) **5g** (89%) **5h** (90%) **5i** (85%)

5j (67%) **5k** (73%) **5l** (77%) **5m** (76%) **5n** (65%)

[a]Reaction conditions: Substituted aromatic amines and heterocycles **4** (0.1 g, 1 equiv.),NH_4SCN (1.5 equiv), $K_2S_2O_8$ (2 equiv.), DCM, (2 mL), reaction time (4 h), rt (24 °C), [b]Isolated yield after column chromatography is given in parenthesis.

In order to make this approach more practical and for the future development, we extended this method on a gram scale under the optimized reaction conditions. GW501516 is a well-known, most potent and selective peroxisome proliferator-activator receptor δ (PPARδ) agonist. The compound **3p** precursor of GW501516 was synthesized using this protocol under optimized reaction conditions on a three gram scale in excellent yield (94%) (Scheme 2.1).



Scheme 2.1 Thiocyanation on a gram scale

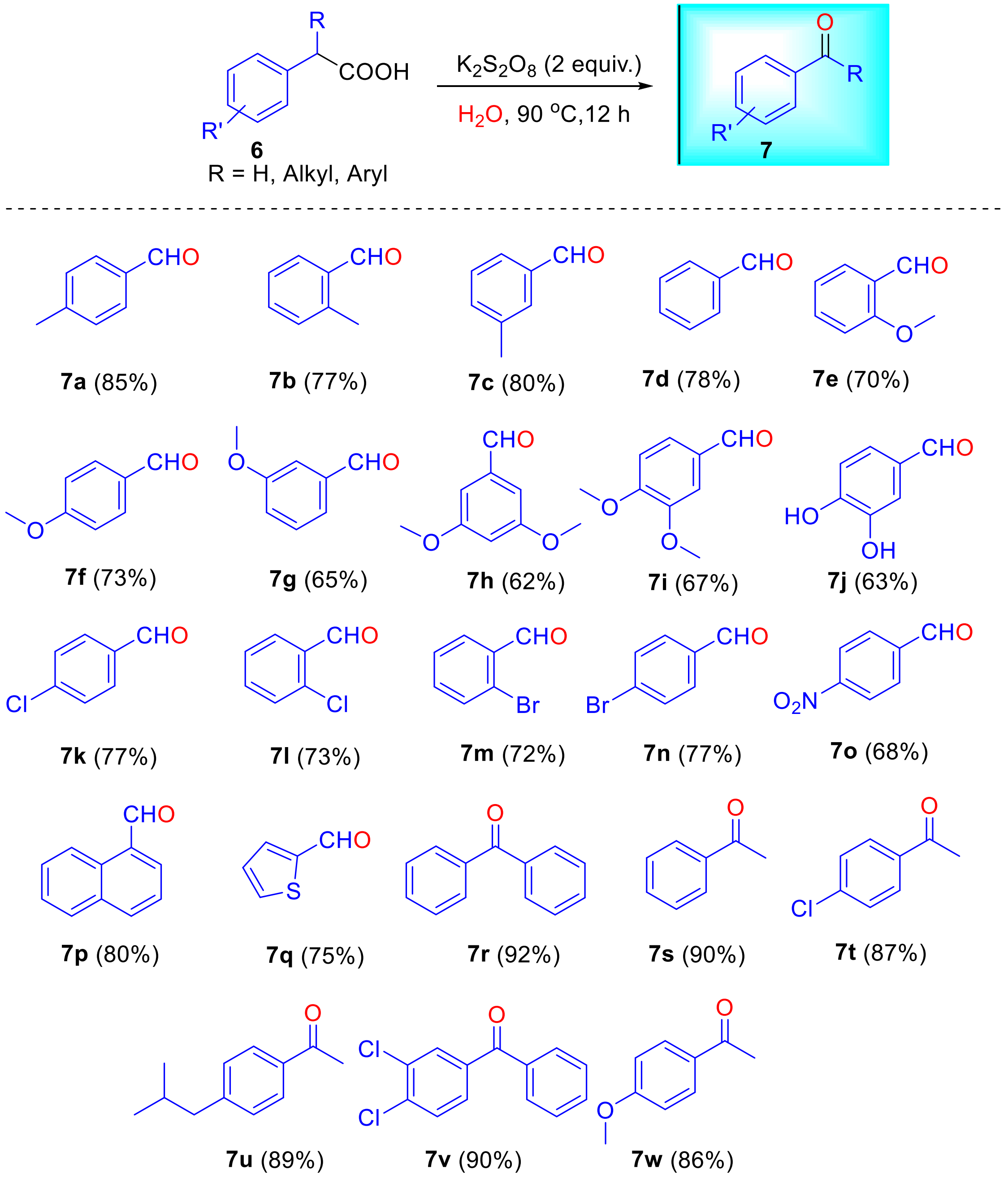
The radical mechanism was confirmed by using the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). In order to investigate and to support the formation of a phenol radical cation intermediate, the UV-Vis spectroscopy studies were carried out.

An expedient and direct transition-metal-free regioselective thiocyanation of phenols, anilines and heterocycles using NH_4SCN and $K_2S_2O_8$ has been developed. The transformation is realized via the direct C-H functionalization under transition-metal-free conditions at an ambient temperature in excellent yields.

Chapter 3: *Oxidative Decarboxylation of Aryl Acetic Acids in Water:One-Pot Transition-Metal-Free Synthesis of Aldehydes and Ketones*

This chapter presents a one-pot transition-metal-free protocol for the synthesis of aldehydes and ketones via oxidative decarboxylation of aryl acetic acids in water. Aldehydes and ketones are very important class of compounds and they have been used extensively in wide areas of chemical synthesis. In this chapter we report an oxidative decarboxylative strategy for the direct and clean synthesis of aldehydes and ketones **7** without over-oxidation into carboxylic acids in water. We commenced our initial work with 4-methyl phenylacetic acid **6a** with $K_2S_2O_8$ as a model reaction. After extensive screening of solvents and different temperatures, the optimum reaction condition was emerged as 4-methylphenyl acetic acid **6a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 90 ^{o}C in water under aerial atmosphere in 12 h.

Table 3.1. Oxidative decarboxylation of arylacetic acids to aldehydes and ketones[a,b]



[a] Reaction conditions: Arylacetic acid **6** (1equiv.), $K_2S_2O_8$ (2 equiv.), water (2 mL) open atmosphere; reaction was monitored by TLC. [b] Isolated yield after purification by column chromatography is given in parenthesis.

Under optimized reaction conditions arylacetic acids (**6a-6p**) possessing the electron-donating group as well as electron withdrawing groups reacted smoothly by affording the corresponding aldehydes (**7a-7p**) in moderate to good yields (Table 3.1). Similarly, the heteroaromatic acid such as 2-thienylacetic acid **6q** under the reaction conditions afforded the 2-thienylcarboxylaldehyde (**7q**). *α*-Substituted phenylacetic acids (**6r-6w**) under optimized reaction conditions afforded the corresponding ketones (**7r-7w**) in excellent yields (Table 3.1).

To make the protocol more general and for the wider applicability we demonstrated the synthesis of benzaldehyde **7d** (83%) and benzophenone **7r** (93%) on a gram scale starting from the corresponding arylacetic acids **6d** and **6r** respectively under optimum reaction conditions.

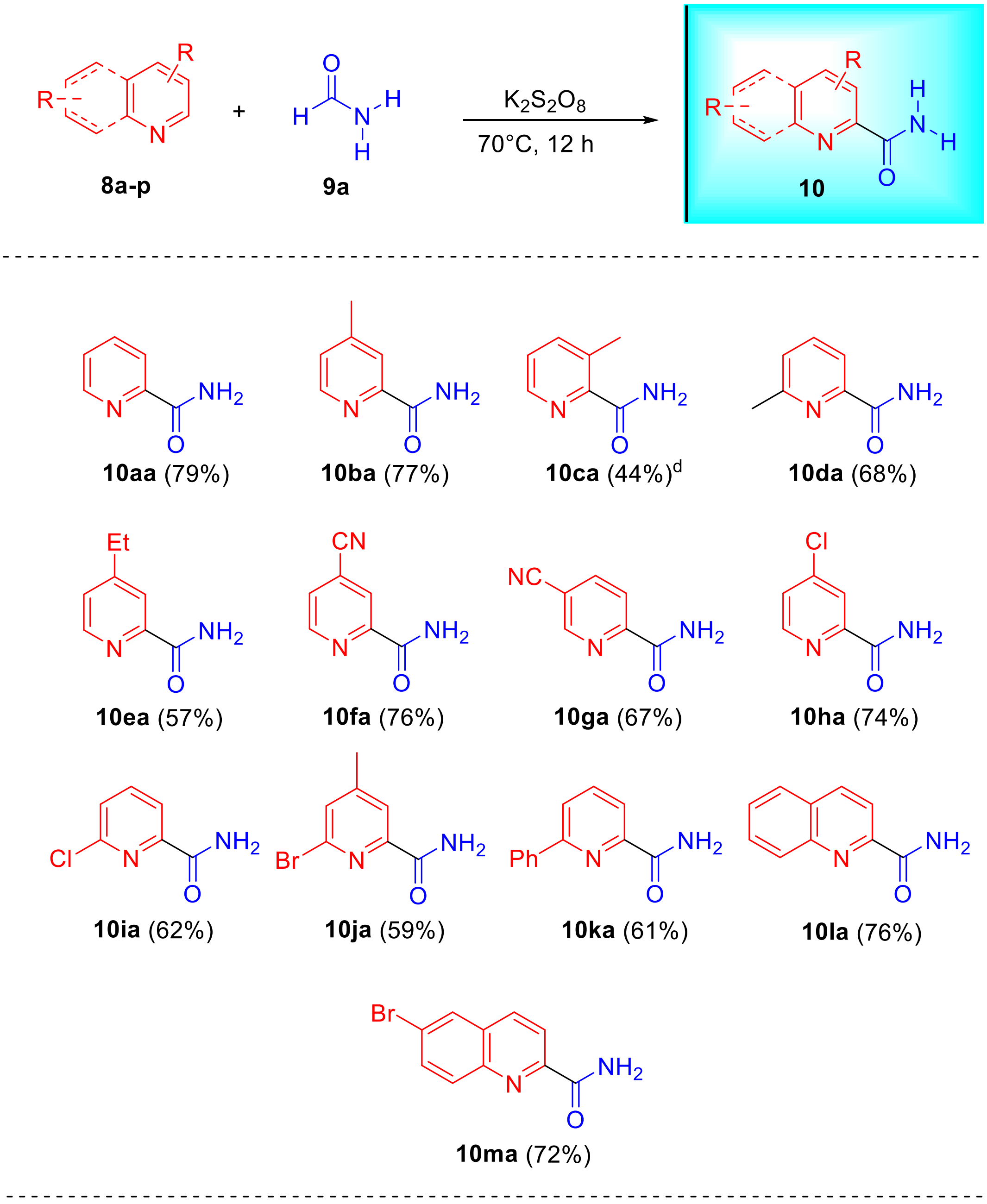
Further, in order to validate and understand the role of water, the reaction was carried out using ^{18}O labeled water ($H_2{}^{18}O$, 97%) under optimized reaction conditions. The ^{18}O labeled product was confirmed by the HRMS and GC-mass spectrometry (^{18}O content was 96.3%). It is very significant to note that this protocol gives a direct access to prepare ^{18}O-labeled aldehydes and ketones quantitatively without resorting to an exchange experiment. The reaction in presence of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) supported the radical pathway.

We have demonstrated a one-pot protocol for the direct and clean transformation of arylacetic acids to aldehydes and ketones in water with minimal waste. The protocol employed environmentally friendly and less expensive $K_2S_2O_8$ as reagent, and commercially available arylacetic acids without any over oxidation. Method also demonstrated the direct access to ^{18}O-labeled aldehydes and ketones without relying on any exchange experiment. Experimental conditions are simple and above all reaction is carried out only in water and it has been demonstrated on a gram scale for wider application.

Chapter 4: *Transition-Metal-Free Synthesis of Primary to Tertiary Carboxamides: A Quick Access to Pro-drug Pyrazinecarboxamide*

This chapter describes a direct aminocarbonylation of heteroaromatics via cross-dehydrogenative coupling approach. This simple and user friendly protocol for aminocarbonylation uses potassium persulfate and formamide/N-methylformamide (NMF)/DMF as reagents to access primary to tertiary carboxamides with high selectivity. This chapter begins with a brief account on aminocarbonylation and related previous approaches. We commenced our initial work with pyridine **8a** and formamide **9a** as model substrates in presence of $K_2S_2O_8$ (2 equiv.) in DCE.

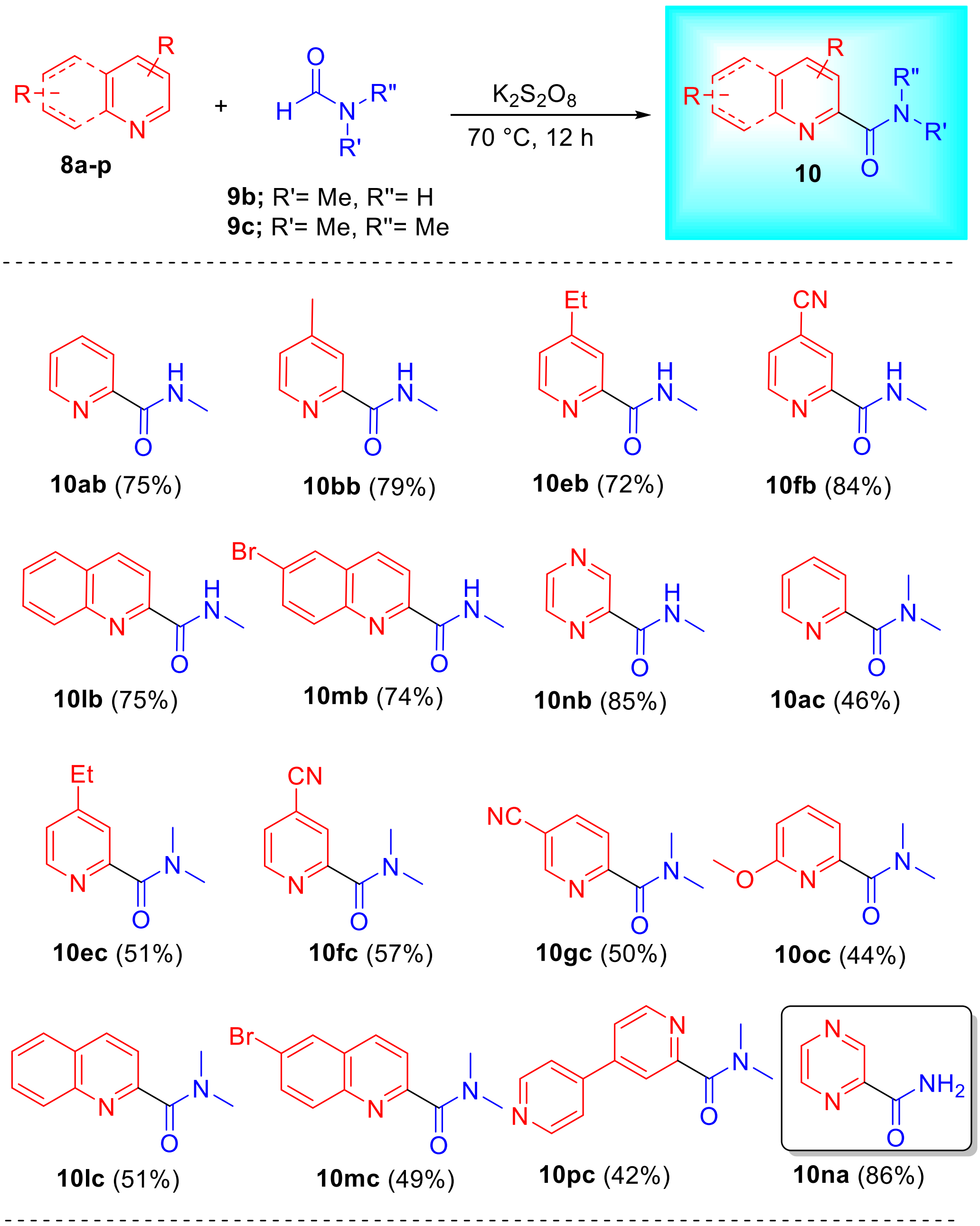
Table 4.1 Synthesis of primary azaheterocyclic carboxamides[a,b]



[a]Reaction Conditions: Heteroaromatics **1** (1 equiv.), Formamide **9a** (20 equiv. 2 mL) potassium persulfate (2 equiv.) under aerial atmosphere for 12 h, [b]Isolated yield after purification by column chromatography is given in parenthesis. [c]**3ca'**(5-methylpicolinamide) was obtained as regioisomer along with **3ca** (**3ca:3ca' 58:42**).

After screening several solvents and temperature conditions optimum reaction condition was emerged as pyridine **8a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 70 ^oC and formamide **9a** (20 equiv, solvent as well as reagent) under aerial atmosphere in 12 h.

Table 4.2. Synthesis of secondary and tertiary azaheterocyclic carboxamides [a,b]



[a]Reaction conditions: Heteroaromatics **1** (1 equiv.), or NMF **9b** or DMF **9c** (20 equiv. 2 mL) potassium persulfate (2 equiv.) under aerial atmosphere for 12 h, [b]Isolated yield after purification by column chromatography is given in parenthesis.

Under the optimized reaction conditions, substrates (**8a-8m**) possessing the electron-donating as well as electron withdrawing groups reacted smoothly with formamide **9a** to afford the corresponding carboxamides (**10aa-10ma**) in moderate to good yields (Table 4.1). Encouraged by this success we explored this protocol for the synthesis of various secondary and tertiary carboxamides (Table 4.2).

The compounds (**8a-b**, **8e-f**) reacted smoothly with the *N*-methyl formamide (NMF) **9b** to afford the corresponding secondary carboxamides (**10ab**, **10bb**, **10eb**, **10fb**) in very good yields (Table 4.2). Further, the protocol was explored on quinoline and its derivatives, and pyrazine (**8l**, **8m**, **8n**) with NMF **9b** under the optimized reaction conditions to afford the secondary carboxamides (**10lb**, **10mb**, **10nb**) in very good yields. Different substrates **8a, 8e-g, 8l-1m, 8o-p** (pyridine, quinoline, bipyridyl derivatives) were treated with the DMF **9c** under optimized reaction conditions to afford the corresponding tertiary carboxamides (**10ac**, **10ec**, **10fc**, **10gc**, **10lc**, **10mc**, **10oc**, **10pc**) in moderate yields.

Pyrazine carboxamide (**10na**) is known as Rifater or Tebrazid and is a prescribed prodrug for the tuberculosis worldwide. The protocol was employed for the synthesis of this drug:pyrazine carboxamide (Rifater) (**10na**) on 2 gram scale starting from pyrazine (**8n**). Further the reaction using radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) supported the radical pathway for this transformation.

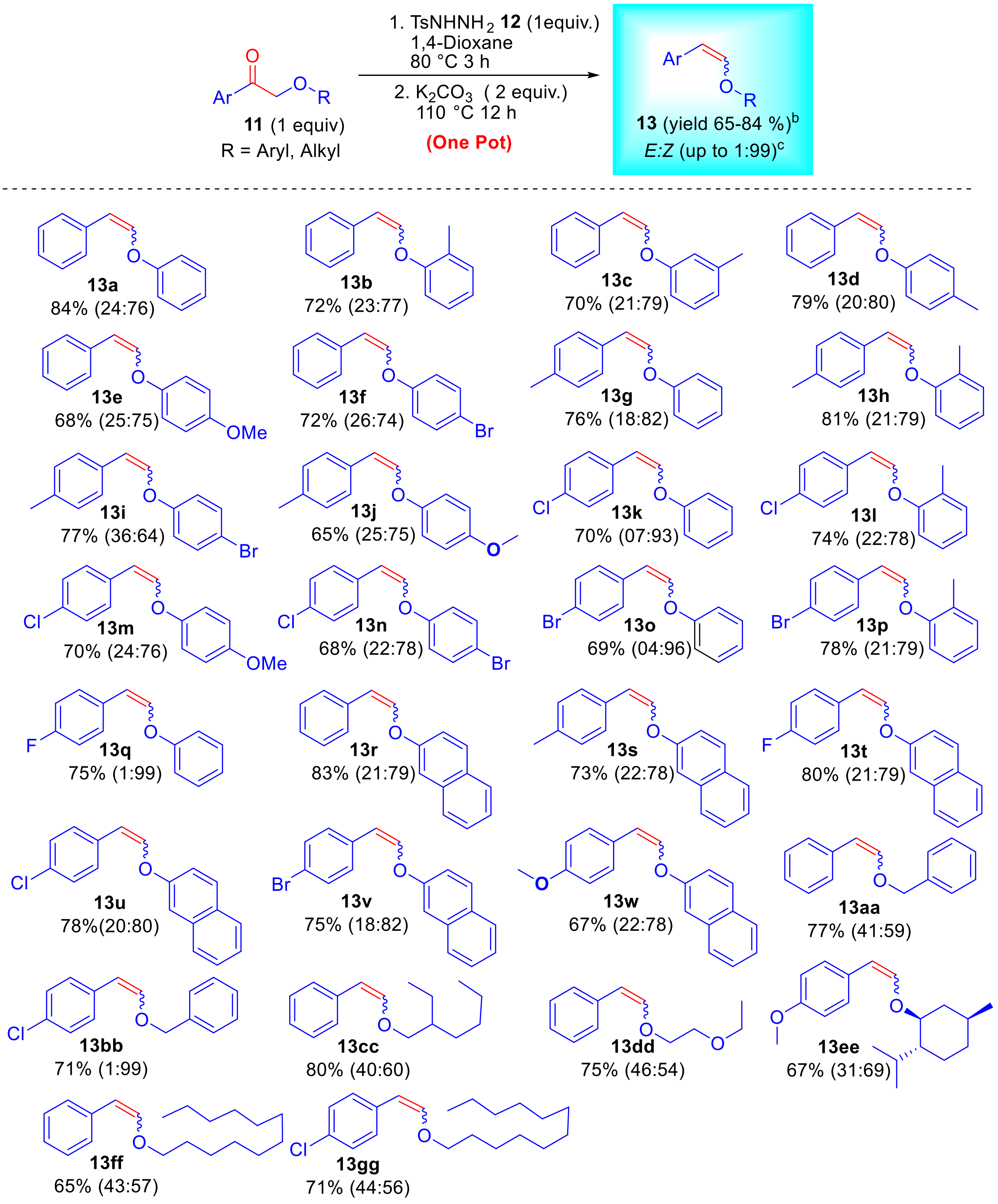
We have developed a transition-metal-free one-pot protocol that enables the direct aminocarbonylation of few heterocycles efficiently. Straightforward and simple protocol gives a direct access to primary to tertiary carboxamides employing user friendly and less expensive $K_2S_2O_8$ as reagent. Protocol works well with usually unreactive substrates such as NMF, DMF and quinoline and other azaheterocycles. Moreover, the protocol is clean and did not give any side products emanating from competing α-amidoalkylation. Pyrazinecarboxamide a prescribed drug has been synthesized using this protocol and the practicality of the protocol was demonstrated on a gram scale for the wider application.

Chapter 5: ***Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones via Bamford-Stevens Reaction***

This chapter presents a transition-metal-free synthesis of styrenyl ethers via Bamford-Stevens reaction. The protocol gave an access to aryl vinyl ethers starting from 2-aryloxy and alkoxy acetophenones and tosyl hydrazide using K_2CO_3 as a base under mild reaction conditions. This chapter gives a brief account on the importance and applications of aryl vinyl ethers and their synthesis. Initially, a model one pot reaction was carried out by heating phenyloxy acetophenone (2- phenoxy-1-phenylethan-1-one) **11a** and tosylhydrazide **12** in DCE at 80 °C for 3 h followed by the addition of K_2CO_3 (2 equiv.). After screening several solvents at different temperatures, we found that heating substrate **11** and tosyl hydrazide **12** (1 equiv.) in 1,4-dioxane at 80 °C for 3 h followed by the addition of K_2CO_3 (2 equiv.) at 110 °C for 12 h was found to be the optimum reaction condition.

Various aromatic substrates containing phenyl, methyl, methoxy, bromo, chloro, fluoro substituents worked smoothly under the optimized reaction conditions to afford the corresponding desired products (**13a-13q)** in moderate to very good yields (see Table 5.1, up to 84% yield). Likewise, ketoethers bearing naphthyl functionality adjacent to oxygen also worked smoothly affording the desired products (**13r-13w**) in moderate to very good yields (67-83%). Further we turned our attention towards the synthesis of aliphatic keto ether substrates. Gratifyingly, a variety of substrates (**11aa-11gg**) worked smoothly under the optimized reaction conditions to afford the corresponding products **13aa-13gg** (see Table 5.1). We observed that styrenyl ethers (**13k, 13o, 13q**) derived from aryloxy acetophenones were highly *Z*-selective (up to *E:Z* = 1:99) while the products derived from alkoxy acetophenones (**13aa**, **13cc-13gg**) were found to be relatively less selective (up to *E:Z* = 31:69). In order to make this approach more practical and for the wider applicability, we demonstrated the synthesis of **13a** on a gram scale starting from the corresponding 2-phenoxy-1-phenylethan-1-one **11a** under optimum reaction conditions.

Table 5. Synthesis of aryl/alkyl styrenyl ethers [a-c]



13a 84% (24:76)
13b 72% (23:77)
13c 70% (21:79)
13d 79% (20:80)
13e 68% (25:75)
13f 72% (26:74)
13g 76% (18:82)
13h 81% (21:79)
13i 77% (36:64)
13j 65% (25:75)
13k 70% (07:93)
13l 74% (22:78)
13m 70% (24:76)
13n 68% (22:78)
13o 69% (04:96)
13p 78% (21:79)
13q 75% (1:99)
13r 83% (21:79)
13s 73% (22:78)
13t 80% (21:79)
13u 78%(20:80)
13v 75% (18:82)
13w 67% (22:78)
13aa 77% (41:59)
13bb 71% (1:99)
13cc 80% (40:60)
13dd 75% (46:54)
13ee 67% (31:69)
13ff 65% (43:57)
13gg 71% (44:56)

[a]Reaction conditions: Step-1: 2-aryloxy/alkoxy acetophenone derivative **11** (1 equiv.), 4-methylbenzenesulfonohydrazide **12** (1 equiv.), 1,4-dioxane (2 mL) in pressure tube at 80 °C for 3 h, Step-2: potassium carbonate (2 equiv.), heated for 12 h, [b]Isolated yield after purification by column chromatography is given in parenthesis. [c]diastereomeric ratio was determined by ^1H NMR.

We developed one transition-metal-free one-pot two step method for the synthesis of styrenyl ethers starting from 2-aryloxy/alkoxy acetophenones. The method works smoothly on both aromatic and aliphatic substrates. The protocol employs mild, commercially available and less expensive K_2CO_3 as base and the desired products were obtained in good to excellent yields.

*****

(*Numbers of substrates and products in the synopsis are different from those in thesis. Please note that compound numbers have been assigned for the convenience in every chapter and number of few compounds may vary from chapter to chapter*)

Publications

1. **Trimbak B. Mete**, Tushar M. Khopade, Ramakrishna G. Bhat, “Transition-metal-free regioselective thiocyanation of phenols, anilines and heterocycles”, *Tetrahedron Lett.*, **2017**, *58*, 415.
2. **Trimbak B. Mete**, Tushar M. Khopade, Ramakrishna G. Bhat, “Oxidative decarboxylation of arylacetic acids in water: one-pot transition-metal-free synthesis of aldehydes and ketones”, *Tetrahedron Lett.*, **2017**, *58*, 2822.
3. **Trimbak B. Mete**, Ankit Singh, Ramakrishna G. Bhat, “Transition-metal-free synthesis of primary to tertiary carboxamides: a quick access to prodrug-pyrazinecarboxamide”, *Tetrahedron Lett.*, **2017**, *58*, 4709.
4. Amar R. Mohite, **Trimbak B. Mete**, Ramakrishna G. Bhat, “An expedient stereoselective synthesis of (*E*)-*α,β*-unsaturated esters and thioesters using $FeCl_3{\cdot}6H_2O$”, *Tetrahedron Lett.*, **2017**, *58*, 770.
5. Prakash R. Sultane, **Trimbak B. Mete**, Ramakrishna G. Bhat, “A convenient protocol for the deprotection of *N*-benzyloxycarbonyl (Cbz) and benzyl ester groups”, *Tetrahedron Lett.*, **2015**, *56*, 2067.
6. Prakash R. Sultane, **Trimbak B. Mete**, Ramakrishna G. Bhat, “Chemoselective *N*-deacetylation under mild conditions”, *Org. Biomol. Chem.*, **2014**, *12*, 261.
7. Tushar M. Khopade, **Trimbak B. Mete**, Ramakrishna G. Bhat, “An adverse effect of higher catalyst loading and longer reaction time on enantioselectivity in organocatalytic multicomponent reaction”, *Chem. Eur. J.* **2018, --, ----.** DOI. 10.1002/chem.201800278
8. **Trimbak B. Mete**, Debashis Laha, Ramakrishna G. Bhat, “Transition-metal-free synthesis of styrenyl ethers from 2-aryloxy/alkoxy acetophenones *via* Bamford-Stevens reaction”, *Manuscript under review.*
9. Lakshmi VR Babu Syamala, **Trimbak B. Mete**, Ramakrishna G. Bhat, “$FeCl_3$. 6H2O catalized selective reduction of C=C in alkylidene carbonyl compounds” *Manuscript under preparation.*
10. Tushar M. Khopade, Prakash K. Warghude, **Trimbak B. Mete**, Ramakrishna G. Bhat, “Direct organocatalytic synthesis of *α,β*-unsaturated carbonyl compounds” *Manuscript under preparation.*

Chapter 1

Introduction to Transition-Metal-Free Reactions

O N E

Image Source of batman : google images of batsman

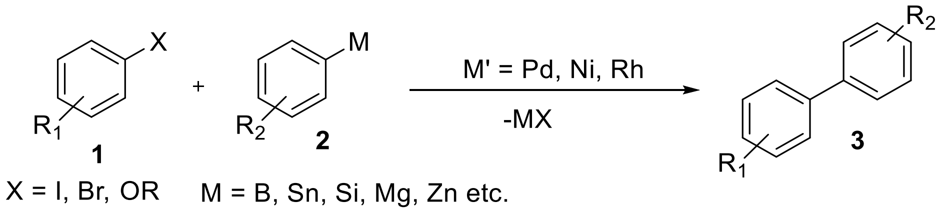
Introduction to Transition-Metal-Free Reactions 1

1.1 Abstract

This chapter presents a brief overview on the importance of transition-metal-free reactions followed by the uses as well as drawbacks of the transition-metal-catalyzed reactions. An account on the synthetic uses of transition-metal-catalyzed reactions and, its limitations and challenges has been presented. Likewise, advantages of transition-metal-free reactions and their classifications based on the reaction pathways have been discussed. Usually, transition-metal-free reactions follow radical, radical cation and carbene pathways. The importance and uses of some of the transition-metal-free reagents including environmentally friendly and less expensive persulfate oxidant have been discussed.

1.2 Transition-metal-catalyzed reactions

Transition-metal-catalyzed reactions have been studied extensively since the very beginning of the past century and they represent a great success in organic chemistry, along with the birth and growth of organometallic chemistry.[1] The transition-metal-catalyzed coupling reactions were initiated in 1960s and they became one of the most efficient and direct strategies for the carbon-carbon bond formation.[2] The extensive variations and modifications of transition-metal-catalyzed coupling reactions enabled wide applications in organic synthesis and were regarded as the most reliable, accurate, and powerful tools in chemists' arsenal.[3] Many coupling reactions utilize organoboron,[4] organotin reagents,[5] and the conventional organometallic reagents, including Grignard reagents,[6] organolithium,[7] organozinc,[8] and organosilane reagents in presence of transition metal catalysts (Scheme 1.1).[9] The Mizoroki-Heck reaction is one of the perfect examples for the direct C-H functionalization of olefins.[10] Great success and significance of transition-metal-catalyzed coupling reactions have been highlighted by the Nobel prize in chemistry.[11]



Scheme 1.1 Traditional transition-metal-catalyzed reactions

1.3 Limitations of transition-metal-catalyzed reactions

Even though, traditional transition-metal-catalyzed reactions have become indispensable to some extent, yet they are facing some challenges and are still limited in applications due to some of the drawbacks of the catalytic systems and due to the inherent properties of heavy metals. Firstly, most of the transition-metal catalysts are generally very expensive,[12] and require supporting ligands during the reactions. The supporting ligands are normally even more expensive and sometimes difficult to synthesize them. Secondly, most of the transition metals are toxic to some extents (though there are exceptions), and removal of trace amounts of transition metal residues from the final products are challenging and quite costly, and this is a serious concern especially in the pharmaceutical industry.[13] Thirdly, many transition metal catalysts are usually sensitive to moisture and oxygen (O_2), hence, very strict manipulation is required during the reaction. Fourthly, in most of the cases, co-catalysts and additives are also critical to promote the efficiency and selectivity of reactions.[14] Finally, the large consumption of transition metals does not meet the requirement of sustainable development.[15]

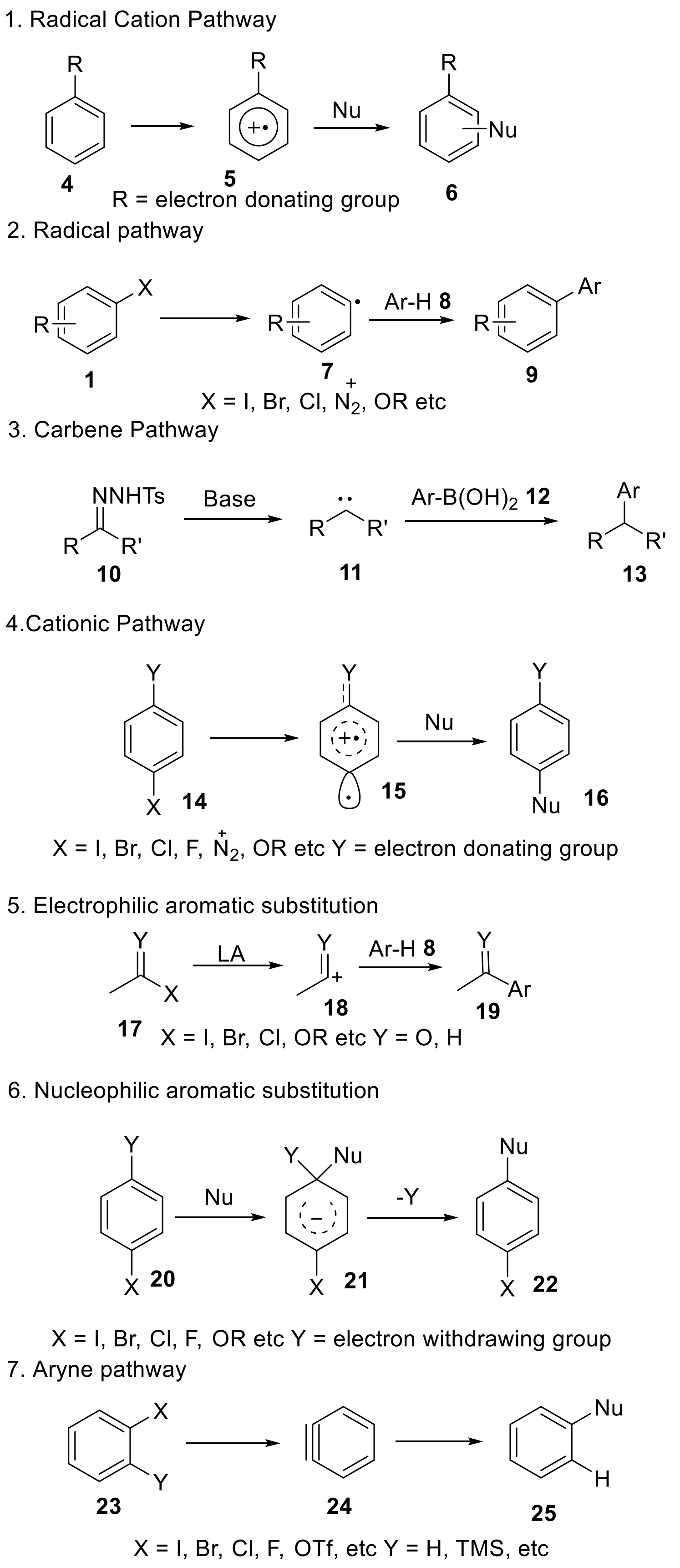
Obviously, alternative pathways to construct C-C and C-X (X = Heteroatom) bonds under transition-metal-free conditions are highly appealing. In this regard, studies on transition-metal-free coupling reactions are of great significance to provide a better understanding of how the reactions work with or without transition metals.

1.4 Transition-metal-free reactions

Transition-metal-free reactions can be defined as “the reactions, where in similar starting materials are used like in transition-metal-catalyzed reactions and affords the similar/same products under transition-metal-free conditions”.[16] Usually, most of the transition-metal-free reagents are commercially available, less expensive, relatively less toxic, not sensitive to oxygen (O_2). In many cases they do not need inert conditions, and the reactions can be performed in water. These many factors make transition-metal-free reactions environmentally benign and thus nowadays gaining importance for many transformations. Undoubtedly, the scope of transition-metal-free reactions is promising and wider. This area of research still needs more investigations and systematic knowledge to explore many interesting transformations under transition-metal-free conditions.

1.5 Classification of transition-metal-free reactions

On the basis of the proposed and proved mechanistic pathways in the literature, transition-metal-free reactions can be broadly classified in to the following classes, namely (1) radical cation pathway, (2) radical pathway, (3) carbene pathway (4) cationic pathway, (5) electrophilic aromatic substitution (Friedel−Crafts reaction) (6) nucleophilic aromatic substitution (Ipso substitution), (7) aryne pathway, and (8) classical organocatalysis pathway (Scheme 1.2).

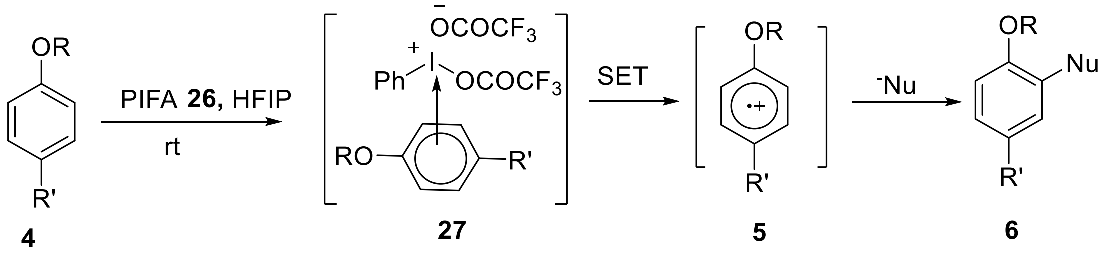


Scheme 1.2 Types of transition-metal-free reactions based on mechanistic pathways

As most of the thesis work is based on radical cation pathway, radical pathway, and carbene pathway, some of the selected examples of these types have been described in this chapter.

1.5.1 Transition-metal-free reactions via radical cation pathway

Earlier, in the year 1994, Kita and co-workers reported hypervalent iodine-induced nucleophilic substitution of *para*-substituted phenyl ethers **4**.[17] The authors described the single-electron-transfer (SET) ability of hypervalent iodine reagent PIFA [phenyliodine(III)bis(trifluoroacetate)] **26** towards phenyl ethers **4** via oxidation process. The reagent promoted the formation of aromatic cation radical **5** starting from aryl ethers **4**, and the radical cation intermediate **5** subsequently underwent an oxidative nucleophilic substitution reaction with various nucleophiles (Scheme 1.3). It’s believed that the electron rich arenes react with PIFA **26** to generate a charge-transfer (CT) complex **27** subsequently leading to radical cation intermediate **5** via SET.

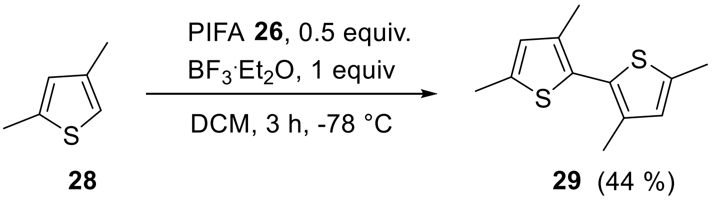


Nu = $\bar{N}_3$, $\bar{O}Ac$, 1,3-dicarbonyls, $\bar{S}CN$, $\bar{S}Ar$ PIFA = $PhI(OCOCF_3)_2$

Scheme 1.3 General process for the hypervalent iodine (III) reagent promoted reactions

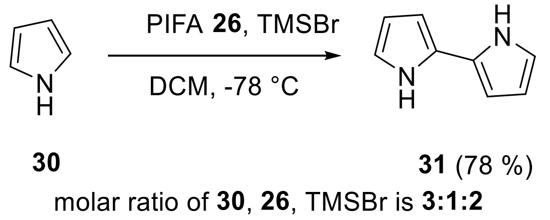
The reactive radical cation can react with various nucleophiles (N_3^-, AcO^-, and 1,3-dicarbonyl compounds) to afford a series of useful products **6** in moderate to good yields (up to 82%). The generation of the reactive radical cationic intermediates **5** was confirmed by UV and ESR spectroscopic studies.[18] Since then, hypervalent iodine (III) reagents have been utilized as selective and efficient SET oxidizing agents for the variety of direct functionalization of electron-rich arenes and heteroarenes under mild conditions.

Kita and co-workers have made significant contributions in hypervalent iodine(III)-promoted reactions, especially on a series of substrates such as aromatic and heteroaromatic compounds (thiophenes, pyrroles, and indoles). They reported the reaction of PIFA [phenyliodine(III) bis(trifluoroacetate)] **26** with 2,4-dimethylthiophene **28** in the presence of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -78 °C to afford the corresponding *α,α*-linked bisthiophene derivative **29** as the sole coupling product in moderate yield (44 %) and the possible *α,β*-linked regioisomers were not detected (Scheme 1.4).[19]



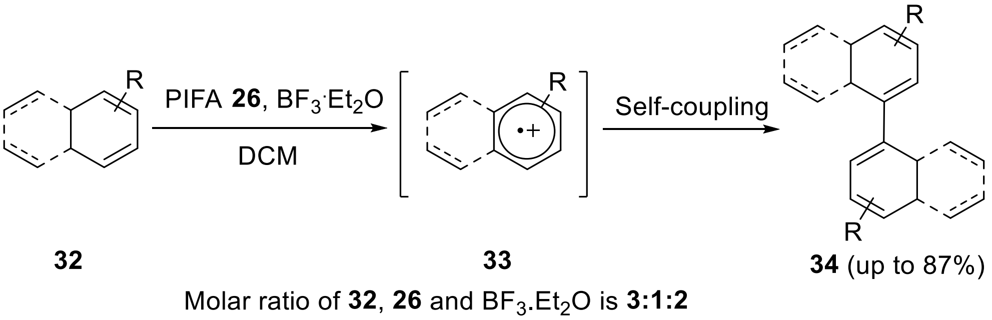
Scheme 1.4 Oxidative coupling of alkyl thiophene

Similarly, bipyrroles are also important structures in dyes, porphyrin analogues, natural products and components for molecular recognition and self-assembly systems.[20] In this regard, various methodologies have been developed for the preparation of these electron-rich bipyrroles.[21] The oxidative coupling of two pyrroles have also been promoted by the hypervalent iodine reagents. Kita and co-workers developed an easy and efficient synthesis of bipyrroles **30** starting from pyrroles **31** in the presence of PIFA **26** and trimethylsilyl bromide (TMSBr) in DCM at -78 °C in good yield (78 %) (Scheme 1.5).



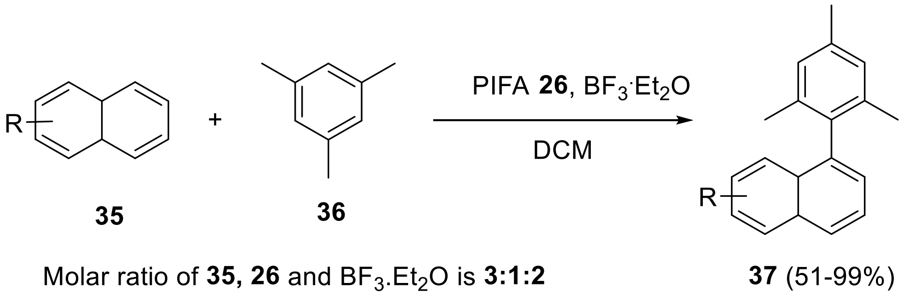
Scheme 1.5 Oxidative coupling of pyrrole

The homobiaryl coupling reaction was further extended to a heterobiaryl coupling version starting from electron-rich aromatic compounds. Kita and co-workers demonstrated the oxidative homocoupling of electron-rich aromatic compounds to afford the biphenyl and binaphthyl dimers **34** in high yields (up to 87% yield) in the presence of PIFA **26** and $BF_3{\cdot}Et_2O$ (Scheme 1.6).[22]



Scheme 1.6 Oxidative self-coupling of electron-rich aromatic compounds

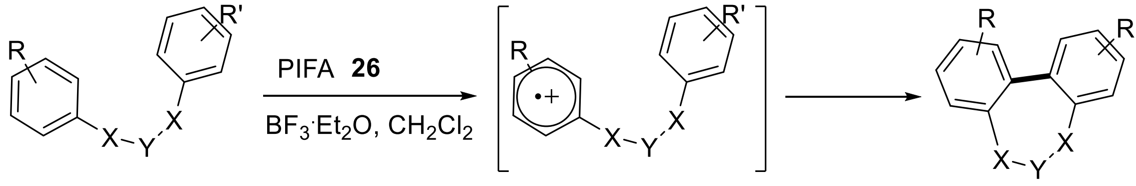
In 2008, Kita and co-workers reported a direct oxidative cross-coupling of naphthalenes **35** and mesitylene **36** in presence of PIFA **26** and $BF_3{\cdot}Et_2O$ to afford the corresponding coupling products **37** in moderate to excellent yields (up to 99%) (Scheme 1.7).[23] This transition-metal-free oxidative cross-coupling is believed to generate a radical cation intermediate *via* single electron transfer (SET).



Scheme 1.7 Oxidative cross-coupling

Further, the biaryl structural motifs in polycyclic systems have been synthesized using hypervalent iodine(III) reagent (PIFA) *via* oxidative coupling strategy. This transition-metal-free coupling tolerated various substrates **38** with different linkages to afford the corresponding biaryls **40** in good yields (up to 79%

yield) (Scheme 1.8).[24] Likewise, the method was extended to the synthesis of symmetrical as well as unsymmetrical biaryls.



38 X = CH_2, O
Y = N, Si, S
R, R' = H, OMe, OCH_2O, OTBS

39

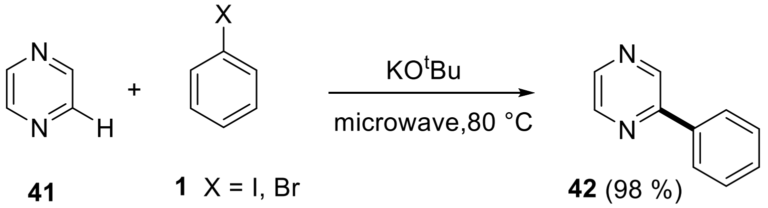
40 (up to 79%)

Molar ratio of **38, 26** and $BF_3{\cdot}Et_2O$ is **3:1:2**

Scheme 1.8 Intramolecular oxidative biaryl coupling reactions

1.5.2 Transition-metal-free reactions via radical pathway

In 2008, Itami and co-workers carried out an iridium-catalyzed arylation of electron-deficient arenes in presence of stoichiometric amount of KO^{t}Bu under microwave irradiation. Interestingly, they unexpectedly observed the coupling reaction of iodobenzene **1** and pyrazine **41** to afford the 2-phenyl pyrazine **42** in 98% yield (Scheme 1.9).[25] Several experimental studies indicated that KO^{t}Bu alone mediates the coupling reaction and it did not require the use of iridium metal catalyst. This reaction is homolytic aromatic substitution (HAS) and is believed to undergo *via* single electron transfer mechanism. The bromobenzene found to be relatively less reactive than iodobenzene and almost no reaction occurred when chlorobenzene or fluorobenzene were used under the reaction conditions.



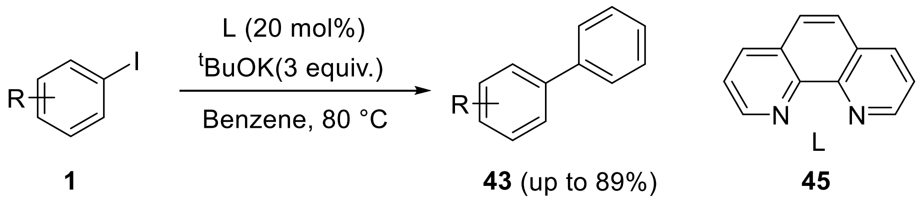
41 **1** X = I, Br **42** (98 %)

Molar ratio: **41**/1/KO^{t}Bu = **40/1/1.5**

Scheme 1.9 Arylation of pyrazine

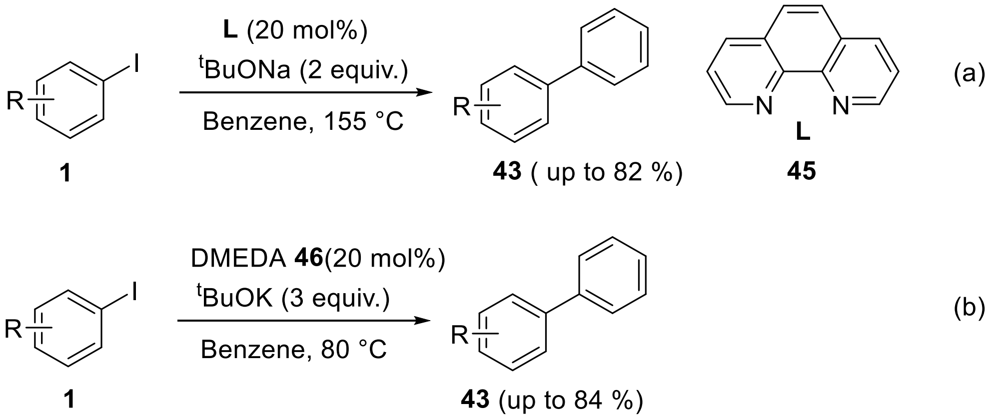
In 2010, Shi and co-workers had initially explored HAS type reaction for the cross-coupling of 4-iodoarenes **1** with benzene in the presence of cobalt salt, 1,10-

phenanthroline **45** as ligand and KO^{t}Bu.[26] Later, the detailed experimental studies revealed that the desired cross-coupling reaction works smoothly in the absence of cobalt catalyst and the desired product was obtained in good yields (up to 89% yield) (Scheme 1.10). The efficiency of the coupling reaction was dramatically enhanced by the use of 4,7-diphenyl-1,10-phenanthroline **44** as ligand.



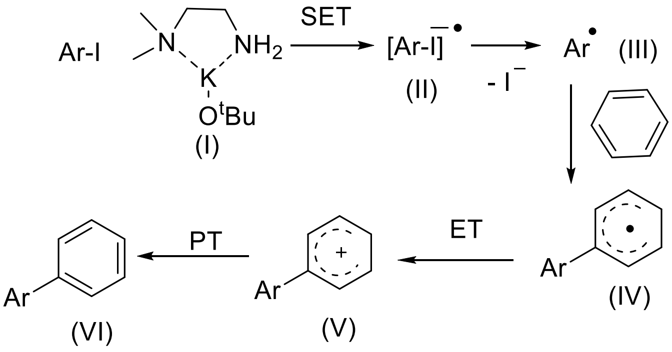
Scheme 1.10 Coupling reaction of iodoarene with benzene

Almost at the same time, Shirakawa and Hayashi[27] as well as Kwong and Lei[28] reported very similar transition-metal free cross-coupling reactions. Shirakawa and Hayashi demonstrated that the arylation of benzene with 4-iodoarenes **1** using NaO^{t}Bu and phenanthroline **45** derivatives as ligand at elevated temperature to afford the corresponding coupled product **43** in good yields (up to 82%) (Scheme 1.11a).[27] Likewise, Kwong and Lei reported the same cross-coupling reaction of 4-iodoarenes **1** with benzene in the presence of NaO^{t}Bu and *N,N′*-dimethylethylene diamine (DMEDA) **46** to afford the desired product **43** in good yields (up to 84%) (Scheme 1.11b).[28]



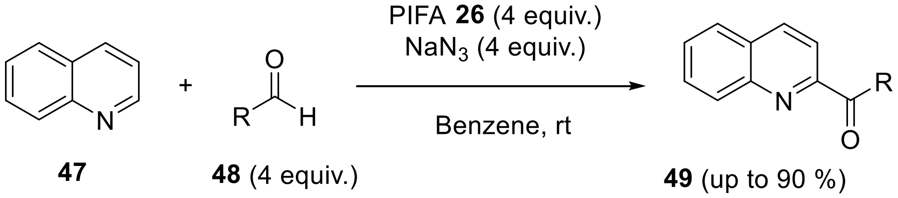
Scheme 1.11 Coupling reactions of iodoarenes with benzene

This base-promoted HAS reaction is believed to generate aryl radical and subsequent addition of aryl radical to arene followed by transfer of electron and proton to afford the corresponding coupling product (Scheme 1.12). The radical anion (II) generated via a single-electron transfer (SET) between aryl halide and KO*t*Bu−ligand complex (I), further leads to the formation of an intermediate aryl radical (III) by the elimination of a halide anion. Further, the reaction of aryl radical (III) with arene furnishes the radical σ-complex (cyclohexadienyl-type radical) (IV), which upon electron transfer (ET) and proton transfer (PT) processes afford the desired biaryl product (VI) (Scheme 1.12).



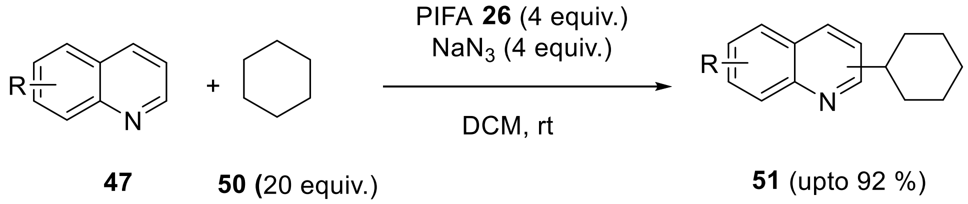
Scheme 1.12 Mechanism of base-promoted HAS reaction

Very recently, Antonchick and co-workers reported a transition-metal-free cross dehydrogenative-coupling of aromatic nitrogen heterocycles **47** with aldehydes **48** using PIFA **26** and $TMSN_3$ as an additive to afford the corresponding product **49** in good yields (up to 90%) (Scheme 1.13).[29] The reaction proceeded via the formation of an acyl radical intermediate.



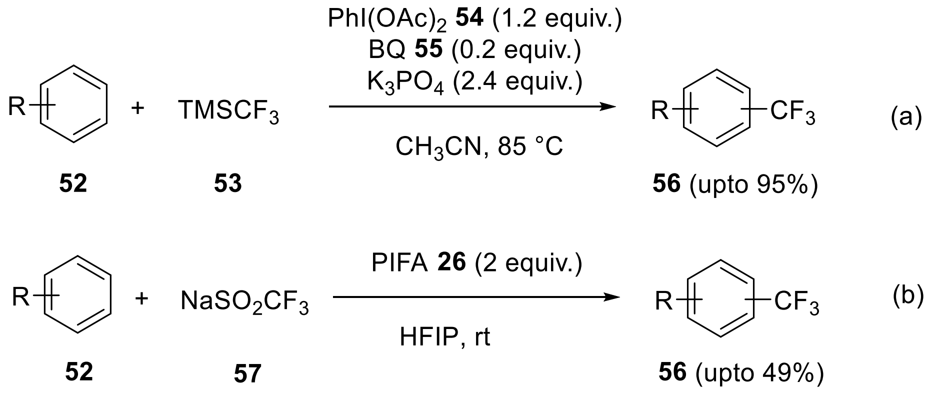
Scheme 1.13 The cross dehydrogenative-coupling of heterocycles with aldehydes

Antonchick and co-workers also reported a direct selective oxidative cross-coupling of simple alkanes with nitrogen containing heteroarenes **47** using PIFA **26** as an efficient hypervalent iodine reagent and NaN_3 as an additive.[30] However, the protocol used an excess amount of alkanes **50** (20 equiv.) to afford the desired products **51** in excellent yields (up to 92 %) (Scheme 1.14)



Scheme 1.14 Oxidative cross-coupling of alkanes with heteroarenes

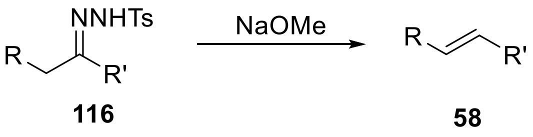
The trifluoromethylated aromatics are very useful precursors in pharmaceuticals, materials and agrochemicals, due to their electron withdrawing character, metabolic stability, and lipophilicity.[31] In this regard, the transition-metal-free trifluoromethylation of aromatic compounds was developed using different trifluoromethyl sources. Qing and co-workers reported a $PhI(OAc)_2$ **54** mediated oxidative trifluoromethylation of arenes **52** using CF_3SiMe_3 **53** under transition-metal-free conditions to afford the corresponding trifluoromethyl derivatives **56** in excellent yields (up to 95%) (Scheme 1.15a).[32] Likewise, Shibata and co-workers utilized sodium trifluoromethanesulfinate ($NaSO_2CF_3$) **57** and PIFA **26** for the trifluoromethilation of arenes **52** to afford the corresponding trifluoromethyl derivatives **56** in modest yields (up to 49%) (Scheme 1.15b).[33] The hypervalent iodine reagents PIDA **54** and PIFA **26** is believed to activate electron rich aromatic compounds as well as promote the generation of CF_3 radical in this transformation.



Scheme 1.15 Trifluoromethylation of arenes

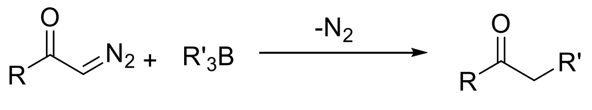
1.5.3 Transition-metal-free reactions via carbene pathway

N-tosylhydrazone is a versatile coupling partner and has been widely used in various cross-coupling reactions. Diazo compounds without an electron-withdrawing group are usually unstable and difficult to handle, while *N*-tosylhydrazones are bench stable, very easy to handle and they can be easily prepared by the condensation of aldehydes or ketones with tosylhydrazides. These tosylhydrazones are the ideal precursors of diazo compounds. The Bamford-Stevens reaction[34] and Shapiro reaction are the earliest examples that explored the use of tosylhydrazones **116** to access useful olefinic compounds **58** (Scheme 1.16).[35] These are the typical base-induced transition-metal-free reactions of *N*-tosylhydrazones to furnish alkenes or substituted alkenes **58**. It is believed that base promotes the reaction of *N*-tosylhydrazone to generate unstable diazo compound that ultimately collapses to produce carbene in situ via the liberation of nitrogen. Then subsequent 1, 2-hydride shift affords the corresponding alkenes.



Scheme 1.16 Bamford-Stevens reaction

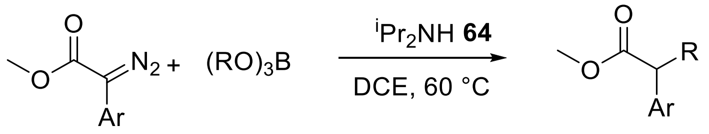
The electron-withdrawing group containing diazo compounds such as, α-diazocarbonyl compounds are generally stable, reactive, and easy to handle. They can directly react with organometallic reagents without any transition metal catalysts. One of the earliest examples of C-C bond forming reactions with alkyl or aryl borane reagents **60** has been reported by Hooz and co-workers.[36] They explored the use of diazonitrile, diazoacetate, and diazoketones **59** by treating them with bulky trialkylboranes **60** to afford the corresponding alkylation products **61** in relatively low yields (up to 52% yield) (Scheme 1.17). The scope of the protocol was further evaluated with more reactive organoboranes such as dialkylchloroboranes, alkyl, alkenyl, or aryldichloroboranes.[37]



59 **60** **61**

Scheme 1.17 Coupling of diazoketones with trialkylboranes

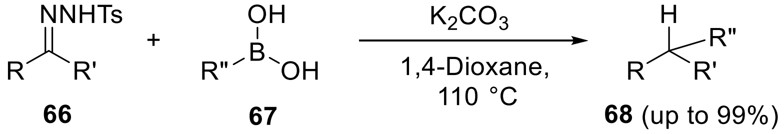
In 2009, Wang and co-workers reported the coupling reaction of α-diazocarbonyl compounds **62** with boroxines **63** in the presence of 3.0 equiv of diisopropylamine (^{i}Pr$_2$NH) **64** and DCE (1,2-dichloroethane) as solvent under transition-metal-free conditions.[38] The reaction of methyl α-diazopropionates **62** with arylboroxines **63** afforded the corresponding phenylation products **65** in good yields (up to 84%) (Scheme 1.18).



62 **63** **65** (up to 84%)

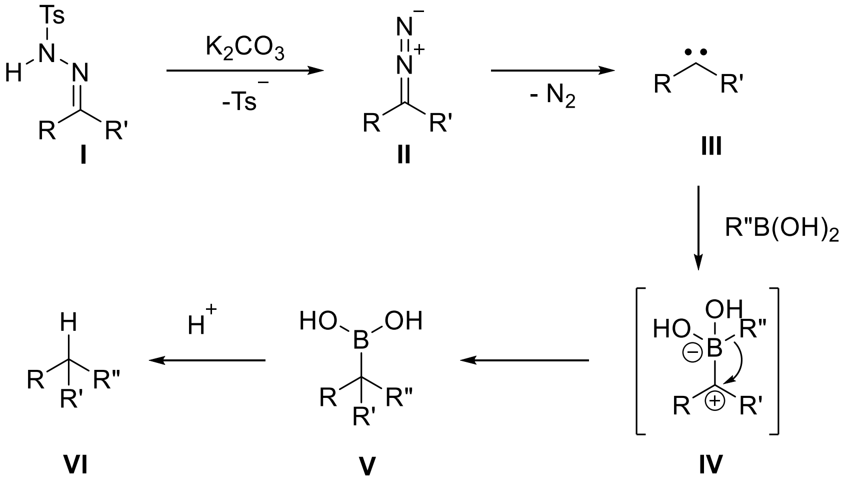
Scheme 1.18 Reactions of α-diazocarbonyl compounds with aryl and alkenyl boroxines

At the same time, Valdes and co-workers reported an efficient transition-metal-free reductive cross coupling of *N*-tosylhydrazones **66** and boronic acids **67** using K_2CO_3 (1.5 equiv) as a base in 1,4-dioxane at 110 °C to afford the corresponding alkylated/arylated products **68** in excellent yields (up to 99%) (Scheme 1.19).[39] The reaction conditions tolerated various functional-groups in both coupling partners. This C-C bond forming reaction between *N*-tosylhydrazones **66** and boronic acids **67** under transition-metal-free conditions gave an access to direct reductive arylation/alkylation of carbonyl compounds in one pot.



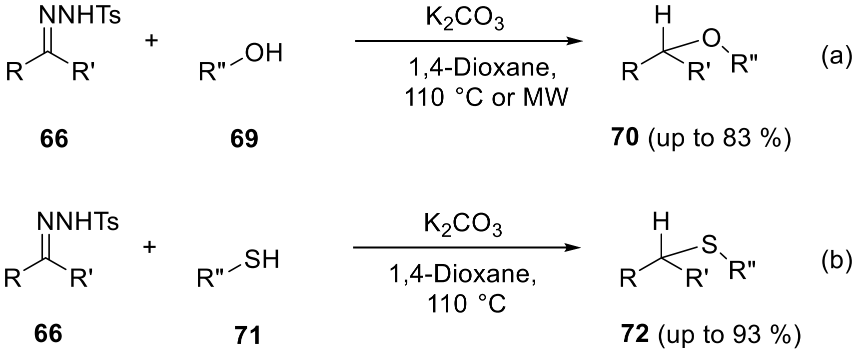
Scheme 1.19 Reductive coupling of *N*-tosylhydrazones with boronic acids

Plausible mechanism of reductive coupling is shown as, *N*-Tosylhydrazones **I** under basic conditions decomposes to afford the diazo compounds **II**, which subsequently forms a highly reactive carbene **III** by the elimination of $N_{2.}$ Further, the nucleophilic carbene intermediate **III** reacts with the boronic acid to form a zwitterionic intermediate **IV**, which further collapses to form benzyl boronic acids **V**. Finally, protodeboronation of the benzyl boronic acid **V** under basic condition leads to the final desired product **VI** (Scheme 1.20).[39]



Scheme 1.20 Plausible mechanism of reductive coupling of *N*-tosylhydrazones with boronic acids

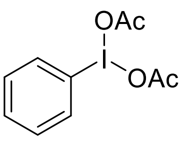
Later in 2010, the same group extended this methodology to prepare ethers **70** via the reductive coupling of *N*-tosylhydrazones **66** with phenols/alcohols **69** under transition-metal-free conditions using K_2CO_3 under conventional heating or microwave (MW) reaction conditions (up to 83 % yield, Scheme 1.21, eq a).[40] More recently, Peng and co-workers carried out the similar cross-coupling reaction of thiophenols **71** and *N*-tosylhydrazones **66** to afford the corresponding unsymmetrical benzylic thioethers **72** in moderate to good yields (up to 93 % yield, Scheme 1.21, eq b).[41]



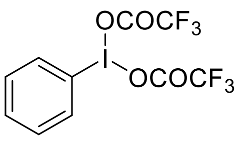
Scheme 1.21 Reductive coupling of *N*-tosylhydrazones with phenols, alcohols and thiophenols

1.6 Transition-metal-free oxidizing reagents

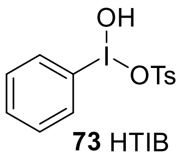
Hypervalent iodine reagents, peroxy reagents, persulfate reagents are the very important class of oxidants and these reagents have recently attracted much attention, and are widely used in modern organic synthesis.[42] In recent decades, trivalent iodine reagents, such as phenyliodine (III) diacetate (PIDA) **54**, phenyliodine(III)bis(trifluoroacetate) (PIFA) **26**, [hydroxy(tosyloxy)iodo] benzene **73** (HTIB, also named as Koser's reagent), Dess-Martin periodinane (DMP) **74**, 2-iodoxybenzoic acid (IBX) **75** and iodosobenzene **76** have exhibited unique reactivity in many synthetic transformations (Figure 1.1). These hyperiodine reagents have exhibited similar or even better oxidative ability than those of traditional high-oxidative-state heavy metals, such as Pb(IV)-, Hg(II)-, Os(IV)-, and Tl(III)-based oxidative reagents. Additionally, due to their low toxicity, high stability, easy handling, and commercial availability, hyperiodine reagents are served as useful synthetic oxidants in organic synthesis.



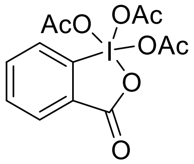
54 PIDA



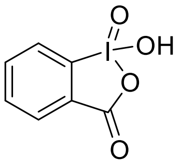
26 PIFA



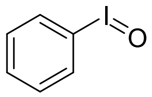
73 HTIB
Koser's reagent



74 DMP



75 IBX

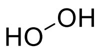


76 Iodosobenzene

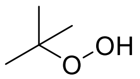
Figure 1.1 Hypervalent iodine reagents

O_2

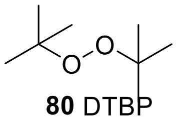
77



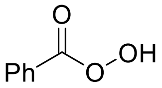
78



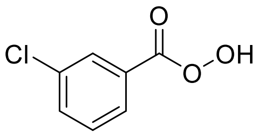
79 TBHP



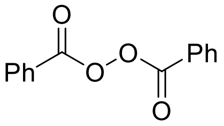
80 DTBP



81 Perbenzoic acid



82 mCPBA



83 Dibenzoyl peroxide

Figure 1.2 Peroxy reagents

$(NH_4)_2S_2O_8$

84 Ammonium Persulfate

$Na_2S_2O_8$

85 Sodium Persulfate

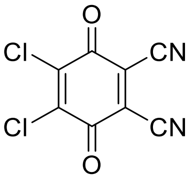
$K_2S_2O_8$

86 Potassium Persulfate

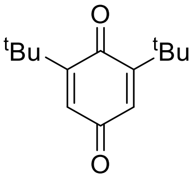
$KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5K_2SO_4$

87 Oxone

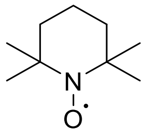
Figure 1.3 Persulfate reagents



88 DDQ



89 DTBQ



90 TEMPO

Figure 1.4 Other common oxidants

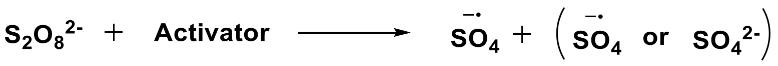
Similarly, various peroxy reagents, such as O_2, H_2O_2, TBHP, DTBP, *m*CPBA, *etc*. **77-83** (Figure 1.2); persulfate reagents like $NH_4S_2O_8$, $K_2S_2O_8$, $Na_2S_2O_8$, oxone **84-87** (Figure 1.3) and some other reagents like DDQ, DTBQ, TEMPO, *etc*. **88-90** (Figure 1.4) have been explored in various organic transformations.

Persulfate reagents are easily available and less expensive. In the subsequent chapters we have explored the use of potassium persulfate for the novel and useful protocols. In this regard, some of the selected methods based on persulfates and its reactivity have been described in brief.

1.7 Introduction to persulfates

Persulfates are commercially available, comparatively less expensive and less toxic. Persulfate anion easily splits into very reactive sulfate anion radical ($SO_4^{-\bullet}$) at room temperature. Persulfates afford water-soluble salts as by-products. Sulfate anion radical ($SO_4^{-\bullet}$) is known for its efficient oxidative properties and has been explored for the degradation of environmental pollutants and due to its strong electron-accepting ability, sulfate anion radical ($SO_4^{-\bullet}$) has been efficiently utilized to destroy soil carbon pollutants. In this regard, the persulfate chemistry has been considered as environmentally friendly and benign. Over the past several years, the persulfate reagents have been employed in various fields such as oxidation, polymerization, gas and oil production, cosmetics, soil stabilization and synthetic organic chemistry.[43] Among many persulfate sources, potassium persulfate ($K_2S_2O_8$) has been proved to be one of the very selective and reactive reagents.[44] As the reagent is also water soluble, reactions can be developed in water as solvent.

The persulfate reagents can be activated by various means to generate highly reactive and useful sulfate anion radical ($SO_4^{-\bullet}$) in situ, that can be used in various organic transformations. Persulfate sources such as $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$ have been utilized in variety of reactions and they can be activated via heat, transition metals, ultraviolet (UV) light, to generate highly reactive sulfate anion radical (Scheme 1.22).[45]



$$S_2O_8^{2-} + \text{Activator} \longrightarrow \overset{-\bullet}{SO_4} + \left(\overset{-\bullet}{SO_4} \text{ or } SO_4^{2-}\right)$$

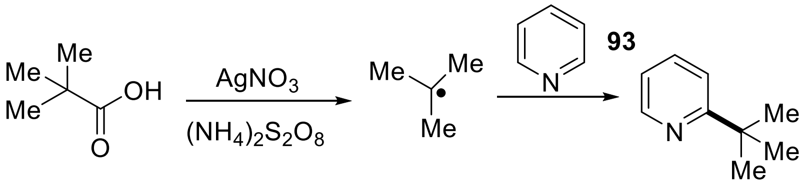
Activator = heat, transition metals, light

Scheme 1.22 Persulfate activation

Although the oxidation potential of $SO_4^{-\bullet}$ is 2.6 eV, the reactivity between organic compounds and $SO_4^{-\bullet}$ is considered to be slow, via a single electron transfer mechanism.[44a,46] Thus, sulfate anion radical can react with alcohols, ethers and hydrocarbons through single electron or hydrogen (H) transfer mechanism. The oxidizing ability of persulfate has been explored in the synthesis of aldehydes, ketones, carboxylic acids, quinones, and a variety of other compounds. Persulfate-based oxidants are potentially attractive alternatives to other oxidants in organic transformations.

1.8 Persulfates in organic transformations under transition-metal-free condition

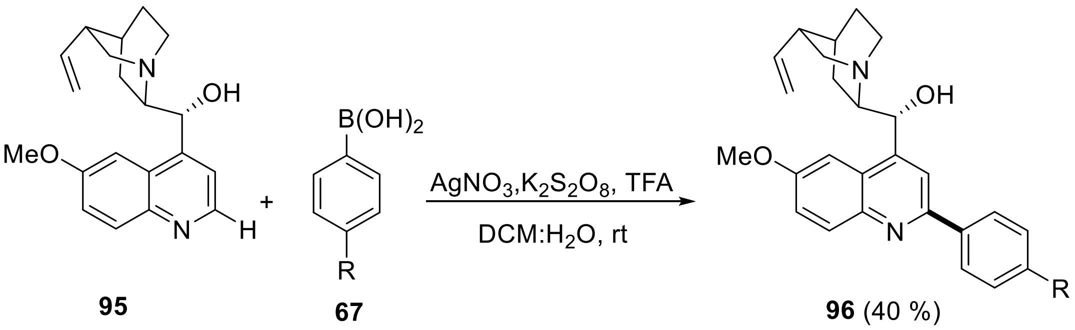
In transition-metal-catalyzed C-H bond functionalization, persulfates have been used to oxidize metals to regenerate them into their original oxidation state for next catalytic cycle.[47] In 1971, F. Minisci found that Ag catalysts are crucial to activate persulfate anion ($S_2O_8^{-2}$) (Scheme 1.23).[48a] In this reaction, $(NH_4)_2S_2O_8$ was used as a source for $SO_4^{-\bullet}$ to generate alkyl radicals **92** from the corresponding carboxylic acids **91** via decarboxylation. In the next couple of years, Minisci's reaction conditions led to the development of several versatile methods for the synthesis of small as well as complex organic molecules.[48b-g]



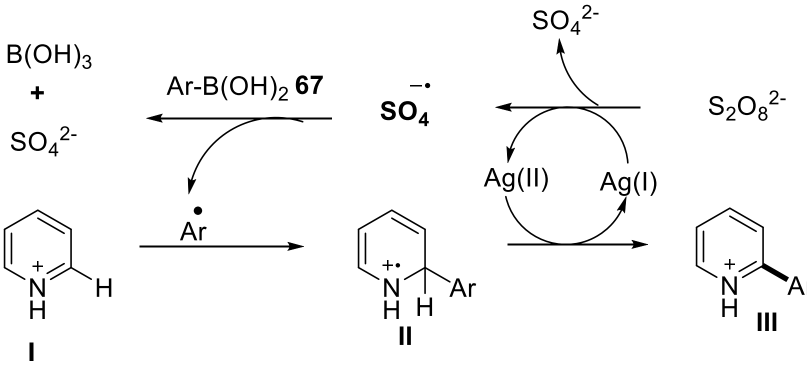
91 **92** **94** (up to 87 %)

Scheme 1.23 Radical addition to heteroaromatics

Recently, Baran and co-workers reported silver(I)-catalyzed addition of aryl boronic acids **67** to various aromatic nitrogen heterocycles including complex molecules such as quinine **95** in 40% yield using $K_2S_2O_8$ following a radical pathway (Scheme 1.24 and Scheme 1.25).[49]

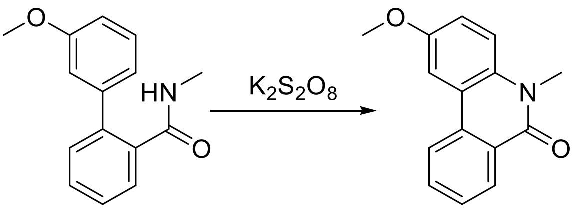


Scheme 1.24 Arylation of quinine with aryl boronic acids



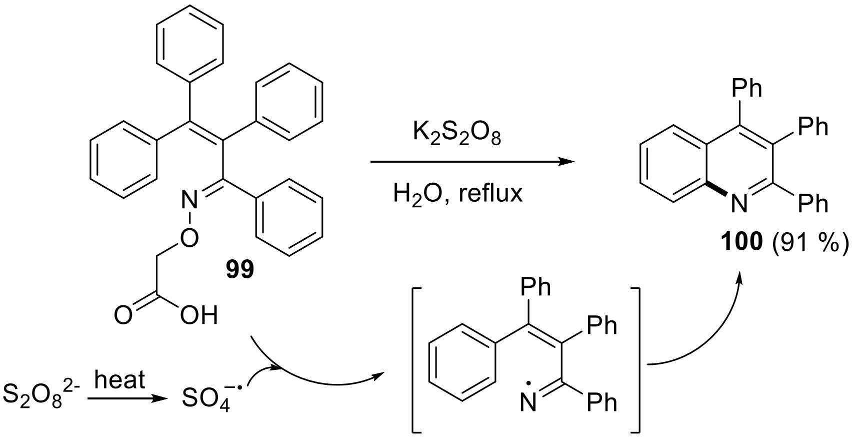
Scheme 1.25: Proposed reaction mechanism

In 1972, Perkins and co-workers developed the synthesis of phenanthridinones **98** by the cyclization of *N*-methylbiphenyl-2-carboxamides **97** *via* the formation of nitrogen centered radical intermediate leading to C-N bond formation in presence of $K_2S_2O_8$ (Scheme 1.26).[50]


97 **98** (73 %)

Scheme 1.26 Phenanthridinone synthesis via C-N bond formation

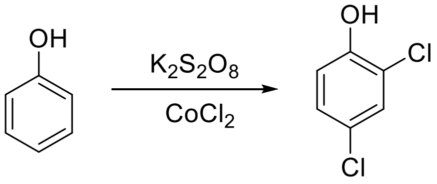
In 1979, Forrester et al. reported the synthesis of quinolines **100** from *o*-hydroxy carbonyl methyl oximes **99** in the presence of $K_2S_2O_8$ in water at refluxing conditions. In this reaction temperature was used as a source to activate the $K_2S_2O_8$ to produce $SO_4^{-\bullet}$. The reaction proceeds via the nitrogen centered radical **101** to afford the quinolines **100** in very good yields (up to 91%) (Scheme 1.27).[51]



99 **100** (91 %) **101**

Scheme 1.27 Homolytic cleavage of N-O bond by persulfate

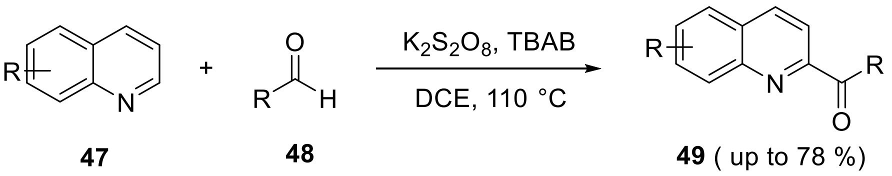
In 2006, Gonzalez and co-workers developed a method for chlorination of phenol **69a** using $CoCl_2$ as chlorinating agent in the presence of potassium persulfate to afford the corresponding chorophenols **102** in very good yields (up to 93%) (Scheme 1.28).[52]



69a **102** (93 %)

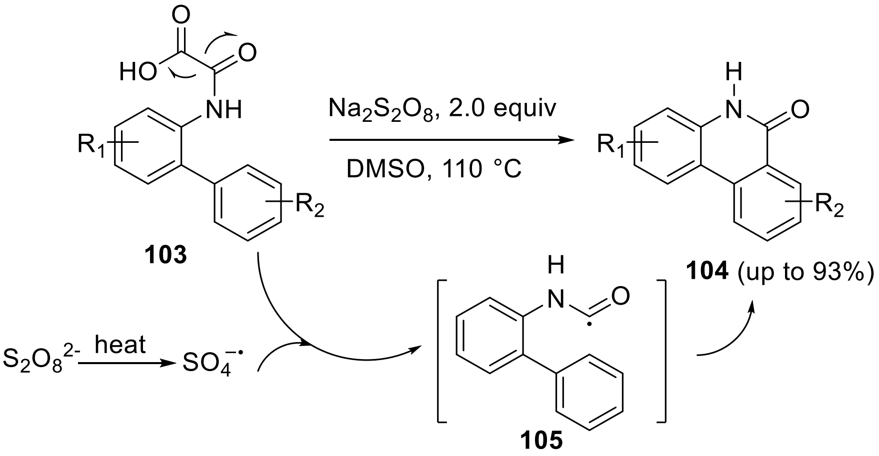
Scheme 1.28 Chlorination of phenol

The transition-metal-free acylation of quinolines **47** (also isoquinoline and quinoxaline derivatives) has been developed by Prabhu and co-workers *via* cross dehydrogenative coupling (CDC) reaction with aldehydes **48** and quinolines **47** in presence of TBAB (tetrabutylammonium bromide, 30 mol%) and $K_2S_2O_8$ as an oxidant to afford the corresponding quinoline derivatives **49** in good yields (up to 78%) (Scheme 1.29).[53] They developed the transition-metal-free version of Minisci reaction and this intermolecular acylation of electron-deficient heteroarenes provides an easy access to heterocyclic compounds **49**.



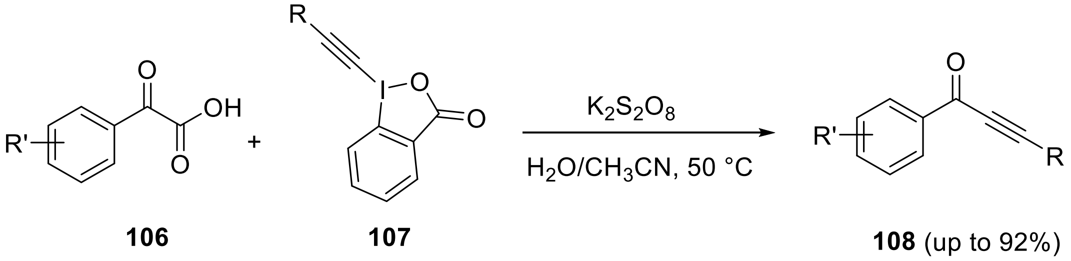
Scheme 1.29 Acylation of electron-deficient heteroarenes

Yuan et. al developed $Na_2S_2O_8$ promoted decarboxylative intramolecular cyclization of biaryl-2-oxamic acid **103** for the synthesis of phenanthridinones **104** in excellent yields (up to 93%) (Scheme 1.30).[54] This is the first example of intramolecular decarboxylative amidation of unactivated arenes under transition-metal-free conditions. This reaction is believed to undergo *via* carbamoyl radical **105** intermediate.



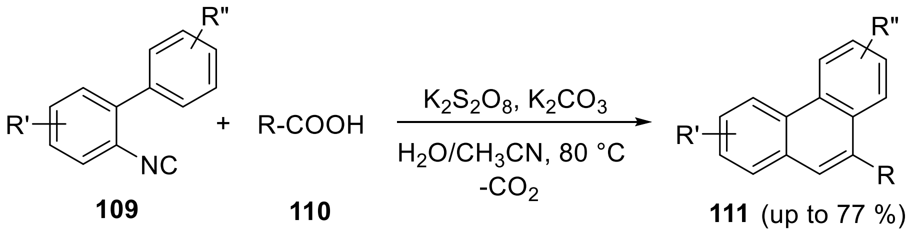
Scheme 1.30 Synthesis of phenanthridinones

Xu and co-workers developed a transition-metal-free synthetic method for the various ynones **108** *via* the decarboxylative alkynylation of α-keto acids **106** using 1-[(triisopropylsilyl)- ethynyl]-1,2-benziodoxol-3(1H)-one **107** in the presence of $K_2S_2O_8$ (Scheme 1.31).[55] The method gives access to ynones **108** under mild reaction conditions and exhibited the remarkable functional group tolerance.



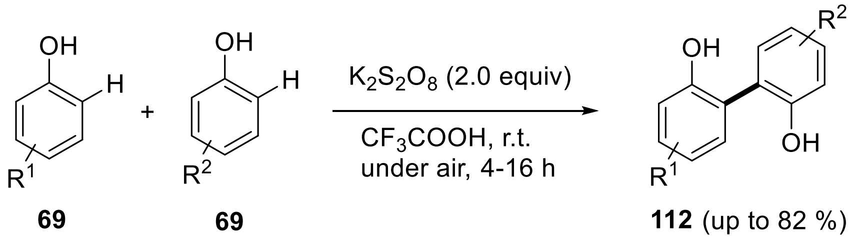
Scheme 1.31 Synthesis of ynones

Zhou and co-workers reported a radical cascade decarboxylation/cyclization of 2-isocyanobiphenyls **109** with aliphatic carboxylic acids as well as aromatic carboxylic acids **110** using $K_2S_2O_8$ under the transition-metal-free conditions (Scheme 1.32).[56] The protocol affords two new C−C bonds under decarboxylation conditions and the method proved to be environmentally friendly to afford 6-alkyl/aryl phenanthridines **111** in moderate to good yields (up to 77 %).



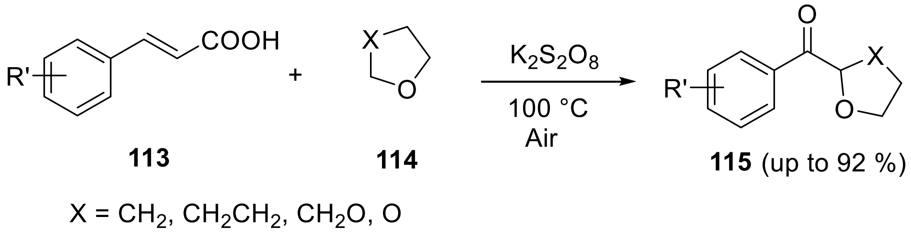
Scheme 1.32 Synthesis of phenanthridines

More et al. developed an efficient oxidative cross-coupling of two different phenols **69** in the presence of $K_2S_2O_8$ and $Bu_4N^+ \cdot HSO_3^-$ (10 mol %) in CF_3COOH at ambient conditions to afford the corresponding unsymmetrical biphenols **112** in good yields (up to 82 %, Scheme 1.33).[57] The cross-coupling of substituted phenols with naphthols (1:1 ratio) and cross-coupling of naphthols with phenol (1:2 ratio) have been explored.



Scheme 1.33 Synthesis of unsymmetrical biphenols

Guo and co-workers developed $K_2S_2O_8$ promoted decarboxylative cross coupling of *α,β*-unsaturated carboxylic acids **113** with cyclic ethers **114** under aerobic conditions to afford the corresponding *α*-oxyalkyl ketones **115** in good yields (up to 92 % Scheme 1.34).[58] The protocol disclosed C–C and C-O bond formation in one step through addition, oxidation, and decarboxylation processes leading to the desired α-oxyalkyl ketones products.



Scheme 1.34 Synthesis of α-oxyalkyl ketones

1.9 Aim and rationale of thesis work

In the past decade, oxidative C-H functionalization to form new C-C, C-N, and C-S bonds has emerged as an elegant and robust synthetic method for accessing useful products, featuring atom economy and straightforwardness. Also oxidative decarboxylative C-C bond cleavage strategies to form new C-C, C-N, C-S and C-O bonds have been developed. However, many of these methods are based on transition metal catalysis, thus relatively increasing the cost and toxicity of the reactions. As an alternative, transition-metal-free versions have become very important for avoiding more expenditure and environmental issues.

$K_2S_2O_8$ is a cheap, environmentally friendly powerful oxidant and has been found useful for C-C, C-N, C-S and C-O bond cleavage. In all these oxidative processes role of sulfate anion radical ($SO_4^{-\bullet}$) is very important. It is one electron oxidant and also sulfate anion radical ($SO_4^{-\bullet}$) is frequently used as an oxidant for the degradation of environmental and soil carbon pollutants and it has been widely used as a radical initiator in a number of industrial applications. The sulfate anion radical can be generated easily from persulfate sources such as $K_2S_2O_8$, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ at room temperature without having any external reagents or sources. In this regard, it is a challenge and demanding to develop novel transition-metal-free synthetic protocols using less expensive and environmentally friendly reagents such as persulfates.

1.10 Conclusions

Transition-metal-free reactions are environmentally benign and thus nowadays gaining importance for many transformations. $K_2S_2O_8$ has been extensively utilized in many reactions as an efficient and useful reagent. $K_2S_2O_8$ can also be explored in many useful transformations as an alternative for transition metal reagent to access synthetic scaffolds. We became interested in exploring novel use of $K_2S_2O_8$ and other transition-metal-free reagents in synthetic transformations to access useful and important compounds. $K_2S_2O_8$ is also commercially available, less expensive and environmentally benign reagent. In the subsequent chapters we have discussed the novel transition-metal-free protocols in detail.

1.11 References

1. For reviews and books on transition-metal-catalyzed reactions, please see:

   (a) Masel RI. *Chemical Kinetics and Catalysis*; Wiley Interscience: New York, 2001;

   (b) Behr A. *Organometallic Compounds and Homogeneous Catalysis: Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2002;

   (c) Elschenbroich C. *Organometallics*; Wiley-VCH: Weinheim, 2006.

2. For reviews and books on transition-metal-catalyzed coupling reactions, please see:

   (a) Diederich F, Stang PJ. *Metal-Catalyzed Cross-Coupling Reactions*; Eds.; Wiley-VCH: Weinheim, 1998;

   (b) Brase S, de Meijere A. de Meijere A, Diederich F. *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*; Eds.; Wiley-VCH: Weinheim, 2004;

   (c) Dyker G. *Handbook of C-H Transformations: Applications in Organic Synthesis*; Ed.; Wiley-VCH: Weinheim, 2005.

3. For reviews and books on applications of transition-metal-catalyzed coupling reactions in organic synthesis, please see:

   (a) Boudier A, Bromm LO. Lotz M, Knochel P. *Angew Chem Int Ed*. 2000;39:4414.

   (b) Eisenstadt A, Ager DJ, Sheldon RA, van Bekkum H. *In Fine Chemicals through Heterogeneous Catalysis*; Eds.; Wiley-VCH: Weinheim, 2001;

   (c) Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem Int Ed*. 2005;44:4442;

   (d) Corbet J-P, Mignani G. *Chem Rev*. 2006;106:2651;

   (e) Magano J, Dunetz JR. *Chem Rev*. 2011;111:2177;

   (f) Crawley ML, Trost BM, Shen HC. *Selected Applications of Transition-Metal-Catalyzed Carbon-Carbon Cross-Coupling Reactions in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, 2012.

4. (a) Miyaura N, Suzuki A. *Chem Commun*. 1979;866;

   (b) Suzuki A. *Acc Chem Res*. 1982;15:178;

   (c) Suzuki A. *Pure Appl Chem*. 1991;63:419.

   (d) Martin R, Yang Y, *Acta Chem Scand*. 1993;4:221;

   (e) Miyaura N, Suzuki A. *Chem Rev*. 1995;95:2457,

   (f) Suzuki A. *J Organomet Chem*. 1999;576:147;

   (g) Molander GA, Ellis N. *Acc Chem Res*. 2007;40:275;

   (h) Molander GA, Canturk B. *Angew Chem Int Ed*. 2009;48:9240.

5. (a) Milstein D, Stille J. *J Am Chem Soc*. 1978;100:3636;

   (b) Stille J. *Angew Chem Int Ed*. 1986;25:508;

(c) Pereyre M, Boston MA, ed *Tin in Organic Synthesis*; Butterworths: 1987;185-207.
(d) Mitchell T. *Synthesis* 1992;803,
(e) Farina V, Krishnamurthy V, Scott WJ. *Org React*. 1997;50:1;
(f) Gallager W, Terstiege I, Malecka RE, Jr. *J Am Chem Soc*. 2001;123:3194.

6. (a) Tamao K. Trost B. ed *Comprehensive Organic Synthesis*; Ed.; Permagon: Oxford, 1991;3:435-480;
(b) Terao J, Kambe N. *Acc Chem Res*. 2008;41:1545;
(c) Knappke CEI, von Wangelin AJ. *Chem Soc Rev* 2011;40:4948.

7. (a) Beak P, Basu A, Gallagher DJ, Park YS, Thayumanavan S. *Acc Chem Soc*. 1996;29:552;
(b) Hoppe D, Hense T. *Angew Chem Int Ed*. 1997;36:2282;
(c) Clayden J. *Organolithiums: Selectivity for Synthesis;* Pergamon: New York, 2002;
(d) Hogson DM. *Organolithiums in Enantioselective Synthesis*; *Ed.; Topics in Organometallic Chemistry*; Springer: New York, 2003; Vol. 5.

8. (a) Negishi E, King A, Okukado N. *J Org Chem*. 1977;42:1821;
(b) Negishi E, *Acc Chem Res*. 1982;15:340;
(c) Knochel P, Singer R. *Chem Rev*. 1993;93:2117;
(d) Knochel P, Langer F, Longeau A, Rottlander M, Studemann T. *Chem. Ber*. 1997;130:1021;
(e) Erdik E. *Tetrahedron* 1998;46:9577;
(f) Knochel P, Dohle W, Gommermann N, Kneisel FF, Kopp F, Korn T, Sapountzis I, Vu VA. *Angew Chem Int Ed*. 2003:42:4302;
(g) Phapale VB, Cardenas DJ. *Chem Soc Rev*. 2009;38:1598.

9. (a) Hatanaka Y, Hiyama T. *Synlett* 1991;845;
(b) Hiyama T, Hatanaka Y. *Pure Appl Chem*. 1994;66:1471;
(c) Hiyama T, Diederich F, Stang J. *In Metal-Catalyzed Cross-Coupling Reactions*;., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10, pp 421-454;
(d) Demnark SE, Sweis RF. *Acc Chem Res*. 2002:35:835;
(e) Denmark SE, Regens CS. *Acc Chem Res*. 2008;41:1486;
(f) Sore HF, Galloway WRJD, Spring DR. *Chem Soc Rev*. 2012;41:1845.

10. (a) Heck RF, Nolley JP, Jr. *J Org Chem*. 1972;37:2320;
(b) Heck RF. *Org React*. 1982;27:345;
(c) de Meijere A, Meyer FE. *Angew Chem Int Ed*. 1994;33:2379;
(d) Cabri W, Candiani I. *Acc Chem Res*. 1995;28:2;

(e) Crisp GT. *Chem Soc Rev*. 1998;27:427;

(f) Amatore C, Jutand A. *Acc Chem Res*. 2000;33:314;

(g) Alonso F, Beletskaya I, Yus M. *Tetrahedron* 2005;61:11771.

11. (a) Negishi Ei. *Angew Chem Int Ed*. 2011;50:6738;

    (b) Suzuki A. *Angew Chem Int Ed* 2011;50:6722;

    (c) Seechurn CCCJ, Kitching MO, Colacot TJ, Snieckus V. *Angew Chem Int Ed*. 2012;51:5062.

12. For the prices of various transition metals, please see the following website: www.metalprices.com.

13. (a) Nair D, Scarpello J, White L, Freista dos Santos L, Vankelecom I, Livingston A. *Tetrahedron Lett*. 2001;42:8219;

    (b) *The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products*; London, 2002;

    (c) Rivera-Utrilla J, Bautista-Toledo I, Ferro-Garcia M, Moreno-Catilla C. *Carbon* 2003;41:323;

    (d) Garett C, Prasad K. *Adv Synth Catal*. 2004;346:889.

14. (a) Gansauer A, Bluhm H. *Chem Rev*. 2000;100:2771;

    (b) Shibasaki M, Yamamoto Y. *Multimetallic Catalysts in Organic Synthesis*; Eds; Wiley-VCH: Weinheim, 2004;

    (c) Wang C, Xi Z. *Chem Soc Rev*. 2007;36:1395;

    (d) Oxgaard J, Tenn WJ, III, Nielsen RJ, Periana RA, Goddard WA, III. *Organometallics* 2007;26:1565

    (e) Boutadla Y, Davies DL, Macgregor SA, *Poblador-Bahamonde AI*. *Dalton Trans*. 2009;5887;

    (f) Boutadla Y, Davies DL, Macgregor SA, *Poblador-Bahamonde AI*. *Dalton Trans*. 2009;5820;

    (g) Lapointe D, Fagnou K. *Chem Lett*. 2010;39:1118;

    (h) Ackermann L. *Chem Rev*. 2011;111:1315.

15. For reviews on green chemistry, see:

    (a) Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998;

    (b) Li C-J, Trost BM. *Proc Natl Acad Sci. USA*. 2008;105:13197;

    (c) Dunn PJ. *Chem Soc Rev*. 2012;41:1452.

16. Sun C-L, Shi Z-J. *Chem Rev*. 2014;114;9219−9280.
17. Kita Y, Tohma H, Hatanaka K, Takada T, Fujita S, Mitoh S, Sakurai H, Oka S. *J Am Chem Soc*. 1994;116:3684.
18. Fritz HP, Gebauer HZ, Naturforsch BJ. *Chem Sci*. 1978;338:702.
19. Dohi T, Ito M, Morimoto K, Minamitsuji Y, Takenaga N, Kita Y. *Chem Commun*. 2007;4152.
20. (a) Kleemann A, Engel J, Kutscher B, Reichert D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001;
    (b) Korostova SE, Mikhaleva AI, Trofimov BA. *Russ Chem Rev*. 1999;68:459;
    (c) Gale PA, Anzenbacher P, Jr. Sessler JL. *Chem. Rev*. 2001;222:57;
    (d) Sessler JL, Seidel D. *Angew Chem Int Ed*. 2003;42:5134.
21. (a) Rapoport H, Castagnoli N, Jr. *J Am Chem Soc*. 1962;84:2178;
    (b) Bordner J, Rapoport H. *J Org Chem*. 1965;30:3824;
    (c) Brown D, Griffiths D, Rider ME, Smith RC. *J Chem Soc Perkin Trans 1*. 1986;455;
    (d) Vogel E, Balci M, Kakumanu P, Kogh P, Lex J, Ermer O. *Angew Chem Int Ed.* 1987;26:928;
    (e) Sessler JL, Cyr MJ, Lynch V, McGhee E, Ibers JA. *J Am Chem Soc*. 1990;112:2810;
    (f) D’Alesssion R, Rossi A. *Synlett* 1996;513;
    (g) Skowronek P, Lightner DA. *Monatsh. Chem*. 2003;134:889;
    (h) Yu M, Pantos GD, Sessler JL, Pagenkopf BL. *Org Lett*. 2004;6:1057;
    (i) Fürstner A, Radkowski K, Peters H. *Angew Chem Int Ed*. 2005;44;2777, and references therein.
22. (a) Tohma H, Morioka H, Takizawa S, Arisawa M, Kita Y. *Tetrahedron* 2001;57:345;
    (b) Tohma H, Iwata M, Maegawa T, Kita Y. *Tetrahedron Lett*. 2002;8:5377.
23. Dohi T, Ito M, Morimoto K, Iwata M, Kita Y. *Angew Chem Int Ed*. 2008;47:1301
24. (a) Kita Y, Gyoten M, Ohtsubo M, Tohma H, Takada T. *Chem Commun*. 1996;1481;
    (b) Takada T, Arisawa M, Gyoten M, Hamada R, Tohma H, Kita Y. *J Org Chem*. 1998;63:7698.
25. Yanagisawa S, Ueda K, Taniguchi T, Itami K. *Org Lett*. 2008;10;4673.
26. Sun C-L, Li H, Yu D-G, Yu M, Zhou X, Lu X-Y, Huang K, Zheng S-F, Li B-J, Shi Z-J. *Nat Chem*. 2010;2:1044.

27. Shirakawa E, Itoh K, Higashino T, Hayashi T. *J Am Chem Soc*. 2010;132:15537.
28. Liu W, Cao H, Zhang H, Zhang H, Chung KH, He C, Wang H, Kwong FY, Lei A. *J Am Chem Soc*. 2010;132:16737.
29. Matcha K, Antonchick AP. *Angew Chem Int Ed*. 2013 ;52:2082.
30. Burgmann L, Antonchick AP. *Angew Chem Int Ed*. 2013;52:3267.
31. (a) Kirsch P, *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004;
    (b) Hird M, *Chem Soc Rev*. 2007;36:2070;
    (c) Kirk KL. *Org Process Res Dev*. 2008;12:305;
    (d) Furuya T, Kamlet AS, Ritter T. *Nature* 2011;473:470;
    (e) Tomashenko OA, Grushin VV. *Chem Rev*. 2011;111:4475;
    (f) Besset T, Schneider C, Cahard D. *Angew Chem Int Ed*. 2012;51:5048;
    (g) Pan F, Shi Z. *Acta Chim Sinica* 2012;70:1679;
    (h) Qing F-L, *Chin J Org Chem*. 2012;32:815;
    (i) Lü C, Shen Q, Liu D. *Chin J Org Chem*. 2012;32:1380;
    (j) Wu XF, Neumann H, Beller M. *Chem-Asian J*. 2012;7:1744;
    (k) Studer A. *Angew Chem Int Ed*. 2012;51:8950;
    (l) Ye Y, Sanford S. *Synlett* 2012;2005.
32. Wua X, Chu L, Qing F-L. *Tetrahedron Lett*. 2013;54:249.
33. Yang Y-D, Iwamoto K, Tokunaga E, Shibata N. *Chem Commun*. 2013;49:5510.
34. Bamford WR, Stevens TS. *J Chem Soc*. 1952;4735.
35. (a) Shapiro RH, Lipton MF, Kolonko KJ, Buswell RL, Capuano LA. *Tetrahedron Lett*. 1975;16:1811
    (b) Adlington RM, Barret AGM. *Acc Chem Res*. 1983;16:55.
36. (a) Hooz J, Linke S. *J Am Chem Soc*. 1968;90:5936;
    (b) Hooz J, Linke S. *J Am Chem Soc*. 1968;90:6891;
    (c) Hooz J, Morrison GF. *Can J Chem*. 1970;48:868;
    (d) Hooz J, Gunn DM. *J Chem Soc Chem. Commun*. 1969;139;
    (e) Hooz J, Gunn DM. *Tetrahedron Lett*. 1969;3455;
    (f) Hooz J, Gunn DM. *J Am Chem Soc*. 1969;91:6195.
37. (a) Brown HC, Midland MM, Levy AB. *J Am Chem Soc*. 1972;94:3662;
    (b) Hooz, J, Bridson JN, Calzada JG, Brown HC, Midland MM, Levy AB. *J Org Chem*. 1973;38:2574.
38. Peng C, Zhang W, Yan G, Wang J. *Org Lett*. 2009;11:1667.
39. Barluenga J, Tomas-Gamasa M, Aznar F, Valdes C. *Nat Chem*. 2009;1:433.

40. Barlueng J, Tomas-Gamasa M, Aznar F, Valdes C. *Angew Chem Int Ed*. 2010;49:4993.
41. Ding Q, Cao B, Yuan J, Liu X, Peng Y. *Org Biomol Chem*. 2011;9:748.
42. For recent reviews and books on hypervalent iodine chemistry, please see:
    (a) Varvoglis A. *Tetrahedron* 1997;53:1179;
    (b) Varvoglis A. *Hypervalent Iodine in Organic Synthesis*; Academic: San Diego, 1997;
    (c) Kitamura T, Fujiwara Y. *Org Prep Proced Int*. 1997;29:409.
    (d) Kirschning A. *Eur J Org Chem*. 1998;11:2267;
    (e) Ochiai M. *In Chemistry of Hypervalent Compounds*; Akiba K. Ed.; Wiley-VCH: New York, NY, 1999; Chapter 12;
    (f) Zhdankin VV, Stang PJ. Chem Rev. 2002;102:2523;
    (g) Wirth T, Ochiai M, Zhdankin VV, Koser GF, Tohma H, Kita Y. *Topics in Current Chemistry:Hypervalent Iodine Chemistry-Modern Developments in Organic Synthesis*; Springer: Berlin, 2003;
    (h) Tohma H, Kita Y. *Adv Synth Catal*. 2004;346:111;
    (i) Moriarty RM. *J Org Chem*. 2005;70:2893;
    (j) Wirth T. *Angew Chem Int Ed*. 2005;44:3656;
    (k) Zhdankin VV; Stang PJ. *Chem Rev*. 2008;108:5299;
    (l) Ochiai M. *Synlett* 2009:159;
    (m) Dohi T, Kita Y. *Chem Commun.* 2009:2073;
    (n) Stang PJ, Zhdankin VV. *Chem Rev*. 1996;96:1123.
43. Ahmad M. Persulfate activation by major soil minerals. Ph.D. Thesis, Department of Civil and Environmental Engineering,Washington State University, August 2009.
44. (a) Devariab S, Shah BA. *Chem Commun.* 2016;52:1490;
    (b) Forrester AR, Gill M, Sadd JS, Thomson RH. *J Chem Soc Perkin Trans. I*, 1979;612;
    (c) Lee M, Sanford MS. *Org Lett.* 2017;19:572.
45. (a) He X, Mezyk SP, Michael I, Fatta-Kassinos D, Dionysiou DD. *J Hazard Mater*. 2014;279:375-383;
    (b) Zhao L, Hou H, Fujii A, Hosomi M, Li FS. *Environ Sci Pollut R*. 2014;21:7457-7465;

(c) Zhang BT, Zhang Y, Teng YH, Fan MH. *Crit Rev Env Sci Tec*. 2015;45:1756 - 1800.

46. Zhang Y, Teuscher KB, Ji H. *Chem Sci*. 2016;7:2111.
47. (a) Dick AR, Kampf JW, Sanford MS. *J Am Chem Soc.* 2005;127:12790;

    (b) Sun CL, Liu J, Wang Y, Zhou X, Li BJ, Shi ZJ. *Synlett* 2011;883;

    (c) Padala k, Jeganmohan M. *Chem Commun*. 2013;49:9651;

    (d) Padala K, Jeganmohan M. *Chem Eur J*. 2014;20:4092;

    (e) Raghuvanshi K, Zell D, Ackermann L. *Org Lett*. 2017;1278;

    (f) Laha JK, Patel KV, Sharma S. *ACS Omega*. 2017;2:3806;

    (g) Xie Z, Cai Y, Hu H, Lin C, Jiang J, Chen Z, Wang L, Pan Y. *Org Lett*. 2013;15:4600;

    (h) Jin J, MacMillan DWC. *Angew Chem Int Ed*. 2015;54:1565.
48. (a) Minisci F, Bernardi R, Bertini F, Galli R, Perchinummo M. *Tetrahedron* 1971;27:3575;

    (b) Minisci F, Vismara V, Fontana F, Morini G, Serravalle M, Giordano C. *J Org Chem.* 1986;51:4411;

    (c) Deb A, Manna S, Modak A, Patra T, Maity S, Maiti D. *Angew Chem Int Ed.* 2013;52:9747;

    (d) For selected reviews on the Minisci reaction, see: Duncton MA. *J Med Chem Commun*. 2011;2:1135;

    (e) Minisci F, Vismara E, Fontana F. *Heterocycles* 1989;28:489;

    (f) Minisci F, Fontana F, Vismara E. *J Heterocycl Chem.* 1990;27:79;

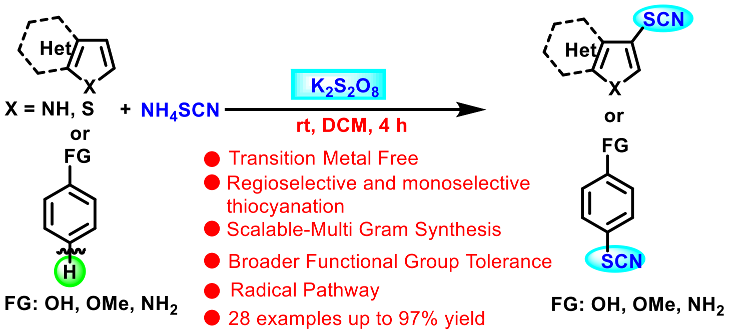
    (g) Harrowven DC, Sutton B. *J Prog Heterocycl Chem.* 2004;16:27.
49. Seiple IB, Su S, Rodriguez RA, Gianatassio R, FujiwaraY, Sobel AL, Baran PS. *J Am Chem Soc.* 2005;132:13194.
50. Hey DH, Jones GH, Perkin MJ. *J C S Perkin I*. 1972;118.
51. Forrester AR, Gill M, Sadd JS, Thomson RH, *J Chem Soc Perkin Trans. I*. 1979;612.
52. Anipsitakis GP, Gonzalez MA. *Environ Sci Technol* 2006;40:1000.
53. SiddarajuY, Lamani M, Prabhu KR. *J Org Chem*. 2014;79:3856.
54. Yuan M, Chen L, Wang JW, Chen SJ, Wang KC, Xue YB, Yao GM, Luo ZW, Zhan YH. *Org Lett*. 2015;17:346.
55. Wang P-F, Feng Y-S, Cheng Z-F, Wu Q-M, Wang G-Y, Liu L-L, Dai J-J, Xu J, Xu H-J. *J Org Chem*. 2015;80:9314.
56. Lu S, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336.

57. More NY, Jeganmohan M. *Org Lett*. 2015;17:3042.

58. Ji P, Liu Y, Xu J, Luo W, Liu Q, Guo C. *J Org Chem*. 2017;82;2965.

Chapter 2

Transition-Metal-Free Regioselective Thiocyanation of Phenols, Anilines and Heterocycles



Transition-Metal-Free Regioselective Thiocyanation of Phenols, Anilines and Heterocycles

2

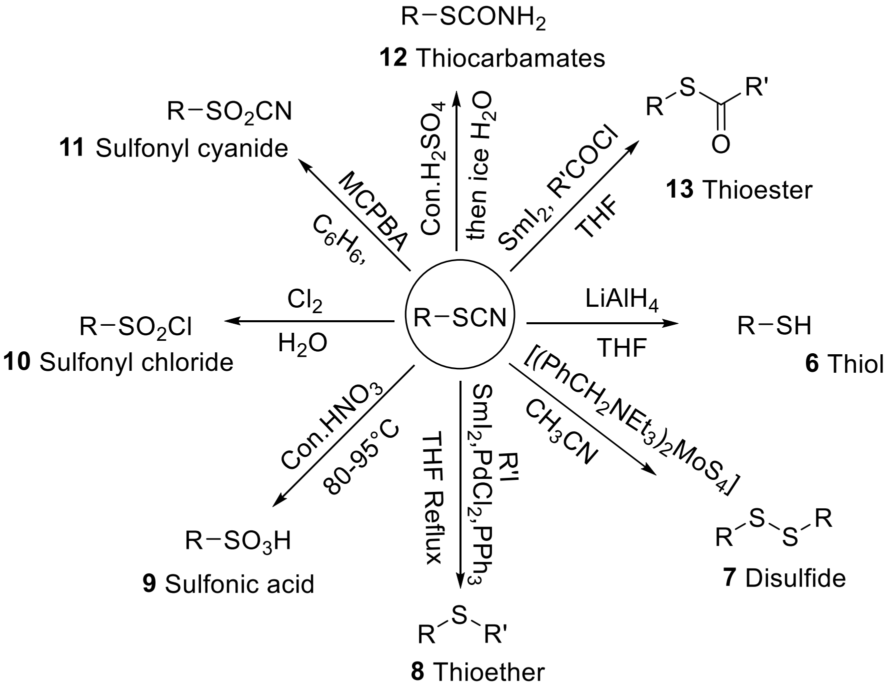
2.1 Abstract:

An expedient, direct and regioselective thiocyanation of phenols, anilines and heterocycles is described. Transformation is realized via the direct C-H functionalization under transition-metal-free conditions at ambient temperature in excellent yields. The method proved to be monoselctive and a variety of functional groups tolerated the reaction conditions. The practicality of the protocol is demonstrated in gram scale synthesis of a precursor of PPAR δ agonist in excellent yield.

2.2 Introduction

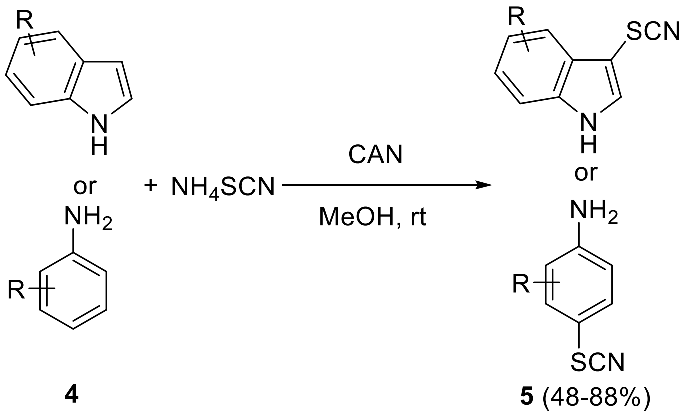
Organosulfur derivatives are very important class of compounds with biological importance. Hence, efforts have been devoted to synthesize organosulfur compounds by directly introducing the sulfur moieties into the organic scaffolds. Among these, direct thiocyanation of aromatic and heteroaromatics is one of the most important and convenient methods for the carbon-sulfur bond formation. Many aryl thiocyanates exhibit potent biological and pharmacological activities and they are the building blocks of many biologically active heterocycles and agrochemicals.[1] Moreover, aryl thiocyantes are the versatile precursors for making various useful organosulfur compounds such as thiols **6**,[2] thioethers **8**,[3] thioesters **13** ,[4] thiocarbamates **12**,[5] disulfides **7**,[6a] sulfonic acids **9**,[6b] sulfonyl chlorides **10**,[6c] sulfonyl cyanides **11**,[6d] sulfur containing heterocycles[7] and many pharamceuticals[1a] (Scheme 2.1). Owing to the importance, efforts have been made to access the thiocyanates by different methods.[8] Usually, thiocyanates are obtained by the direct electrophilic thiocyanation of arenes or nucleophilic substitution reaction of the corresponding organic molecules. Even though these traditional methods contributed to various synthetic transformations, use of toxic transition metal reagents, corrosive molecular halogen and halogen based reagents, harsher reaction conditions impede their wide utility. Certainly, these are the some of the limiting factors for the successful and wider applications of many traditional methods of thiocyanation. Some of the other reagents that have been explored for the thiocyanation under various conditions are ceric ammonium nitrate (CAN)/ammonium thiocyante,[8c] antimony (V) chloride/lead

(II)thiocyanate,[9] arylthallium bistrifluoroacetate/potassium thiocyanate,[10] $Zn(SCN)_2/Cl_2$,[11] $Mn(OAc)_3$,[12] $Cu(SCN)_2/Cl_2$,[13] $NaSCN/Br_2$.[14]



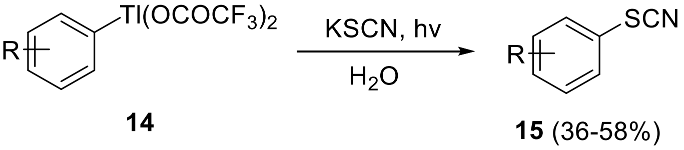
Scheme 2.1. Reactions of thiocyanate

In 1999 Nair et al. reported the thiocyanation reaction of indoles/anilines **4** by treating with ammonium thiocyanate and ceric ammonium nitrate (CAN) in methanol at room temperature to afford thiocyanatoindoles/thiocyanato anilines[8c] **5** in good yields (up to 88%, Scheme 2.2).



Scheme 2.2. Thiocyanation of indoles and anilines using CAN/NH_4SCN

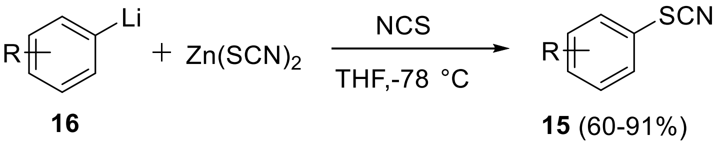
Taylor et al. disclosed a photochemical method starting from arylthallium bis-trifluoroacetates **14** in aqueous potassium thiocyanate solution under photolytic conditions to afford the corresponding aryl thiocyanate **15** in moderate yields (Scheme 2.3).[10]



Scheme 2.3. Photochemical thiocyanation of aromatic compounds

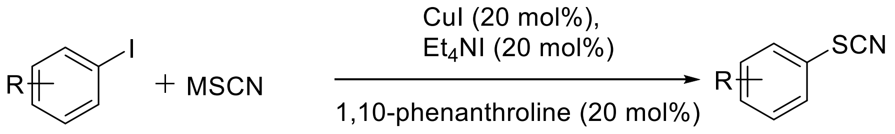
Most of the methods greatly rely either on the use of heavy and toxic transition metals, or on corrosive halogen and stronger oxidants. Use of these reagents, oxidants in stoichiometric amount and in turn generation of a large amount of heavy metal waste is the real drawbacks of these methods. Most of these thiocyanation methods have been focused on limited substrates, mostly on electron rich indoles and closely related *N*-bearing heterocycles which are of high reactivity. Some of these methods have been also accompanied by low regio- and chemo-selectivity. In the recent years, efforts have been made to improvise these classic protocols using specialized reagents.

Takagi et al. reported the reaction of aryl lithium **16** and $Zn(SCN)_2$ in presence of *N*-chloro succinamide (NCS) as an oxidant to afford arylthiocyanates **15** in good yields (up to 91%, Scheme 2.4).[15]



Scheme 2.4. Thiocyanation of aryl lithium compounds.

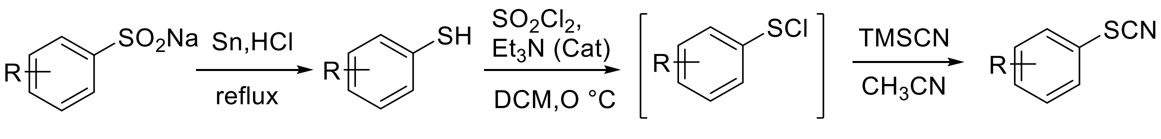
Wang et al. developed a copper catalyzed thiocyanation of aryl iodides **17** by the treatment with sodium or potassium thiocyantes to afford the corresponding arylthiocyanates **15** in good yields (up to 83%). The reaction proceeded via the nucleophilic displacement of iodide by thiocyanide (Scheme 2.5).[16]



17

Scheme 2.5. Thiocyanation of aryl iodides

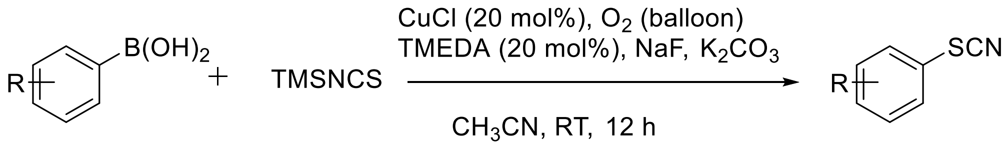
The direct cyanation of organosulfur compounds **19** was reported by Watson and co-workers using sulfonyl chloride and trimethylsilyl cyanide (TMSCN) to afford the corresponding arylthiocyanates **15** in very good yields[17] (up to 96%, Scheme 2.6).



18 **19** **20** **15** (78-96%)

Scheme 2.6 Cyanation of organosulfur compounds

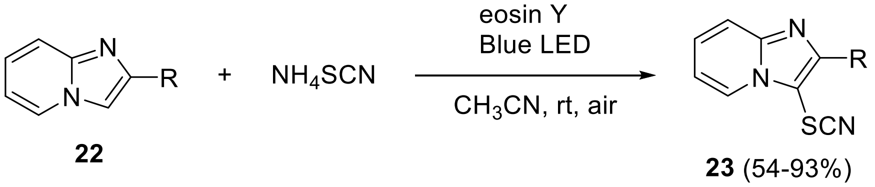
Sun et al. developed a strategy for the transformation of arylboronic acids **21** to the corresponding aryl thiocyanates **15** based on the copper catalyzed oxidative cross-coupling reaction between arylboronic acids **21** and trimethylsilylisothiocyanate (TMSNCS) under oxygen atmosphere.[18] This catalytic protocol gave a direct access to aryl thiocyanates starting from arylboronic acids in good yields (up to 89 %, Scheme 2.7)



21 **15** (45-89%)

Scheme 2.7. Cross-coupling reaction of arylboronic acids with TMSNCS

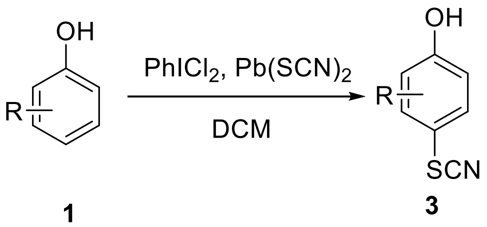
However, these methods are not devoid of the use of transition metals or harsh reaction conditions and they also generate transition metal waste in these processes. Efforts have also been focused on the transition-metal-free and visible light promoted thiocyanation in elegant ways.[8g,19] A visible light mediated, metal-free process for the thiocyanation of imidazoheterocycles **22** has been developed by Hajra and co-workers using eosin Y as a photoredox catalyst under ambient air at room temperature to afford the corresponding thiocyanates **23** in very good yields (up to 93%, Scheme 2.8). [19]



Scheme 2.8. Visible light promoted thiocyanation of imidazoheterocycles

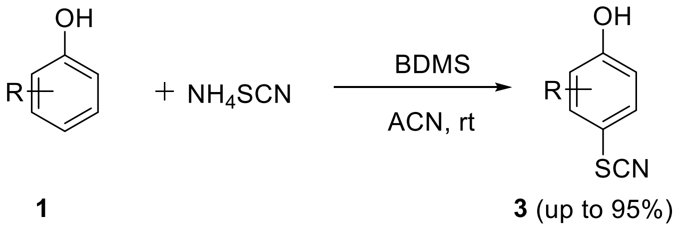
However, most of the protocols of thiocyanation available in the literature are executed on indoles, imidazoheterocycles and nitrogen containing activated heterocycles.[8a-g, 12, 19] Also, thiocyanation of aromatic amines and nitrogen heterocycles are reported to be facile. On the other hand, interestingly thiocyanation of phenols are less explored[20] and not studied extensively possibly due to its intrinsic electronic nature. Practical use of some of these available methods is seriously limited due to the use of toxic metal reagents such as $Pb(SCN)_{2,}$[20e] molecular halogen, and above all formation of side products.

Singh and co-workers developed thiocyanation of phenols **1** using a reagent combination of (dichloroiodo)-benzene and $Pb(SCN)_2$ in dry dichloromethane to afford the thiocyanated phenol derivatives **3** in good yield (up to79%, Scheme 2.9).[20e]



Scheme 2.9. Thiocyanation of phenol using $PhI(Cl)_2/Pb(SCN)_2$

Bhalerao et al. reported thiocyanation of various phenols **1** by using a combination of bromodimethylsulfonium bromide (BDMS) and ammonium thiocyanate at ambient temperature to afford the corresponding thiocyanated phenol derivatives **3** in very good yields (up to 95%, Scheme 2.10).[20f]



Scheme 2.10. thiocyanation of phenols using BDMS

Thiocyanation of phenols have been found to be not facile and especially with electron withdrawing groups on phenols and the most of the protocols have limited substrate scope.

Practical, efficient and highly selective transition-metal-free transformations are gaining a great importance for the last few years.[21] Synthetic organic chemists have been focusing on the approaches that are transition-metal-free in nature and they are increasingly becoming popular. Hence, efforts are being made for the transition-metal-free direct C-H functionalization of organic molecules. Phenol and heterocycle scaffolds are core to many bioactive molecules and pharmaceuticals. In this regard, development of transition-metal-free, more efficient and practical protocol for the direct thiocyanation of diverse phenol, aniline and heterocycle derivatives is highly desirable.

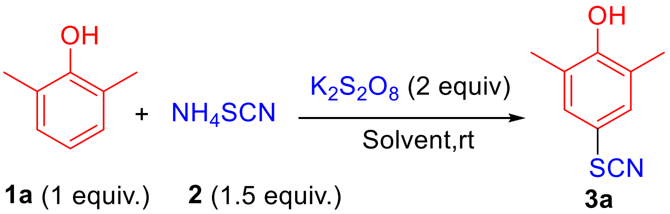
Herein, in this chapter novel, practical and direct transition-metal-free regioselective thiocyanation of phenols, aromatic amines and heterocycles using inexpensive potassium persulfate and NH_4SCN under mild conditions is described. This method has several advantages such as broad substrate scope and transition-metal-free reaction conditions.

2.3 Results and discussion

2.3.1 Optimization studies

At the outset of our investigation, we selected 2,6-dimethyl phenol **1a** and ammonium thiocyanate **2** as model substrates. In order to optimize the reaction conditions different oxidants, solvents and reaction conditions were explored. In presence of 2 equiv. of oxone in DCE at room temperature, the reaction afforded trace amount of the expected product **3a**. Several solvents such as CH_3CN, THF, DCM were screened; however, reaction did not afford the expected product. Later, the reaction of **1a** and **2** in presence of $K_2S_2O_8$ in acetic acid at room temperature afforded the thiocyanated product **3a** in 70% yield (entry 4, **Table 2.1**). The reaction proceeded in acetonitrile affording **3a** in 85% yield. Gratifyingly, the reaction proceeded smoothly in DCM by affording **3a** in excellent yield (95%) in 4 h at room temperature (entry 6 **Table 2.1**). Notably, the reaction also proceeded smoothly in water yielding **3a** in 68%. After screening several solvents, DCM was found to be the best solvent for the reaction. Based on further investigation, we observed that both $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ were effective for the direct thiocyanation of the **1a**. Further studies revealed that 2 equiv. of $K_2S_2O_8$ were crucial for the transformation and for the higher yield. However, we observed the incomplete conversion when the amount of $K_2S_2O_8$ was reduced to 1-1.5 equivalents. Importantly, the reaction did not work in the absence of oxidant $K_2S_2O_8$. The oxidants such as molecular oxygen and *tert*-butyl hydroperoxide (TBHP) did not facilitate the reaction. Based on the exhaustive screening, phenols **1** (1 equiv.) and ammonium thiocyanate **2** (1.5 equiv.) and $K_2S_2O_8$ (2 equiv.) in DCM at room temperature found to be the optimum reaction condition for the effective thiocyantion of phenols.

Table 2.1 Optimization of the reaction conditions[a,b]



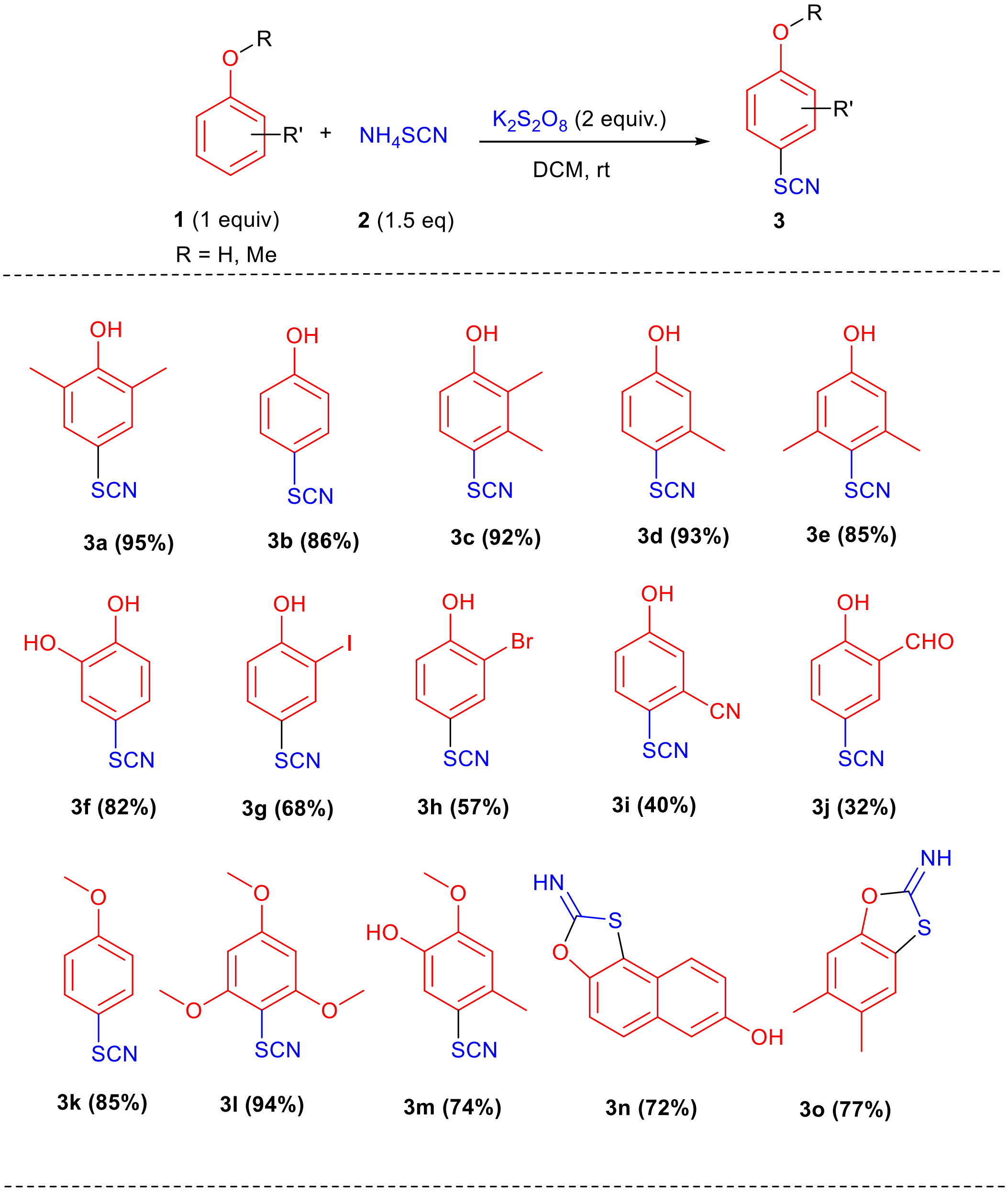
Entry	Oxidant[a]	Solvent	Time (h)	Yield[b] (%)
1	Oxone	DCM	12	trace
2	TBHP	DCM	12	NR
3	O_2	DCM	12	NR
4	$K_2S_2O_8$	Acetic acid	12	70
5	$K_2S_2O_8$	Acetonitrile	12	85
6	**$K_2S_2O_8$**	**DCM**	**4**	**95**
7	$K_2S_2O_8$	DCE	4	93
8	$K_2S_2O_8$	THF	12	50
9	$K_2S_2O_8$	water	6	68
10	$K_2S_2O_8$	Methanol	12	73
11	$K_2S_2O_8$	1,4-dioxane	12	60
12	$K_2S_2O_8$	DMF	12	trace
13	$(NH_4)_2S_2O_8$	DCM	4	94
14	$Na_2S_2O_8$	DCM	4	93

[a]Reaction conditions: **1a** (0.1 g)**, 2** (1.5 equiv), Oxidant (2 equiv, 1.64 mmol), solvent (2 mL), rt (24 °C), 4 h, [b]Isolated yield after column chromatography.

2.3.2 Substrate scope of phenol derivatives

With the optimized reaction conditions in hand, to generalize the methodology, the substrate scope of this transition-metal-free direct thiocyanation was investigated (**Table 2.2**). To our delight, various substrates underwent a facile direct and regioselective thiocyanation under optimized reaction conditions by affording the desired products in good to excellent yields. Various phenols and anisole derivatives with electron-donating and -withdrawing groups reacted smoothly under the optimized reaction conditions to afford the corresponding desired products in moderate to excellent yields (entry **3a-3m, Table 2.2**). It is noteworthy that direct thiocyanation exclusively occurred at the *para*

Table 2.2 Direct regioselective thiocyanation of phenol derivatives[a,b]



[a]Reaction conditions: Substituted phenols and anisoles **1** (1 equiv, 0.1 g). NH_4SCN **2** (1.5 equiv), $K_2S_2O_8$ (2 equiv), DCM (2 mL), reaction time (4 h), rt (24 ^{o}C), [b]Isolated yields after column chromatography given in brackets.

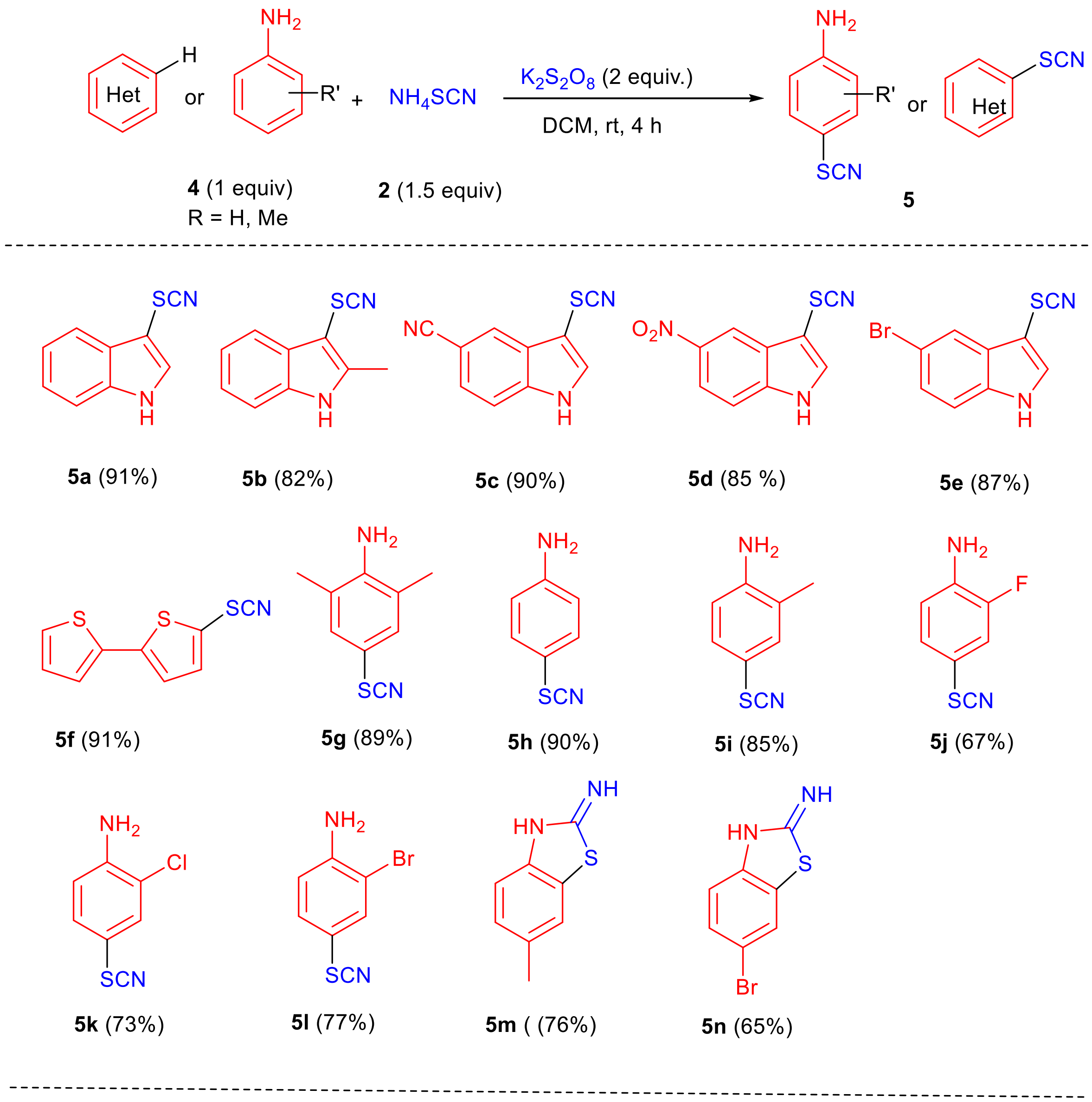
position. The reaction found to be facile, monoselective and did not form any disubstituted products. Phenols bearing electron withdrawing groups such as iodo, bromo, cyano, aldehyde resulted in relatively lower yields of the corresponding products (**3g-3j, Table 2.2**) and unreacted starting materials were observed. However, cyano and aldehyde functional groups tolerated the reaction conditions, while the *o*-nitrophenol did not react under the optimized reaction condition. The thiocyanate functional group was confirmed by the characteristic IR absorption peak (~2160 cm^{-1}) and ^{13}C NMR data. We did not observe the formation of any isothiocyanates. Further, the reactions of naphthalene derivative (**1n**) and 3,4-dimethyl phenol (**1o**) under the optimum reaction conditions resulted in the corresponding stable oxathioimines (**3n**, **3o**).

2.3.3 Substrate scope of indole and aniline derivatives

Encouraged by this initial success on relatively less reactive phenol derivatives, we turned our attention towards the relatively more reactive anilines and heterocycles. Different indole derivatives (**4a-4e**) under the optimized conditions underwent direct C-3 thiocyanation easily to afford corresponding thiocyananto indole derivatives in excellent yields (**5a-5e**, **Table 2.3**). Indoles bearing -CN, -NO_2, -Br groups reacted regioselectively to afford the corresponding thiocyanted products (**5c-5e**) in good to excellent yields. Notably, 2, 2'-bithiophene (**4f**) reacted with ease to afford the corresponding C-2 mono thiocyanated product **5f** in excellent yield (91%).

Later, we explored the reactivity of various aniline derivatives under optimized reaction conditions. All the aniline derivatives under the reaction conditions afforded thiocyanted products (**5g-5l**) in good to excellent yields (see Table 2.3). It is very important to note that direct thiocyanation was highly regioselective and occurred at *para* position. Substrates bearing electron withdrawing groups afforded the thiocyanated products in good yields. However, *para* substituted anilines resulted in the formation of the corresponding stable azathioimines (**5m, 5n**) *via ortho* thiocyanation.

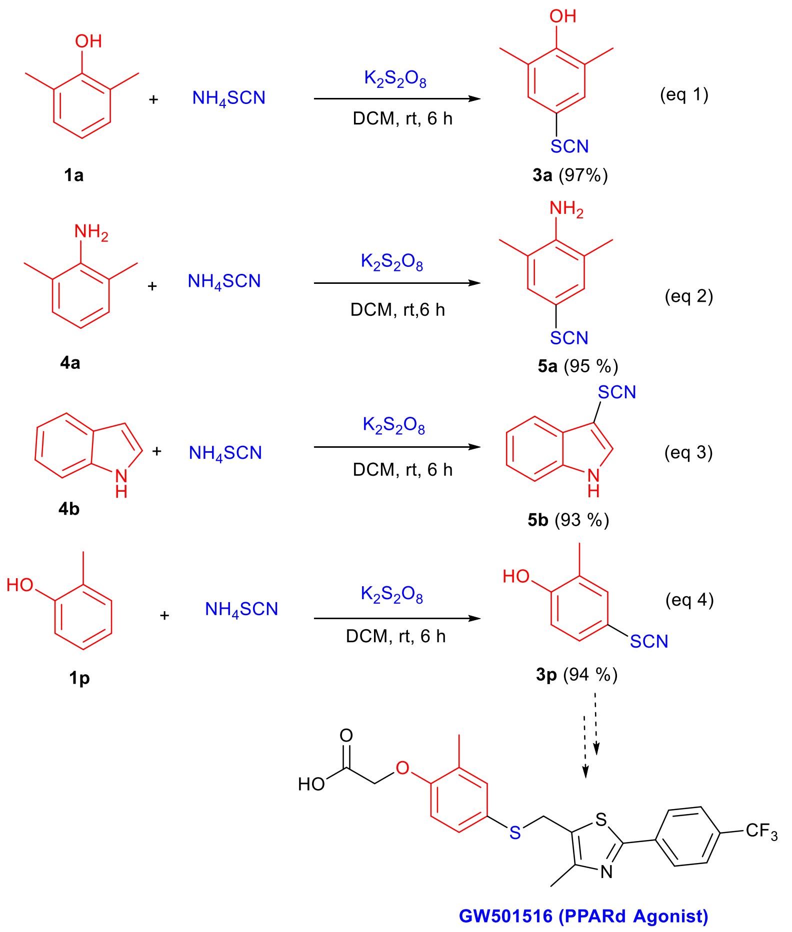
Table 2.3 Direct and regioselective thiocyanation of anilines and heterocycles[a,b]



[a] Reaction conditions: Substituted Aromatic amines and Heterocycles **4** (1 equiv. 0.1 g) NH_4SCN (1.5 equiv), $K_2S_2O_8$ (2 equiv) DCM, (2 mL), reaction time (4 h), rt (24 °C), [b] Isolated yields after column chromatography given in brackets.

2.3.4 Gram scale synthesis

In order to make this approach more practical and for the future development, we extended this method on gram scale under the optimized reaction conditions (Scheme 2.11).



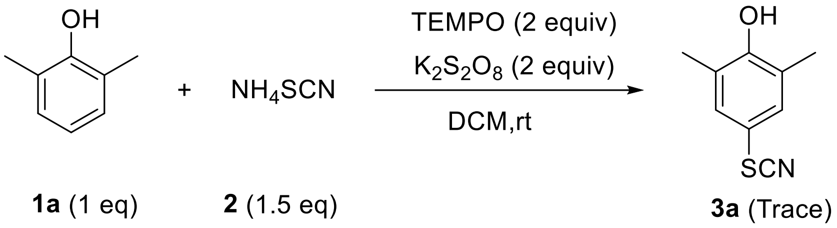
Scheme 2.11 Thiocyanation on a gram Scale

2,6-dimethyl phenol **1a**, 2,6-dimethyl aniline **4a** and indole **4b** afforded the corresponding thiocyanated products (**3a, 5a, 5b**, eq. 1-3) in excellent yields under the optimum reaction conditions. GW501516 is a well known, most potent and selective peroxisome proliferator-activator receptor δ (PPARδ) agonist (Scheme 2.11). Compound **3p** the precursor of GW501516 was earlier synthesized using NaSCN and molecular bromine. Using our protocol we synthesized compound **3p** under optimized reaction condition on a gram scale (3 g) in excellent yield (94%, eq 4, Scheme 2.11). Easy, practical and transition-metal-free reaction conditions demonstrated the practical utility of this method for the direct thiocyanation.

2.4 Mechanistic study

2.4.1 Radical quenching experiment

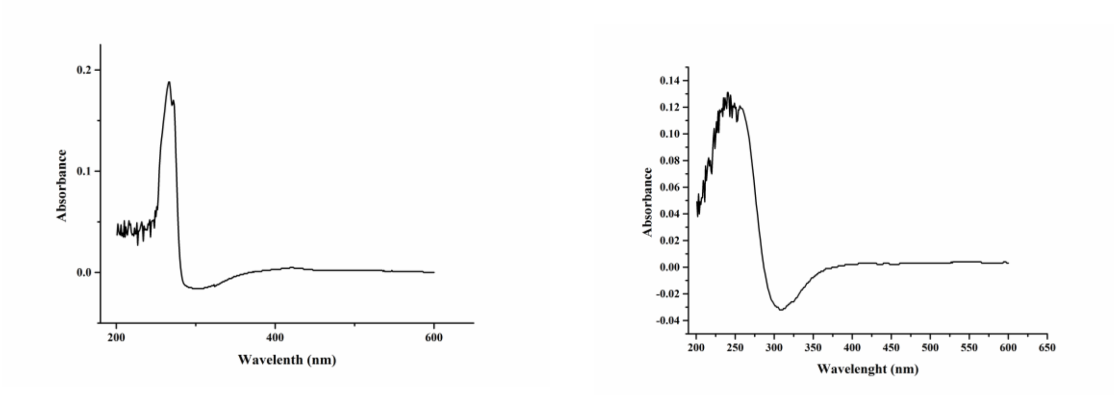
In order to gain further insight into the mechanism, we treated the reaction mixture with the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The thiocyanation reaction did not proceed even after prolonged reaction time (Scheme 2.12) and this indicated that most likely free radical pathway might have been involved during the course of the reaction.



Scheme 2.12. Radical quenching experiment

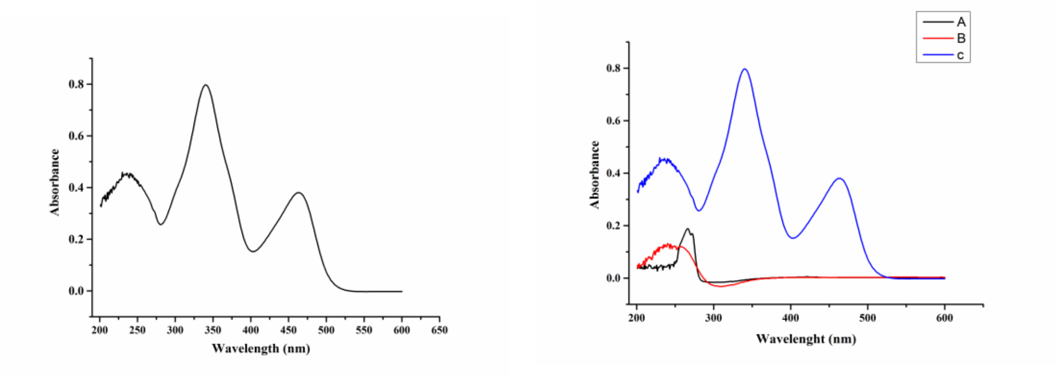
2.4.2 UV-Vis study to detect phenol radical cation intermediate.

$K_2S_2O_8$ is known to generate a strong, short-lived oxidant-sulfate radical anion ($SO_4^{\bullet-}$) easily. The sulfate radical anion (E^o = 2.6 V) is known to generate radical cation on interaction with the low ionization potential aromatics.[22] In order to investigate and to support the formation of a phenol radical cation intermediate, the UV-Vis spectroscopy studies were carried out. An intense absorption band was observed in the visible region between 400 to 500 nm during the reaction of phenol **1a** with $K_2S_2O_8$ at room temperature in CF_3COOH (**Fig 2.1**). This observation strongly supported the formation of a radical cationic intermediate during the course of the reaction. This observation was in accordance with the earlier reports by Kita et al. and Kochi et al.[23a-b]



(A) Substrate-Starting Material

(B) Product



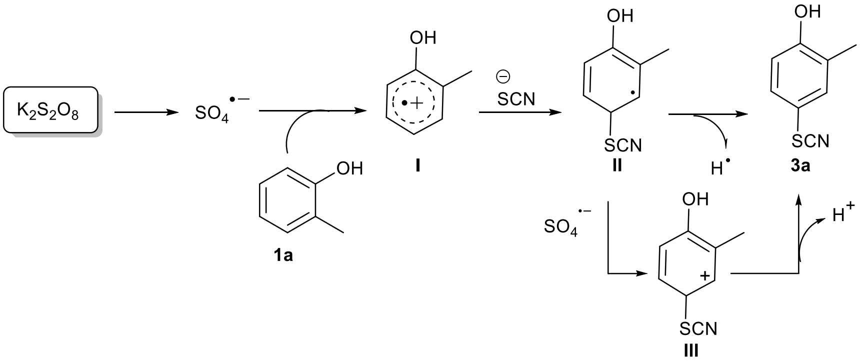
(C) Reaction Mixture

(D)Stacking-Comparison

Fig 2.1. UV-Vis spectroscopic study at ambient temperature

2.5 Proposed mechanism

Based on these investigations and previous literature,[23a-b] the plausible mechanism has been proposed (Scheme 2.13). Potassium persulfate would decompose to generate very strong oxidant sulfate radical anion ($SO4^{\bullet -}$), which in turn oxidizes the aromatics to form radical cation intermediate **I**. Simultaneous nucleophilic addition of thiocyanate anion to the cation intermediate would lead to the formation of radical intermediate **II**. Ultimately the loss of hydrogen radical from **II** would afford the desired compound **3a**. Alternatively, further oxidation of the intermediate **II** will lead to the formation of cation intermediate **III**. Finally, the elimination of H^+ from this intermediate afford the desired product **3a** (Scheme 2.13).



Scheme 2.13 Proposed mechanism for the direct thiocyanation

2.6 Conclusions

In conclusions, we have demonstrated the transition-metal-free regioselective and monoselective thiocyantion of phenols, anilines and other nitrogen bearing heterocycles under mild conditions. To the best of our knowledge for the first time direct thiocyanation of phenols has been achieved using commercially available and inexpensive $K_2S_2O_8$. Most importantly, this protocol proved to be scalable on a multi gram quantity. The desired products were obtained in good to excellent yields and a wide range of functional groups were tolerated. Initial understandings suggested that reaction proceeded via radical cation intermediate. This protocol presents a new and viable path to access thiocyanated aromatics and precursors of bioactive molecules.

2.7 Experimental section

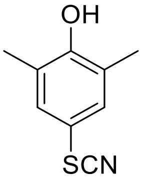
2.7.1 General

All reagents were purchased from commercial sources and were used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminium backed plates (2.5 mm). ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$, Methanol-d_4, and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. All reactions were carried out in dried glassware. Dichloromethane was used for the reaction. All purchased chemicals were used without further purification. Column chromatography was carried out using silica gel. Melting points were measured in open glass capillary and values are uncorrected.

2.7.2 General procedure A: synthesis of thiocyanatophenols, thiocyanatoanilines and thiocyanatoindoles:

In an oven dried round bottom flask containing a mixture of 2,6-dimethyl phenol **1a** (100 mg, 0.82 mmol), ammonium thiocyanate **2** (94 mg, 1.23 mmol) and potassium persulfate (443 mg, 1.64 mmol) in DCM (2 mL) were stirred for 4 h. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered through sintered funnel containing silica and sodium sulfate. The Filtrate concentrated under reduced pressure to afford the crude product **3a**. This was purified by column chromatography (EtOAc:Hexane) to furnish the pure compound **3a** as a white solid (139 mg, 95% yield). Similar procedure was used for the thiocynation of anisoles, anilines and heterocycles.

2, 6-dimethyl-4-thiocyanatophenol (3a):



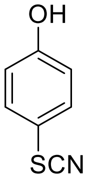
3a

The compound **3a** was obtained as a as a white solid (139 mg, 95% yield). mp = 103-106 °C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3351, 2157, 1584, 1311; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 5.05 (s, 1H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 132.6, 125.6, 112.9, 112.2, 16.0; HRMS (ESI) calcd. for C_9H_9NOS $[M + H]^+$ 180.0483, found 180.0489.

Gram scale synthesis of (3a)

Similarly the compound **3a** was synthesized on gram scale starting from **1a** (2g, 16.37 mmol) following the general procedure **A** described for **3a**; the compound **3a** was obtained as a white solid (2.85g, 97% yield).

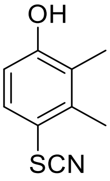
4-thiocyanatophenol (3b)



3b

The compound **3b** was synthesized starting from **1b** following the general procedure **A** described for **3a**; The compound **3b** was obtained as a brown solid (139 mg, 86% yield). mp = 51-53 °C, R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3344, 2160, 1586, 1493, 1220; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 134.4, 117.6, 113.3, 112.4; HRMS (ESI) calcd for $C_7H_5ClN_2S$ $[M + H]^+$ 152.0170, found 152.0173.

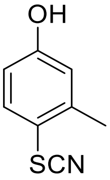
2,3-dimethyl-4-thiocyanatophenol (3c):



3c

The compound **3c** was synthesized starting from **1c** following the general procedure **A** described for **3a**; The compound **3c** was obtained as a white solid (135 mg, 92% yield). mp = 97-99 °C; R_f = 0.5, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}:3371, 2158, 1573, 1281; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 5.69 (s, 1H), 2.50 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 141.5, 132.8, 125.7, 114.3, 113.6, 112.3, 18.1, 12.7; HRMS (ESI) calcd for C_9H_9NOS $[M + H]^+$ 180.0483, found 180.0489.

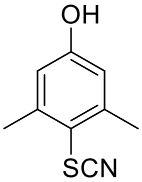
3-methyl-4-thiocyanatophenol (3d):



3d

The compound **3d** was synthesized starting from **1d** following the general procedure **A** described for **3a**; The compound **3d** was obtained as a yellow solid (142 mg, 93% yield). mp = 75-78 °C; R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3350, 2159, 1577, 1234; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.24 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 143.5, 136.2, 118.7, 115.1, 112.7, 112, 21.1; HRMS (ESI) calcd. for C_8H_7NOS $[M + H]^+$ 166.0326, found 166.0330.

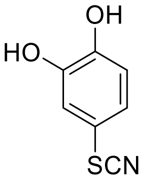
3, 5-dimethyl-4-thiocyanatophenol (3e):



3e

The compound **3e** was synthesized starting from **1e** following the general procedure **A** described for **3a**; The compound **3e** was obtained as a white solid (127 mg, 87%). mp = 131-133 ^{o}C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}:3351, 2157, 1584, 1311; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2H), 5.71 (s, 1H), 2.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 145.2, 116.4, 112.7, 111.8, 22.2; HRMS (ESI) calcd for C_9H_9NOS [M + H] $^{+}$ 180.0483, found 180.0481.

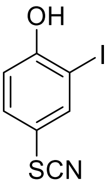
4-thiocyanatobenzene-1,2-diol (3f) :



3f

The compound **3f** was synthesized starting from **1f** following the general procedure **A** described for **3a**; The compound **3f** was obtained as a black solid (125 mg, 82% yield). mp = 138-141 ^{o}C; R_f = 0.3, (EtOAc:Hexane 30:70); IR (neat) cm^{-1}:3743, 3288, 2161, 1513, 1280; ^{1}H NMR (400 MHz, CD_3OD) δ 7.01 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (101 MHz, MeOD) δ 149.2, 148, 125.4, 119.9, 117.7, 113.2, 113.1; HRMS (ESI) calcd for $C_7H_5NO_2S$ [M + H] + 168.0119, found 168.0115

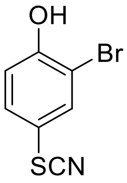
2-iodo-4-thiocyanatopheno(3g):



3g

The compound **3g** was synthesized starting from **1g** following the general procedure **A** described for **3a**; The compound **3g** was obtained as a white solid (86 mg, 68% yield). mp = 100-102 ^{o}C; R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3308, 2161, 1625, 1393, 1285; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 141.8, 134.3, 116.6, 115.4, 111.2, 86.6; HRMS (ESI) calcd. for C_7H_4INOS [M + H]$^{+}$ 277.9136, found 277.9122.

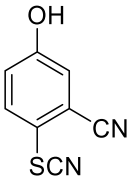
2-bromo-4-thiocyanatophenol (3h):



3h

The compound **3h** was synthesized starting from **1h** following the general procedure **A** described for **3a**; The compound **3h** was obtained as a white solid (75 mg, 57% yield). mp = 157-159 ^{o}C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}:3103, 2147, 1582, 1225, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 2.3 Hz, 1H), 7.46 (dd, J = 8.5, 2.3 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 135.7, 133.3, 117.9, 115.2, 111.5, 111; HRMS (ESI) calcd. for C_7H_4BrNOS [M + H]$^{+}$ 226.0538, found 226.0532.

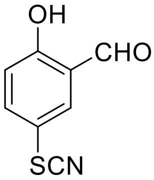
5-hydroxy-2-thiocyanatobenzonitrile (3i):



3i

The compound **3i** was synthesized starting from **1i** following the general procedure **A** described for **3a**; The compound **3i** was obtained as a white solid (60 mg, 40% yield). mp = 103-106 ^{o}C; R_f = 0.5, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}:3283, 2923, 2227, 2176, 1579, 1427; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 2.8 Hz, 1H), 7.17 (dd, J = 8.7, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 137.7, 121.9, 121.6, 118, 116.1, 115.2, 111.5; HRMS ESI (-ve ion mode) calcd for $C_8H_4N_2OS$ [M - H]$^{-}$ 174.9966, found 174.9995.

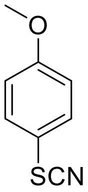
2-hydroxy-5-thiocyanatobenzaldehyde (3j):



3j

The compound **3j** was synthesized starting from **1j** following the general procedure **A** described for **3a**; The compound **3j** was obtained as a white solid (47 mg, 32% yield). mp = 94-97 ^{o}C; R_f = 0.5, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3393, 2856, 2150, 1652, 1465, 1282; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.92 (s, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 163.2, 140.3, 137.7, 121.6, 120.5, 113.9, 110.7; HRMS ESI (-ve ion mode) calcd. for $C_8H_5NO_2S$ [M - H]$^-$ 177.9963, found 177.9996.

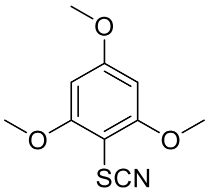
1-methoxy-4-thiocyanatobenzene (3k):



3k

The compound **3k** was synthesized starting from **1k** following the general procedure **A** described for **3a**; The compound **3k** was obtained as a yellow solid (130 mg, 85% yield). mp = 131-134 ^{o}C; R_f = 0.5, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 2925, 2155, 1589, 1493, 1252; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 133.9, 116, 114, 111.7, 55.7; HRMS (ESI) calcd for C_8H_7NOS [M + H]$^+$ 166.0326, found 166.0323

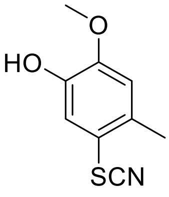
1,3,5-trimethoxy-2-thiocyanatobenzene (3l):



3l

The compound **3l** was synthesized starting from **1l** following the general procedure **A** described for **3a**; The compound **3l** was obtained as a white solid (125 mg, 94% yield). mp = 106-108 ^{o}C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3319, 2187, 1576, 1395, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 2H), 3.92 (s, 6H), 3.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 161.5, 112, 91.4, 89.7, 56.6, 55.7; HRMS (ESI) calcd. for $C_{10}H_{11}NO_3S$ [M + H]$^+$ 226.0538, found 226.0537.

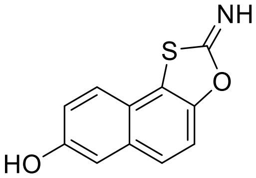
2-methoxy-4-methyl-5-thiocyanatophenol (3m):



3m

The compound **3m** was synthesized starting from **1m** following the general procedure **A** described for **3a**; The compound **3m** was obtained as a white solid (105 mg, 74% yield). mp = 127-130 °C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm-1: 3407, 2154, 1508, 1270; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.77 (s, 1H), 5.60 (s, 1H), 3.90 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 144.8, 133.3, 119.6, 113.5, 113.4, 111.2, 56.2, 20.5; HRMS (ESI) calcd. for $C_9H_9NO_2S$ $[M + H]^+$ 196.0432, found 196.0432

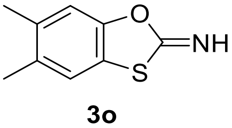
2-Iminonaphtho[1,2-d][1,3]oxathiol-7-ol (3n):



3n

The compound **3n** was synthesized starting from **1n** following the general procedure **A** described for **3a**; The compound **3n** was obtained as a brown solid (97 mg, 72% yield). mp = °C; R_f = 0.4, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3743, 3282, 2363, 2322, 1693, 1531; ^{1}H NMR (400 MHz, MeOD) δ 7.56 (d, J = 9.0 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.20 – 7.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 147.2, 133.8, 127.1, 125.9, 122.9, 121.3, 118.9, 112.6, 111.4; HRMS (ESI) calcd. for $C_{11}H_7NO_2S$ [M + H] + 218.0275, found 218.0278.

5, 6-dimethylbenzo[d][1,3]oxathiol-2-imine (3o):

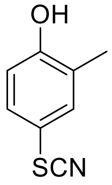


3o

The compound **3o** was synthesized starting from **1o** following the general procedure **A** described for **3a**; The compound **3o** was obtained as a white solid (113 mg, 77% yield). mp = 96-99 °C; R_f = 0.6, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3325, 1584, 1311; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.91 (s, 1H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 167.1, 149.4, 135.9, 133.1, 122.2, 120.5, 112.2, 20.1, 19.6; HRMS (ESI) calcd. for C_9H_9NOS $[M + H]^+$ 180.0483, found 180.0485.

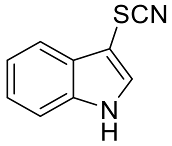
Gram Scale Synthesis of 2-methyl-4-thiocyanatophenol (3p):



3p

The compound **3p** was synthesized on gram scale starting from **1p** (3g, 27.74 mmol) following the general procedure **A** described for **3a**; The compound **3p** was obtained as a yellow solid (4.32g, 94% yield). mp = 73-75 °C; R_f = 0.5, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3350, 2159, 1577, 1234; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.26 (d, *J* = 8.4 Hz 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.79 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 135.2, 131.64, 127.0, 116.8, 113.0, 112.4, 15.9; HRMS (ESI) calcd for C_8H_7NOS $[M + H]^+$ 166.0326, found 166.0330.

3-thiocyanato-1H-indole (5a):



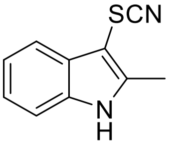
5a

The compound **5a** was synthesized starting from **4a** following the general procedure **A** described for **3a**; The compound **5a** was obtained as a white solid (135 mg, 91% yield). mp = 123-125 °C; R_f = 0.5, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3325, 2155, 1410, 1236, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.82 – 7.78 (m, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.33 – 7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 131.1, 127.8, 124, 122, 118.9, 112.2, 112.1, 92.4; HRMS (ESI)(-ve ion mode) calcd. for $C_9H_6N_2S$ $[M - H]^-$ 173.0174, found 173.0172.

Gram scale synthesis of 5a :

Similarly the compound **5a** was synthesized on gram scale starting from **4a** (2g, 17.07 mmol) following the general procedure **A** described for **3a**; The compound **5a** was obtained as a white solid (2.78 g, 93% yield).

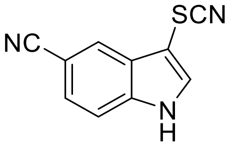
2-methyl-3-thiocyanato-1H-indole (5b):



5b

The compound **5b** was synthesized starting from **4b** following the general procedure **A** described for **3a**; The compound **5b** was obtained as a brownish solid (118 mg, 82% yield). mp = 102-104 ^{o}C; R_f = 0.6, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3321, 2154, 1516, 1405, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.68 – 7.66 (m, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.19 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 135.2, 128.8, 123.1, 121.7, 118.2, 112.1, 111.3, 89.2, 12.2; HRMS (ESI) (-ve ion mode) calcd. for $C_{10}H_8N_2S$ $[M - H]^-$ 187.0330, found 187.0330.

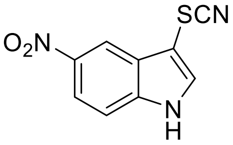
3-thiocyanato-1H-indole-5-carbonitrile (5c):



5c

The compound **5c** was synthesized starting from **4c** following the general procedure **A** described for **3a**; The compound **5c** was obtained as a white solid (126 mg, 90% yield). mp = 217-218 ^{o}C; R_f = 0.3, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3271, 2361, 2321, 2155, 1515; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.21 (s, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.2, 135.8, 127.3, 125.7, 123.3, 119.82, 114.2, 111.9, 103.4, 91.5; HRMS (ESI) (-ve ion mode) calcd. for $C_{10}H_5N_3S$ $[M - H]^-$ 198.0126, found 198.0123.

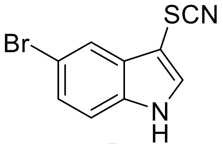
5-nitro-3-thiocyanato-1H-indole (5d):



5d

The compound **5d** was synthesized starting from **4d** following the general procedure **A** described for **3a**; The compound **5d** was obtained as a yellow solid (115 mg, 85% yield). mp = 220-221 ^{o}C; R_f = 0.3, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3357, 3122, 2361, 2322, 2160, 1529, 1396; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.63 (s, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 8.28 (s, 1H), 8.13 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 142.1, 139.5, 137, 126.9, 118.1, 114.4, 113.7, 111.9, 93.1; HRMS (ESI) (-ve ion mode) calcd. for $C_9H_5N_3O_2S$ [M - H]$^-$ 218.0024, found 218.0027.

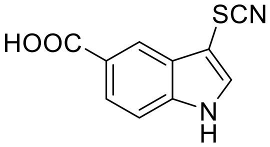
5-bromo-3-thiocyanato-1H-indole (5e):



5e

The compound **5e** was synthesized starting from **4e** following the general procedure **A** described for **3a**; The compound **5e** was obtained as a brownish solid (112 mg, 87% yield). mp = 141-143 °C; R_f = 0.4, (EtOAc:Hexane 50:50);IR (neat) cm^{-1}: 3314, 3118, 2157, 1453, 1001, 800; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.78 (s, 1H), 7.92 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 2.9 Hz, 1H), 7.39 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.8, 132.2, 129.5, 127.2, 121.6, 115.6, 113.7, 111.6, 92.3; HRMS (ESI) (-ve ion mode) calcd. for $C_9H_5BrN_2S$ [M - H]$^-$ 250.9279, found 250.9280.

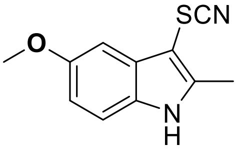
3-thiocyanato-1H-indole-5-carboxylic acid (**5f**):



5f

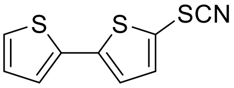
The compound **5f** was synthesized starting from **4f** following the general procedure A described for **3a**; The compound **5f** was obtained as a yellow solid (125 mg, 92% yield). mp = 113-116 °C; R_f = 0.3, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3347, 3314, 3118, 2159, 1453; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.30 (s, 1H), 8.31 (s, 1H), 8.11 (d, *J* = 2.8 Hz, 1H), 7.88 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.8, 138.9, 134.9, 127.1, 124.0, 123.7, 120.0, 112.8, 112.2, 91.3; HRMS (ESI) (+ve ion mode) calcd. for $C_{10}H_6N_2O_2S$ [M + Na]$^+$ 241.0047, found 241.0049.

5-methoxy-2-methyl-3-thiocyanato-1H-indole (5g):


5g

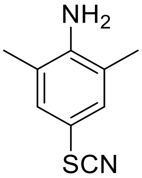
The compound **5g** was synthesized starting from **4g** following the general procedure **A** described for **3a**; The compound **5g** was obtained as a white solid (128 mg, 94% yield). mp = 210-214 ^{o}C; R_f = 0.4, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3325, 3150, 2153, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.90 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 142.5, 129.9, 129.7, 113.2, 112.1, 112.2, 100.1, 88.8, 56.0, 12.3; HRMS (ESI) (+ve ion mode) calcd. for $C_{11}H_{10}N_2OS$ [M + H]$^{+}$ 219.0592, found 219.0592.

5-thiocyanato-2, 2'-bithiophene(5h)


5h

The compound **5h** was synthesized starting from **4h** following the general procedure **A** described for **3a**; The compound **5h** was obtained as a white solid (122 mg, 91% yield). mp = 143-146 ^{o}C; R_f = 0.4, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.23 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.11 (d, *J* = 4.0 Hz, 1H), 7.05 (dd, *J* = 5.0, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 138.8, 135.6, 128.3, 126.4, 125.5 , 124.4, 116.1, 110.4; HRMS (ESI)(-ve ion mode) calcd. for $C_9H_5NS_3$ [M - H]$^{-}$ 221.9500, found 221.9502.

2,6-dimethyl-4-thiocyanatoaniline (5i):


5i

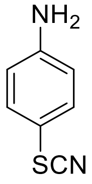
The compound **5i** was synthesized starting from **4i** following the general procedure **A** described for **3a**; The compound **5i** was obtained as a brown solid (131 mg, 89% yield). mp = 80-82 ^{o}C; R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}:3485, 3391, 2152, 1624, 1474; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 3.85 (s, 2H), 2.16 (s, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 145.4, 133, 123.3, 112.8, 108.7, 17.6; HRMS (ESI calcd for $C_9H_{10}N_2S$ $[M + H]^+$ 179.0643, found 179.0646.

Gram scale synthesis of (5i)

The compound **5i** was synthesized on gram scale starting from **4i** (2g, 16.50 mmol) following the general procedure **A** described for **3a**; The compound **5g** was obtained as a brown solid (2.80 g, 95% yield).

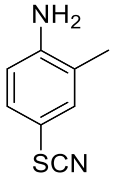
4-thiocyanatoaniline (5j):



5j

The compound **5j** was synthesized starting from **4j** following the general procedure **A** described for **3a**; The compound **5j** was obtained as a brown solid (145 mg, 90% yield). mp = 67-69 °C; R_f = 0.5, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3470, 3373, 2152, 1625, 1495, 1299, 822; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 3.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149, 134.6, 116.2, 112.5, 109.7; HRMS (ESI) (-ve ion mode) calcd for $C_7H_6N_2S$ $[M - H]^-$ 149.0174, found 149.0169.

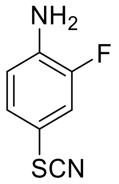
2-methyl-4-thiocyanatoaniline (5k):



5k

The compound **5k** was synthesized starting from **4k** following the general procedure **A** described for **3a**; The compound **5k** was obtained as a brownish solid (130 mg, 85% yield). mp = 71-73 °C; R_f = 0.5, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3451, 3370, 2151, 1632, 1492, 1299, 815; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 135.2, 132.2, 124, 115.9, 112.7, 109.4, 17.3; HRMS (ESI) (-ve ion mode) calcd. for $C_8H_8N_2S$ $[M - H]^-$ 163.0330, found 163.0326.

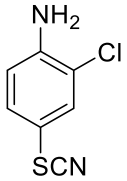
2-fluoro-4-thiocyanatoaniline (5l)



5l

The compound **5l** was synthesized starting from **4l** following the general procedure **A** described for **3a**; The compound **5l** was obtained as a colourless oil (102 mg, 67 % yield). R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3387, 3076, 2363, 2155, 1641, 1463, 846, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (dd, 1H), 7.17 (ddd, *J* = 8.4, 2.1, 1.0 Hz, 1H), 6.78 (t,1H), 4.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.8, 137.4 (d, *J* = 12.5 Hz), 129.7 (d, *J* = 3.3 Hz), 119.9, 119.7, 117.3 (d, *J* = 4.3 Hz), 111.6 , 109.6 (d, *J* = 7.5 Hz); HRMS (ESI) (-ve ion mode) calcd for $C_7H_5FN_2S$ $[M - H]^-$ 167.0079, found 167.0076.

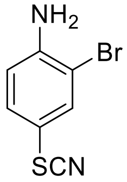
2-chloro-4-thiocyanatoaniline (5m)



5m

The compound **5m** was synthesized starting from **4m** following the general procedure **A** described for **3a**; The compound **5m** was obtained as a colourless oil (105 mg, 73 % yield). R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3457, 3099, 2361, 2157, 1630, 1531, 814, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 134.0, 132.7, 119.8, 116.5, 111.8, 110.2; HRMS (ESI) (-ve ion mode) calcd. for $C_7H_5ClN_2S$ $[M - H]^-$ 182.9784, found 182.9781.

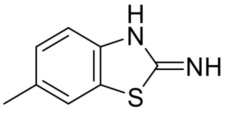
2-bromo-4-thiocyanatoaniline (5n)



5n

The compound **5n** was synthesized starting from **4n** following the general procedure **A** described for **3a**; The compound **5n** was obtained as a white solid (103 mg, 77% yield). mp = 95-97 ^{o}C; R_f = 0.3, (EtOAc:Hexane 20:80); IR (neat) cm^{-1}: 3448, 3092, 2363, 2159, 1529, 859; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 2.2 Hz, 1H), 7.29 (dd, J = 8.5, 2.2 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 136.9, 133.3, 116.2, 111.9, 110.0, 109.2; HRMS (ESI) (-ve ion mode) calcd. for $C_7H_5BrN_2S$ [M - H]$^-$ 226.9279, found 226.9278.

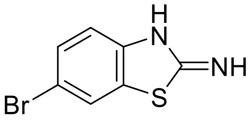
6-methylbenzo[d]thiazol-2(3H)-imine (5o):



5o

The compound **5o** was synthesized starting from **4o** following the general procedure **A** described for **2a**; The compound **5o** was obtained as a brownish solid (116 mg, 76% yield). mp = 131-134 ^{o}C; R_f = 0.2, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3298, 3130, 1623, 1534, 1464, 813; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.2 Hz, 1H), 7.37 (s, 1H), 7.10 (dd, J = 8.2, 1.2 Hz, 1H), 5.60 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 149.8, 132.2, 131.6, 127.3, 121.1, 118.8, 21.4; HRMS (ESI) (-ve ion mode) calcd for $C_8H_8N_2S$ [M - H]$^-$ 163.0330, found 163.0329.

6-bromobenzo[d]thiazol-2(3H)-imine (5p):



5p

The compound **5p** was synthesized starting from **4p** following the general procedure **A** described for **3a**; The compound **5p** was obtained as a white solid (86 mg, 65% yield). mp = 212-214 ^{o}C; R_f = 0.3, (EtOAc:Hexane 50:50); IR (neat) cm^{-1}: 3448, 3092, 2363, 1529, 859; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 2.1 Hz, 1H), 7.60 (s, 2H), 7.32 (dd, J = 8.5, 2.1 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 152, 133.1, 128.2, 123.2, 119.1, 112; HRMS (ESI) (-ve ion mode) calcd. for $C_7H_5BrN_2S$ [M - H]$^-$ 226.9279, found 226.9278.

2.8 Appendix I: ^1H, ^{13}C spectral data of representative compounds

Compound No.	**Figure AII.X**	**Data**	**Page No.**
3a	Figure II.1 and II.2	^1H and ^{13}C	63
3b	Figure II.3 and II.4	^1H and ^{13}C	64
5a	Figure II.5 and II.6	^1H and ^{13}C	65
5g	Figure II.7 and II.8	^1H and ^{13}C	66
5h	Figure II.9 and II.10	^1H and ^{13}C	67
5i	Figure II.11 and II.12	^1H and ^{13}C	68
5j	Figure II.9 and II.8	^1H and ^{13}C	69

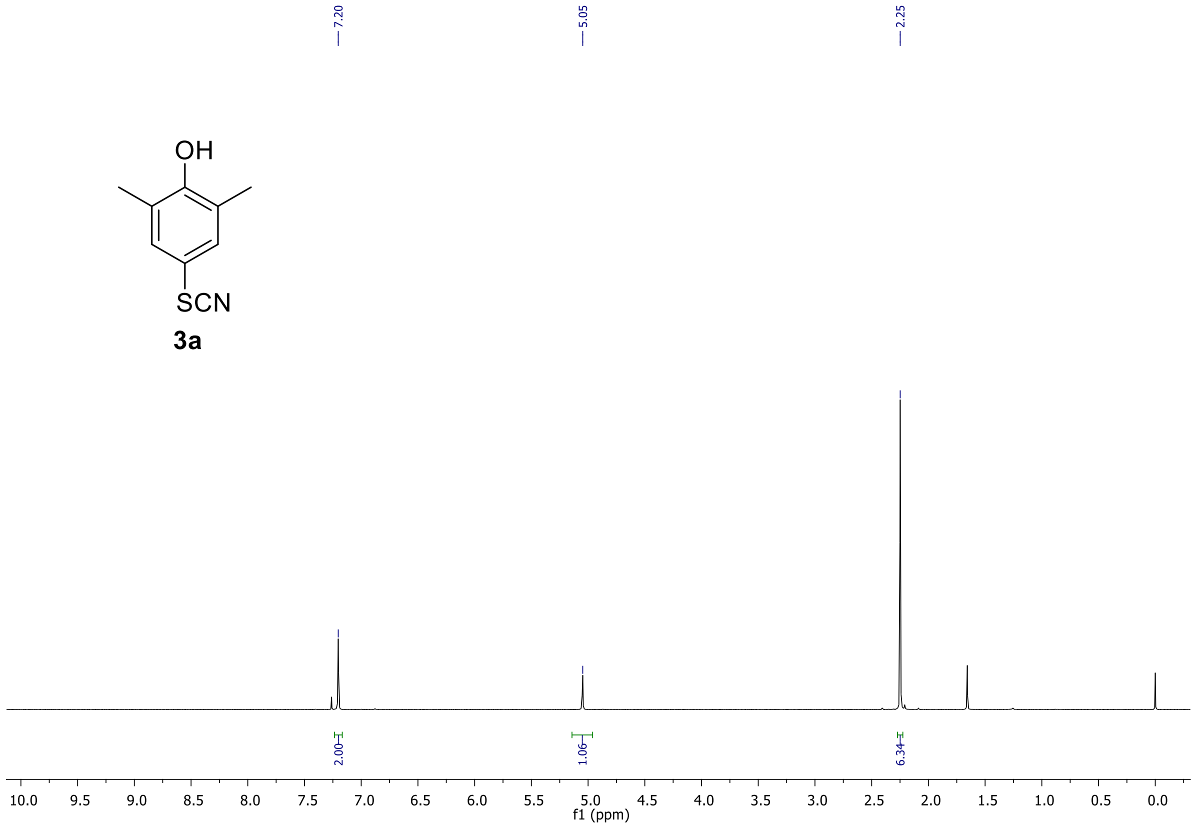


Figure II.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

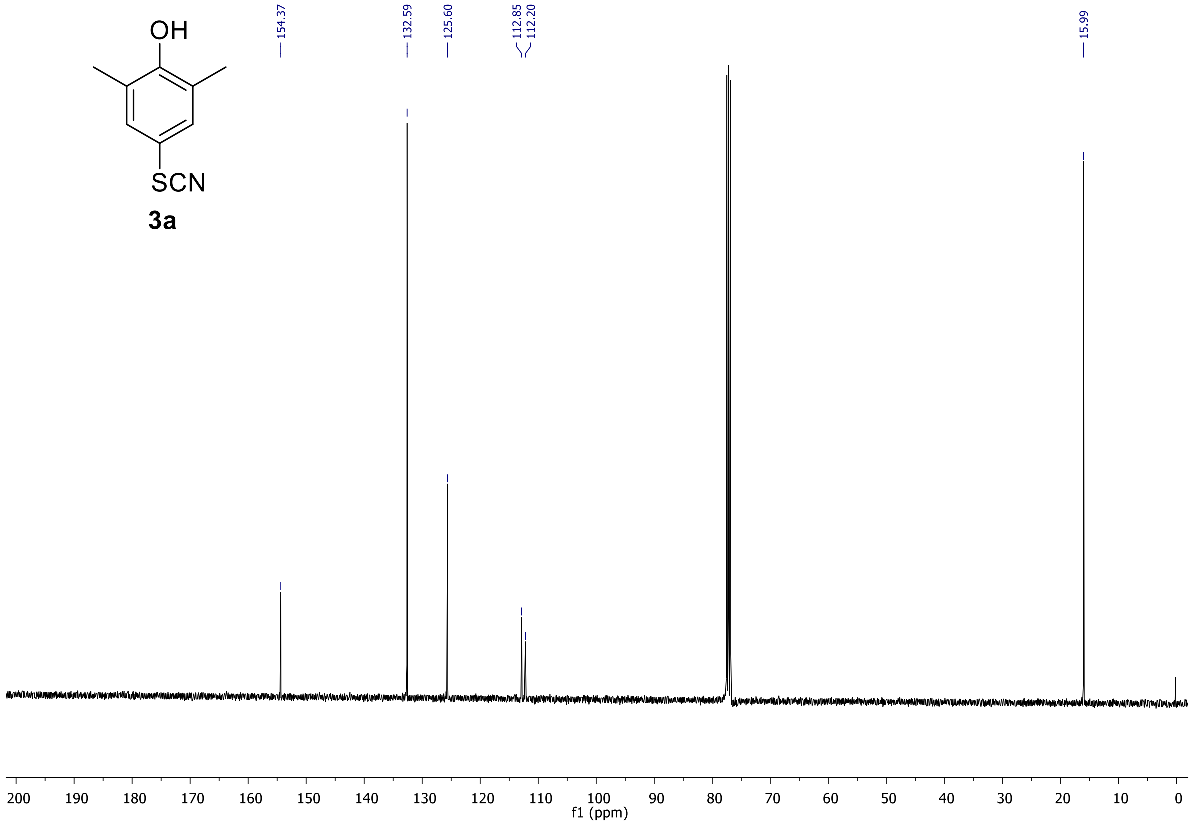


Figure II.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

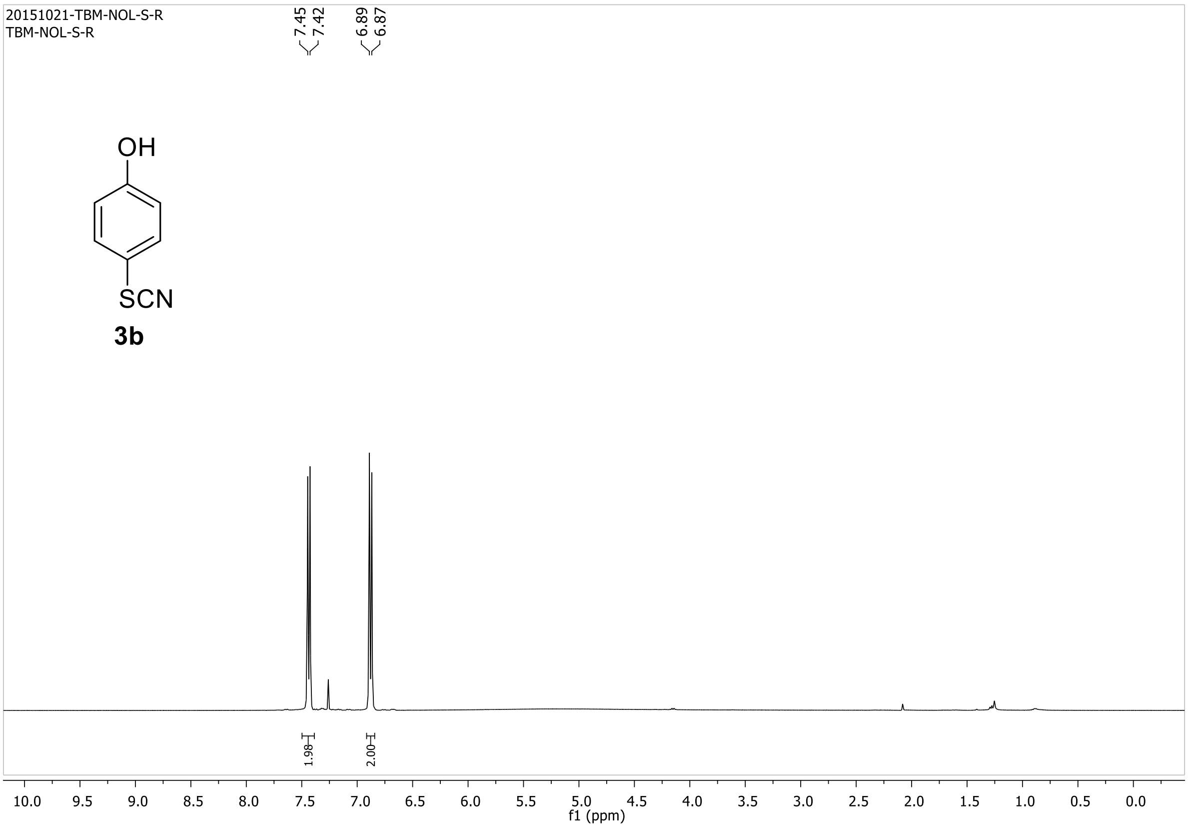


Figure II.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3b**

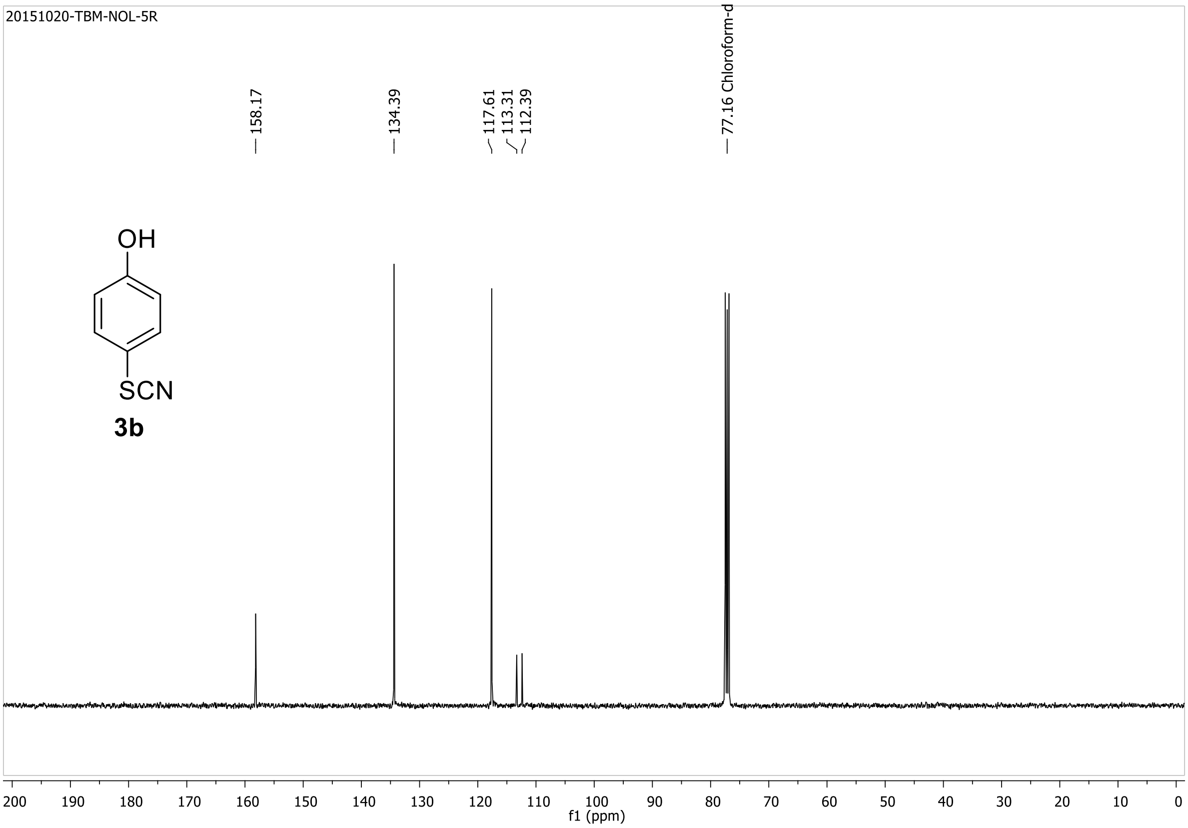


Figure II.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3b**

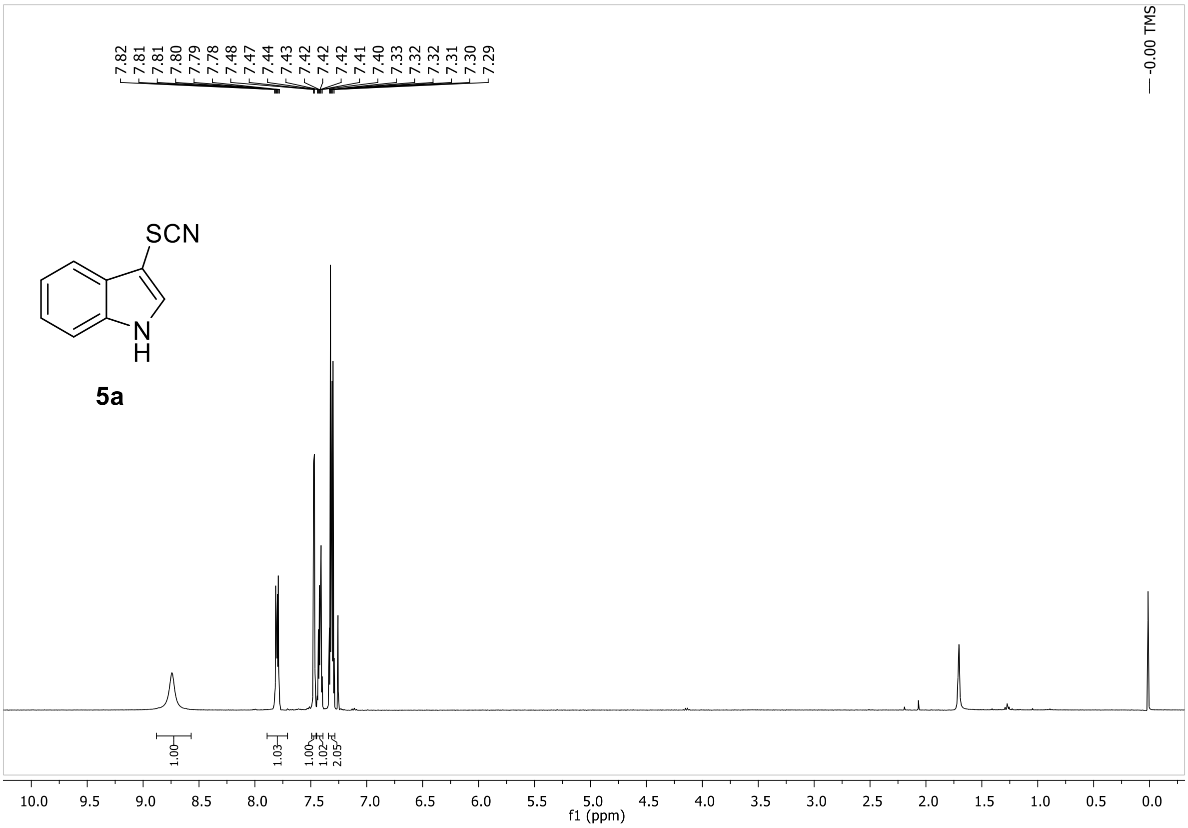


Figure II.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a**

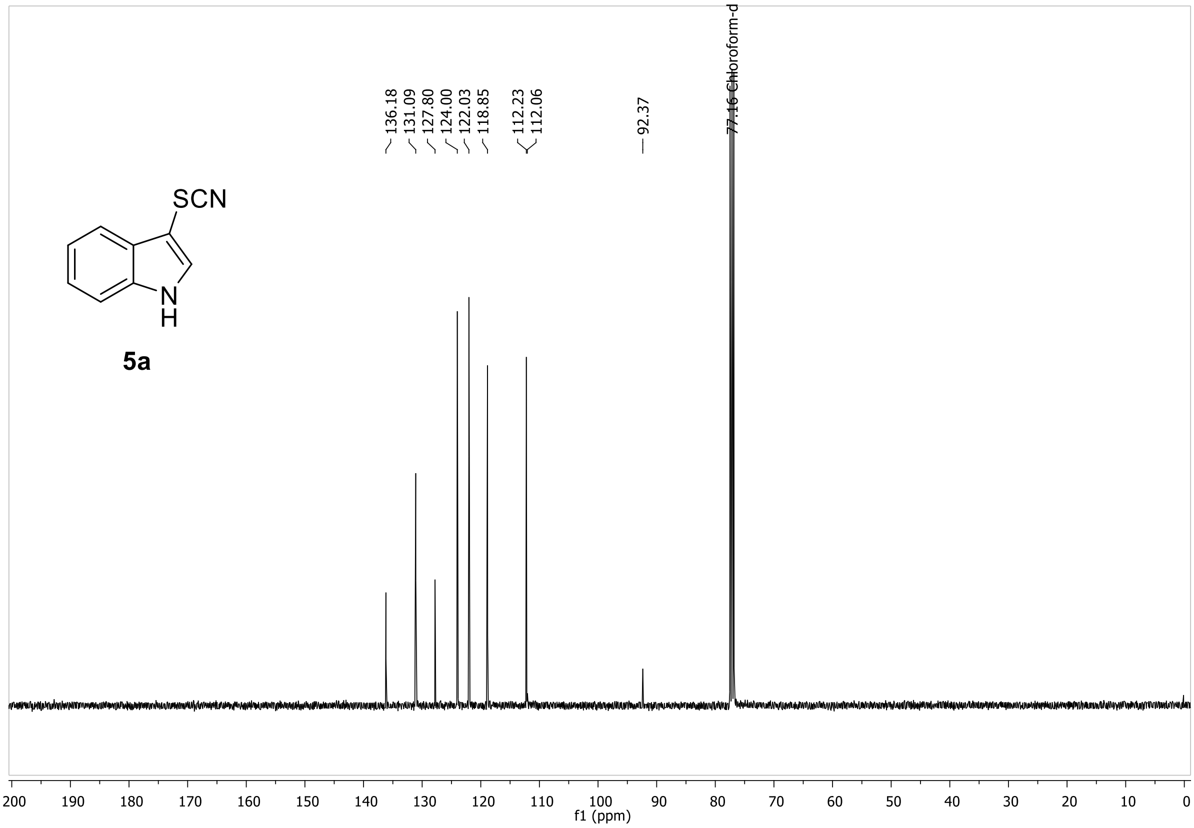


Figure II.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5a**

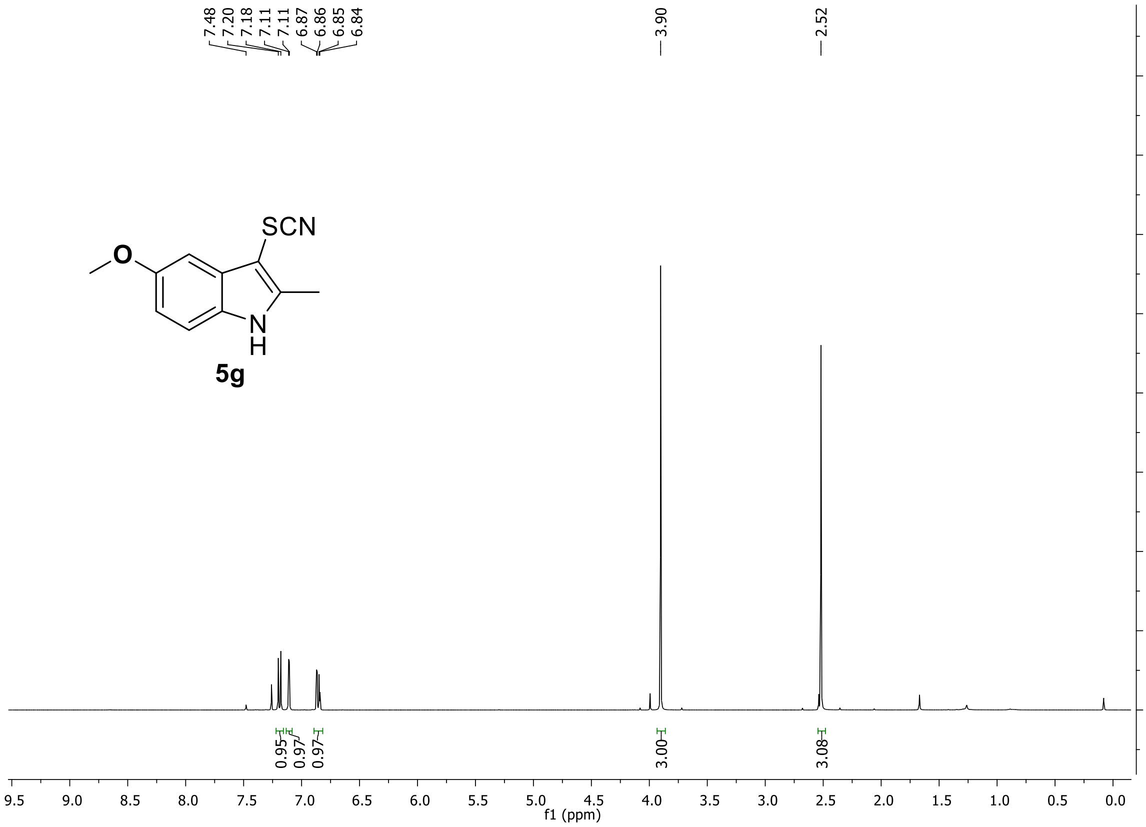


Figure II.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5g**

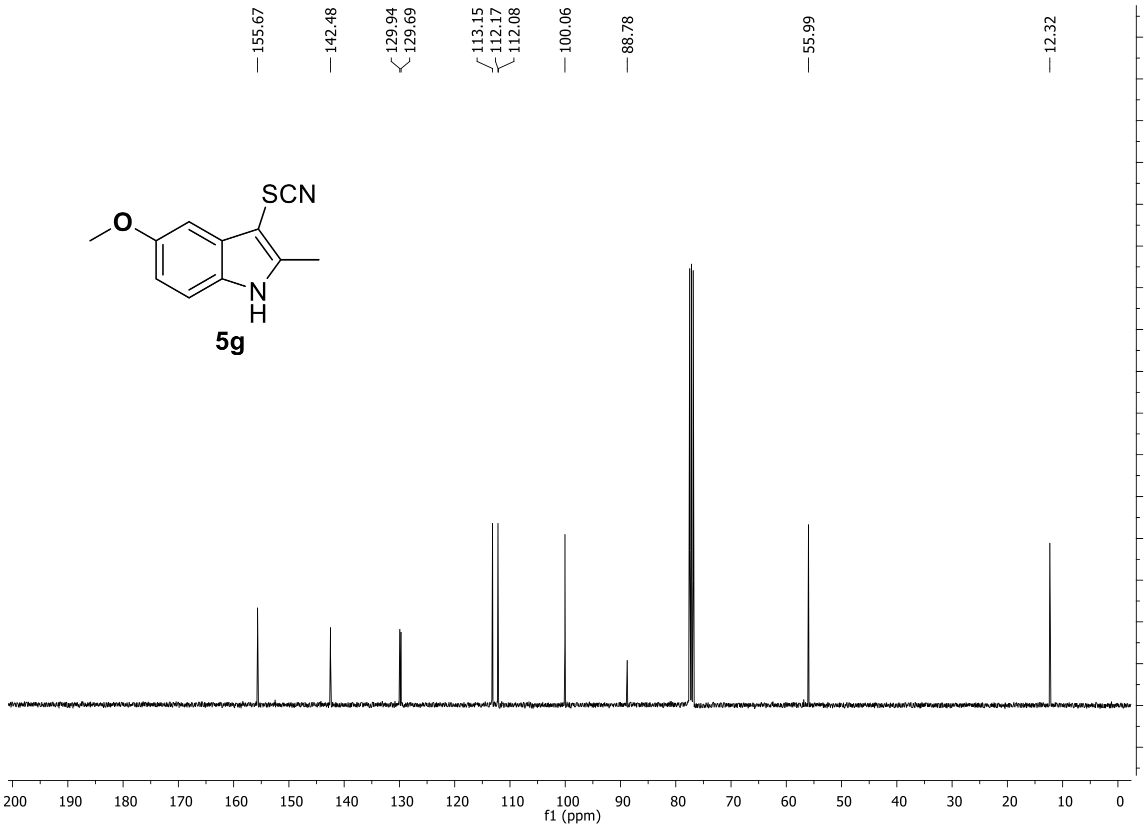


Figure II.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5g**

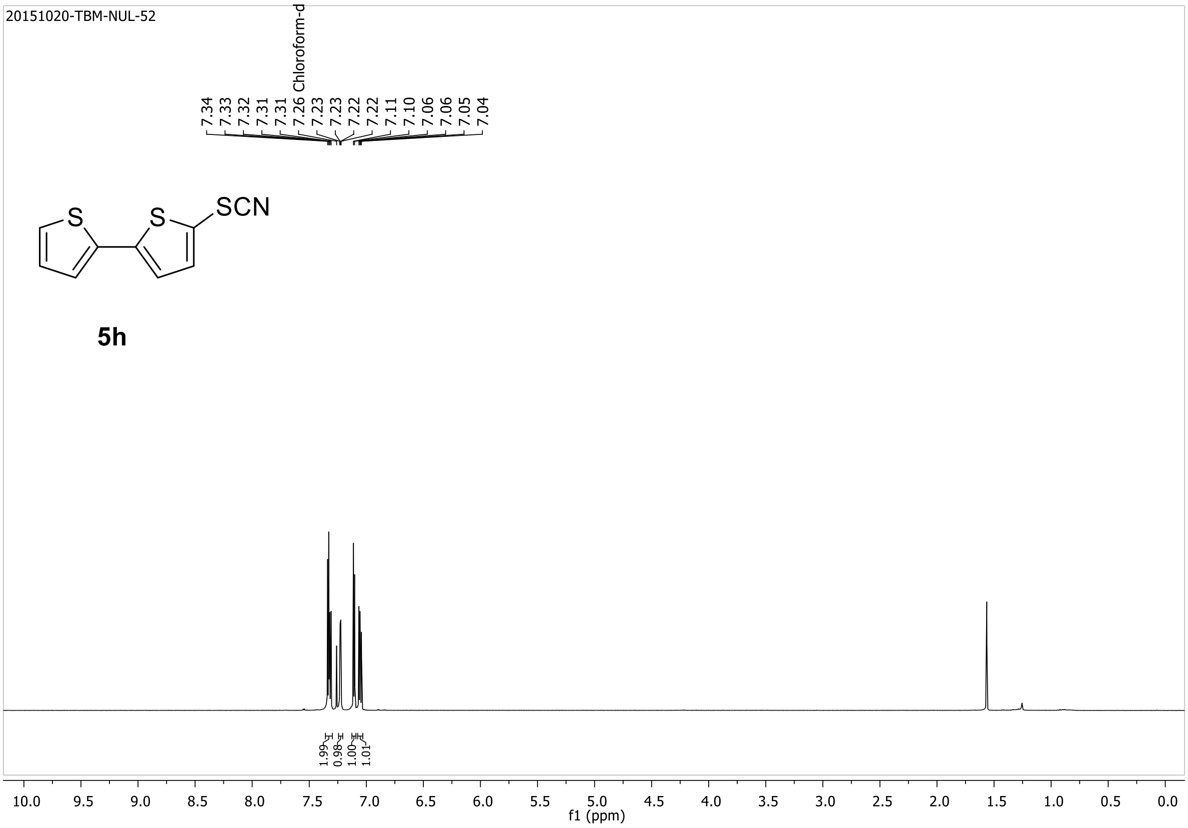


Figure II.9: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **5h**

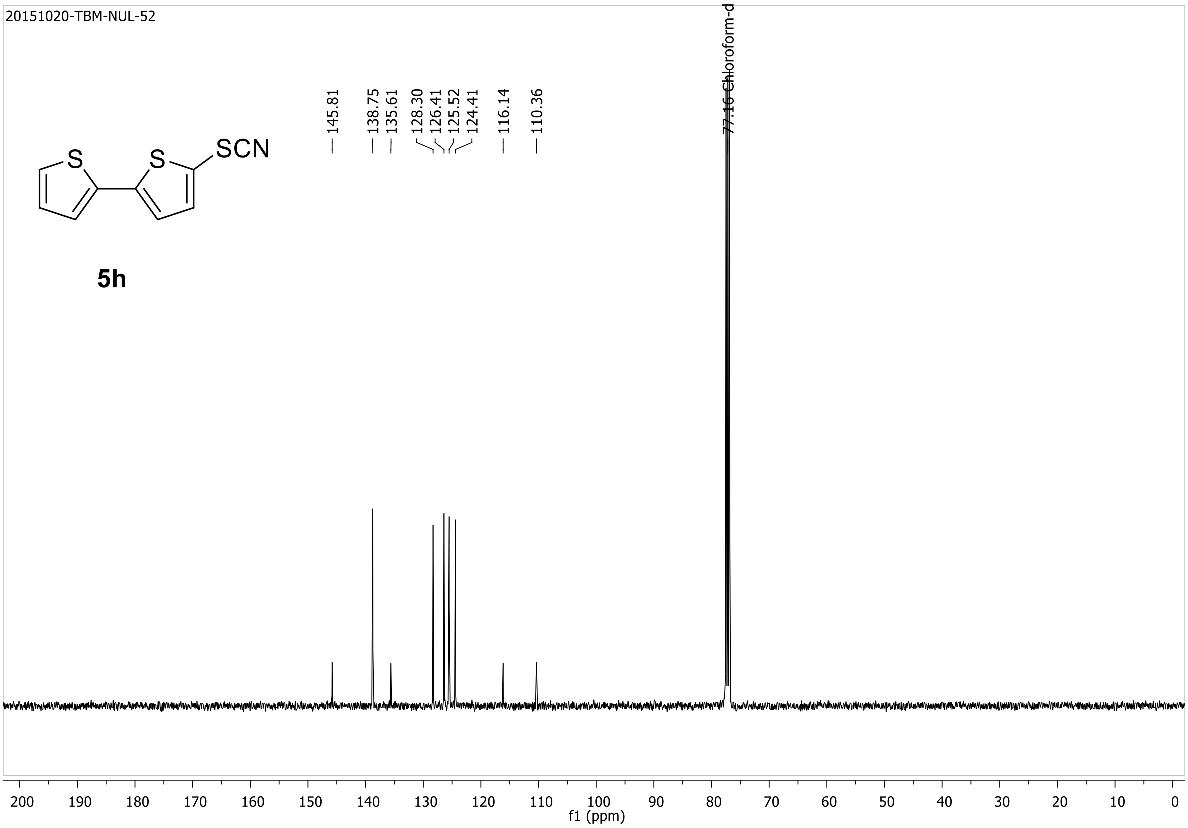


Figure II.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **5h**

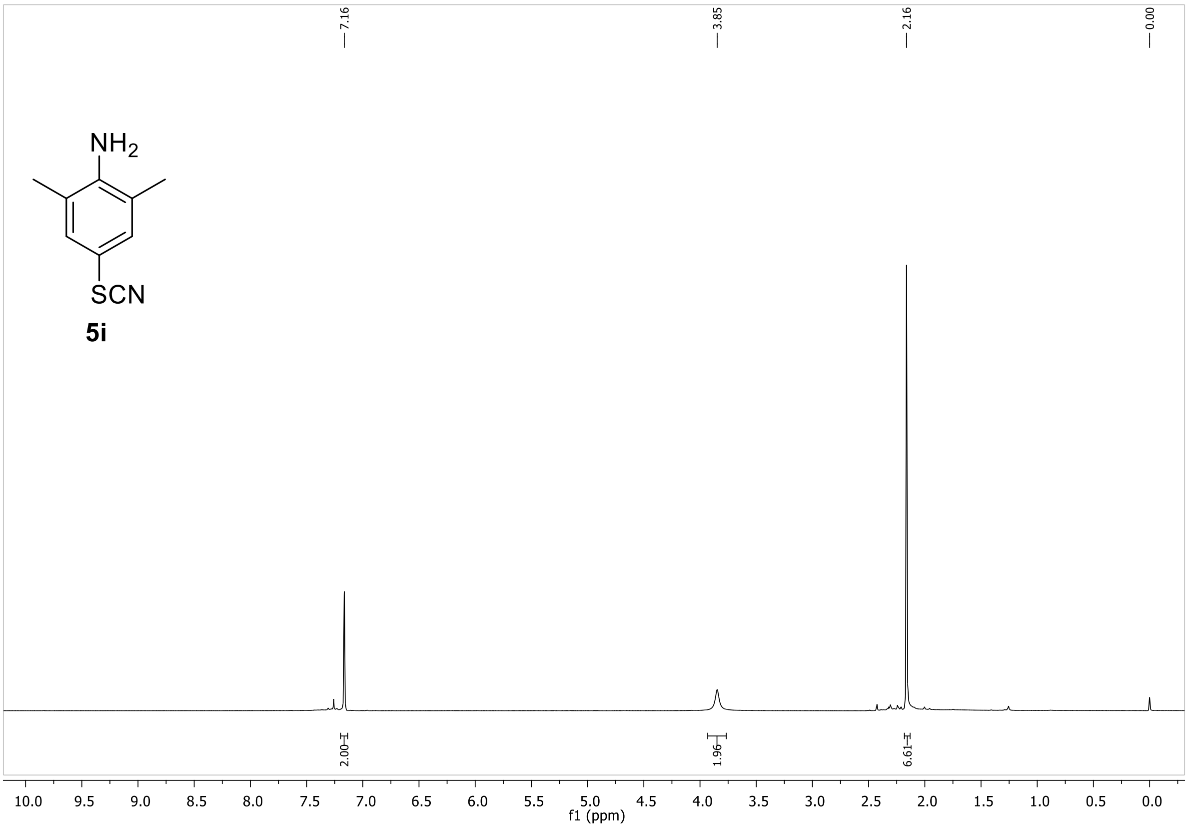


Figure II.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5i**

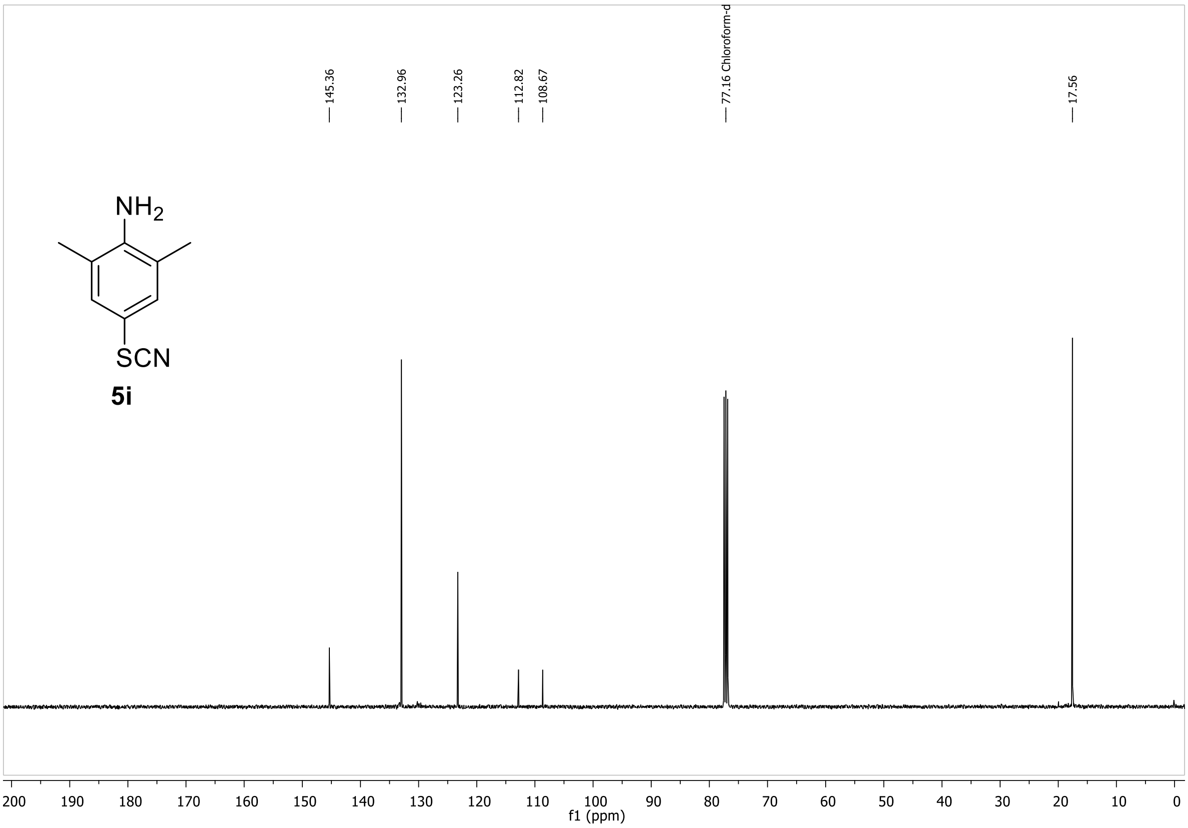


Figure II.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5i**

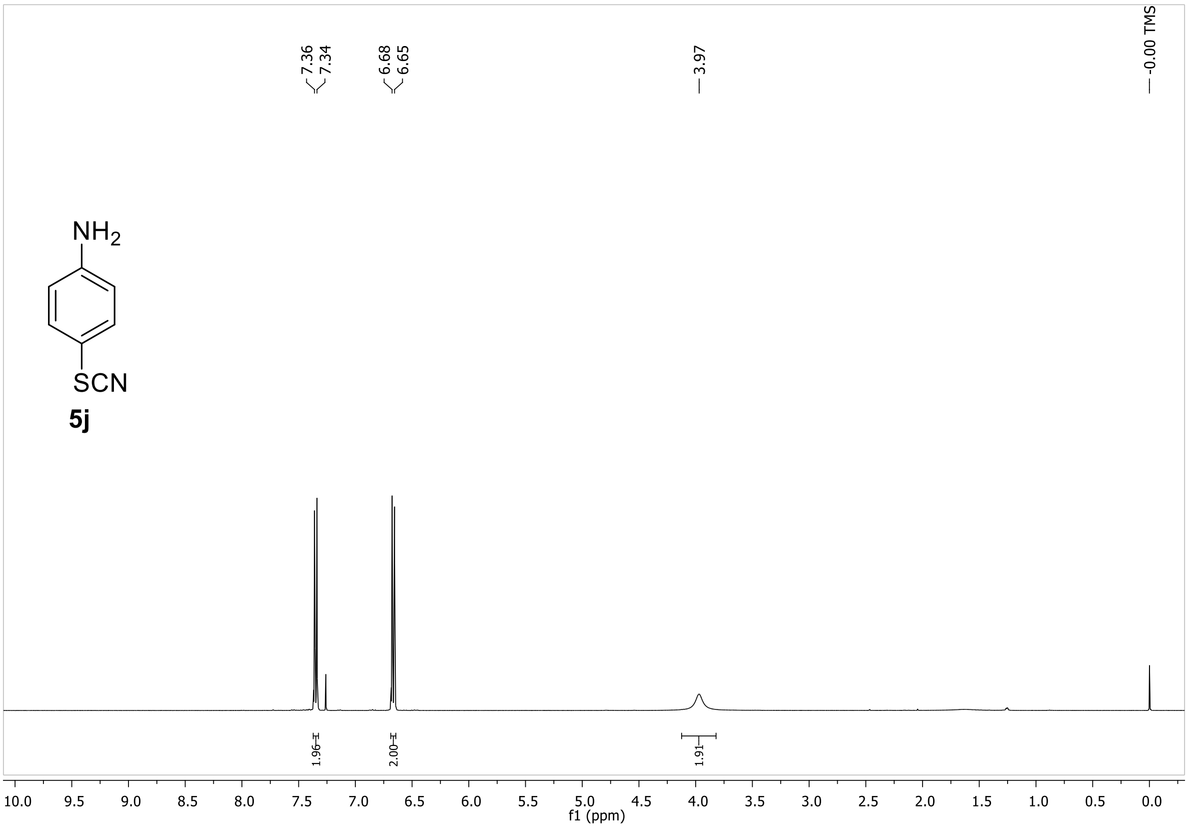


Figure II.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5j**

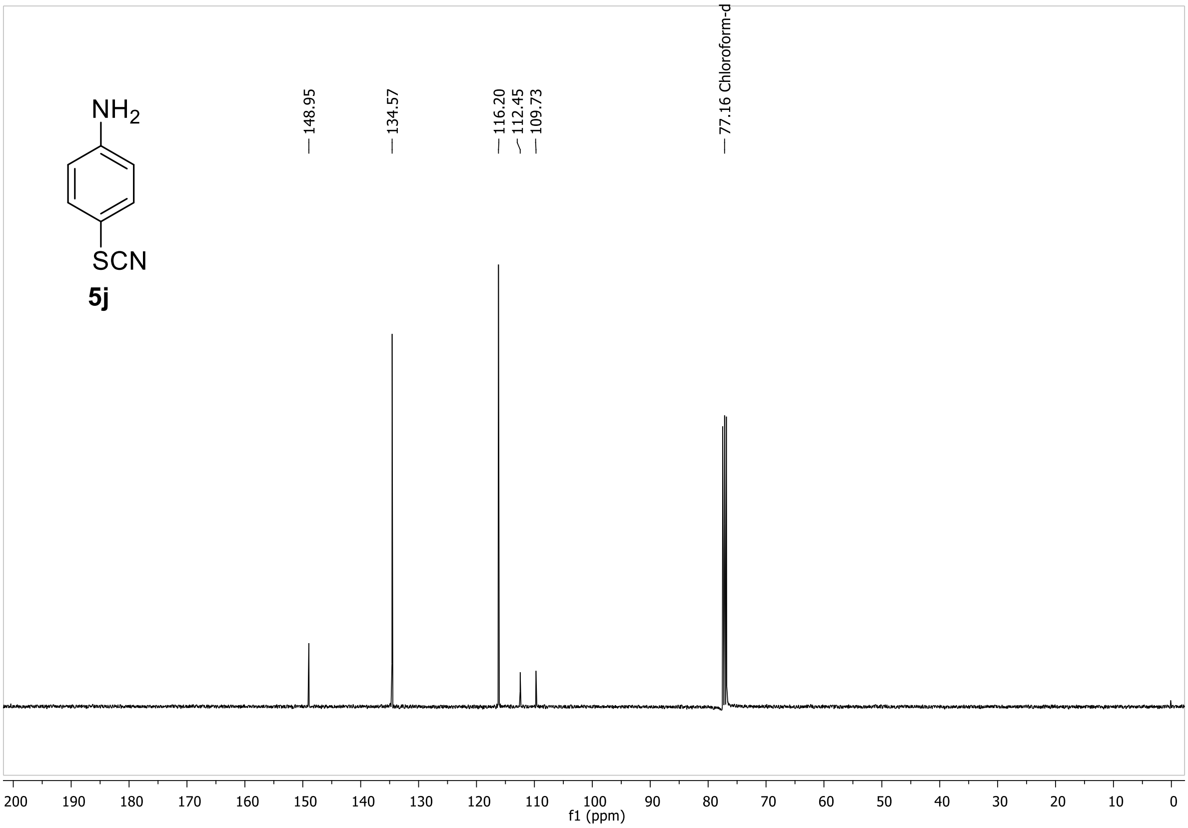


Figure II.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5j**

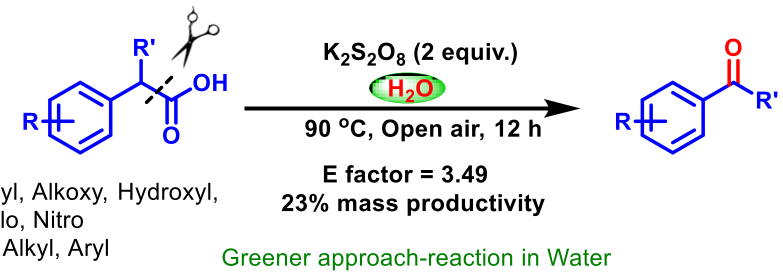
2.9 References and notes

1. (a) Guy RG. In: Patai S, ed. *The Chemistry Cyanates and their Thioderivatives, Part 2*. New York: John Wiley and Sons; **1977**:819 [chapter 18];
   (b) Owens RG. In: Torgeson DC, ed. *In Fungicide: An Advanced Treatise*. New York: Academic Press; 1967:147 [chapter 5];
   (c) Houmam A, Hamed EM, Still IWJ. *J Am Chem Soc*. 2003;125:7258;
   (d) Mackinnon DL, Farrell AP. *Environ Toxicol Chem*. 1992;11:1541.
2. Wei ZL, Kozikowski AP. *J Org Chem*. 2003;68:9116.
3. Verkruijsse HD, Brandsma L. *Synthesis*. 1991;818.
4. (a) Kitagawa I, Ueda Y, Kawasaki T, Mosettig E. *J Org Chem*. 1963;46:3335;
   (b) Toste FD, LaRaronde F, Still IWJ. *Tetrahedron Lett*. 1995;36:2949.
5. (a) Riemschneider R, Wojahn F, Orlick G. *J Am Chem Soc*. 1951;73:5905;
   (b) Riemschneider R. *J Am Chem Soc*. 1956;78:844.
6. Prabhu KR, Ramesha AR, Chandrasekaran S. *J Org Chem*. 1995;60:7142.
7. (a) Wood JL. *Organic Reactions*, Vol 3. New York: Wiley; 1967. 240;
   (b) Kelly TR, Kim MH, Certis ADM. *J Org Chem*. 1993;58:5855.
8. (a) Grant MS, Snyder HR. *J Am Chem Soc*. 1960;82:2742;
   (b) Nair V, Nair LG. *Tetrahedron Lett*. 1998;39:4585;
   (c) Nair V, George TG, Nair LG, Panicker SB. *Tetrahedron Lett*. 1999;40:1195;
   (d) Yadav JS, Reddy BVS, Murali Krishna BB. *Synthesis*. 2008;2008:3779;
   (e) Toste FD, De Stefano V, Still IWJ. *Synth Commun*. 1995;25:1277;
   (f) Nikoofar K. *Chem Sci Trans*. 2013;2:691;
   (g) Fan W, Yang Q, Xu F, Li P. *J Org Chem*. 2014;79:10588;
   (h) Zhu D, Chang D, Shi L. *Chem Commun*. 2015;51:7180;
   (i) Khazaei A, Zolfigol MA, Mokhlesi M, Pirveysian M. *Can J Chem*. 2012;90:427;
   (j) Wu G, Liu Q, Shen Y, Wu W, Wu L. *Tetrahedron Lett*. 2005;46:5831.
9. Uemura S, Onoe A, Okazaki H, Okano M. *Bull Chem Soc Jpn*. 1975;48:619.
10. Taylor EC, Kienzle F. *Synthesis*. 1972;38.
11. Bacon RGR, Guy RG. *J Chem Soc*. 1960;318.
12. Pan X-Q, Lei M-Y, Zou J-P, Zhang W. *Tetrahedron Lett*. 2009;50:347.
13. Kaufmann HP, Kulchler KA. *Eur J Inorg Chem*. 1934;67:944.

14. Kaufmann HP, Oehring W. *Eur J Inorg Chem*. 1926;59:187.
15. Takagi K, Takachi H, Sasaki K. *J Org Chem.* 1995;60:6552.
16. Wang YF, Zhou Y, Wang JR, Liu L, Guo QX. *Chin Chem Lett*. 2006;17:1283.
17. Still IWJ, Watson IDJ. *Synth Commun*. 2001;31:1355.
18. Sun N, Che L, Mo W, Hu B, Shen Z, Hu X. *Org Biomol Chem*. 2015;13:691.
19. Mitra S, Ghosh M, Mishra S, Hajra A. *J Org Chem.* 2015;80:8275.
20. (a) Kaufmann HP, Oehring W. *Ber.* 1926;59B:187;
    (b) Likhosherstov MV, Petrov AA. *J Gen Chem (USSR).* 1933;3:183;
    (c) Kaufmann HP, Kulchler KA. *Ber.* 1934;67B:944;
    (d) Kita Y, Takeda Y, Okuno T, et al. *Chem Pharm Bull*. 1887;1997:45;
    (e) Prakash O, Kaur H, Pundeer R, Dhillon RS, Singh SP. *Synth Commun*. 2003;33:4037.
    (f) Bhalerao DS, Akamanchi KG. *Synlett* 2007;19:2952.
21. (a) Wang H, Guo L-N, Duan X-H. *Org Lett*. 2013;15:5254;
    (b) Lin J-P, Zhang F-H, Long Y-Q. *Org Lett*. 2014;16:2822;
    (c) Siddaraju Y, Lamani M, Prabhu KR. *J Org Chem*. 2014;79:3856;
    (d) Shichao L, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336;
    (e) Yang H, Duan X-H, Zhao J-F, Guo L-N. *Org Lett*. 2015:17;1998;
    (f) Gesu A, Pozzoli C, Torre E, Aprile S, Pirali T. *Org Lett*. 1992;2016:18;
    (g) Yang D, Yan K, Wei W, et al. *J Org Chem*. 2015;80:11073.
22. (a) Minisci F, Citterio A. *Acc Chem Res*. 1983;16:27;
    (b) Hey DH, Jones GH, Perkins MJ. *J C S Perkin* I. 1972;118.
23. (a) Kita Y, Tohma H, Hatanaka K, et al. *J Am Chem Soc*. 1994;116:3684;
    (b) Sankararaman S, Haney WA, Kochi JK. *J Am Chem Soc*. 1987;109:7824.

Chapter 3

Oxidative Decarboxylation of Arylacetic Acids in Water: One-Pot Transition-Metal-Free Synthesis of Aldehydes and Ketones



R = Alkyl, Alkoxy, Hydroxyl,
Halo, Nitro
R' = H, Alkyl, Aryl

Greener approach-reaction in Water
Direct access to Aldehydes and Ketones from aryl acetic acids
24 examples with high yields (up to 92%)
Gram Scale Synthesis
Easy access to ^{18}O-labelled Ketones and Aldehydes

Oxidative Decarboxylation of Arylacetic Acids in Water: One-Pot Transition-Metal-Free Synthesis of Aldehydes and Ketones

3

3.1 Abstract

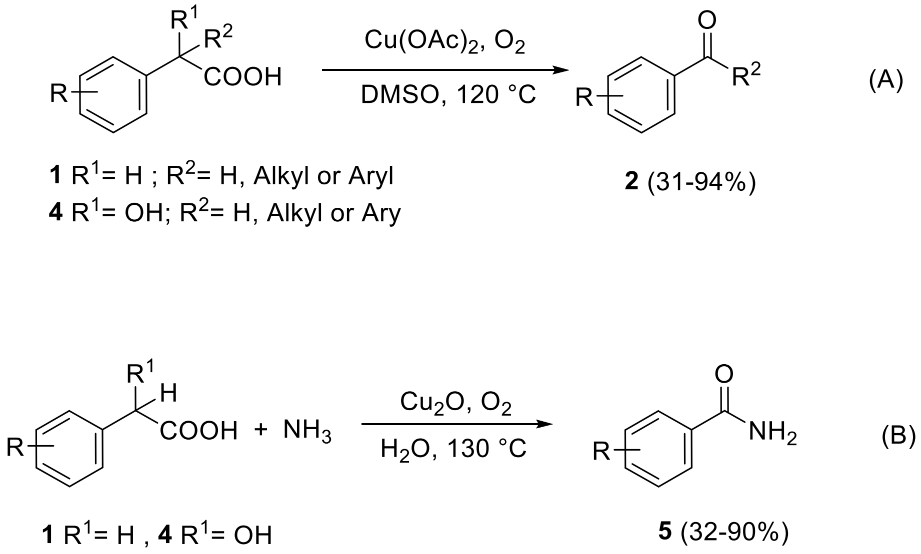
One-pot transition-metal-free synthesis of aromatic aldehydes and ketones via oxidative decarboxylation of arylacetic acids in water is developed. The protocol relies on the direct decarboxylation of sp^3*-hybridized carbon in water without any over oxidation into carboxylic acids with minimal waste. The reaction mechanism is investigated and the application of this protocol is demonstrated on a gram scale.*

3.2 Introduction

Aldehydes and ketones are very important class of compounds and they have been used extensively in wide areas of chemical synthesis.[1] Evidently, the effort towards the quick and short synthesis of aldehydes and ketones always has been desirable. Traditional synthesis of aldehydes and ketones rely on activating the carboxylic acid into a Weinreb amide[2] or into an acyl halide[3] with subsequent nucleophilic attack with hydrides or organometallic species. One-step synthesis of ketones starting from carboxylic acids can be achieved using excess of organolithium reagents; however formation of tertiary alcohols is unavoidable.[4] These harsh conditions can lead to the erosion of stereochemical purity thus leading to partial racemization.[5] Nevertheless, efforts have been made to improvise the existing methods. Cyanocuprates have been explored to convert the carboxylic acids directly into ketones.[6] Quick and efficient cleavage of carbon-carbon bond is one of the most important challenges in organic synthesis.[7]

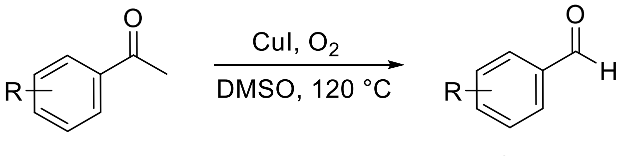
The selective cleavage of C-C σ bond has greatly attracted the attention of researchers in the recent times due to its inert nature. Undoubtedly, development of an efficient protocol for the selective cleavage of C-C σ bond is a great challenge and still much to be explored for the effective utilization. Transition-metal-catalyzed decarboxylation via C-C bond cleavage has been gaining a great importance due its significant role in decarboxylative reactions.[8] Elegant and valuable protocols are developed in this area for making carbon-carbon and carbon-heteroatom bonds starting from carboxylic acids and by cleaving the C-C bond α to the carboxylate group.[9] Also, decarboxylation reactions were carried out at neutral reaction conditions and importantly carbon dioxide liberated as a sole non-toxic by-product. Transition-metal-catalyzed decarboxylation at sp^{2-}hybridized carbon is mostly explored in the literature and more strikingly, decarboxylation at sp^{3-}hybridized carbon to introduce a functional group is relatively rare and challenging.[10]

Very recently transition-metal-catalyzed synthesis of aldehydes and ketones **2** were reported by Song and co-workers using aerobic oxidative decarboxylation of phenylacetic acids **1** and α-hydroxyphenylacetic acids **4**. This transformation was performed using copper acetate and oxygen as a sole oxidant to afford the corresponding aldehydes and ketones in modest to excellent yields (Scheme 3.1A). [11] Likewise, a Cu_2O-catalyzed decarboxylative ammoxidation of phenylacetic acids **1** and α-hydroxyphenylacetic acids **4** with ammonia in water was also developed by Song and co-workers to afford the corresponding amides **5** in modest to excellent yields (Scheme 3.1B).[12] This transformation involved the sequential decarboxylation, dioxygen activation, oxidative C-H bond functionalization and amidation reactions in one-pot to afford the corresponding primary aromatic amides **5**.



Scheme 3.1 Synthesis of aldehydes, ketones and amides

Zang et al. explored the reactivity of cuprous salt for the novel synthesis of aldehydes starting from methyl ketones in presence of oxygen.[13] A wide range of aromatic as well as aliphatic methyl ketones **6** were subjected to this copper-catalyzed reaction under oxygen atmosphere at relatively higher temperature (120 °C) to afford the corresponding aldehydes **2** in good to excellent yields **(**Scheme 3.2**)**. This oxidative transformation terminates at the aldehyde **2** stage, by releasing hydrogen (H_2) and carbon dioxide (CO_2) as by-products.

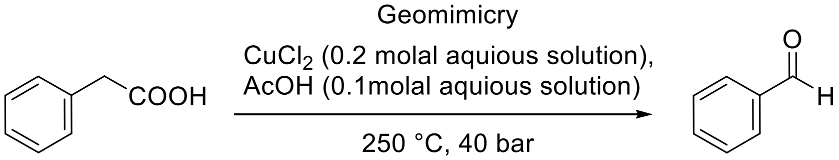


6

2 (64-97%)

Scheme 3.2 Synthesis of aldehydes from methyl ketones

Yang et al. described a decarboxylative non-aerobic oxidation of phenylacetic acid **1d** to benzaldehyde **2d** using cupric salts at high temperature and pressure in water (250 °C and 40 bar) (Scheme 3.3).[14] The protocol mimicked the geochemically relevant conditions to achieve the decarboxylative conditions to access aldehyde.

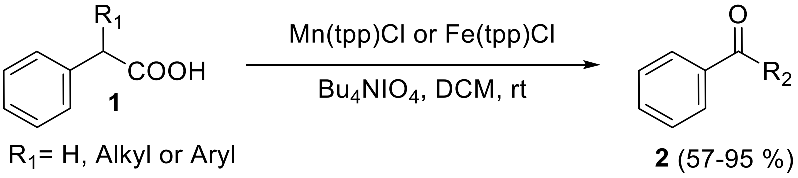


1d

2d

Scheme 3.3 Decarboxylative oxidation using geomimicry

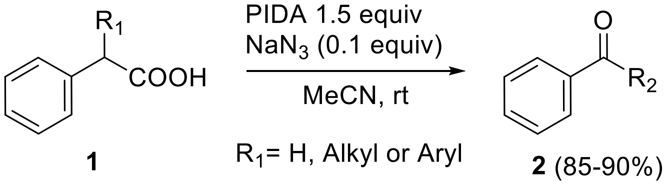
Mirkhani and co-workers utilized the combination of iron(III)/manganese(III) tetraphenylprorphyrins and tetrabutylammonium periodate as an oxidant for the effective decarboxylation of carboxylic acids **1** to afford aldehydes and ketones **2** in 1,4-dioxane under refluxing condition (Scheme 3.4).[16] The protocol gave a direct access to aldehydes and ketones in moderate to excellent yields (57- 95 %).



Scheme 3.4 Iron/Manganese catalyzed decarboxylation to access aldehydes and ketones

All of these above mentioned protocols rely on transition metals, viz. copper, iron and manganese for catalyzing the transformations.[15] However, there are only countable protocols for the oxidative decarboxylation of aryl carboxylic acids under transition-metal-free conditions.

Telvekar et al. demonstrated the synthetic utility of hypervalent iodine reagent, (diacetoxyiodo)benzene (PIDA) and catalytic amount of sodium azide in acetonitrile for oxidative decarboxylation of 2-aryl carboxylic acids **1** into the corresponding aldehydes and ketones **2** in good to excellent yields (up to 90 %, Scheme 3.5).[17]



Scheme 3.5 PIDA/NaN$_3$ mediated decarboxylation to afford aldehydes and ketones

Thus development of more easier, practical and non-hazardous protocol for the synthesis of aldehydes and ketones via oxidative decarboxylation under transition-metal-free conditions are highly desirable. There are ambiguities in defining a true 'green method'. However, some of the most accepted guiding principles such as minimal waste, higher mass productivity; lower E-factor, non-toxicity etc. define the greener methods. Practical, efficient and highly selective transition-metal-free transformations using environmentally benign, less expensive and readily available reagents are gaining a great importance for the last few years.[18] As a part of our ongoing efforts to develop transition-metal-free protocols,[19] we herein, report an oxidative decarboxylative strategy for the direct and clean synthesis of aldehydes and ketones without over oxidation into carboxylic acids in water with a minimal waste and lower E-factor. This simple protocol uses potassium persulfate as a reagent and makes the novel use of it for the synthesis of aldehydes and ketones starting from arylacetic acids.

3.3 Results and discussion

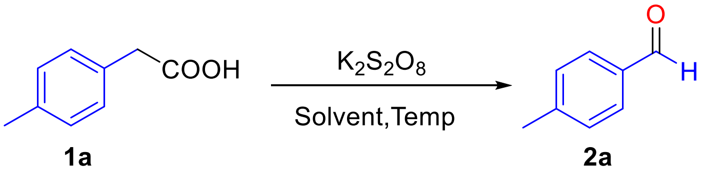
3.3.1 Optimization studies

In order to explore the transition-metal-free decarboxylative strategy for the direct synthesis of aldehydes and ketones, we commenced our initial work with 4-methyl phenylacetic acid **1a** with $K_2S_2O_8$ as a model reaction (Table 3.1). Attempted reaction of **1a** with $K_2S_2O_8$ (2 equiv.) in CH_3CN/H_2O (1:1) at room temperature (both in air and inert condition) did not work even after prolonged reaction time (entry 1, Table 3.1). Interestingly, when the reaction was carried out at elevated temperature (80 $^{\circ}$C), to our delight, the desired product, 4-methylbenzaldehyde **2a** was formed in 75% isolated yield (Table 3.1, entry 2) in 12 h. With this initial result in hand, further the reaction was screened in different solvent conditions. However, the reaction was sluggish in CH_3CN and DCE (entry 3 - 6) and afforded only a trace amount of desired product **2a**. However, the reaction in DCE/H_2O at 80 ^{o}C afforded the desired product in 60% yield (entry 7). Interestingly, the model reaction worked efficiently only in water at 80 $^{\circ}$C affording the desired product 4-methyl benzaldehyde **2a** in 75% yield (entry 8).

Gratifyingly, with the elevated temperature (90 ^{o}C) under aerial condition reaction afforded the compound **2a** in excellent yield of 85% (entry 9). Oxidants such as PIDA, PIFA and Oxone were found to be ineffective reagents for the desired transformation (entry 10-12). Attempts to lower the reaction temperature resulted in lower yield with incomplete conversion of the starting material (entry 13). Reactions under oxygen or open air atmosphere did not change the course of the reaction and also did not have any significant effect on the yield or reaction time (entry 9, 14). Reaction did not work in the absence of potassium persulfate (entry 15). After extensive screening of solvents and different temperatures, the optimum reaction condition was emerged as 4-methylphenyl acetic acid **1a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 90 ^{o}C in water under aerial atmosphere (entry 9, Table 3.1) in 12 h.

It is also important to note that persulfates are very popular for their ability to oxidize variety of contaminants in ground water via ‘in situ chemical oxidation’ (ISCO).[20] Persulfates are known to be benign, eco-friendly or green and low cost reagent.[21]

Table 3.1. Optimization of the reaction conditions[a-c]



Entry	**Reagent**	**Solvent**	**Temp (°C)**	**Atm**	**Yield[b] (%)**
1	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	rt	air	NR
2	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	80	air	75
3	$K_2S_2O_8$	CH_3CN	reflux	air	trace
4	$K_2S_2O_8$	CH_3CN	reflux	O_2	trace
5	$K_2S_2O_8$	MeOH	reflux	air	NR
6	$K_2S_2O_8$	DCE	90	O_2	Trace
7	$K_2S_2O_8$	DCE/ H_2O (1:1)	80	air	60
8	$K_2S_2O_8$	H_2O	80	air	75
9	**$K_2S_2O_8$**	**H_2O**	**90**	**air**	**85**
10	PIDA	H_2O	90[c]	air	27
11	PIFA	H_2O	90[c]	air	21
12	Oxone	H_2O	90[c]	air	15
13	$K_2S_2O_8$	H_2O	50	air	20
14	$K_2S_2O_8$	H_2O	90	O_2	83
15	-	H_2O	90	air	-

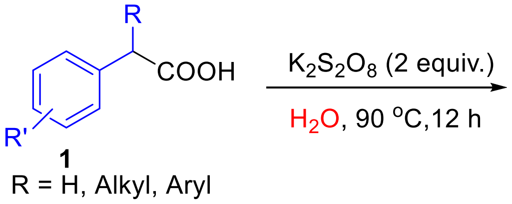
[a]Reaction conditions: 4-methylphenyl acetic acid **1a** (1 equiv.), potassium persulfate (2 equiv.), solvent (2 mL) under corresponding atmosphere for 12 h, [b]Isolated yield after purification by column chromatography. [c]reactions did not work at rt.

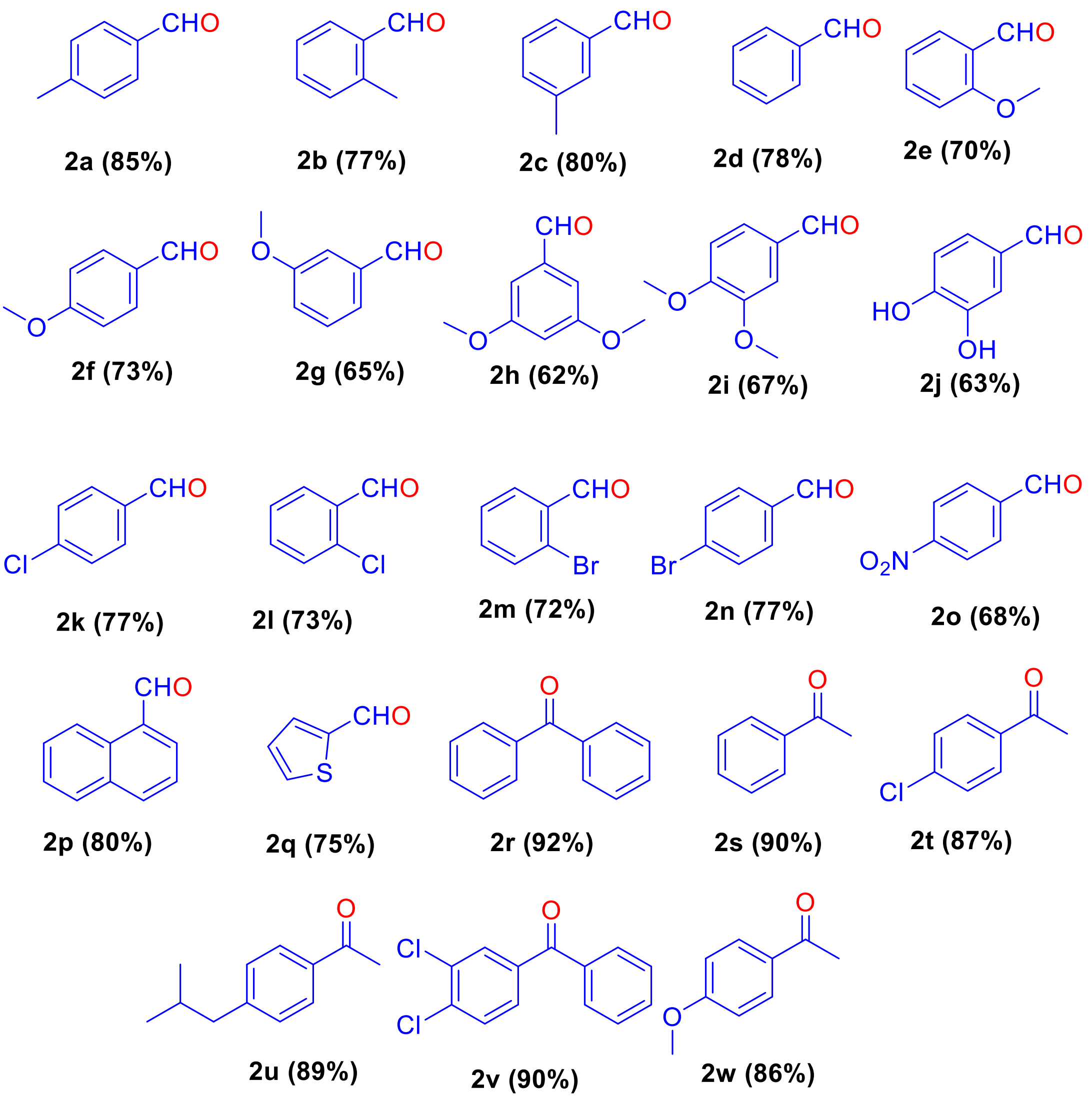
3.3.2 Substrate scope for aldehydes and ketones

Encouraged by the initial success and with an optimized reaction condition in hand; we explored the substrate scope of the method. Under optimum reaction conditions arylacetic acids (**1a-1o**) possessing the electron-donating as well as electron withdrawing groups reacted smoothly by affording the corresponding aldehydes (**2a-2o**) in moderate to good yields (Table 3.2). 1-naphthylacetic acid **1p** reacted smoothly and gave the corresponding naphthaldehyde **2p** in 80% yield. Similarly, the heteroaromatic acid such as 2-thienylacetic acid **1q** under reaction conditions afforded the 2-thienylcarboxylaldehyde (**2q**). α-Substituted phenyl acetic acids (**1r-1w**) under optimum reaction conditions afforded the corresponding ketones (**2r-2w**) in excellent yields (86-92%, Table 3.2).

The anti-inflammatory drug, ibuprofen **1u** afforded the corresponding ketone[22] **2u** in excellent yield as well. Interestingly, the amino acid phenyl glycine **1x** afforded benzaldehyde **2d** instead of the anticipated amide. Probably, imine might have formed during the course of reaction, which upon hydrolysis resulted in **2d**. The position of the substituents on the ring had no significant and noticeable effect on the reaction rate and yields. Functional group such as hydroxyl, chloro, bromo, methoxy and nitro were well tolerated. However, unfortunately, attempted reactions of aliphatic acids such as 3-butenoic acid, *tert*-butyl acetic acid and valeric acid did not afford the desired products.

Table 3.2. Oxidative decarboxylation of arylacetic acids to aldehydes and ketones[a,b]





2a (85%) **2b** (77%) **2c** (80%) **2d** (78%) **2e** (70%)

2f (73%) **2g** (65%) **2h** (62%) **2i** (67%) **2j** (63%)

2k (77%) **2l** (73%) **2m** (72%) **2n** (77%) **2o** (68%)

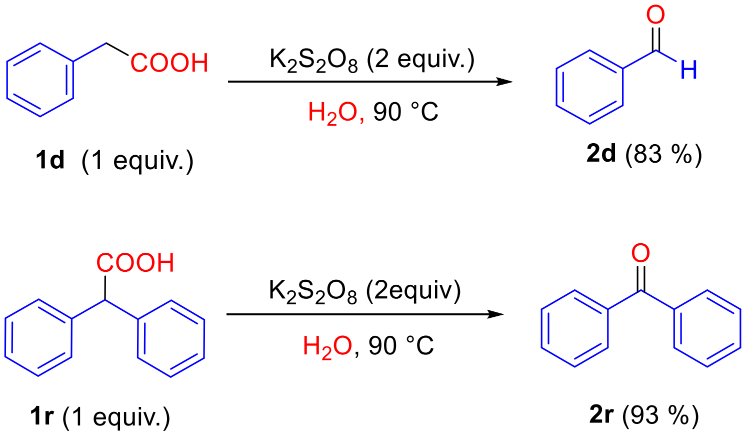
2p (80%) **2q** (75%) **2r** (92%) **2s** (90%) **2t** (87%)

2u (89%) **2v** (90%) **2w** (86%)

[a] Reaction conditions: arylacetic acid **1** (1equiv.), potassium persulfate (2 equiv.), water (2 mL) open atmosphere; reaction was monitored by TLC. [b] Isolated yield after purification by column chromatography.

3.3.3 Gram Scale Synthesis

To make the protocol more general and for the wider applicability we demonstrated the synthesis of benzaldehyde **2d** (83%) and benzophenone **2r** (93%) on a gram scale starting from the corresponding arylacetic acids **1d** and **1r** respectively under optimum conditions (Scheme 3.6).

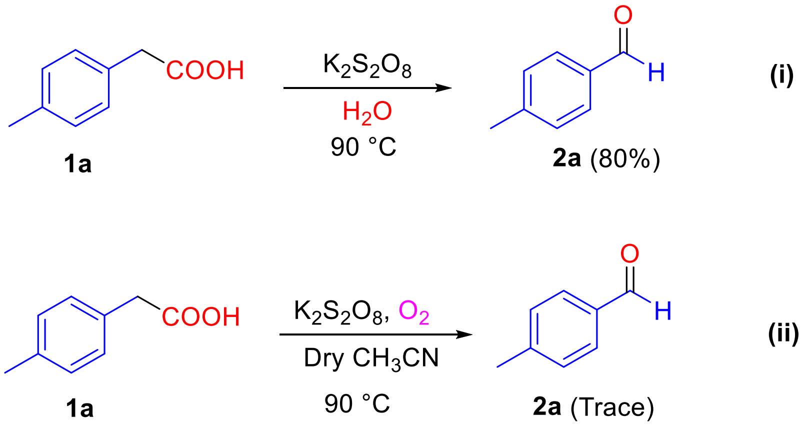


Scheme 3.6 Gram scale synthesis of benzaldehyde and benzophenone

During the optimization we observed that reaction worked efficiently in water under atmosphere of air as well as oxygen. Effective minimization of reagents in this protocol led to a minimal waste (free from halogen and transition metals), thus producing only 3.5 g of waste for every 1 g of the product formed. It is also gratifying to note that this one pot reaction with E (environmental) factor of 3.49[23] and mass productivity of 23% (mass intensity 4.5)[23] satisfies the defined metrics[24] for the cleaner and greener chemical processes (see Experimental Section, **3.7.2** for the calculation details).

3.4 Mechanistic Investigations

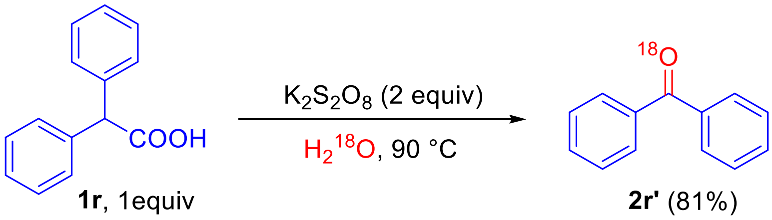
In order to investigate and elucidate the reaction mechanism few control experiments were carried out. Compound **1a** when treated with $K_2S_2O_8$ (2 equiv.) in water under inert conditions afforded the corresponding aldehyde **2a** in good yield (80%, eq i, Scheme 3.7**)**. This experiment indicates that oxygen did not have any role in the reaction mechanism. Interestingly, reaction did not work in the absence of water (eq ii, Scheme 3.7).



Scheme 3.7 Control experiments

3.4.1 ^{18}O labelling experiment

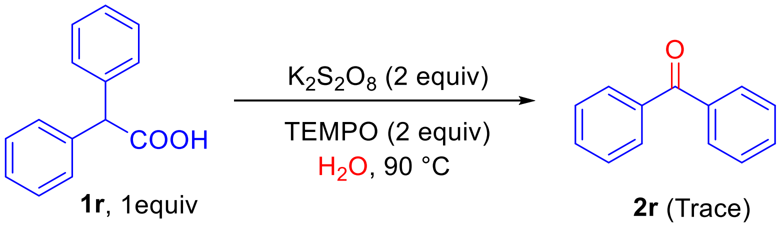
To validate the role of water in the reaction, compound **1r** was treated with $K_2S_2O_8$ (2 equiv.) in labeled water ($H_2^{18}O$, 97%) under inert condition for 12 hours. To our delight we isolated the corresponding **2r'** in excellent yield (81%, Scheme 3.8). Presence of ^{18}O was confirmed by the HRMS and GC-mass spectrometry (^{18}O content 96.3%, see Experimental Section, **3.7.4**). It is very significant to note that this protocol gives a direct access to prepare ^{18}O-labeled aldehydes and ketones quantitatively without resorting to an exchange experiment (Scheme 3.8).



Scheme 3.8 ^{18}O labelling experiment

3.4.2 Radical quenching experiment

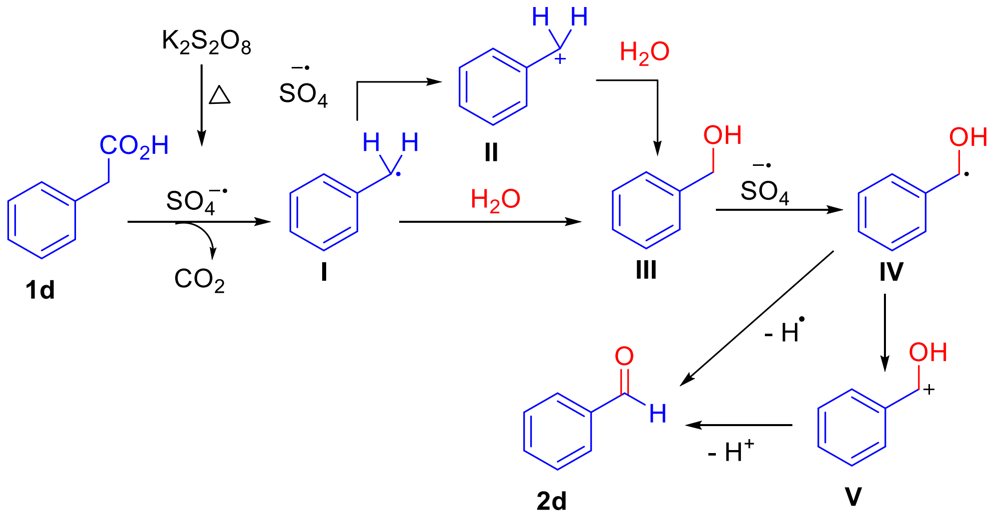
Later, to gain further insight into the mechanism, diphenylacetic acid **1r** was treated with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard optimum reaction conditions. The result showed that reaction did not proceed even after prolonged reaction time indicating that TEMPO inhibited the radical pathway (Scheme 3.9).



Scheme 3.9 Radical quenching experiment

3.5 Proposed Mechanism

Based on our investigations and previous literature[25] we propose that sulfate anion radical ($SO_4^{\bullet -}$) (produced by the decomposition of potassium persulfate) upon reaction with phenylacetic acid **1d** generates benzyl radical **I** by the extrusion of carbon dioxide



Scheme 3.10. Plausible mechanism for the formation of aldehyde and ketones

(Scheme 3.10). $SO_4^{\bullet -}$ further oxidizes the benzyl radical **I** to the corresponding benzyl carbocation **II** via one electron oxidation. This reactive species reacts with water to form the corresponding benzyl alcohol **III**. The persulfate anion radical further oxidizes benzyl alcohol to the corresponding intermediates **IV** and **V**. Ultimately, the loss of proton from **V** would afford the desired product, benzaldehyde **2d**. Alternatively, intermediate **IV** would directly afford benzaldehyde **2d** by the loss of hydrogen radical (Scheme 3.10).

3.6 Conclusions

In conclusion we have demonstrated a one-pot protocol for the direct and clean transformation of arylacetic acids to aldehydes and ketones in water with minimal waste. The protocol employed environmentally friendly and less expensive $K_2S_2O_8$ as reagent, and commercially available arylacetic acids without any over oxidation. Method also demonstrated the direct access to ^{18}O-labeled aldehydes and ketones without relying on any exchange experiment. Experimental conditions are simple and above all reaction is carried out only in water and it has been demonstrated on a gram scale for wider application.

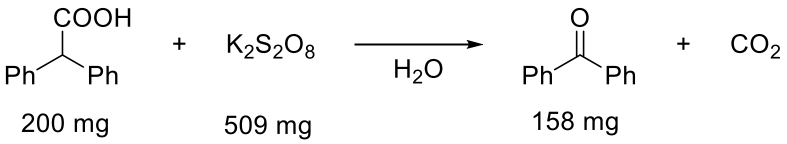
3.7 Experimental Section

3.7.1 General

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminium backed plates (2.5 mm). ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR data are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of Chloroform-d. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF (+ ve ion mode). IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. All reactions were carried out in dried glassware. Distilled water was used for the reaction. All purchased chemicals were used without further purification. Column chromatography was carried out using silica gel.

3.7.2 E Factor, Mass Productivity and Mass Intensity for Aldehyde and Ketone-Representative Examples:

For the synthesis of Benzophenone 2r:



Total amount of reactant = 200mg + 509mg = 709mg
Amount of product = 158mg
Amount of waste = 709mg - 158mg = 551mg

$$\text{E Factor} = \frac{\text{Amount of waste}}{\text{Amount of product}} = \frac{551}{158}$$

E Factor = 3.49

$$\text{Mass productivity} = \frac{\text{Amount of product}}{\text{Total amount of reactant}} \text{ X } 100$$

$$= \frac{158}{709} \text{ X } 100$$

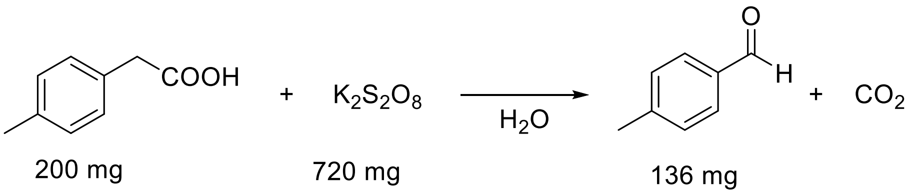
Mass productivity = 22.58 %

$$\text{Mass Intensity} = \frac{\text{Total amount of reactant}}{\text{Amount of product}}$$

$$= \frac{709}{158}$$

Mass Intensity = 4.48

For the synthesis of 4-methyl benzaldehyde 2a:



Total amount of reactant = 200mg + 720mg = 920mg
Amount of product = 136mg
Amount of waste = 920mg - 136mg = 784mg

$$\text{E Factor} = \frac{\text{Amount of waste}}{\text{Amount of product}} = \frac{784}{136}$$

E Factor = 5.76

$$\text{Mass productivity} = \frac{\text{Amount of product}}{\text{Total amount of reactant}} \text{ X } 100$$

$$= \frac{136}{920} \text{ X } 100$$

Mass productivity = 14.78 %

$$\text{Mass Intensity} = \frac{\text{Total amount of reactant}}{\text{Amount of product}}$$

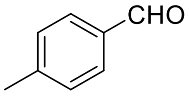
$$= \frac{920}{136}$$

Mass Intensity = 6.76

3.7.3 General Procedure for the preparation of Aldehydes and Ketones from Aryl acetic acids:

In an oven dried tube containing a mixture of 4-methyl phenyl acetic acid **1a** (200 mg, 1.33 mmol) and potassium persulfate (360 mg, 2.66 mmol), water (2 mL) was added and heated at 90 °C for 12 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature (24 ^{o}C) and it was extracted with ethyl acetate (3 x 5 mL). The crude product was purified by column chromatography to furnish compound **2a** as colorless liquid (136 mg, 85% yield).

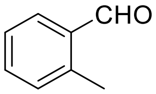
4-methylbenzaldehyde (2a):



2a

IR (neat) cm^{-1}: 2827, 2734, 1689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 145.7, 134.3, 129.8, 130.0, 22.0; HRMS (ESI TOF) *m/z* calcd for C_8H_8O $[M + H]^+$ 121.0653, found 121.0654.

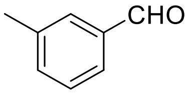
2-methylbenzaldehyde (2b):



2b

The compound **2b** was synthesized starting from **1b** following the general procedure described for **2a**; the compound **2b** was obtained as a colourless liquid. (124 mg, 77%yield). IR (neat) cm^{-1}: 2857, 2736, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.80 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 140.7, 134.3, 133.8, 132.2, 131.9, 126.4, 19.7; HRMS (ESI TOF) *m/z* calcd for C_8H_8O $[M + H]^+$ 121.0653, found 121.0658.

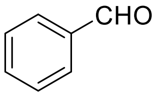
3-methylbenzaldehyde (2c):



2c

The compound **2c** was synthesized starting from **1c** following the general procedure described for **2a**; the compound **2c** was obtained as a colourless oil (129 mg, 80% yield). IR (neat) cm^{-1}: 2826, 2728, 1694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.68 – 7.66 (m, 2H), 7.45 – 7.39 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.67, 139.0, 136.6, 135.4, 130.1, 129.0, 127.3, 21.3;HRMS (ESI TOF) *m/z* calcd for C_8H_8O $[M + H]^+$ 121.0653, found 121.0657.

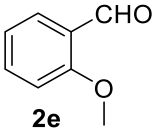
Benzaldehyde(2d):



2d

The compound **2d** was synthesized starting from **1d** following the general procedure described for **2a**; the compound **2d** was obtained as a colourless liquid (121 mg, 78% yield). IR (neat) cm^{-1}:2818, 2738, 1694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89 – 7.87 (m, 2H), 7.65 – 7.61 (m, 1H), 7.55 – 7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 136.5, 134.6, 129.9, 129.1; HRMS (ESI TOF) *m/z* calcd for C_7H_6O $[M + H]^+$ 107.0497, found 107.0501.

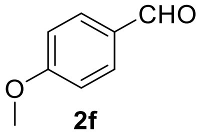
2-methoxy benzaldehyde (2e):



2e

The compound **2e** was synthesized starting from **1e** following the general procedure described for **2a**; the compound **2e** was obtained as a yellowish liquid (115 mg, 70% yield). IR (neat) cm^{-1}: 2849, 2763, 1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.81 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.03 – 6.97 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 161.9, 136.1, 128.6, 124.9, 120.7, 111.7, 55.7; HRMS (ESI TOF) *m/z* calcd for $[M + H]^+$ 137.0602, found 137.0605.

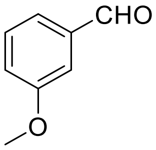
4-methoxy benzaldehyde (2f):



2f

The compound **2f** was synthesized starting from **1f** following the general procedure described for **2a**; the compound **2f** was obtained as a yellowish liquid (120 mg, 73% yield). IR (neat) cm^{-1}: 2838, 2740, 1681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 164.7, 132.1, 130.0, 114.4, 55.7; HRMS (ESI TOF) *m/z* calcd for $C_8H_8O_2$ $[M + H]^+$ 137.0602, found 137.0607.

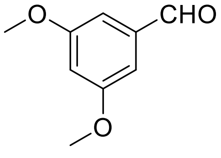
3-methoxy benzaldehyde (2g):



2g

The compound **2g** was synthesized starting from **1g** following the general procedure described for **2a**; the compound **2g** was obtained as a yellowish liquid (107 mg, 65% yield). IR (neat) cm^{-1}: 2838, 2731, 1695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.46 – 7.42 (m, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.19 – 7.16 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 160.3, 137.9, 130.2, 123.7, 121.7, 112.1, 55.6; HRMS (ESI TOF) *m/z* calcd for $C_8H_8O_2$ $[M + H]^+$ 137.0602, found 137.0607.

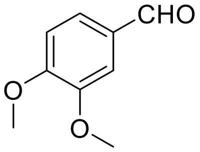
3,5-dimethoxy benzaldehyde (2h):



2h

The compound **2h** was synthesized starting from **1h** following the general procedure described for **2a**; the compound **2h** was obtained as a light yellow solid (110 mg, 62% yield) m.p.: 47-49°C; IR (neat) cm^{-1}: 2840, 2729, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.99 (s, 2H), 6.69 (s, 1H), 3.83 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 161.3, 138.5, 107.3, 107.2, 55.7; HRMS (ESI TOF) *m/z* calcd for $C_9H_{10}O_3$ $[M + H]^+$ 167.0708, found 167.0712.

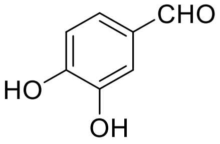
3,4-dimethoxy benzaldehyde (2i):



2i

The compound **2i** was synthesized starting from **1i** following the general procedure described for **2a**; the compound **2i** was obtained as a pale yellow solid (112 mg, 67% yield). m.p.: 41-43°C; IR (neat) cm^{-1}: 2838, 2755, 1678; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.47 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 154.5, 149.6, 130.2, 127.0, 110.4, 108.9, 56.2, 56.0; HRMS (ESI TOF) *m/z* calcd for $C_9H_{10}O_3$ $[M + H]^+$ 167.0708, found 167.0713.

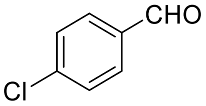
3,4-dihydroxy benzaldehyde (2j):



2j

The compound **2j** was synthesized starting from **1j** following the general procedure described for **2a**; the compound **2j** was obtained as a pale yellow solid (104 mg, 63% yield). m.p.: 152-155°C; IR (neat) cm^{-1}: 3285, 3217, 2958, 2913, 1649; ^1H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.27 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.24 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.2, 152.2, 146.0, 129.0, 124.6, 115.6, 114.4; HRMS (ESI TOF) *m/z* calcd for $C_7H_6O_3$ $[M + H]^+$ 139.0395, found 139.0394.

4-Chloro benzaldehyde (2k)

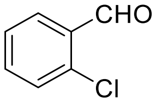


2k

The compound **2k** was synthesized starting from **1k** following the general procedure described for **2a**; the compound **2k** was obtained as a white solid (126 mg, 77% yield).
m.p.: 47-49 °C; IR (neat) cm^{-1}: 2858, 2761, 1688; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

191.0, 141.1, 134.8, 131.0, 129.6; HRMS (ESI TOF) *m/z* calcd for C_7H_5ClO [M + H]$^+$ 141.0107, found 141.0112.

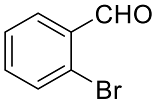
2-chloro benzaldehyde (2l):



2l

The compound **2l** was synthesized starting from **1l** following the general procedure described for **2a**; the compound **2l** was obtained as a colourless liquid (121 mg, 73% yield). IR (neat) cm^{-1}: 2870, 2755, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.92 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.3, 7.1, 1.8 Hz, 1H), 7.45 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.38 (td, *J* = 7.9, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 138.1, 135.3, 132.5, 130.7, 129.5, 127.4; HRMS (ESI TOF) *m/z* calcd for C_7H_5ClO [M + H] +141.0107, found 141.0112.

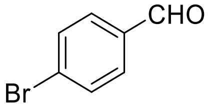
2-bromo benzaldehyde (2m):



2m

The compound **2m** was synthesized starting from **1m** following the general procedure described for **2a**; the compound **2m** was obtained as a colourless liquid (124 mg, 72% yield). IR (neat) cm^{-1}: 2863, 2750, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.92 – 7.89 (m, 1H), 7.64 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.45 – 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 135.5, 134.0, 133.6, 130.0, 128.0, 127.2; HRMS (ESI TOF) *m/z* calcd for C_7H_5BrO [M + H]$^+$ 184.9602, found 184.9604.

4-Bromo benzaldehyde (2n) :

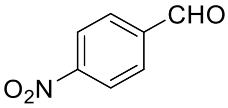


2n

The compound **2n** was synthesized starting from **1n** following the general procedure described for **2a**; the compound **2n** was obtained as a light yellow solid (132 mg, 77% yield). m.p: 55-57°C; IR (neat) cm^{-1}: 2823, 2727, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ

9.98 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 135.2, 132.6, 131.1, 129.9; HRMS (ESI TOF) *m/z* calcd for C_7H_5BrO [M + H]$^+$ 184.9602, found 184.9604.

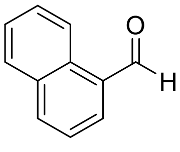
4-nitro benzaldehyde (2o):



2o

The compound **2o** was synthesized starting from **1o** following the general procedure described for **2a**; the compound **2o** was obtained as a yellow solid (113 mg, 68% yield). m.p.: 104-106°C; IR (neat) cm^{-1}: 2848, 2733, 1706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.40 (d, *J* = 8.7 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 151.2, 140.2, 130.6, 124.5; HRMS (ESI TOF) *m/z* calcd for $C_7H_5NO_3$ [M + H]$^+$ 152.0348, found 152.0352.

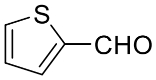
1-naphthaldehyde (2p):



2p

The compound **2p** was synthesized starting from **1p** following the general procedure described for **2a**; the compound **2p** was obtained as a colourless liquid (134 mg, 80% yield). IR (neat) cm^{-1}: 2852, 2727, 1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.26 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.72-7.68 (m, 1H), 7.65 – 7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 136.9, 135.4, 133.8, 131.5, 130.6, 129.2, 128.6, 127.1, 125.0; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_8O$ [M + H]$^+$ 157.0653, found 157.0658.

Thiophene-2-carboxaldehyde (2q):

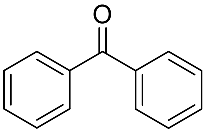


2q

The compound **2q** was synthesized starting from **1q** following the general procedure described for **2a**; the compound **2q** was obtained as a yellow liquid (119 mg, 75% yield).

IR (neat) cm^{-1}: 2820, 2714, 1677; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.93 (s, 1H), 7.78 – 7.75 (m, 2H), 7.22 – 7.19 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.1, 144.1, 136.4, 135.2, 128.4; HRMS (ESI TOF) *m/z* calcd for C_5H_4OS [M + H]$^+$ 113.0061, found 113.0070.

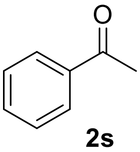
Benzophenone (2r):



2r

The compound **2r** was synthesized starting from **1r** following the general procedure described for **2a**; the compound **2r** was obtained as a white solid (158 mg, 92% yield) m.p.:47-49°C; IR (neat) cm^{-1}: 1655. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 – 7.80 (m, 4H), 7.61 – 7.57 (m, 2H), 7.48 (t, *J* = 7.7 Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.9, 137.7, 132.5, 130.2, 128.4; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{10}O$ [M + H]$^+$ 183.0815, found 183.0816.

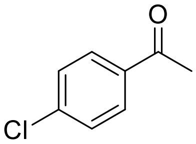
Acetophenone (2s):



2s

The compound **2s** was synthesized starting from **1s** following the general procedure described for **2a**; the compound **2s** was obtained as a colourless liquid (144 mg, 90% yield). IR (neat) cm^{-1}: 1680; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 – 7.94 (m, 2H), 7.58 – 7.54 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.3, 137.2, 133.2, 128.7, 128.4, 26.7; HRMS (ESI TOF) *m/z* calcd for C_8H_8O [M + H]$^+$ 121.0653, found 121.0655.

4-chloroacetophenone (2t):

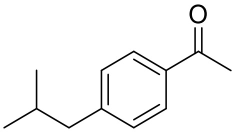


2t

The compound **2t** was synthesized starting from **1t** following the general procedure described for **2a**; the compound **2t** was obtained as a colourless liquid (186 mg, 87%

yield). IR (neat) cm^{-1}:1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 139.7, 135.5, 129.8, 129.0, 26.7; HRMS (ESI TOF) *m/z* calcd for C_8H_7ClO $[M + Na]^+$ 177.0082, found 177.0083.

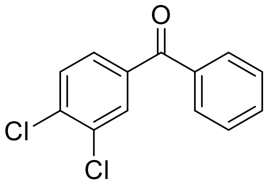
1-(4-isobutylphenyl)ethan-1-one (2u):



2u

The compound **2u** was synthesized starting from **1u** following the general procedure described for **2a**; the compound **2u** was obtained as a colourless liquid (152 mg, 89% yield). IR (neat) cm^{-1}: 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 2.59 (s, 3H), 2.53 (d, *J* = 7.2 Hz, 2H), 1.89 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 147.7, 135.0, 129.4, 128.4, 45.5, 30.2, 26.7, 22.4; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{16}O$ $[M + H]^+$177.1279, found 177.1284.

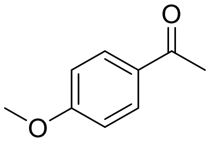
(3,4-dichlorophenyl)(phenyl)methanone (2v):



2v

The compound **2v** was synthesized starting from **1v** following the general procedure described for **2a**; the compound **2v** was obtained as a white solid (160 mg, 90% yield).
m.p.: 99-103°C; IR (neat) cm^{-1}: 1660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.9 Hz, 1H), 7.78 – 7.76 (m, 2H), 7.65 – 7.60 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 137.3, 137.2, 136.8, 133.1, 132.0, 130.6, 130.1, 129.2, 128.7; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_8Cl_2O$ $[M + H]^+$ 251.0030, found 251.0033.

1-(4-methoxyphenyl)ethan-1-one (2w):

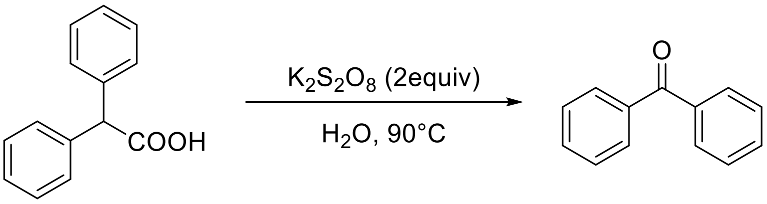


2w

The compound **2w** was synthesized starting from **1w** following the general procedure described for **2a**; the compound **2w** was obtained as a colourless liquid (144 mg, 86% yield). IR (neat) cm^{-1}: 1672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 163.6, 130.7, 130.4, 113.8, 55.5, 26.4; HRMS (ESI TOF) *m/z* calcd for $C_9H_{10}O_2$ $[M + H]^+$ 151.0759, found 151.0766.

Gram Scale Synthesis of Benzophenone 2r:

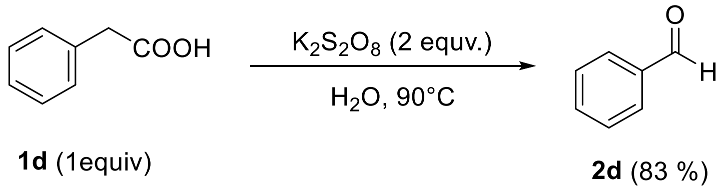
In an oven dried tube containing a mixture of diphenyl acetic acid **1r** (1 g, 4.71 mmol) and potassium persulfate (2.55 g, 9.42mmol), water (10 mL) was added and heated at 90 °C for 12 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature (24 ^{o}C) and it was extracted with ethyl acetate (3 x 15 mL). The crude product was purified by column chromatography to furnish compound **2r** as a white solid (0.809 g, 93% yield).



1r, 1equiv **2r**, 93%

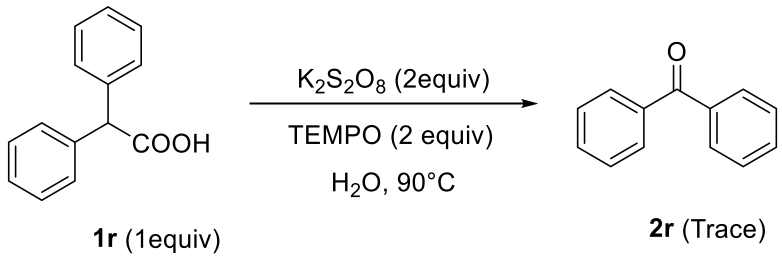
Gram Scale Synthesis of Benzaldehyde 2d:

In an oven dried tube containing a mixture of phenyl acetic acid **1a** (1 g, 7.34 mmol) and potassium persulfate (3.97g, 14.69 mmol), water (10 mL) was added and heated at 90 °C for 12 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature (24 ^{o}C) and it was extracted with ethyl acetate (3 x 15 mL). The crude product was purified by column chromatography to furnish compound **2a** as a colourless liquid (0.648 g, 83% yield).



Radical Quenching Experiment:

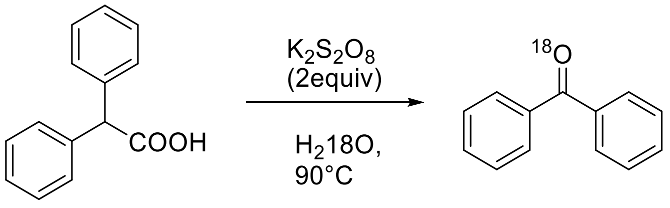
In an oven dried tube containing a mixture of diphenyl acetic acid **1r** (50 mg, 0.24 mmol), potassium persulfate (127 mg, 0.47 mmol) and TEMPO (74 mg, 0.47 mmol), water (0.5 mL) was added and heated at 90 °C for 12 h. Reaction gave trace amount of **2r.**



3.7.4 General Procedure for ^{18}O labelling experiment:

In an oven dried glass vial containing a mixture of diphenyl acetic acid **1r** (20 mg, 0.09 mmol) and potassium persulfate (51 mg, 0.19 mmol), ^{18}O-water ($H_2{}^{18}O$) (50 µL) was added. The reaction was heated at 90°C for 12 h under inert atmosphere. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature (24 ^{o}C) and it was extracted with ethyl acetate (3 x 2 mL). The crude product was purified by column chromatography to furnish pure compound **2r’** (^{18}O labelled Benzophenone) as a white solid (14 mg, 81% yield).

Product was confirmed by using HRMS and GC-MS.



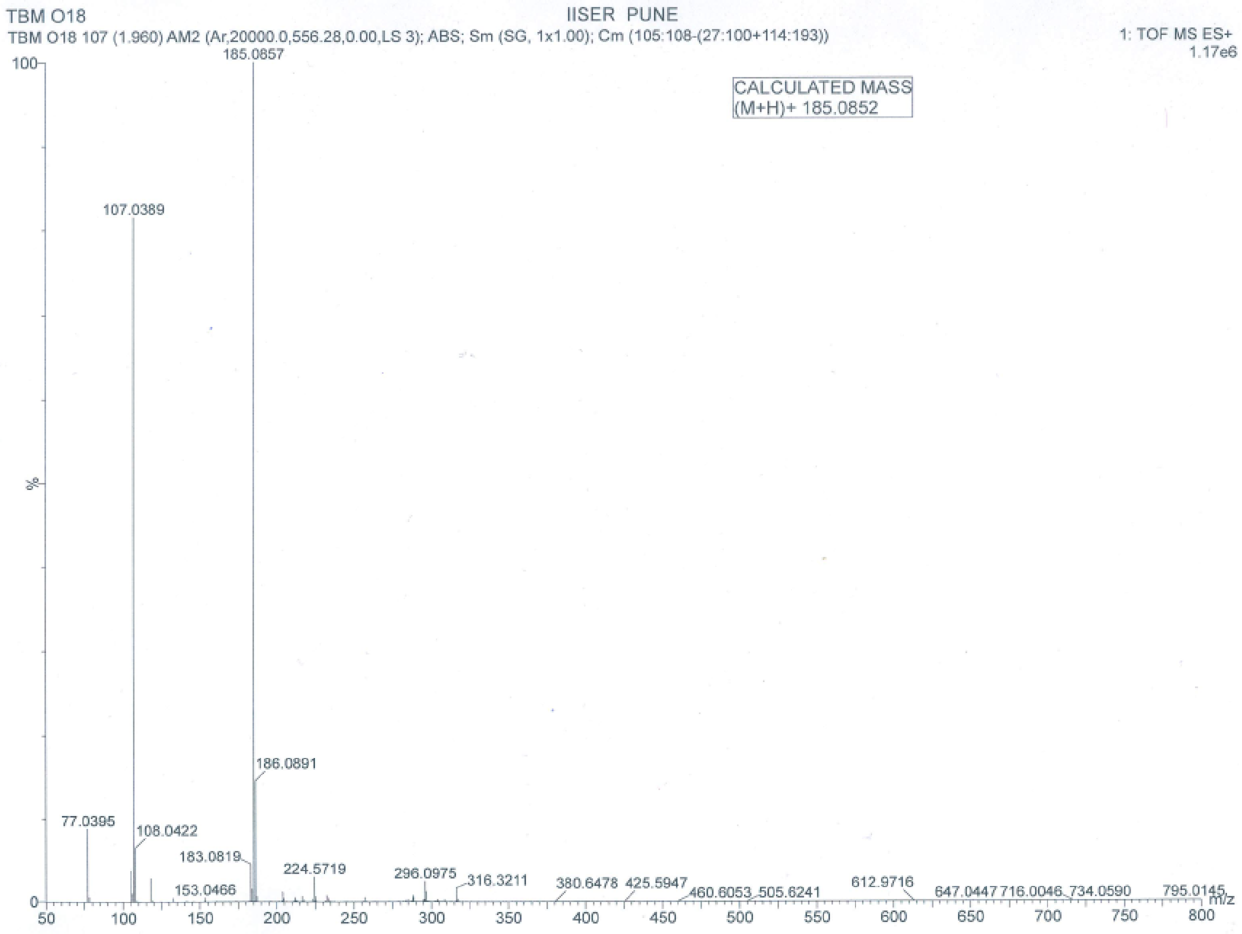
1r 1equiv

2r' (81%)

HRMS:

HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{10}O$ [M + H] + 185.0852, found 185.0857.

(See page S14 and S15 for spectra)

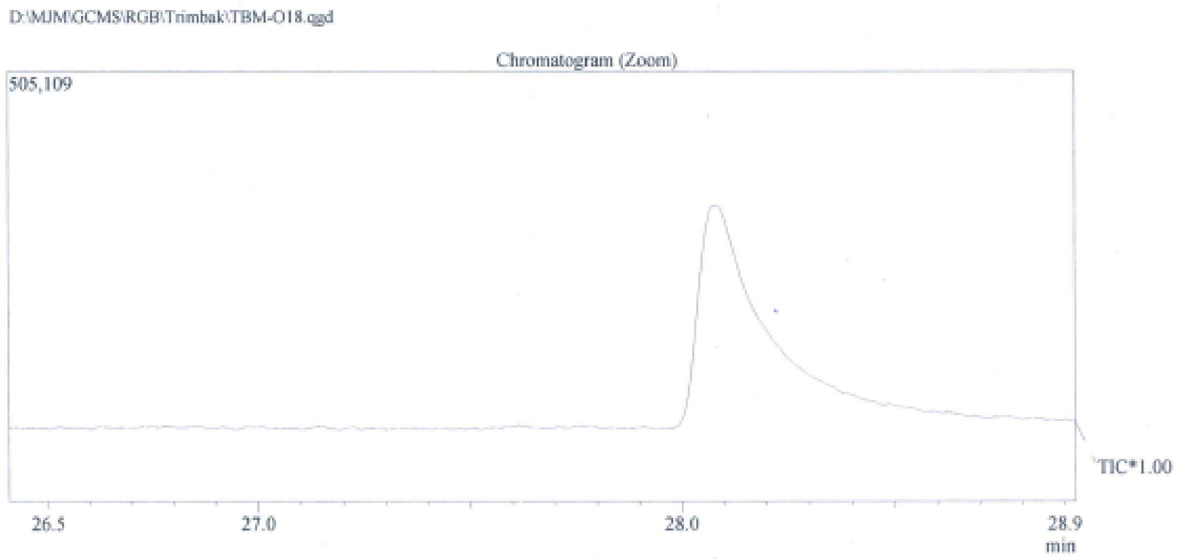


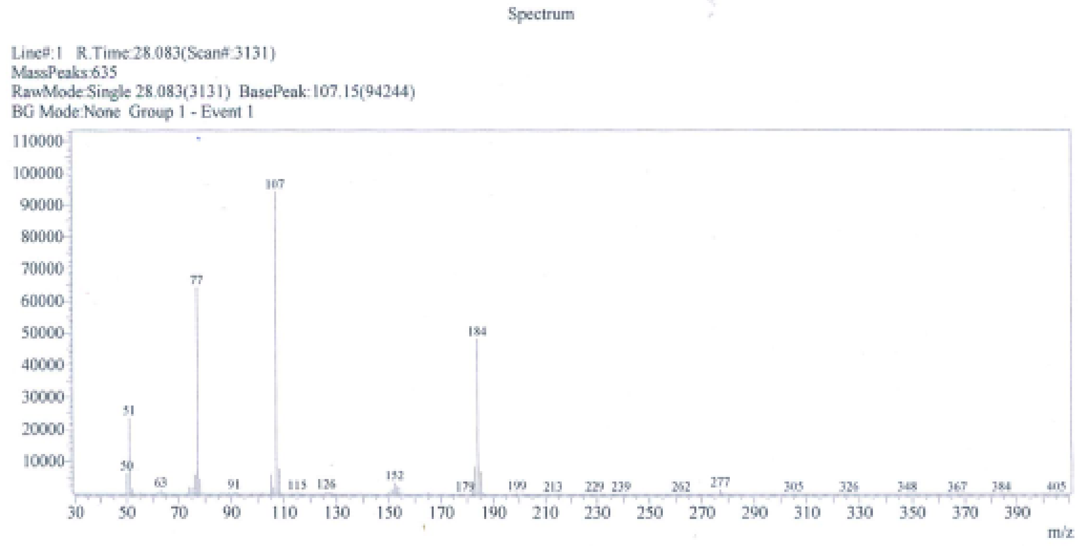
^{18}O content 96.3%

Labelled Water ($H_2{}^{18}O$) used is 97%

GC-MS:

Molecular ion peak M$^+$ at 184 and M/Z at 107 indicate ^{18}O-labeled benzophenone as a product.




Spectrum

Line#:1 R.Time:28.083(Scan#:3131)
MassPeaks:635
RawMode:Single 28.083(3131) BasePeak:107.15(94244)
BG Mode:None Group 1 - Event 1

3.8 Appendix II: ^{1}H, ^{13}C spectral data of representative compounds

Compound No.	**Figure AII.X**	**Data**	**Page No.**
2a	Figure III.1 and III.2	^{1}H and ^{13}C	100
2e	Figure III.3 and III.4	^{1}H and ^{13}C	101
2u	Figure III.5 and III.6	^{1}H and ^{13}C	102
2v	Figure III.7 and III.8	^{1}H and ^{13}C	103

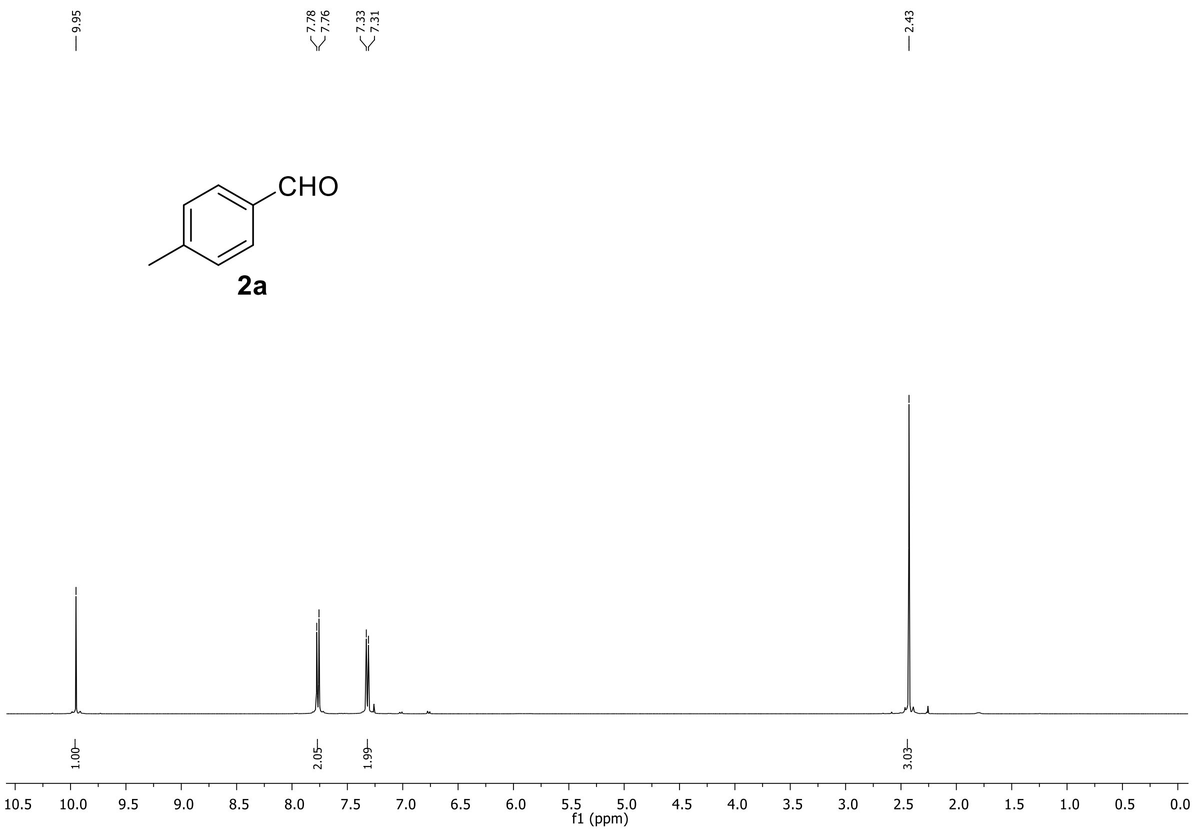


Figure III.1 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2a**

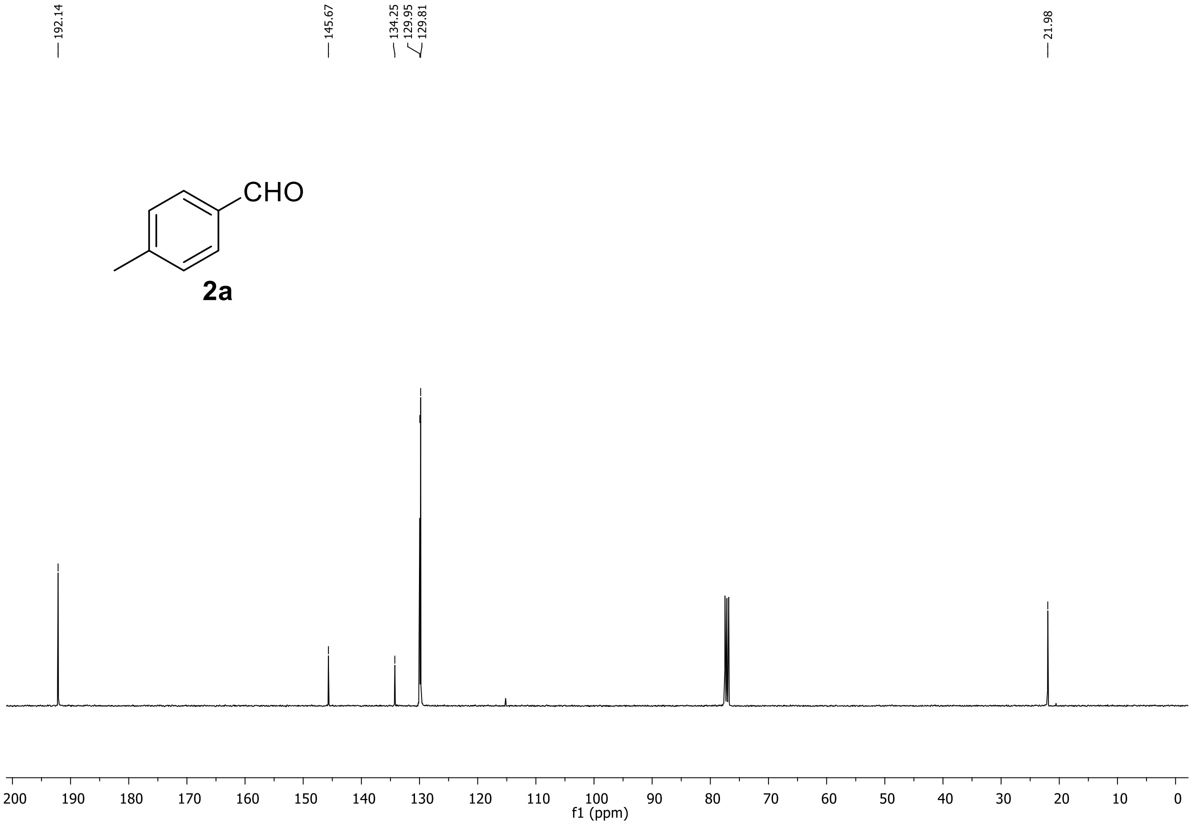


Figure III.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2a**

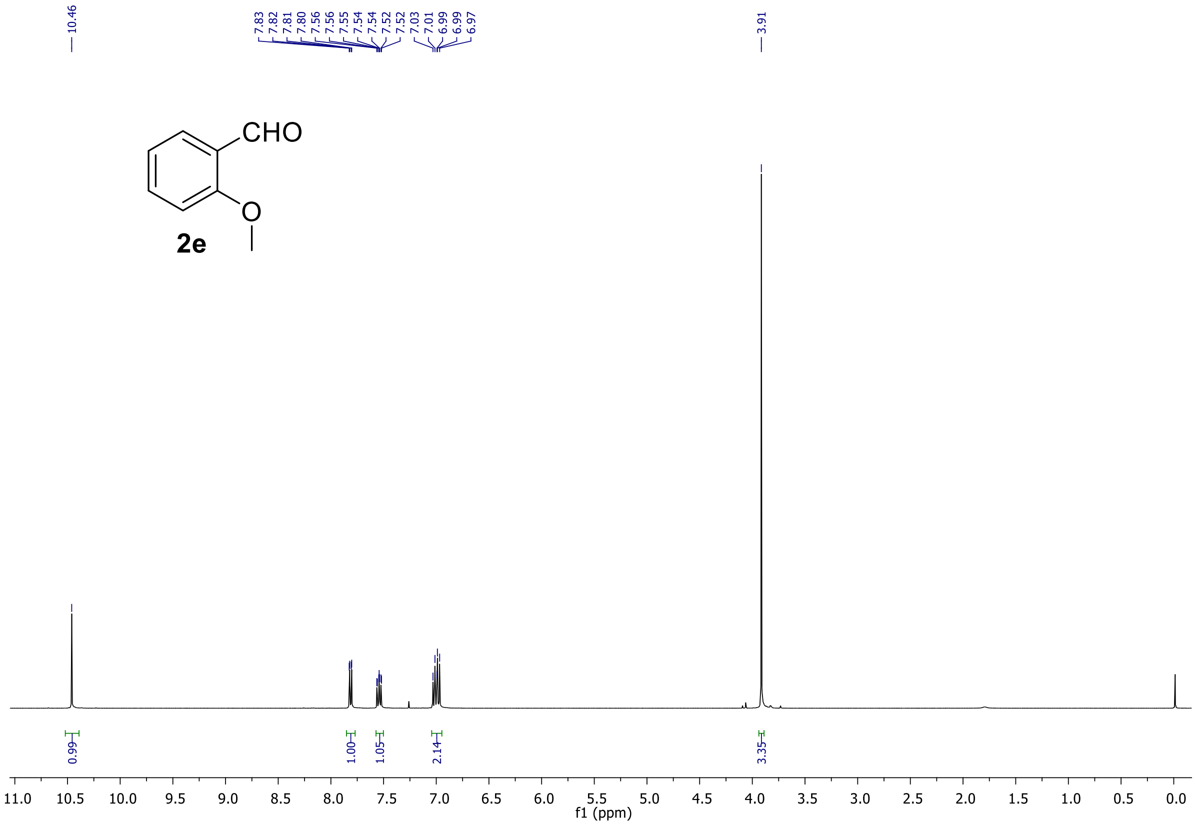


Figure III.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2e**

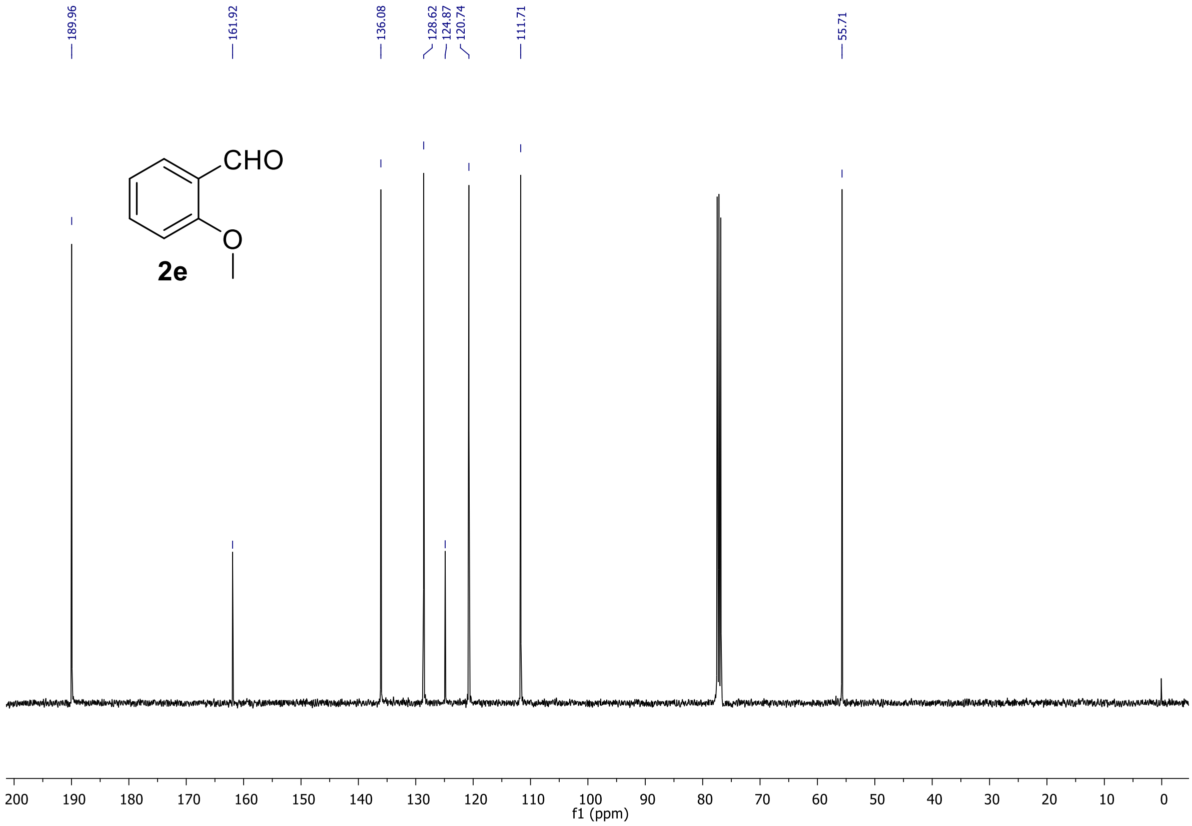


Figure III.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2e**

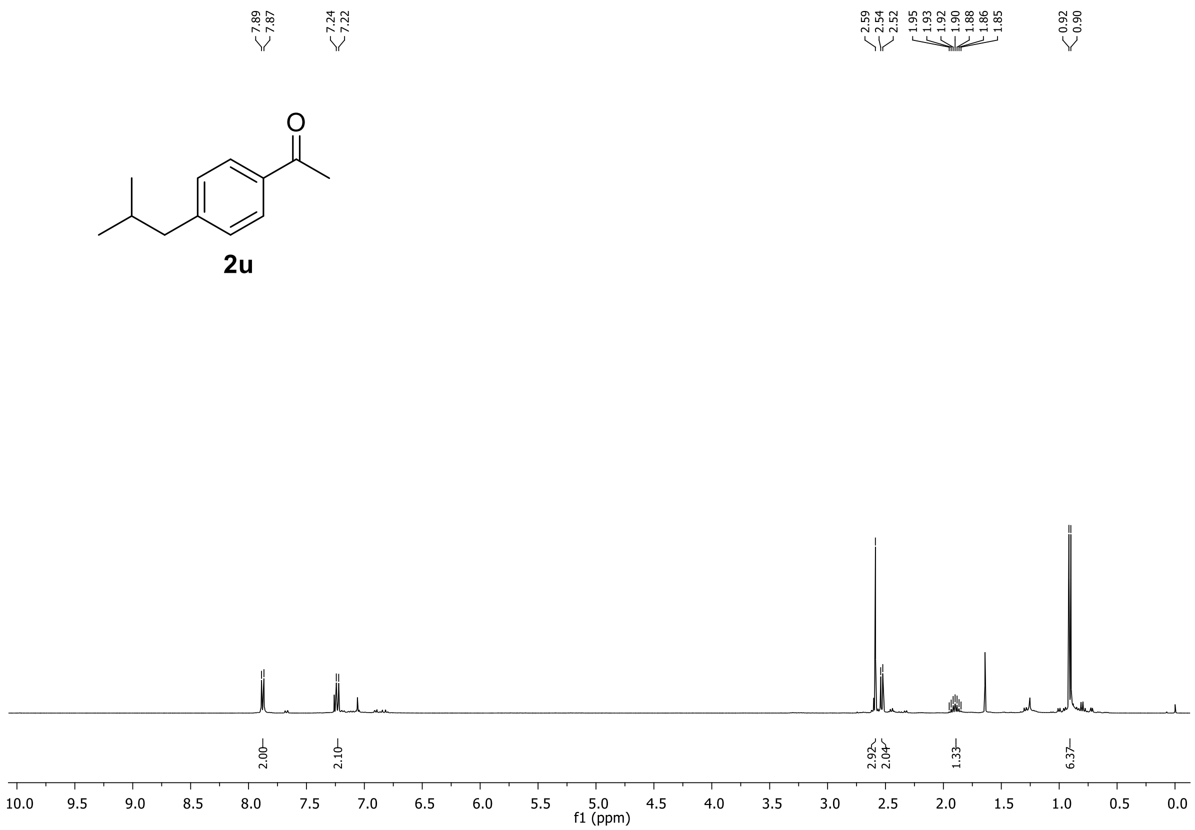


Figure III.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2u**

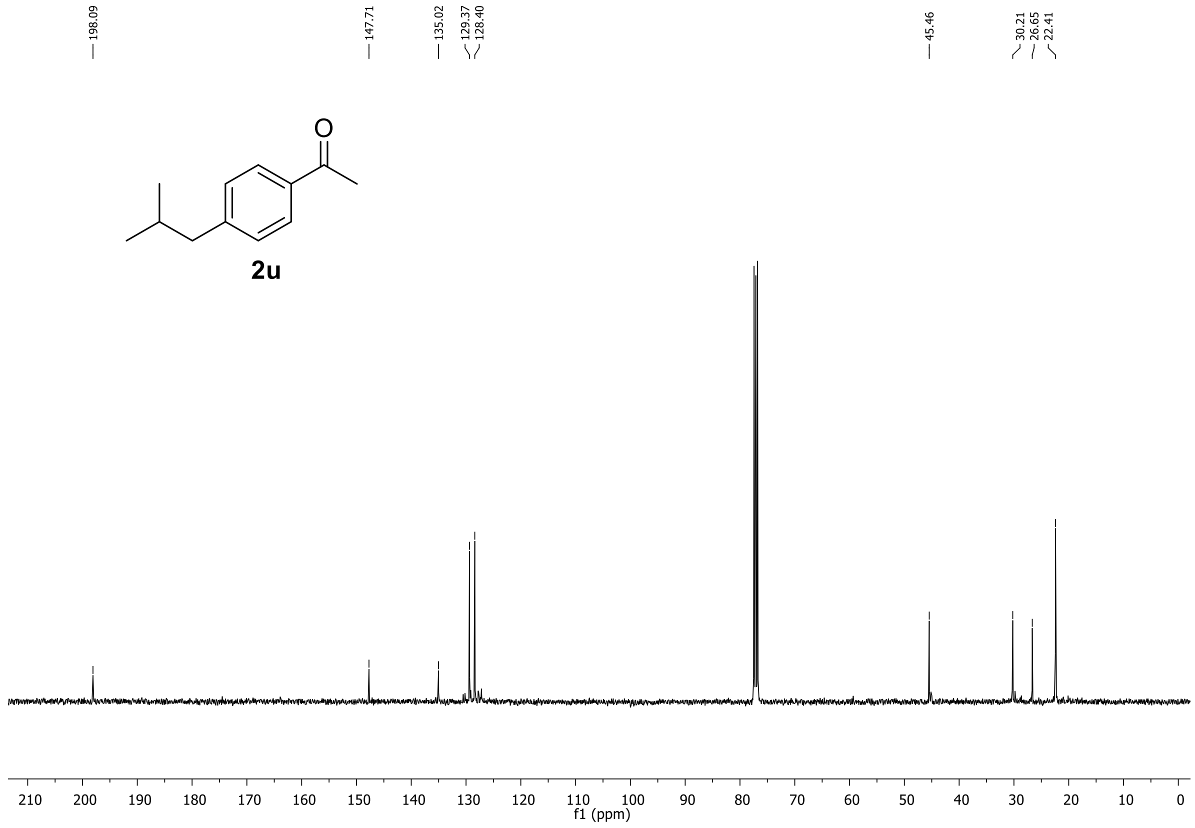


Figure III.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2u**

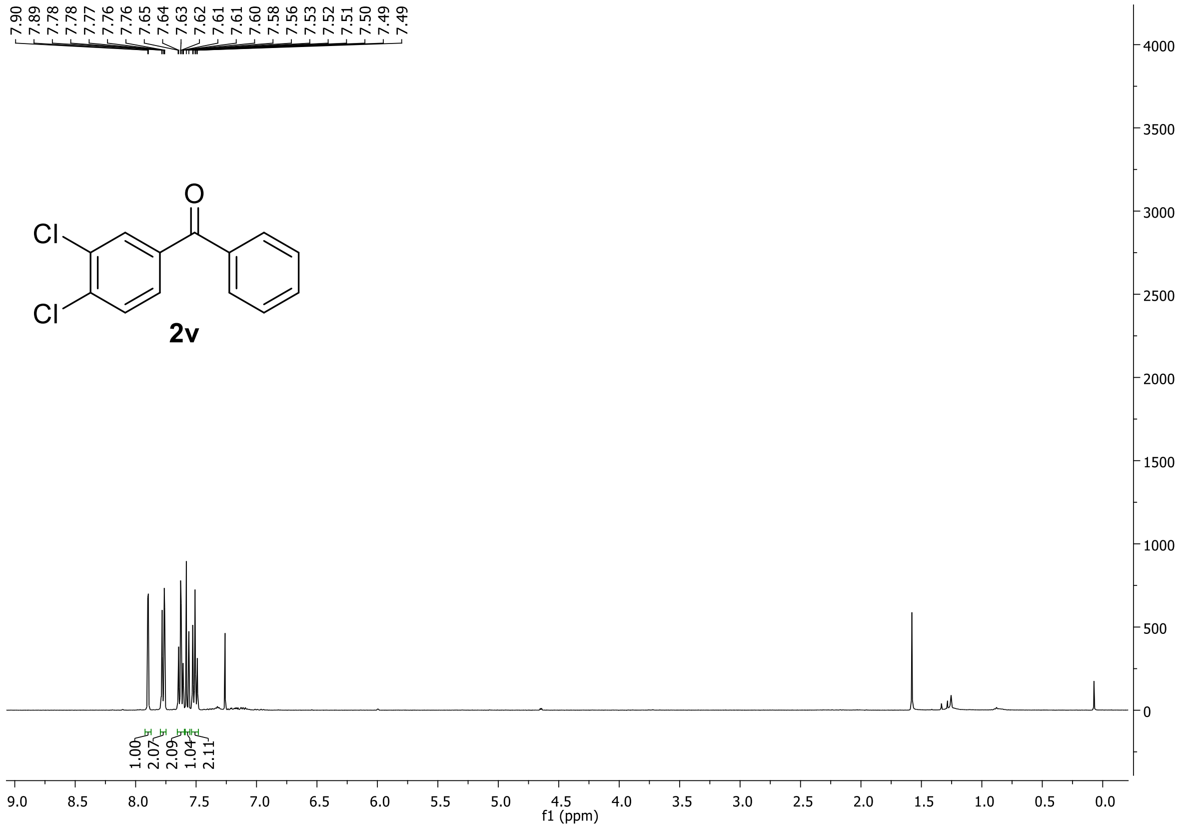


Figure III.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2v**

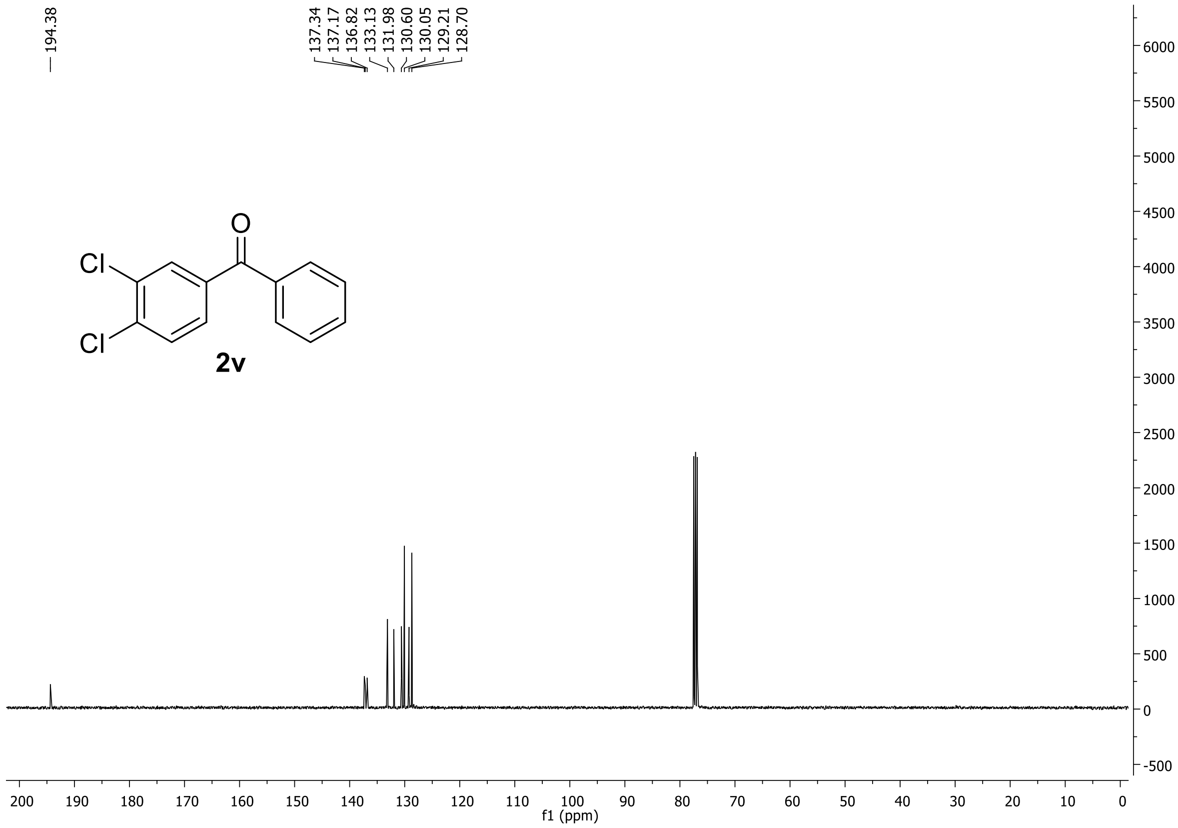


Figure III.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2v**

3.9 References and notes

1 (a) Larock RC. *Comprehensive Organic Transformations.* New York: Wiley-VCH; 1989;

(b) Otera J, ed. *Modern Carbonyl Chemistry*. Weinheim: Wiley-VCH; 2000;

(c) Wilkinson MC. Org Lett. 2011;13:2232–2235;

(d) Nicholson JW, Wilson AD. *J Chem Educ*. 2004;81:1362–1366;

(e) Park A, Park K, Kim Y, Lee S. *Org Lett*. 2011;13:944–947.

2 (a) Qu B, Collum DB. *J Org Chem.* 2006;71:7117–7119;

(b) Nahm S, Weinreb SM. *Tetrahedron Lett.* 1981;22:3815–3818;

(c) Kanagani CO, Kelley DE, Day BW. *Tetrahedron Lett*. 2006;47:6289–6292.

3 (a) Posner GH, Whitten CE, McFarland PE. *J Am Chem Soc*. 1972;94:5106–5108;

(b) Dieter RK. *Tetrahedron Lett*. 1999;55:4177–4236;

(c) Wang X, Zhang L, Sun X, Xu Y, Krishnamurthy D, Senanayake CH. *Org Lett.* 2005;7:5593–5595;

(d) Ryu I, Ikebe M, Sonoda N, Yamato S, Yamamura G, Komatsu M. *Tetrahedron Lett*. 2002;43:1257–1259.

4 (a) Gilman H, van Ess PR. *J Am Chem Soc*. 1933;55:1258–1261;

(b) Tegner C. *Acta Chem Scand*. 1952;6:782–790;

(c) Jorgenson MJ. *Org Synth*. 1973;5:775–779;

(d) Lubell WD, Rapoport H. *J Am Chem Soc*. 1988;110:7447–7455;

(e) Alonso F, Lorenzo E, Yus M. *J Org Chem*. 1996;61:6058–6059.

5 Mislow K, Brenner J. *J Am Chem Soc*. 1953;75:2318–2322.

6 Genna DT, Posner GH. *Org Lett*. 2011;13:5358–5361.

7 (a) Crabtree RH. *Chem Rev*. 1985;85:245–269;

(b) Jun C-H. *Chem Soc Rev*. 2004;33:610–618;

(c) Tobisu M, Chatani N. *Chem Soc Rev*. 2008;37:300–307;

(d) Masarwa A, Marek I. *Chem Eur J.* 2010;16:9712–9721;

(e) Murakami M, Matsuda T. *Chem Commun*. 2011;47:1100–1105.

8 (a) Song Q, Feng Q, Zhou M. *Org Lett*. 2013;15:5990–5993;

(b) Mai S, Zhaoa Y, Song Q. *Org Biomol Chem*. 2016;14:8685–8690.

9 (a) Tanaka D, Romeril SP, Myers AG. *J Am Chem Soc*. 2005;127:10323–10333;

(b) Myers AG, Tanaka D, Mannion MR. *J Am Chem Soc*. 2002;124:11250–11251;

(c) Goossen LJ, Rodríguez N, Goossen K. *Angew Chem Int Ed*. 2008;47:3100–3120;

(d) Goossen LJ, Rodríguez N, Melzer B, Linder C, Deng G, Levy LM. *J Am Chem Soc*. 2007;129:4824–4833;

(e) Forgione P, Brochu M-C, St-Onge M, Thesen KH, Bailey MD, Bilodeau F. *J Am Chem Soc*. 2006;128:11350–11351;

(f) Bilodeau F, Brochu M-C, Guimond N, Thesen KH, Forgione P. *J Org Chem*. 2010;75:1550–1560.

10 (a) Torregrosa RRP, Ariyarathna Y, Chattopadhyay K, Tunge JA. *J Am Chem Soc*. 2010;132:9280–9282;

(b) Zhang C, Seidel D. *J Am Chem Soc*. 2010;132:1798–1799;

(c) Shang R, Ji D-S, Chu L, Fu Y, Liu L. *Angew Chem Int Ed*. 2011;50:4470–4474;

(d) Shang R, Yang Z-W, Wang Y, Zhang S-L, Liu L. *J Am Chem Soc*. 2010;132:14391–14393.

11 Feng Q, Song Q. *J Org Chem*. 2014;79:1867–1871.

12 Song Q, Feng Q, Yang K. *Org Lett*. 2014;16:624–627.

13 Zhang L, Bi X, Guan X, et al. *Angew Chem Int Ed*. 2013;52:11303–11307.

14 Yang Z, Hartnett HE, Shock EL, Gould IR. *J Org Chem*. 2015;80:12159–12165.

15 Even though it is assumed that salts of copper and nickel can be green and sustainable alternatives, a recent report suggests that they do possess significant toxicities: Egorova KS, Ananikov VP. *Angew Chem Int Ed*. 2016;55:12150–12162.

16 Tangestaninejad S, Mirkhani V. *J Chem Res*. 1998;820–821.

17 Telvekar VN, Sasane KA. *Synlett*. 2010;2778–2779.

18 (a) Wang H, Guo L-N, Wang S, Duan X-H. *Org Lett*. 2015;17:3054–3057;

(b) Yuan M, Chen L, Wang J, et al. *Org Lett*. 2015;17:346–349;

(c) Lu S, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336–9352;

(d) Mi X, Wang C, Huang M, Wu Y, Wu Y. *J Org Chem*. 2015;80:148–155;

(e) Wei W, Wen J, Yang D, et al. *J Org Chem*. 2014;79:4225–4230;

(f) Jiang Q, Shenga W, Guo C. *Green Chem*. 2013;15:2175–2179;

(g) Kim SM, Kim DW, Yang JW. *Org Lett*. 2014;16:2876–2879.

19 Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:415–418.

20 (a) Tsitonaki A, Petri B, Crimi M, Mosbaek H, Siegrist RL, Bjerg PL. *Environ Sci Technol*. 2010;40:55–91 (In Situ Chemical Oxidation of Contaminated Soil and

Groundwater Using Persulfate);

(b) Sra KS, Thomson NR, Barker JF. *Environ Sci Technol*. 2010;44:3098–3104;

(c) Liu H, Bruton TA, Li W, et al. *Environ Sci Technol*. 2016;50:890–898.

21 Syed S. *Hydrometallurgy*. 2006;82:48–53.

22 Interestingly, this ketone is also a natural metabolite of Ibuprofen drug following the similar oxidative decarboxylation pathway during drug metabolism: Komuro M, Nagatsu Y, Higuchi T, Hirobe M. *Tetrahedron Lett*. 1992;33:4949–4952.

23 Calculation of E (environmental) factor, mass productivity and mass intensity of representative examples are given in Supporting information.

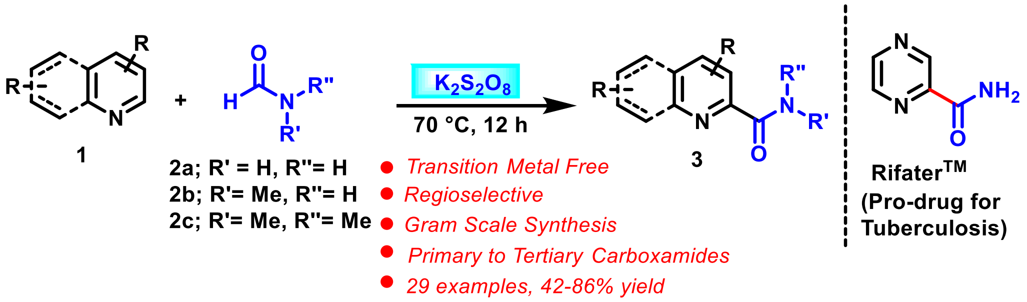
24 (a) Sheldon RA. *Chem Commun*. 2008;3352–3365;

(b) Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*. New York: Oxford University Press; 1998. 30.

25 Tanner DD, Osman SA. *J Org Chem*. 1987;52:4689–4693.

Chapter 4

Transition-Metal-Free Synthesis of Primary to Tertiary Carboxamides: A Quick Access to Prodrug-Pyrazinecarboxamide



- *Transition Metal Free*
- *Regioselective*
- *Gram Scale Synthesis*
- *Primary to Tertiary Carboxamides*
- *29 examples, 42-86% yield*

Transition-Metal-Free Synthesis of Primary to Tertiary Carboxamides: A Quick Access to Prodrug-Pyrazinecarboxamide

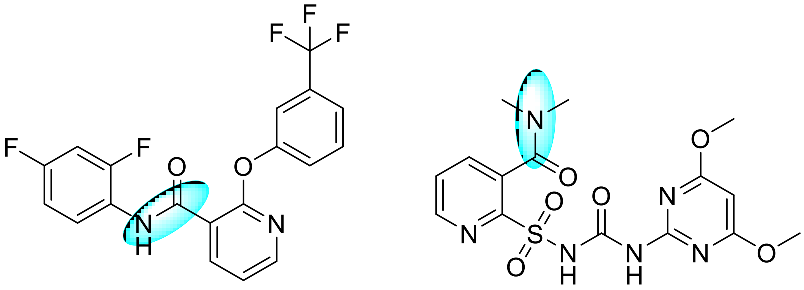
4

4.1 Abstract

One-pot expedient and direct carbamolyation of nitrogen heterocyclics is described. The transformation is realized via the direct dehydrogenative aminocarbonylation of heterocyclic compounds under transition-metal-free conditions. This method is regioselective and the protocol is proved to be scalable in gram quantity. Further, the therapeutically useful antitubercular agent pyrazinecarboxamide is successfully synthesized by employing this protocol.

4.2 Introduction

Carboxamide is a very important and useful functional group and heterocyclic carboxamides are significant structural scaffolds in many materials, natural products and bioactive compounds.[1] Diflufenican **4** (Figure 4.1) is a selective herbicide for both pre-emergence and early post-emergence weed control in winter cereals. It is effective against a wide range of herbaceous weeds.[1d] Likewise, nicosulfuron **5** (Figure 4.1) is a sulfonylurea herbicide used for selective post emergence control of annual and perennial grasses in corn.[1f]

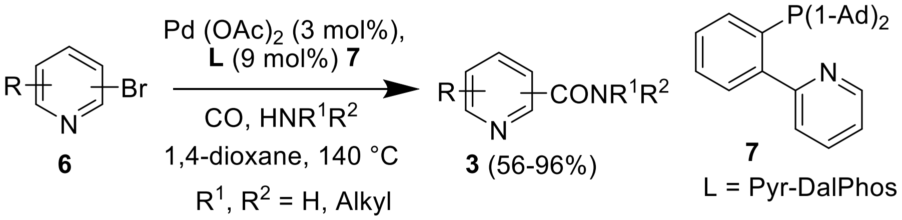

Diflufenican **4**

Nicosulfuron **5**

Figure 4.1. Bioactive compounds containing carboxamides

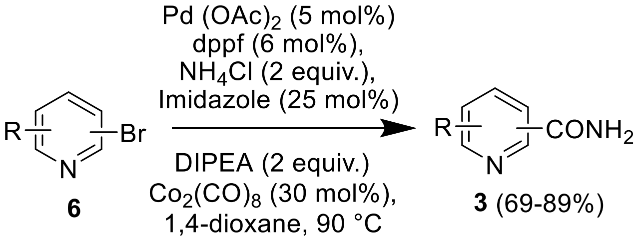
Carboxamides are also useful synthetic building blocks for many pharmaceuticals and agrochemicals.[2] Along with the traditional or conventional condensation reaction of carboxylic acids/carboxylic acid derivatives and amines under harsher basic conditions or using coupling reagents, many alternative strategies have been developed for the synthesis of carboxamides in the recent years. Some of the various strategies including cross-dehydrogenative coupling, amine dehydrogenation or oxidation reactions, transamidation reactions, aldehyde-amine coupling reactions, and C-N coupling reactions have been developed for the carboxamide synthesis in recent years.[2] Alternatively, transition-metal-catalyzed protocols such as aminocarbonylation of aromatic and heteroaromatic halides, direct carbamolyation of pyridines, and hydration of nitriles have been developed in pursuit of achieving newer methods.[3]

Alsabeh et al. reported a palladium catalyzed direct aminocarbonylation of (hetero)aryl bromides **6**.[3a] The reaction of (hetero)aryl bromides **6** in presence of carbon monoxide (CO), ammonia (NH_3) and primary/secondary alkyl amines as reactive partners and catalytic amount of $Pd(OAc)_2$ and ligand Pyr-DalPhos **7** afforded the corresponding (hetero)arylcarboxamides **3** in moderate to excellent yields (Scheme 4.1).



Scheme 4.1 Palladium catalyzed aminocarbonylation

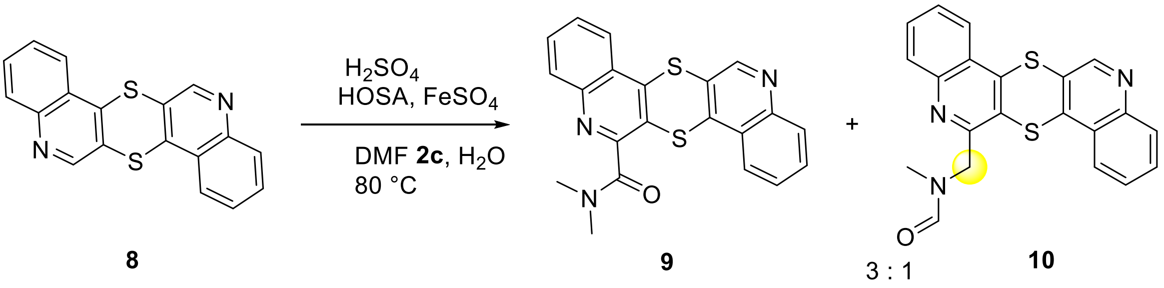
In order to avoid the direct use of CO and NH_3 an alternative sources of CO and NH_3 were utilized for the synthesis of carboxamides. Suresh et al. reported a palladium catalyzed aminocarbonylation of aryl and hetero aryl halides **6** using solid $Co_2(CO)_8$ and NH_4Cl as sources of CO and NH_3 respectively to the synthesize primary amides **3** in good yields (69-89%, Scheme 4.2).[3c]



Scheme 4.2 Aminocarbonylation of heteroaryl bromides

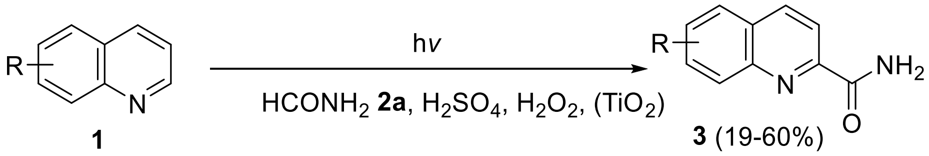
However, these methods rely on transition metal salts and some of these methods require the use of toxic and corrosive gases such as carbon monoxide and ammonia or alternatively ammonia equivalents such as aqueous ammonia, ammonium carbamate and other amine bases. All these methods require the use of transition metals and most of them need pre-activated aryl/heteroaryl halides. However, the limitation of some of these methods is that they are confined to primary carboxamides only with limited scope on pyridines and found to be not suitable for the synthesis of secondary and tertiary carboxamides. Likewise, methods did not work on quinoline and other heteroaromatics. Altough aminocarbonylation via direct activation of *N*-protected formamide is known[4] yet transition-metal-free carbamolyation of heteroaromatics via direct activation of formamide and *N*, *N*-dimethylformamide has not been of much success till date. Some of the examples of direct aminocarbonylation suffer from lower yields, mixture of aminocarbonylated and dominating *α*-amidoalkylated side products, limited substrate scope (mostly with pyridines and formamide), lower chemoselectivity, and moreover methods were not studied in a great detail for the substrate scope.[5]

Michalic and co-workers reported a coupling reaction of thioquinanthrene **8** with DMF **2c** in the presence of hydroxylamine-*O*-sulfonic acid (HOSA) and ferrous sulfate to afford the corresponding carboxamide **9**. However, this reaction afforded *N*-methylamidoalkylated product **10** along with monocarbamoylation product **9** in 3:1 (9:10) ratio **(**Scheme 4.3).[5a]



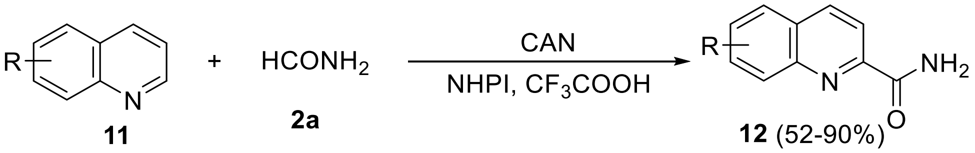
Scheme 4.3 Coupling reaction of thioquinanthrene with DMF

Sunlight induced carbamoylation of quinoline **1** in the presence of TiO_2 and H_2O_2 was reported by Caronna et al. using formamide **2a** as a coupling partner to afford the corresponding primary carboxamides **3** in low to moderate yields (Scheme 4.4).[5b]



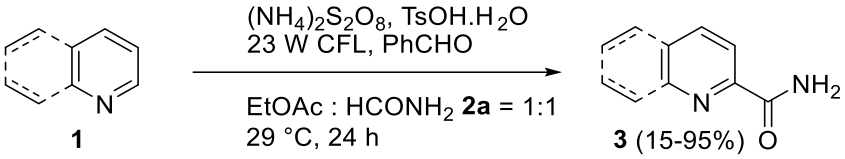
Scheme 4.4 Sunlight induced carbamoylation of quinolone

Minisci et al. utilized ceric ammonium nitrate, *N*-hydroxyphthalimide (CAN-NHPI) and formamide **2a** for the direct carbamoylation of heteroaromatic bases **11**. Ce(IV)-NHPI system effectively generated nucleophilic carbamoyl radical by the oxidation of formamide to afford the corresponding carboxamides **12** in moderate to very good yields (Scheme 4.5).[5c]



Scheme 4.5 Carbamoylation of heteroaromatic bases by Ce(IV) oxidation

Zang et al. described benzaldehyde-mediated photoredox cross-dehydrogenative coupling (CDC) reactions of nitrogen-containing heteroaromatics **1** with formamide **2a** to afford the corresponding carboxamides **3** in excellent yields (up to 95%, Scheme 4.6).[5d]



Scheme 4.6 Photoredox CDC reaction

Practical and expedient transition-metal-free protocols are gaining a great importance[6] and are promising alternatives to the traditional methods as the contamination due to the residual transition metals can be avoided at lower costs. Thus it is more desirable to develop a sustainable transition-metal-free practical protocol for the direct access of primary to tertiary carboxamides of different heteroaromatics. We have shown considerable interest in developing transition-metal-free protocols[7] and our ongoing research activities prompted us to evaluate the method for the direct aminocarbonylation using formamide, *N*-methylformamide and *N*,*N*-dimethylformamide by functionalizing the C-H bond.

Based on the earlier literature,[8] and our previous experience it is known that persulfate is an efficient oxidant and is a very good radical initiator and it could be explored for the homolytic cleavage of formamide and other amides. Interestingly, persulfates are known to be mild and benign and eco-friendly low cost reagents.[9]

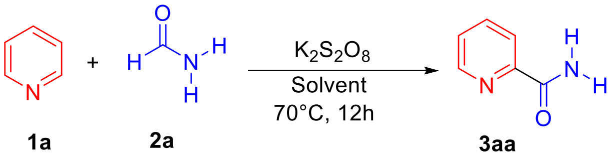
As a part of our ongoing research programme on transition-metal-free protocols, we herein in this chapter, report the direct aminocarbonylation of heteroaromatics via cross-dehydrogenative coupling approach. This simple and user friendly protocol for aminocarbonylation uses potassium persulfate and formamide/N-methylformamide (NMF)/DMF as reagents to access primary to tertiary carboxamides with high selectivity.

4.3 Results and discussion

4.3.1 Optimization studies

We commenced our initial work with pyridine **1a** and formamide **2a** as model substrates (Table 4.1). The initial reaction of pyridine **1a** and formamide **2a** in presence of $K_2S_2O_8$ (2 equiv.) in DCE at room temperature (both in air and inert condition) did not work even after prolonged reaction condition (entry 1, Table 4.1). However, at 50 °C trace amount of product **3aa** formed (entry 2, Table 4.1).While, heating the reaction mixture at

Table 4.1. Screening and Optimization for the aminocarbonylation of pyridine[a-d]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	DCE	rt	12	NR[d]
2	DCE	50	12	trace
3	DCE	70	12	40
4	Formamide[b]	rt	12	NR
5	Formamide[b]	50	12	50
6	**Formamide**[b]	**70**	**12**	**79**
7	H_2O	70	12	30
8	THF	70	6	24
9	CH_3CN	70	12	45
10	Formamide	100	12	Decomposed

[a]Reaction conditions: Pyridine **1a** (1 equiv.), Formamide **2a** (10 equiv.) potassium persulfate (2 equiv.), solvent (2 mL) under aerial atmosphere for 12 h, [b]Formamide **2a** was used as substrate as well as solvent (20 equiv.), [c]Isolated yield after purification by column chromatography. [d]reactions did not work at rt.

70 °C afforded modest yield of the desired product **3aa** (entry 3, Table 4.1). Interestingly, when formamide **2a** was used as solvent as well as substrate the reaction proceeded smoothly at elevated temperature (70 °C), to afford the desired product **3aa** in 79% isolated yield (entry 6, Table 4.1) in 12 h. Whereas water, THF and acetonitrile were found to be not good solvents for the desired transformation. After screening several solvents and different temperature conditions optimum reaction condition was emerged as pyridine **1a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 70 °C and formamide **2a** (20 equiv, solvent as well as reagent) under aerial atmosphere (entry 6, Table 4.1) in 12 h. With this optimized result in hand, we explored the substrate scope of the method with different substrates and primary to tertiary amides.

4.3.2 Synthesis of primary to tertiary heteroaryl carboxamides

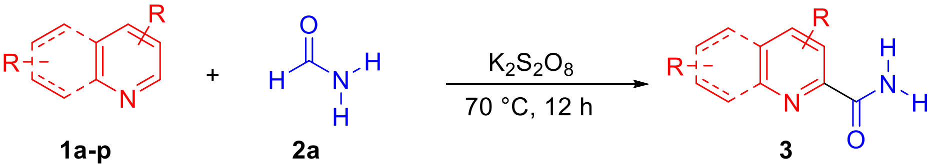
Under optimum reaction conditions, substrates (**1a-1m**) possessing the electron-donating as well as electron withdrawing groups reacted smoothly with formamide **2a** to afford the corresponding carboxamides (**3aa-3ma**) in moderate to good yields (Table 4.2). Encouraged by this success we planned to explore the generality of the protocol by exploring various substrates with secondary and tertiary formamides. Under the optimum reaction conditions, substrates (**1a-b, 1e-f**) reacted smoothly with the *N*-methyl formamide (NMF) **2b** to afford the corresponding secondary carboxamides (**3ab, 3bb, 3eb, 3fb**) in very good yields (see Table 4.3).

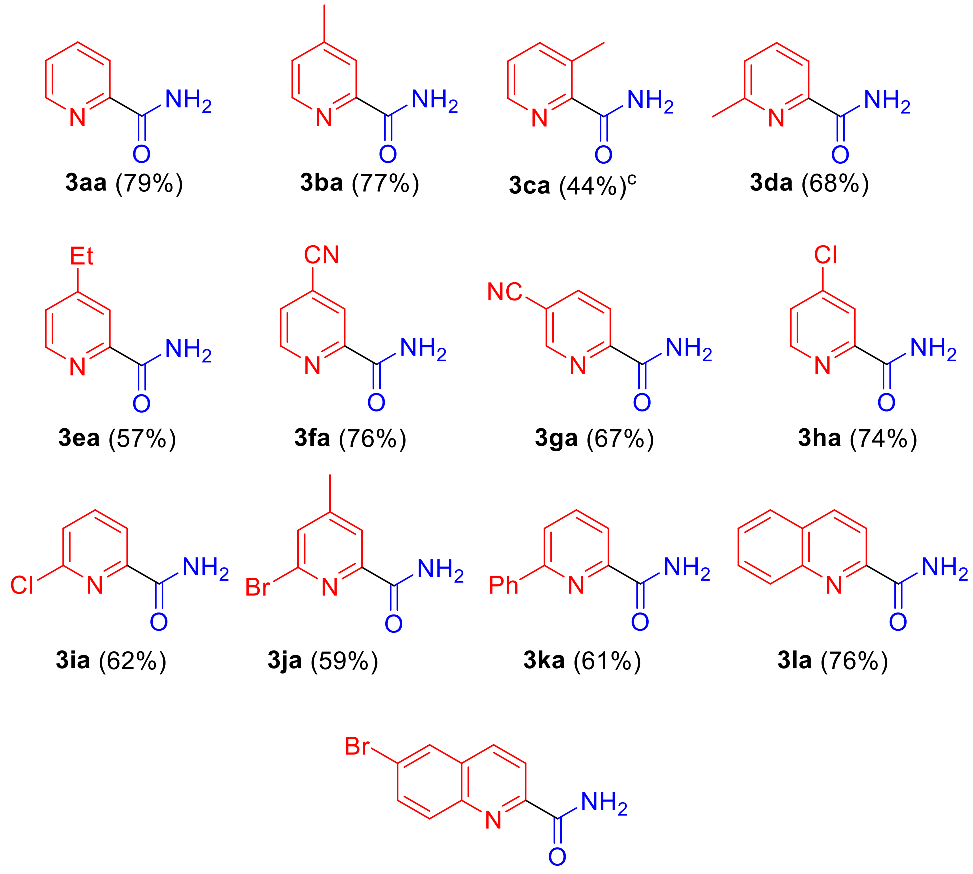
Further, the protocol was explored on quinoline and its derivatives (**1l**, **1m)** and pyrazine (**1n**) with NMF **2b** under the reaction conditions to afford the secondary carboxamides (**3lb, 3mb, 3nb**) in very good yields (up to 85% yield, See Table 4.3). Further, the strength of the protocol was explored to access tertiary carboxamides using DMF.

Earlier, in the literature it was observed that DMF **2c** is relatively unreactive towards the aminocarbonylation and known to give side products emanating from *α*-amidoalkylation as major products. Different substrates **1a, 1e-g, 1l-1m, 1o-p** (pyridine, quinoline, bipyridyl derivatives) were treated with the DMF **2c** under optimum reaction conditions to afford the corresponding tertiary carboxamides (**3ac, 3ec, 3fc, 3gc, 3lc, 3mc,**

3oc, 3pc) in moderate yields (See Table 4.3) . It is very important to note that we did not observe any α-amidoalkylation side products. The position of the substituents on the ring

Table 4.2. Synthesis of primary to tertiary heteroaryl caboxamides[a,b]





3aa (79%) **3ba** (77%) **3ca** (44%)[c] **3da** (68%)

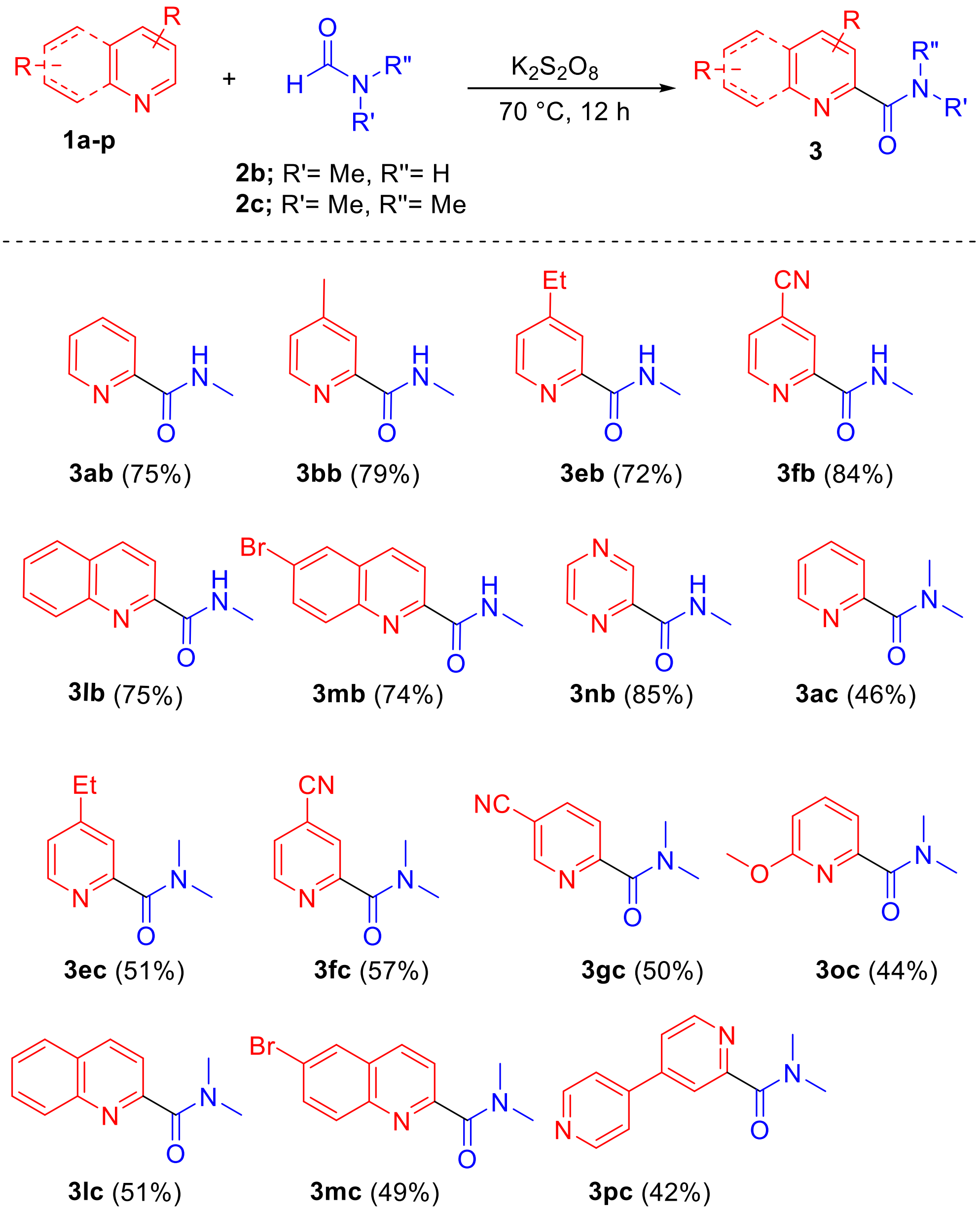
3ea (57%) **3fa** (76%) **3ga** (67%) **3ha** (74%)

3ia (62%) **3ja** (59%) **3ka** (61%) **3la** (76%)

3ma (72%)

[a]Reaction conditions: Heteroaromatics **1** (1 equiv.), Formamide **2a** (20 equiv. 2 mL) potassium persulfate (2 equiv.) under aerial atmosphere for 12 h, [b]Isolated yield after purification by column chromatography. [c]**3ca'** (5-methylpicolinamide) was obtained as regioisomer along with **3ca** (**3ca:3ca' 58:42**).

Table 4.3. Synthesis of secondary and tertiary heteroaryl caboxamides[a,b]



1a-p + **2b**; R'= Me, R"= H **2c**; R'= Me, R"= Me → **3**

3ab (75%) **3bb** (79%) **3eb** (72%) **3fb** (84%)

3lb (75%) **3mb** (74%) **3nb** (85%) **3ac** (46%)

3ec (51%) **3fc** (57%) **3gc** (50%) **3oc** (44%)

3lc (51%) **3mc** (49%) **3pc** (42%)

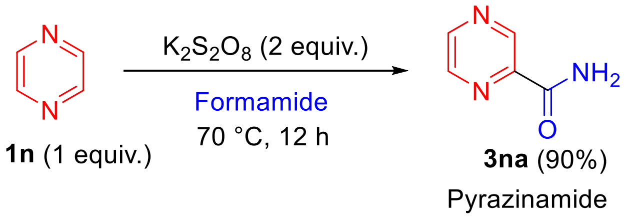
[a]Reaction conditions: Heteroaromatics **1** (1 equiv.),NMF **2b** or DMF **2c** (20 equiv. 2 mL) potassium persulfate (2 equiv.) under aerial atmosphere for 12 h, [b]Isolated yield after purification by column chromatography.

had no significant and noticeable effect on the reaction rate and yields. Different functional group such as bromo, chloro, methoxy and cyano were well tolerated under the reaction conditions. Method proved to be regio- and chemoselective for the *α*-aminocarbonylation only and we did not observe any *γ*-carboxamides and *α*-

amidoalkylated side products. It is very significant to note that protocol gave access to primary to tertiary carboxamides on various substrates including DMF and quinolines.

4.3.3 Gram scale synyhesis

Pyrazine carboxamide is known as Rifater or Tebrazid and is a prescribed prodrug for the tuberculosis worldwide. In order to make this protocol practical and for the wider applicability we demonstrated the synthesis of pyrazine carboxamide **3na** (86% yield) starting from **1n** and formamide **2a** using optimum reaction conditions (Scheme 4.7). Further, we synthesized pyrazine carboxamide **3na** in a gram scale and the method proved to be scalable. The method is simple and straightforward unlike the conventional methods such as coupling of pyrazine carboxylic acid and formamide **2a** via the activation either by acid chloride or by coupling agents such as DCC/EDC·HCl.

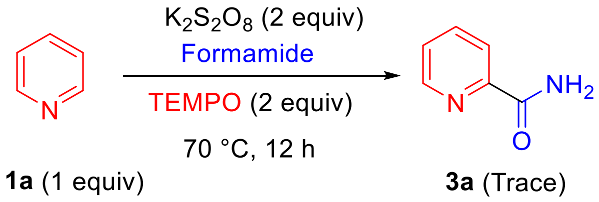


Scheme 4.7. Gram scale synthesis of Pyrazine carboxamide

4.4 Mechanistic study

4.4.1 Radical quenching experiment

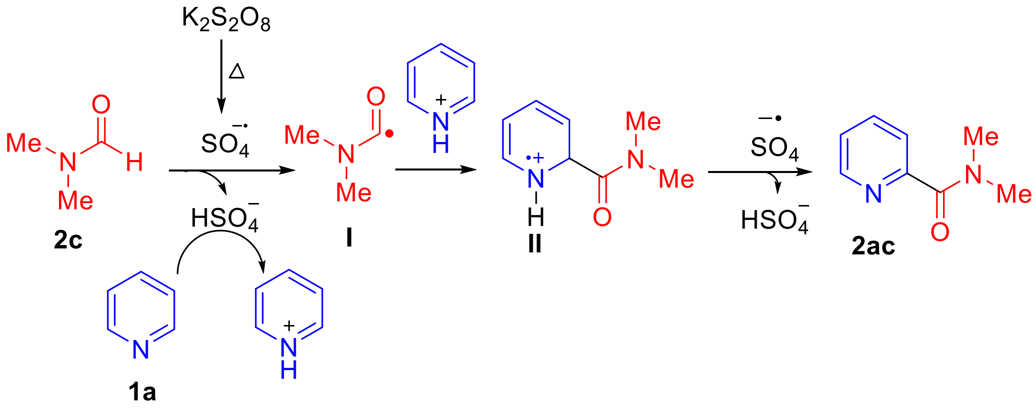
In order to understand and to gain further insight into the mechanism, pyridine **1a** and formamide **2a** were treated with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard optimum reaction conditions. We observed that reaction did not proceed even after prolonged reaction time thus indicating that the possible radical pathway was inhibited by the TEMPO (Scheme 4.8).



Scheme 4.8 Control experiment to understand the mechanistic pathway

4.5 Proposed reaction mechanism

Based on the literature precedence[10] and on our experimental observations we propose that sulfate radical anion ($SO_4^{\bullet-}$) (produced in situ by the decomposition of potassium persulfate under the reaction conditions) reacts with the amide such as DMF **2c** to generate the carbamoyl radical **I** thus forming bisulfate anion (Scheme 4.9). In turn alkaline pyridine is protonated and further undergoes the radical reaction with carbomyl species **I** to generate the intermediate **II**. This reactive species further gets aromatized by reacting with the sulfate radical anion to afford the desired product **2ac** (Scheme 4.9).



Scheme 4.9 Plausible mechanism for the formation of carboxamide

4.6 Conclusions

In summary, we have developed a transition-metal-free one-pot protocol that enables the direct aminocarbonylation of few heterocycles. Straightforward and simple protocol gives a direct access to primary to tertiary carboxamides employing user friendly and less expensive $K_2S_2O_8$ as reagent. The protocol works well with usually unreactive substrates such as NMF, DMF and quinoline and other heterocycles. Moreover, the protocol is clean and did not give any side products emanating from competing *α*-amidoalkylation. Pyrazine carboxamide a prescribed drug and this has been synthesized using our protocol and the practicality of the protocol was demonstrated on a gram scale for the wider application.

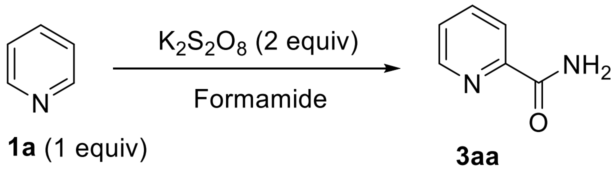
4.7 Experimental section

4.7.1 General

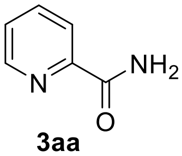
All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-$d_{6.}$ Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of Chloroform-d. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. All reactions were carried out in dried glassware. All purchased chemicals were used without further purification. Column chromatography was carried out using silica gel.

4.7.2 General experimental procedure for the synthesis primary carboxamides

In an oven dried glass tube containing a mixture of pyridine **1a** (100 mg, 1.26 mmol), and potassium persulfate (683 mg, 2.53 mmol), formamide **2a** (2 ml) was added and the reaction mixture was heated at 70 °C. Upon the completion of the reaction (monitored by TLC), saturated sodium bicarbonate solution (5 mL) was added and the crude product was extracted in ethyl acetate (3 X 5 mL). The crude product was purified by column chromatography to furnish compound **3aa** as a white crystalline solid (122 mg, 79% yield)



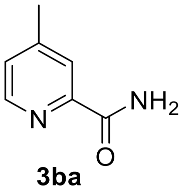
Picolinamide (3aa)



3aa

m.p.: 109-111 °C; IR (neat) cm^{-1}: 3417, 3169,1659, 1584, 1389; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.5 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.45 – 7.41(m, 1H), 6.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.6, 148.4, 137.5, 126.6, 122.5. HRMS (ESI TOF) *m/z* calcd for $C_6H_6N_2O$ $[M + H]^+$ 123.0558, found 123.0564.

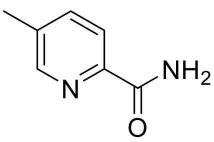
4-methylpicolinamide(3ba)



3ba

The compound **3ba** was synthesized starting from **1b** following the general procedure described for **3aa**; the compound **3ba** was obtained as a white solid (113 mg, 77% yield) m.p.: 125-128 °C; IR (neat) cm^{-1}: 3374, 3182, 2923,1681,1601,1363; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.9 Hz, 1H), 8.02 (s, 1H), 7.87 (s, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 6.16 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 149.5, 148.9, 148.2, 127.4, 123.4, 21.2; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ $[M + H]^+$ 137.0715, found 137.0721

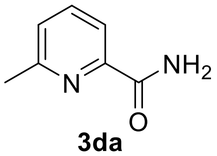
3-methylpicolinamide(3ca)



3ca

The compound **3ca** was synthesized starting from **1c** following the general procedure described for **3aa**; the compound **3ca** was obtained as a white solid (109 mg, 75% yield) m.p.: 117-121 °C; IR (neat) cm^{-1}: 3425, 3190, 2923, 1686, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.65 (d, *J* = 6.5 Hz, 1H), 5.69 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 148.9, 147.2, 137.8, 136.9, 122.2, 29.8; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ [M + H]$^+$ 137.0715, found 137.0722

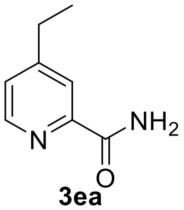
3-methylpicolinamide(3da)



3da

The compound **3da** was synthesized starting from **1d** following the general procedure described for **3aa**; the compound **3da** was obtained as a white solid (99 mg, 68% yield) m.p.: 115-118 °C; IR (neat) cm^{-1}: 3436, 3150,1687,1585,1381; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.87 (s, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 6.20 (s, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 157.5, 149.0, 137.5, 126.2, 119.5, 24.3; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ [M + H]$^+$ 137.0715, found 137.0721

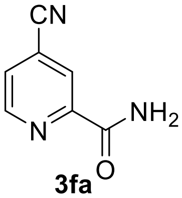
4-ethylpicolinamide (3ea)



3ea

The compound **3ea** was synthesized starting from **1e** following the general procedure described for **3aa**; the compound **3ea** was obtained as a white solid (75 mg, 57% yield). m.p.: 90-91 °C; IR (neat) cm^{-1}: 3446, 3234, 2970, 1665, 1598, 1368; ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.43 (d, *J* = 4.9 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.26 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.23 (s, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 154.8, 149.6, 148.4, 126.2, 122.2, 28.4, 14.3; HRMS (ESI TOF) *m/z* calcd for $C_8H_{10}N_2O$ [M + H]$^+$ 151.0871, found 151.0876.

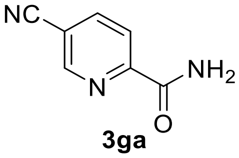
4-cyanopicolinamide (3fa)



3fa

The compound **3fa** was synthesized starting from **1f** following the general procedure described for **3aa**; the compound **3fa** was obtained as a white solid (107mg, 76% yield) m.p.: 250-254 °C; IR (neat) cm^{-1}: 3402, 3178, 2924, 2315, 2241, 1704, 1599, 1368; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.89 (dd, *J* = 5.0, 0.9 Hz, 1H), 8.34 (dd, *J* = 1.5, 0.9 Hz, 1H), 8.27 (s, 1H), 8.08 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 151.4, 149.8, 128.2, 123.8, 121.0, 116.4; HRMS (ESI TOF) *m/z* calcd for $C_7H_5N_3O$ [M + H]$^+$ 148.0511, found 148.0518.

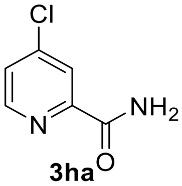
5-cyanopicolinamide (3ga)



3ga

The compound **3ga** was synthesized starting from **1g** following the general procedure described for **3aa**; the compound **3ga** was obtained as a white solid (95mg, 67% yield) m.p.: 185-189 °C; IR (neat) cm^{-1}: 3738, 3461, 2169, 1709, 1513; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.06 (d, *J* = 1.8 Hz, 1H), 8.47 (dd, *J* = 8.2, 1.9 Hz, 1H), 8.28 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.7, 152.9, 151.6, 141.9, 121.9, 116.7, 111.3; HRMS (ESI TOF) *m/z* calcd for $C_7H_5N_3O$ [M + H]$^+$ 148.0511, found 148.0518.

4-chloropicolinamide (3ha)

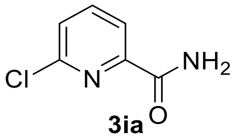


3ha

The compound **3ha** was synthesized starting from **1h** following the general procedure described for **3aa**; the compound **3da** was obtained as a white solid (102 mg, 74% yield) m.p.: 115-118 °C; IR (neat) cm^{-1}: 3351, 3175, 1684, 1425, 1177; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.47 (d, *J* = 5.5 Hz, 1H), 8.20 (d, *J* = 1.9 Hz, 1H), 7.84 (s, 1H), 7.45 (dd, *J* = 5.3, 2.1 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 150.9, 149.4, 146.0, 126.9, 123.3; HRMS (ESI TOF) *m/z* calcd for $C_6H_5ClN_2O$ $[M + H]^+$ 157.0168, found 157.0175.

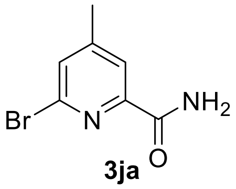
6-chloropicolinamide (3ia)



3ia

The compound **3ia** was synthesized starting from **1i** following the general procedure described for **3aa**; the compound **3ia** was obtained as a yellow solid (86 mg, 62% yield) m.p.: 93-96 °C; IR (neat) cm^{-1}: 3459, 3186, 2908, 1685, 1569, 1383, 1182; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.5 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.72 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 6.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 150.3, 149.9, 140.2, 127.6, 121.4; HRMS (ESI TOF) *m/z* calcd for $C_6H_5ClN_2O$ $[M + H]^+$ 157.0168, found 157.0175.

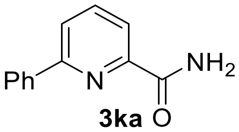
6-bromo-4-methylpicolinamide (3ja)



3ja

The compound **3ja** was synthesized starting from **1j** following the general procedure described for **3aa**; the compound **3ja** was obtained as a brown solid (74 mg, 59% yield). m.p.: 151-153 °C; IR (neat) cm^{-1}: 3425, 3147, 1704, 590, 1349, 815; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.66 (s, 1H), 7.45 (s, 1H), 6.02 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 151.9, 150.2, 140.8, 131.5, 122.9, 21.0; HRMS (ESI TOF) *m/z* calcd for $C_7H_7BrN_2O$ $[M + H]^+$ 214.9820, found 214.9828.

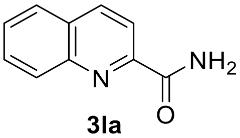
6-phenylpicolinamide (3ka)



3ka

The compound **3ka** was synthesized starting from **1k** following the general procedure described for **3aa**; the compound **3ka** was obtained as a white crystalline solid (79 mg, 61% yield). m.p.: 175-177 °C; IR (neat) cm^{-1}: 3454, 3242, 1649, 1594; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.03– 8.00 (m, 3H), 7.93– 7.88(m, 2H), 7.53 – 7.44 (m, 3H), 5.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 156.3, 149.5, 138.4, 138.3, 129.6, 129.0, 127.1, 123.4, 120.9; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{10}N_2O$ [M + H]$^+$ 199.0871, found 199.0879.

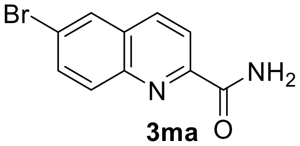
quinoline-2-carboxamide (3la)



3la

The compound **3la** was synthesized starting from **1l** following the general procedure described for **3aa**; the compound **3la** was obtained as a white crystaline solid (102 mg, 76% yield). m.p.: 130-132 °C; IR (neat) cm^{-1}: 3430, 3138, 1686, 1566, 1387; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.88 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.77 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.64 – 7.60 (m, 1H), 6.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.5, 146.7, 137.6, 130.3, 130.0, 129.5, 128.2, 127.9, 118.9; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_8N_2O$ [M + H]$^+$ 173.0715, found 173.0719.

6-bromoquinoline-2-carboxamide (3ma)



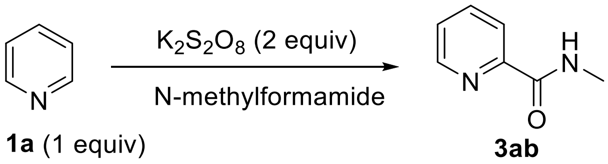
3ma

The compound **3ma** was synthesized starting from **1m** following the general procedure described for **3aa**; the compound **3ma** was obtained as a white solid (88 mg, 72% yield) m.p.: 228-230 °C; IR (neat) cm^{-1}: 3442, 3151, 2920, 1702, 1383; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.84 (dd, *J* = 9.0, 2.2 Hz, 1H), 5.74 (s, 1H); ^{13}C NMR (100 MHz,

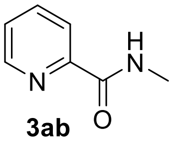
$CDCl_3$) δ 166.6, 149.8, 145.3, 136.6, 133.9, 131.6, 130.5, 130.0, 122.5, 119.9; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_7BrN_2O$ $[M + H]^+$ 228.1137, found 228.1138.

4.7.3 General experimental procedure for the synthesis secondary carboxamides

In an oven dried glass tube containing a mixture of pyridine **1a** (100 mg, 1.26 mmol), and potassium persulfate (683 mg, 2.53 mmol), *N*-methylformamide **2b** (2 mL) was added and the reaction mixture was heated at 70 °C. Upon the completion of the reaction (monitored by TLC), saturated sodium bicarbonate solution (5 mL) was added and the crude product was extracted in ethyl acetate (3 X 5 mL). The crude product was purified by column chromatography to furnish compound **3ab** as yellow oil (129 mg, 75% yield).



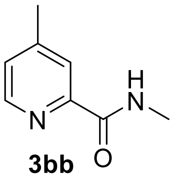
N-methylpicolinamide (3ab)



3ab

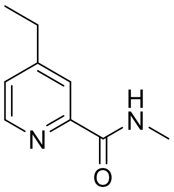
IR (neat) cm^{-1}: 3402, 3149, 1645, 1389; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.6 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 8.03 (s, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 7.7, 4.9, 1.2 Hz, 1H), 3.00 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 150.0, 148.1, 137.4, 126.1, 122.2, 26.2; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ $[M + H]^+$, 137.0715 found 137.0721.

N,4-dimethylpicolinamide (3bb)


3bb

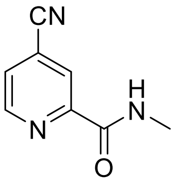
The compound **3bb** was synthesized starting from **1b** following the general procedure described for **3ab**; the compound **3bb** was obtained as a yellow liquid (128 mg, 79 % yield). IR (neat) cm^{-1}: 3360, 3162, 1665, 1351; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (d, *J* = 4.9 Hz, 1H), 7.99 (s, 2H), 7.19 (d, *J* = 4.9 Hz, 1H), 2.99 (d, *J* = 5.1 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.3, 149.8, 148.9, 147.9, 126.9, 123.0, 26.2, 21.2; HRMS (ESI TOF) *m/z* calcd for $C_8H_{10}N_2O$ [M + H]$^+$, 151.0871 found 151.0877.

4-ethyl-*N*-methylpicolinamide (3eb)


3eb

The compound **3eb** was synthesized starting from **1e** following the general procedure described for **3ab**; the compound **3eb** was obtained as a yellow liquid (110 mg, 72% yield). IR (neat) cm^{-1}: 3432, 3219, 2955, 1650, 1355; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.38 (d, *J* = 4.9 Hz, 1H), 8.02 (d, *J* = 0.9 Hz, 2H), 7.21 (dd, *J* = 5.0, 1.7 Hz, 1H), 3.00 (d, *J* = 5.1 Hz, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.3, 154.8, 150.0, 148.1, 125.8, 121.8, 28.4, 26.2, 14.3; HRMS (ESI TOF) *m/z* calcd for $C_9H_{12}N_2O$ [M + H]$^+$, 165.1028 found 165.1035.

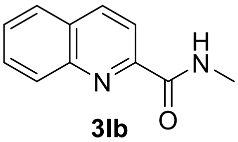
4-cyano-*N*-methylpicolinamide (3fb)


3fb

The compound **3fb** was synthesized starting from **1f** following the general procedure described for **3ab**; the compound **3fb** was obtained as a white solid (130 mg, 84% yield). m.p.: 134-136 °C; IR (neat) cm^{-1}: 3390, 3162, 2907, 2301, 2231, 1688, 1583, 1350; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.4 Hz, 1H), 8.41 (d, *J* = 1.1 Hz, 1H), 7.94 (s, 1H), 7.65 (dd, *J* = 4.9, 1.6 Hz, 1H), 3.05 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 151.4, 149.2, 127.6, 124.1, 122.1, 116.1, 26.4; HRMS (ESI TOF) *m/z* calcd for $C_8H_7N_3O$ [M + H]$^+$, 162.0667 found 162.0673.

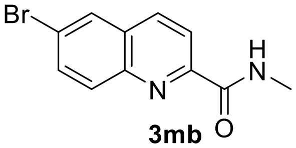
***N*-methylquinoline-2-carboxamide (3lb)**



3lb

The compound **3lb** was synthesized starting from **1l** following the general procedure described for **3ab**; the compound **3lb** was obtained as a white solid (108 mg, 75% yield). m.p.: 118-120 °C; IR (neat) cm^{-1}: 3418, 3119, 1668, 1550, 1365; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (q, 2H), 8.25(s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.62 – 7.58 (m, 1H), 3.09 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 150.0, 146.6, 137.6, 130.2, 129.7, 129.4, 127.9, 127.9, 118.9, 26.3; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_{10}N_2O$ [M + H]$^+$, 187.0871 found 187.0878.

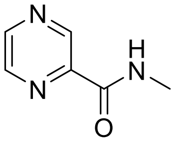
6-bromo-*N*-methylquinoline-2-carboxamide (3mb)



3mb

The compound **3mb** was synthesized starting from **1m** following the general procedure described for **3ab**; the compound **3mb** was obtained as a white solid (94 mg, 74% yield). m.p.: 158-160 °C; IR (neat) cm^{-1}: 3433, 3139, 2909, 1688, 1380; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.80 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.09 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 150.3, 145.1, 136.6, 133.8, 131.3, 130.4, 129.9, 122.1, 119.8, 26.4; HRMS (ESI TOF) *m/z* calcd for $C_{11}H_9BrN_2O$ [M + H]$^+$, 264.9976 found 264.9977.

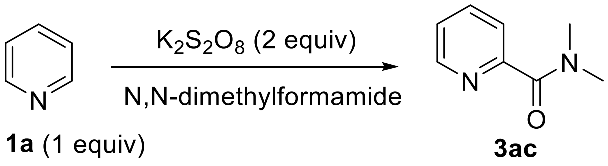
N-methylpyrazine-2-carboxamide (3nb)


3nb

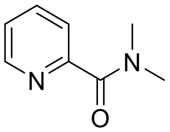
The compound **3nb** was synthesized starting from 3**n** following the general procedure described for **3ab**; the compound **3nb** was obtained as a white solid (145 mg, 85% yield). m.p.: 97-100 °C; IR (neat) cm^{-1}: 3211, 2923, 1632, 1501, 1349; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 1.4 Hz, 1H), 8.72 (d, *J* = 2.5 Hz, 1H), 8.49 (dd, *J* = 2.3, 1.6 Hz, 1H), 7.82 (s, 1H), 3.03 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 147.3, 144.6, 144.4, 142.6, 26.2; HRMS (ESI TOF) *m/z* calcd for $C_6H_7N_3O$ $[M + H]^+$, 138.0667 found 138.0673.

4.7.4 General experimental procedure for the synthesis tertiary carboxamides

In an oven dried glass tube containing a mixture of pyridine **1a** (100 mg, 1.26 mmol), and potassium persulfate (683 mg, 2.53 mmol), *N*,*N*-dimethylformamide **2c** (2 mL) was added and the reaction mixture was heated at 70 °C. Upon the completion of the reaction (monitored by TLC), saturated sodium bicarbonate solution (5 mL) was added and the crude product was extracted in ethyl acetate (3 X 5 mL). The crude product was purified by column chromatography to furnish compound **3ac** as yellow oil (87 mg, 46% yield)



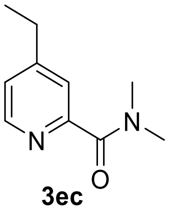
N,N-dimethylpicolinamide (3ac)


3ac

IR (neat) cm^{-1}: 2926, 2849, 1634, 1401; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.2 Hz, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 3.14 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 154.6, 148.3, 137.2,

124.5, 123.7, 39.2, 35.9; HRMS (ESI TOF) *m/z* calcd for $C_8H_{10}N_2O$ [M + H]$^+$ 151.0851, found 151.0874.

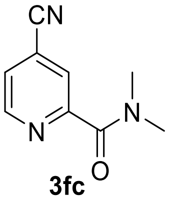
4-ethyl-*N,N*-dimethylpicolinamide (3ec)



3ec

The compound **3ec** was synthesized starting from **1e** following the general procedure described for **3ac**; the compound **3ec** was obtained as a pale yellow oil (85 mg, 51% yield). IR (neat) cm^{-1}: 2924, 2854, 1621, 1494, 1227; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.1 Hz, 1H), 7.46 (d, *J* = 0.8 Hz, 1H), 7.16 (dd, *J* = 5.0, 1.2 Hz, 1H), 3.13 (s, 3H), 3.06 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.30 – 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 154.5, 148.2, 124.2, 123.2, 39.2, 35.8, 28.4, 14.2; HRMS (ESI TOF) *m/z* calcd for $C_{10}H_{14}N_2O$ [M + H]$^+$ 179.1184, found 179.1188.

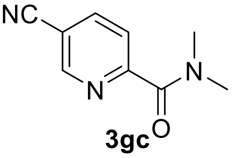
4-cyano-*N,N*-dimethylpicolinamide (3fc)



3fc

The compound **3fc** was synthesized starting from **1f** following the general procedure described for **3ac**; the compound **3fc** was obtained as a white solid (97 mg, 57% yield). m.p.: 38-40 °C; IR (neat) cm^{-1}: 2934, 2842, 2240, 1640, 1507, 1377; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.89 (d, *J* = 1.1 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.13 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (10o MHz, $CDCl_3$) δ 166.8, 155.8, 149.1, 125.9, 125.8, 121.7, 116.0, 39.1, 36.1; HRMS (ESI TOF) *m/z* calcd for $C_9H_9N_3O$ [M + H]$^+$ 176.0824, found 176.0826.

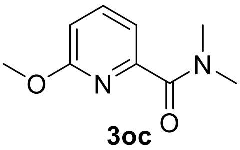
5-cyano-*N,N*-dimethylpicolinamide (3gc)



3gc

The compound **3gc** was synthesized starting from **1g** following the general procedure described for **3ac**; the compound **3gc** was obtained as a white solid (84 mg, 50% yield). m.p.: 105-107 °C; IR (neat) cm^{-1}: 2925, 2855, 2233, 1633, 1404, 1090; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.85 (d, *J* = 1.3 Hz, 1H), 8.07 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 3.15 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.1, 157.5, 151.0, 140.4, 124.0, 116.2, 110.6, 39.1, 36.1; HRMS (ESI TOF) *m/z* calcd for $C_9H_9N_3O$ [M + H]$^+$ 176.0824, found 176.0826.

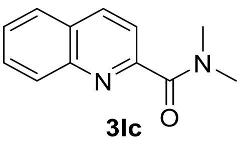
6-methoxy-*N,N*-dimethylpicolinamide (3oc)



3oc

The compound **3oc** was synthesized starting from **1o** following the general procedure described for **3ac**; the compound **3oc** was obtained as a pale yellow oil (75 mg, 44% yield). IR (neat) cm^{-1}: 2925, 2837, 1633, 1582, 1461, 1025; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 – 7.61 (m, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H), 3.12 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.8, 162.8, 151.8, 139.3, 116.5, 112.0, 53.7, 39.1, 36.0; HRMS (ESI TOF) *m/z* calcd for $C_9H_{12}N_2O_2$ [M + H]$^+$ 181.0977, found 181.0978.

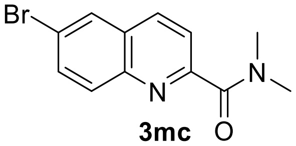
N,N-dimethylquinoline-2-carboxamide (3lc)



3lc

The compound **3lc** was synthesized starting from **1l** following the general procedure described for **3ac**; the compound **3lc** was obtained as a pale yellow oil (91 mg, 51% yield). IR (neat) cm-1: 2925, 2856, 1628, 1494, 1397, 1083; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 3.18 (s, 3H), 3.14 (d, *J* = 3.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 154.2, 146.6, 137.3, 130.2, 129.7, 128.1, 127.7, 127.6, 120.6, 39.2, 35.9; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{12}N_2O$ [M + H]$^+$ 201.1028, found 201.1032.

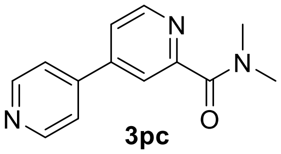
6-bromo-*N,N*-dimethylquinoline-2-carboxamide (3mc)



3mc

The compound **3mc** was synthesized starting from **1m** following the general procedure described for **3ac**; the compound **3mc** was obtained as a pale yellow solid (66 mg, 49% yield). m.p.: 90-93 °C; IR (neat) cm^{-1}: 2924, 2855, 1634, 1481, 871; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.82 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 3.20 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.5, 145.1, 136.1, 133.6, 131.3, 129.7, 129.1, 121.6, 39.1, 35.9; HRMS (ESI TOF) *m/z* calcd for $C_{12}H_{11}BrN_2O$ [M + H]$^+$ 279.0133, found 279.0138.

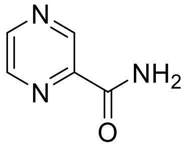
N,N-dimethyl-[4,4'-bipyridine]-2-carboxamide (3pc)



3pc

The compound **3pc** was synthesized starting from **1p** following the general procedure described for **3ac**; the compound **3pc** was obtained as a brown solid (611 mg, 42% yield). m.p.: 142-145 °C; IR (neat) cm^{-1}: 2935, 2860, 1629, 1388, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.5, 1.7 Hz, 2H), 8.68 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.89 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.57-7.54 (m, 3H), 3.14 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 155.5, 150.5, 149.2, 146.7, 145.3, 122.1, 121.6, 121.6, 39.2, 36.0; HRMS (ESI TOF) *m/z* calcd for $C_{13}H_{13}N_3O$ [M + H]$^+$ 228.1137, found 228.1138.

pyrazine-2-carboxamide (3na)



3na

The compound **3na** was synthesized starting from **1n** following the general procedure described for **3aa**; the compound **3na** was obtained as a white solid (133mg, 86% yield) m.p.: 186-189 °C; IR (neat) cm^{-1}: 3224, 2935, 1646, 1516, 1367; ^1H NMR (400 MHz, DMSO-d_6) δ 9.18 (d, *J* = 1.5 Hz, 1H), 8.85 (d, *J* = 2.5 Hz, 1H), 8.71 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.26 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 147.4, 145.1, 143.6, 143.4; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ $[M + H]^+$ 124.0511, found 124.0516.

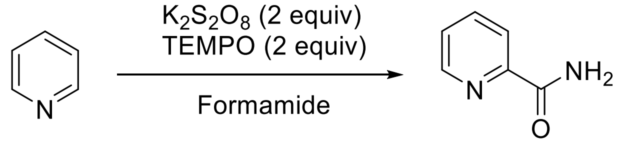
Gram scale synthesis

In an oven dried glass tube containing a mixture of pyrazine **1n** (2 g, 25 mmol), and potassium persulfate (13.50 g, 50 mmol), formamide **2a** (22 mL) was added and the reaction mixture was heated at 70 °C. Upon the completion of the reaction (monitored by TLC), saturated sodium bicarbonate solution (50 mL) was added and the crude product was extracted in ethyl acetate (3 X 40 mL). The crude product was purified by column chromatography to furnish compound **3na** as a white crystalline solid (2.59g, 84% yield)

m.p.: 186-189 °C; IR (neat) cm^{-1}: 3224, 2935, 1646, 1516, 1367; ^1H NMR (400 MHz, DMSO-D6) δ 9.18 (d, *J* = 1.5 Hz, 1H), 8.85 (d, *J* = 2.5 Hz, 1H), 8.71 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.26 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-D6) δ 165.1, 147.4, 145.1, 143.6, 143.4; HRMS (ESI TOF) *m/z* calcd for $C_7H_8N_2O$ $[M + H]^+$ 124.0511, found 124.0516.

Radical quenching experiment

In an oven dried glass tube containing a mixture of pyridine **1a** (100 mg, 1.26 mmol), potassium persulfate (683 mg, 2.53 mmol) and TEMPO (395 mg, 2.53 mmol), formamide **2a** (2 mL) was added and the reaction mixture was heated at 70 °C. Progress of the reaction was monitored by TLC. After prolong reaction time (24 h) we observed only trace amount of product **3ab**.



1a (1 equiv)

3ab Traces

4.8 Appendix III: ^{1}H, ^{13}C spectral data of representative compounds

Compound No.	**Figure AII.X**	**Data**	**Page No.**
3aa	Figure IV.1 and IV.2	^{1}H and ^{13}C	134
3ba	Figure IV.3 and IV.4	^{1}H and ^{13}C	135
3eb	Figure IV.5 and IV.6	^{1}H and ^{13}C	136
3fb	Figure IV.7 and IV.8	^{1}H and ^{13}C	137
3oc	Figure IV.9 and IV.10	^{1}H and ^{13}C	138
3lc	Figure IV.11 and IV.12	^{1}H and ^{13}C	139

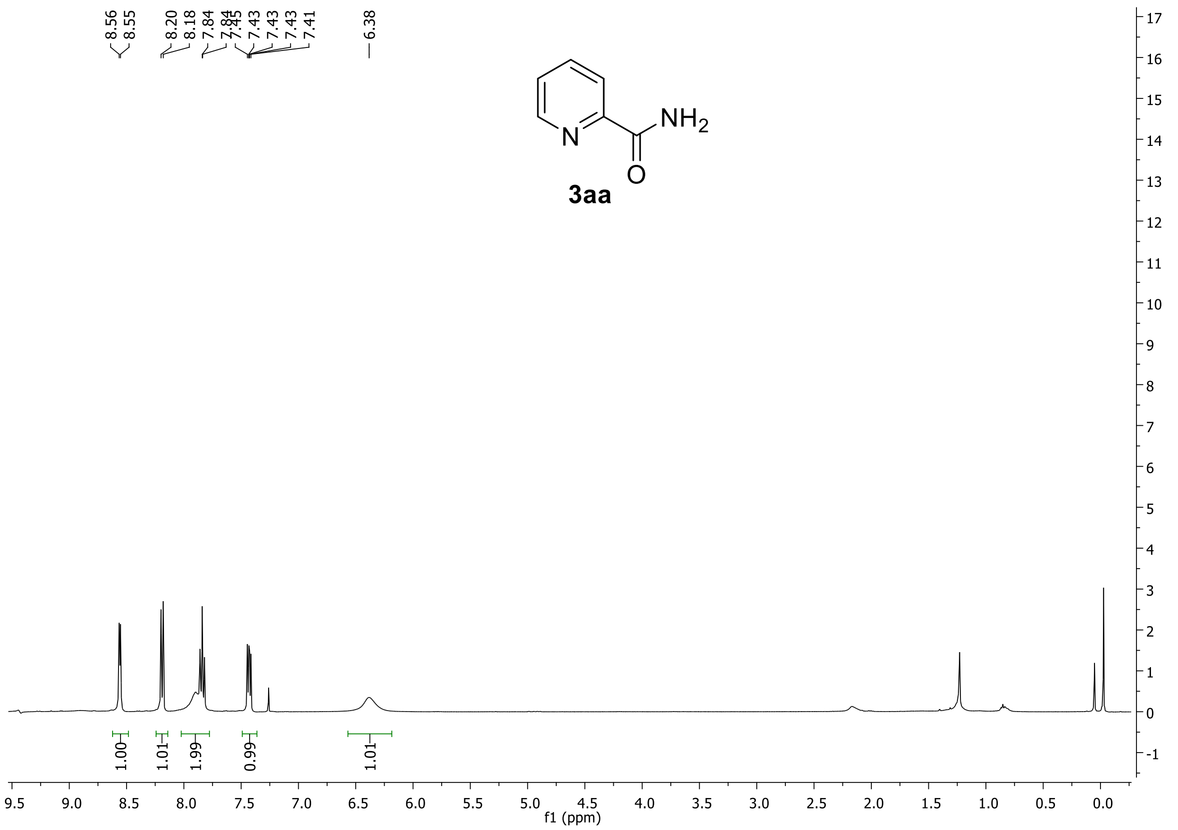


Figure IV.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

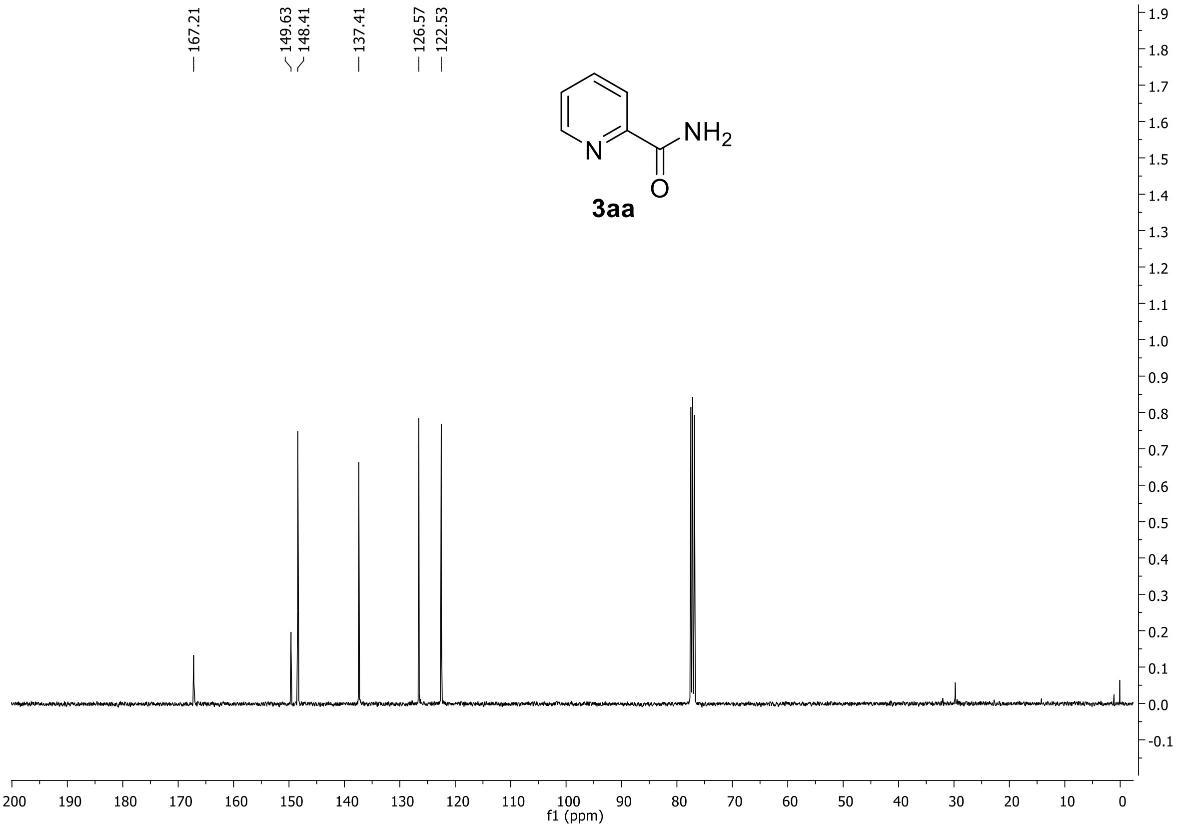


Figure IV.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

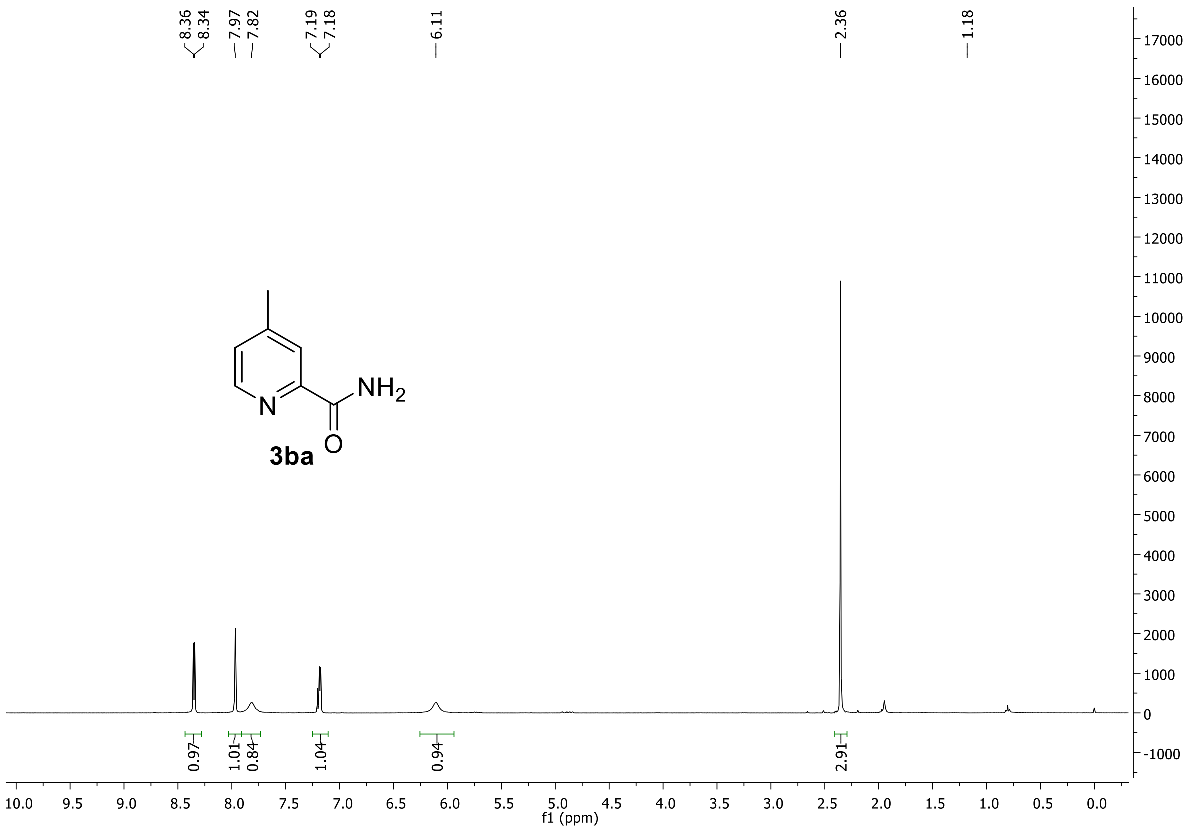


Figure IV.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3ba**

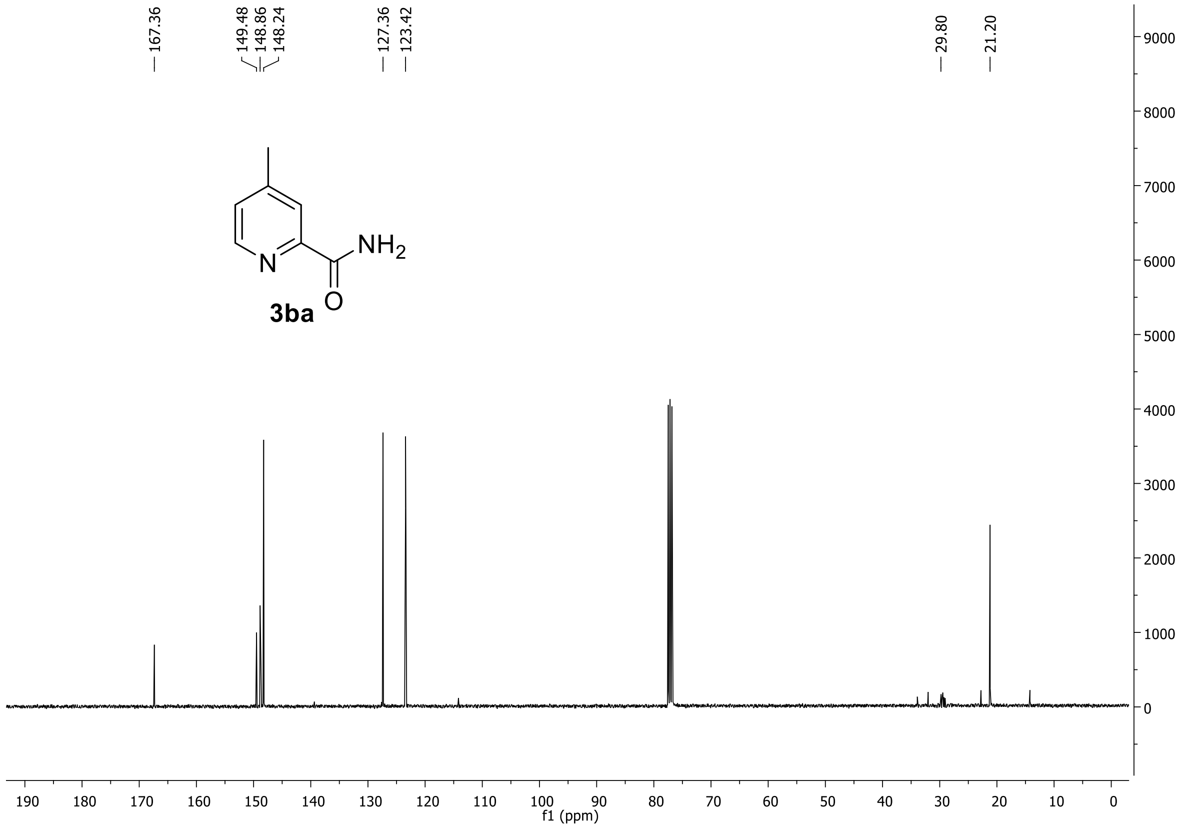


Figure IV.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3ba**

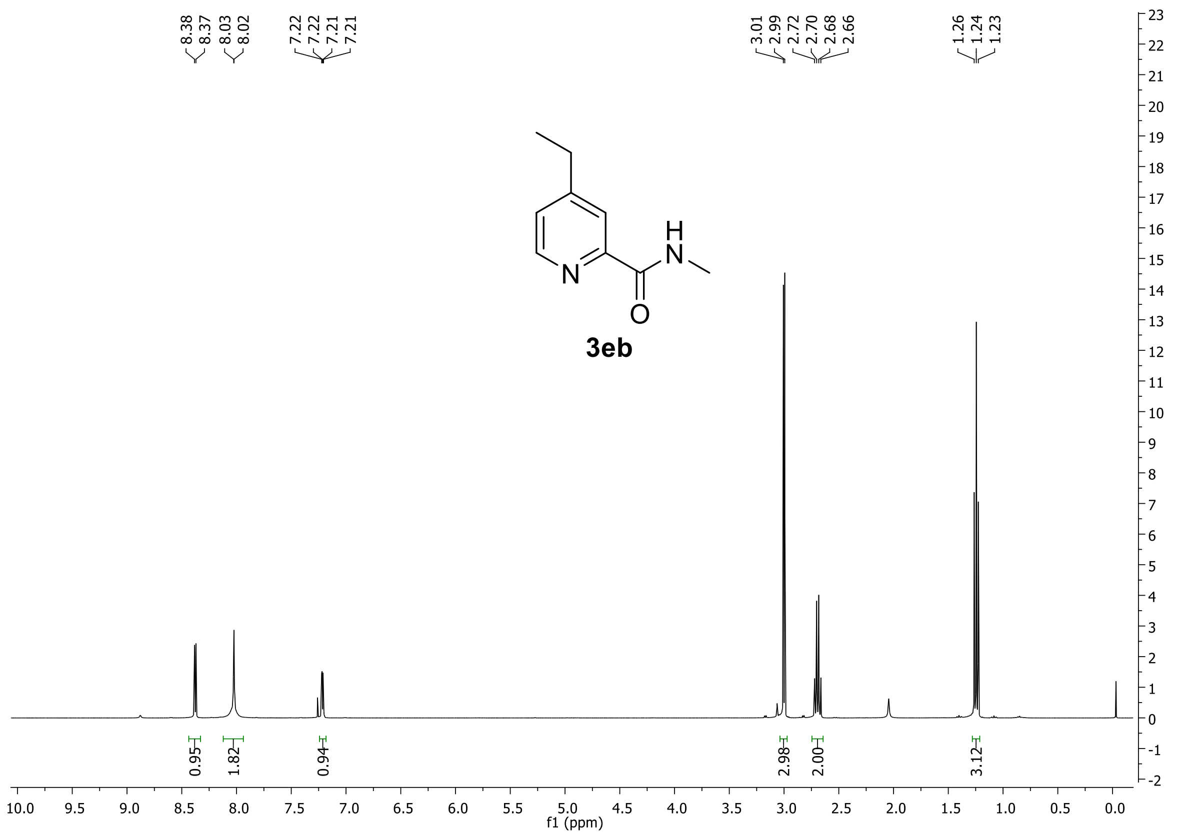


Figure IV.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3eb**

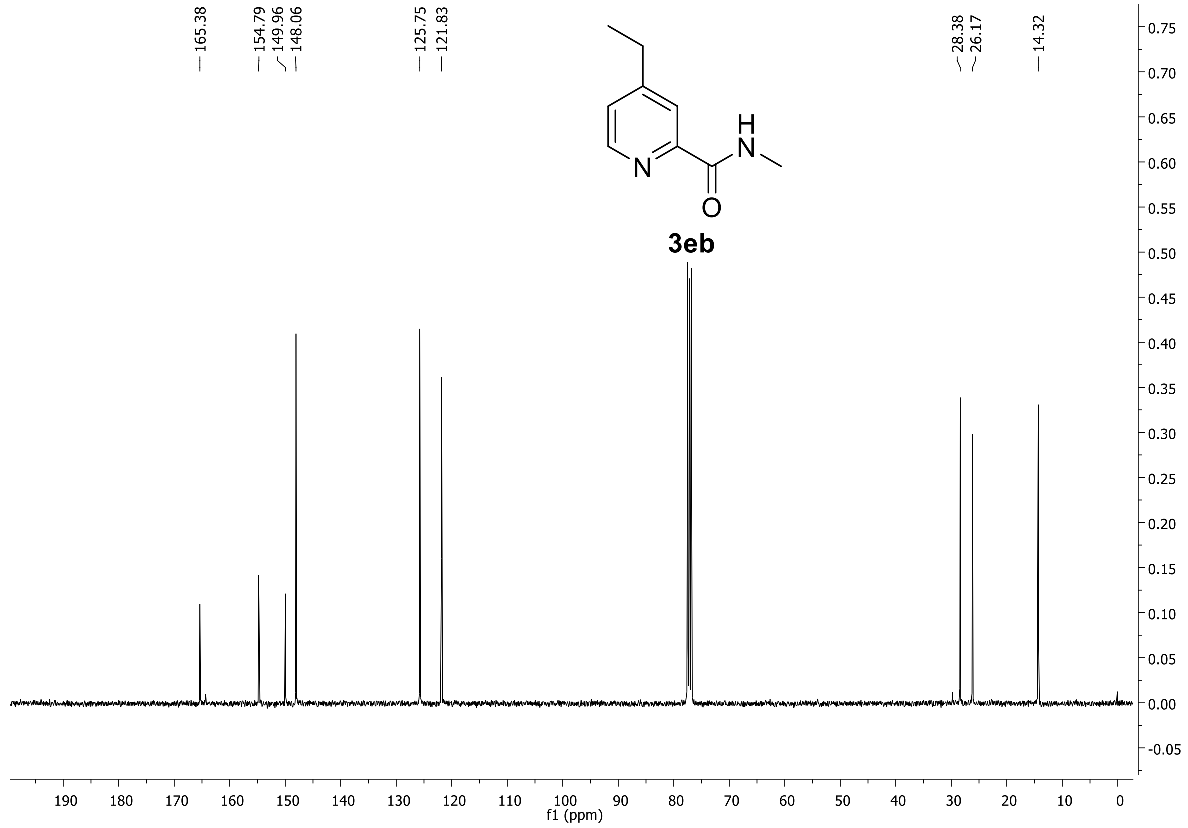


Figure IV.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3eb**

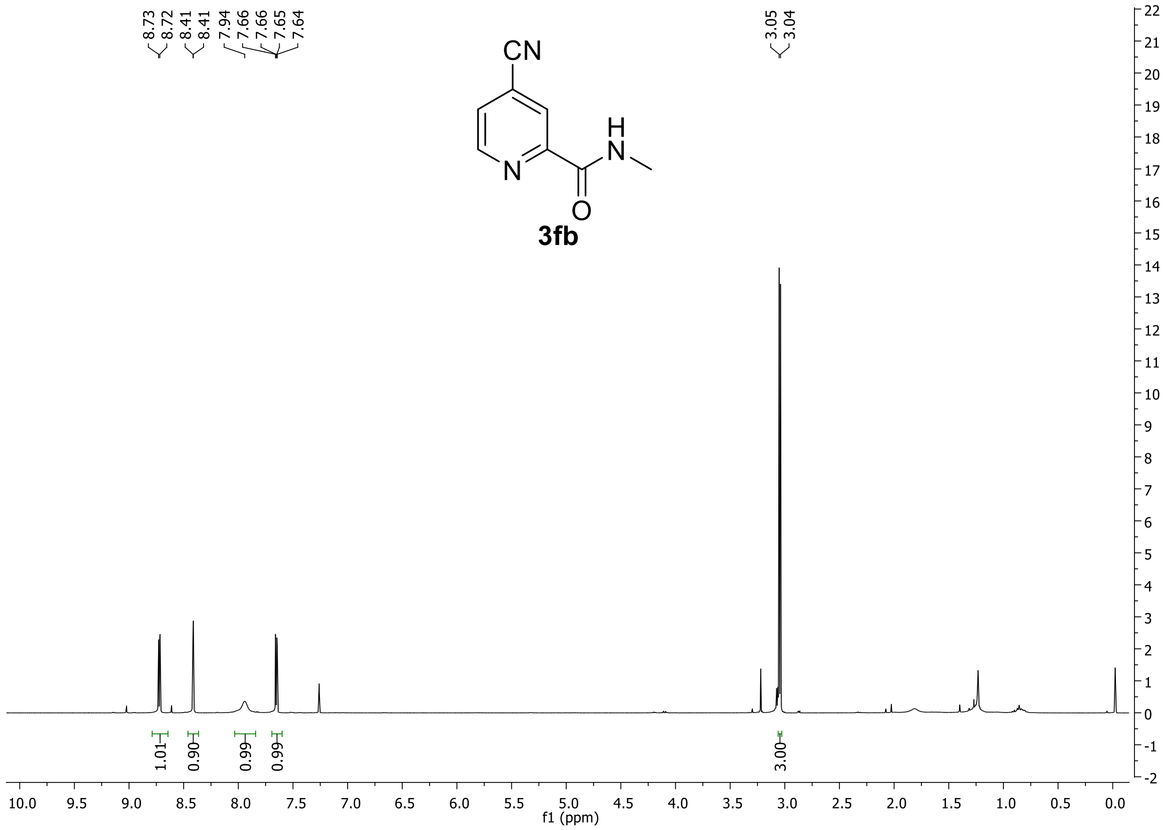


Figure IV.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3fb**

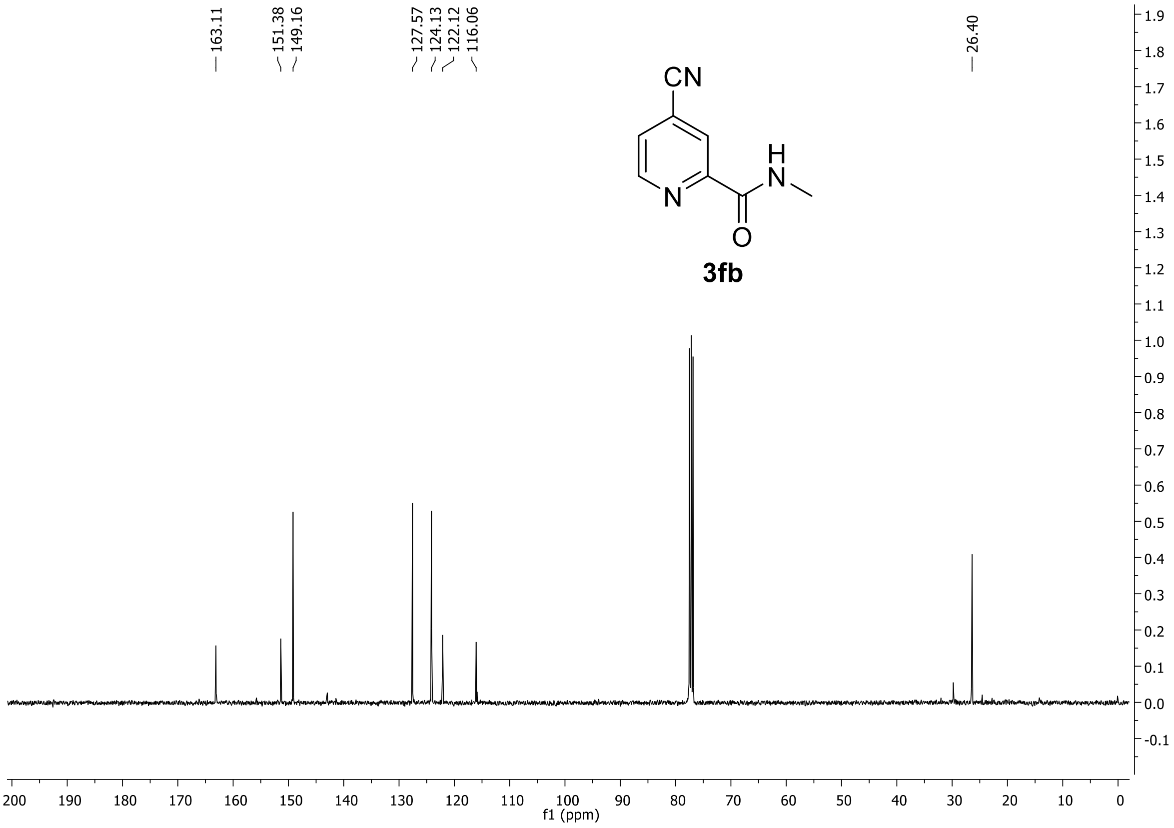


Figure IV.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3fb**

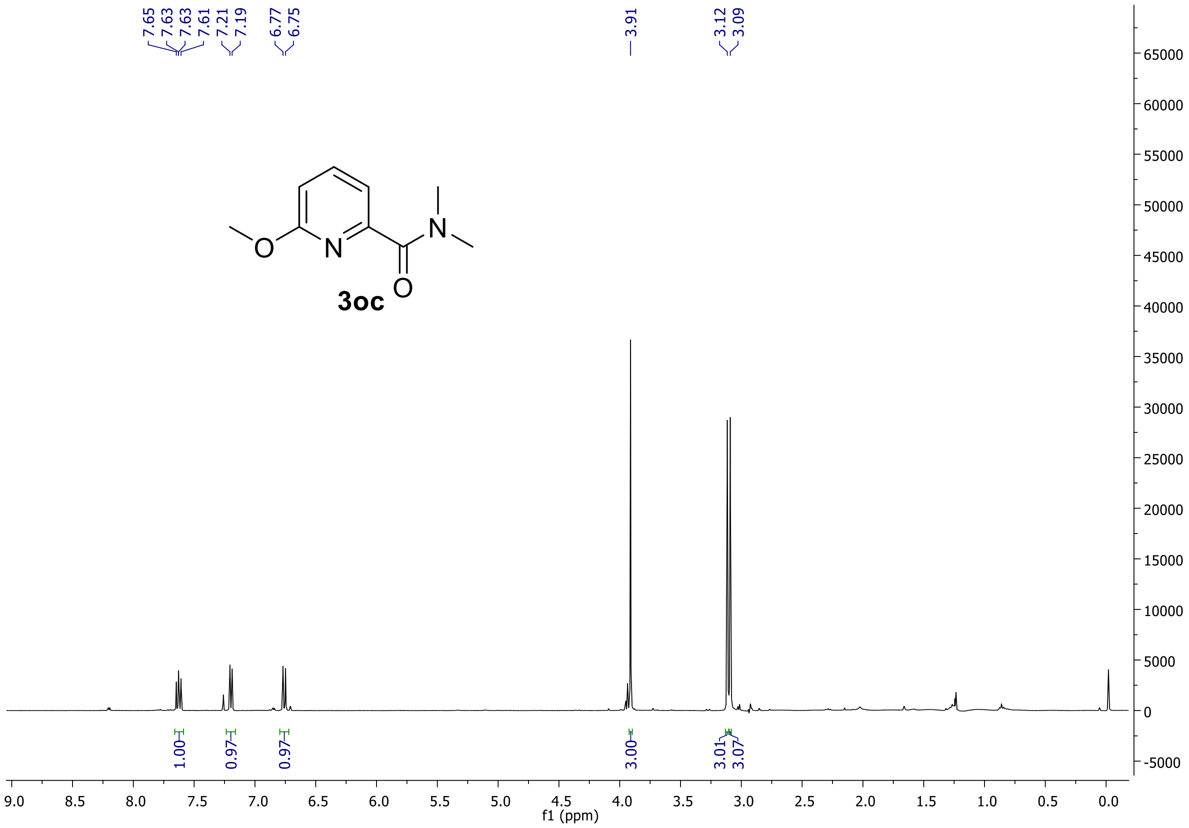


Figure IV.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3oc**

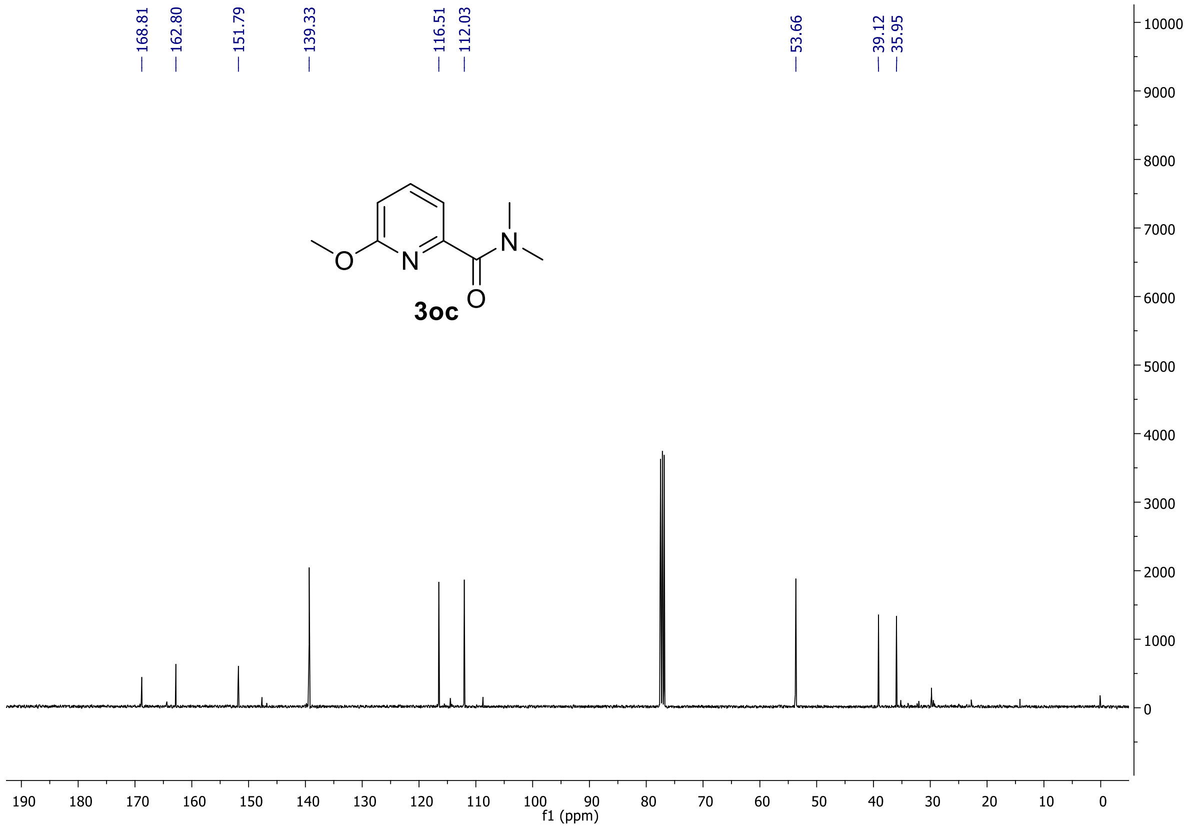


Figure IV.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3oc**

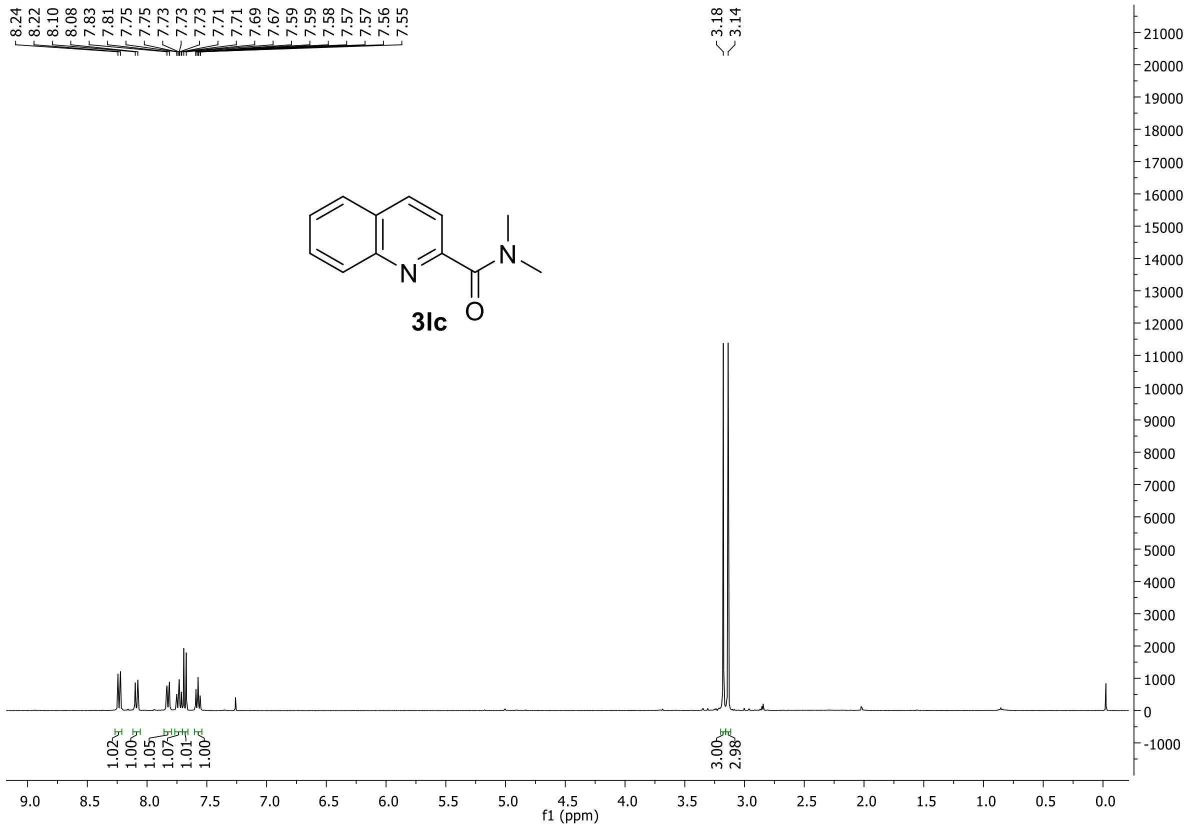


Figure IV.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3lc**

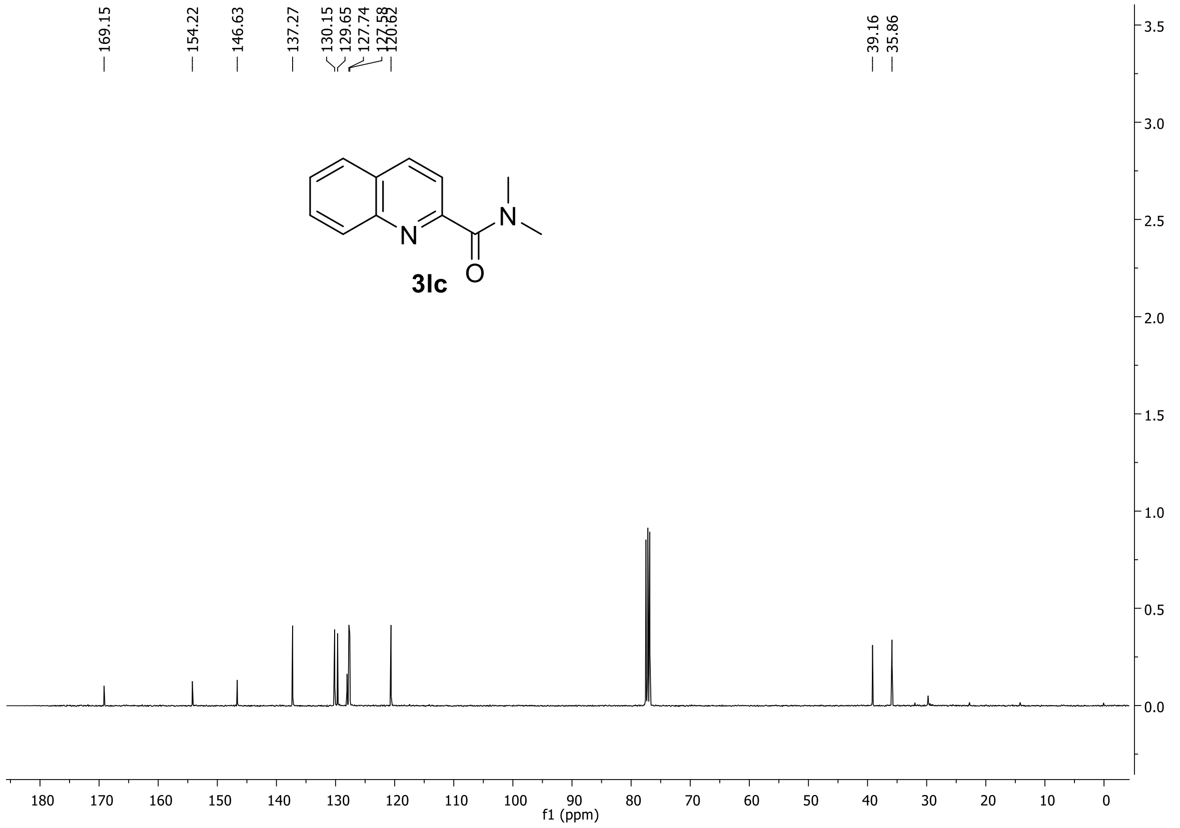


Figure IV.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3lc**

4.5.7 References and notes

1. (a) Johansson I, ed. *Kirk-Othmer Encyclopedia of Chemical Technology*, 2. New York: John Wiley & Sons; 2004:442–463;
   (b) Abicky J, ed. *The Chemistry of Amides*. New York: WileyInterscience; 1970;
   (c) Greenberg A, Breneman CM, Liebman JF, eds. *The Amide inkage: Structural Significance in Chemistry, Biochemistry and Materials Science*. New York: John Wiley & Sons; 2000;
   (d) Haynes C, Kirkwood RC. *Pestic Sci*. 1992;35:161–165;
   (e) Constable DJC, Dunn PJ, Hayler JD, et al. *Green Chem*. 2007;9:411–420;
   (f) Regitano JB, Koskinen WC. *J Agric Food Chem*. 2008;56:5801–5805.
2. (a) *Metabolic Pathways of Agrochemicals: Part 2: Insecticides and Fungicides* (Ed.: Roberts TR., Hutson DH), Royal Society of Chemistry.;
   (b) Arthur G. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*. Wiley-Interscience; 2000;
   (c) Pattabiraman VR, Bode JW. *Nature*. 2011;480:471–479;
   (d) Roy S, Roy S, Gribble W. *Tetrahedron*. 2012;68:9867–9923;
   (e) Carey JS, Laffan D, Thomson C, Williams MT. *Org Biomol Chem*. 2006;4:2337–2347;
   (f) Allen CL, Williams JMJ. *Chem Soc Rev*. 2011;40:3405–3415;
   (g) Chen C, Hong SH. *Org Biomol Chem*. 2011;9:20–26;
   (h) Ekoue-Kovi K, Wolf C. *Chem Eur J*. 2008;14:6302–6315;
   (i) Izumi Y, Ichihashi H, Shimazu Y, Kitamura M, Sato H. *Bull Chem Soc Jpn*. 2007;80:1280–1287;
   (j) Gunanathan C, Ben-David Y, Milstein D. *Science*. 2007;317:790–792;
   (k) Crochet P, Cadierno V. *Chem Commun*. 2015;51:2495–2505.
3. (a) Alsabeh PG, Stradiotto M, Neumann H, Beller M. *Adv Synth Catal*. 2012;354:3065–3070;
   (b) Gadge ST, Bhanage BM. *Synlett*. 2014;25:85–88;
   (c) Suresh AS, Baburajan P, Ahmed M. *Tetrahedron Lett*. 2015;56:4864–4867;
   (d) Nielsen DU, Tanning RH, Lindhardt AT, Gogsig TM, Skrydstrup T. *Org Lett*. 2011;13:4454–4457;
   (e) Han W, Jin F, Zhao Q, Du H, Yao L. *Synlett*. 2016;27:1854–1859;
   (f) Kukushkin VY, Pombeiro AJL. *Chem Rev*. 2002;102:1771–1802;

(g) Caronna T, Gambarotti C, Palmisano L, Punta C, Recupero F. *Chem Commun*. 2003;18:2350–2351;

(h) Cunico RF, Maity BC. *Org Lett*. 2002;4:4357–4359.

4. (a) Ding ST, Jiao N. *Angew Chem Int Ed*. 2012;51:9226–9237;

(b) Muzart J. *Tetrahedron*. 2009;65:8313–8323.

5. (a) Maslankiewicz A, Michalik E. *J Heterocyclic Chem*.1997;34:401;

(b)Caronna T, Gambarotti C, Palmisano L, Punta C, Recupero F. *Chem Commun*. 2003;18:2350;

(c) Minisci F, Recupero F, Punta C, et al. *Chem Commun*. 2002;2496;

(d) Zhang Y, Teuscher KB, Ji H. *Chem Sci*. 2016;7:2111;

(e) Minisci F, Gardini GP, Galli R, Bertini F. *Tetrahedron Lett*. 1970;11:15–16;

(f) Amrollahi Biyouki MA, Smith RAJ, Bedford JJ, Leader JP. *Synth Commun*. 1998;28:3817.

6. (a) Jiang Q, Shenga W, Guo C. *Green Chem*. 2013;15:2175–2179;

(b) Mi X, Wang C, Huang M, Wu Y, Wu Y. *J Org Chem*. 2015;80:148–155;

(c) Yuan M, Chen L, Wang J, et al. *Org Lett*. 2015;17:346–349;

(d) Kim SM, Kim DW, Yang JW. *Org Lett*. 2014;16:2876–2879;

(e) Lu S, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336–9352;

(f) Wei W, Wen J, Yang D, Liu X, Guo M, Dong R, Wang H. *J Org Chem*. 2014;79:4225–4230;

(g) Wang H, Guo L-N, Wang S, Duan X-H. *Org Lett*. 2015;17:3054–3057.

7. (a) Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:415–418;

(b) Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:2822–2825.

8. (a) Tanaka T. *Sci Am*. 1981;244:124–136;

(b) Xia R, Xie M-S, Niu H-Y, Qu G-R, Guo H-M. *Org. Lett*. 2014;16:444–447;

(c) Guo X, Qiu K, Feng X. *Chin J Polym Sci*. 1989;7:165–173.

9. Tanner DD, Osman SA. *J Org Chem*. 1987;52:4689–4693.

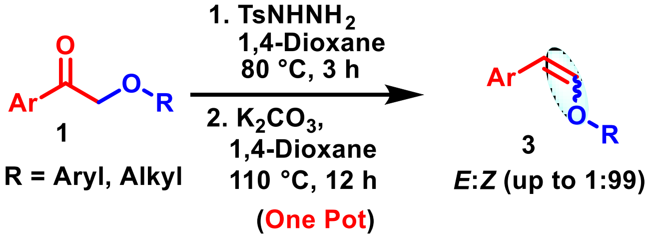
10. (a) Gardini GP, Minisci F, Palla G, Arnone A, Galli R. *Tetrahedron Lett.* 1971;59–62;

(b) Minisci F. *Synthesis*. 1973;1973:1–24;

(c) Tauber J, Imbri D, Opatz T. *Molecules*. 2014;19:16190–16222.

Chapter 5

One Pot Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones via Bamford-Stevens Reaction



- Transition-Metal-Free
- *Z*-selective
- Gram Scale Synthesis
- 30 examples up to 84% yield

One Pot Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones via Bamford-Stevens Reaction

5

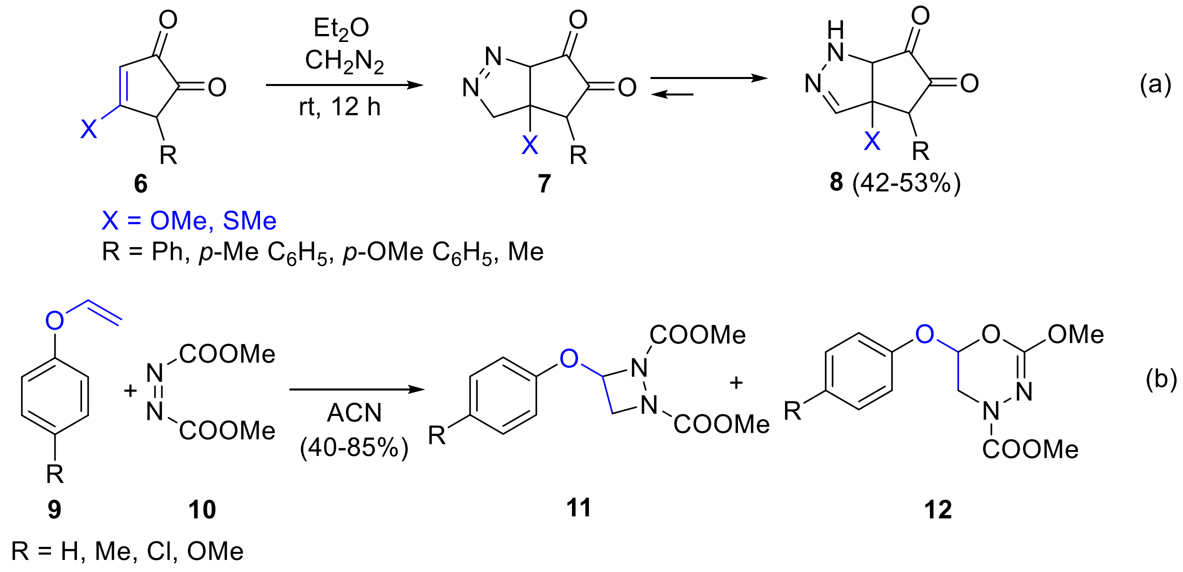
5.1 Abstract

A one-pot transition-metal-free synthesis of styrenyl ethers starting from 2-aryloxy/alkoxy acetophenones is described. The protocol explores the use of tosyl hydrazide and potassium carbonate via Bamford-Stevens reaction to synthesize the styrenyl ethers. The protocol proved to be scalable in gram quantity. The protocol is very simple, practical and uses mild reaction conditions with simple reaction set-up.

5.2 Introduction

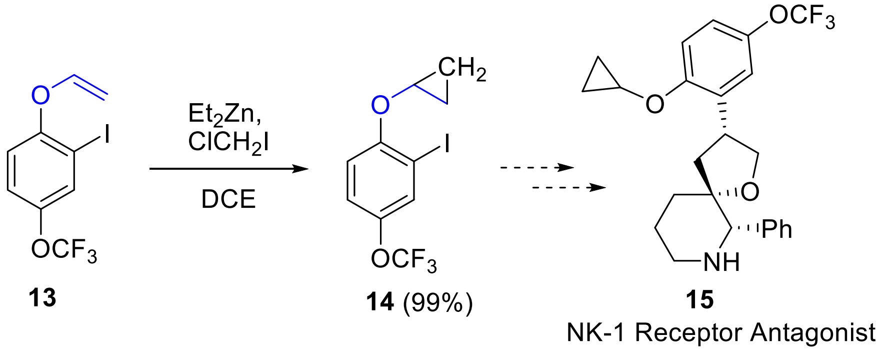
The vinyl functionality is very important and useful in organic synthesis as well as in polymer and pharmaceutical industries. Aryl vinyl/styrenyl ethers have been explored as nucleophiles in many organic reactions such as cycloaddition reactions,[1] ene and aldol-type additions,[2] cyclopropanations[3] and metathesis reactions[4] and are commonly used as acyl anion equivalents.[5]

El-Nabi et al. reported the cycloaddition reaction of the pyrrol-2,3-diones **6** and equimolar amount of diazomethane to afford the corresponding intermediate **7**, which upon subsequent reaction steps furnished 5,6-dioxo-1H pyrrolo[2,3-d]pyrazole derivatives **8** in good yields (42-53%, Scheme 5.1a).[1a] Likewise, Sommer and co-workers reported the reaction of phenylvinyl ethers **9** with dimethyl azodicarboxylate **10** to furnish the corresponding compounds **11** and **12** via (2 + 2) and (2 + 4) cycloaddition reactions (40-85%, Scheme 5.1 b).[1b]



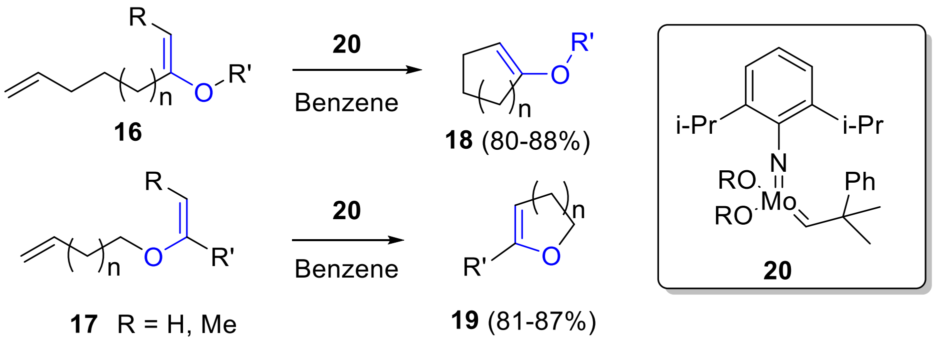
Scheme 5.1 Cycloaddition reactions

Maligres et al. reported the synthesis of a spirobicyclic NK-1 receptor antagonist antipode **15** starting from styrenyl ether **13** (Scheme 5.2).[3] The compound **13** under Simmon Smith reaction conditions afforded the corresponding aryl cyclopropyl ether **14** in excelent yields (99%) and this has been subsequently used as a precursor for the synthesis of NK-1 receptor antagonist **15** (Scheme 5.2).



Scheme 5.2 Cyclopropanation of aryl vinyl ethers

Grubbs and co-workers developed a catalytic ring-closing metathesis of acyclic olefinic enol ethers **16** and **17** using molybdenum alkylidene complex **20** as a catalyst to afford the corresponding carbocyclic enol ethers **18** and heterocycles **19** respectively in very good yields (80-88%). The protocol also demonstrated the synthesis of benzofurans (Scheme 5.3).[4]

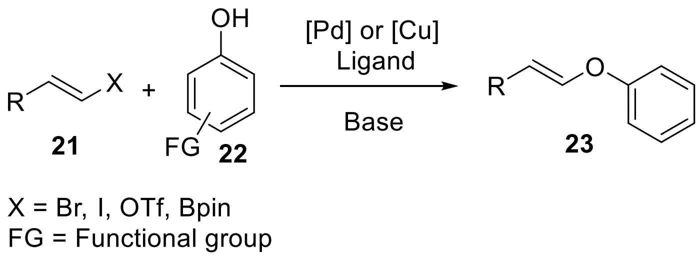


Scheme 5.3 Ring closing olefin metathesis

Apart from the above mentioned synthetic transformations, aryl vinyl/styrenyl ethers have also been widely used in various polymerization reactions and also vinyl/styrenyl ethers have also been explored as protecting groups for the phenol derivatives.[7]

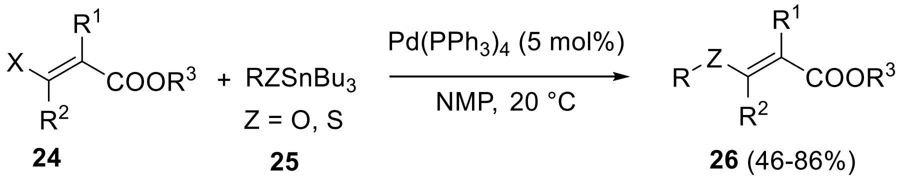
Considering the importance of this scaffold (vinyl/styrenyl ether) and its applications, many research groups have developed transition-metal-catalyzed cross coupling reactions as well as the traditional multi-step strategies for the synthesis of aryl vinyl ethers.[8]

Many scientists have reported the transition-metal-catalysed (copper/palladium) cross-coupling reaction of vinyl halides **21** and phenols **22** to afford the vinyl aryl ethers **23** (Scheme 5.4).[9] Some of the selected methods have been described.



Scheme 5.4 Metal catalyzed cross coupling reactions

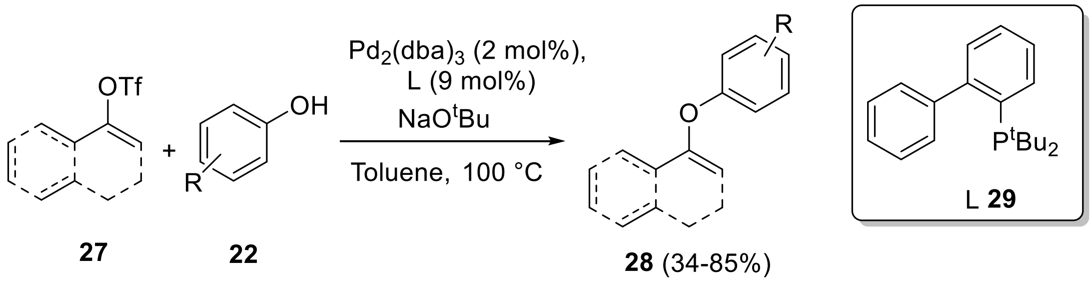
In 1997 Rossi et al. reported the palladium catalyzed C-O and C-S bond forming reactions starting from 3-bromopropenoates **24**. The reaction of 3-bromopropenoates **24** with Bu_3SnZR **25** (Z = O, S) was carried out in the presence of $Pd(PPh_3)_4$ in *N*-methyl-2-pyrrolidone (NMP) to afford the corresponding 3-alkoxy, 3-arylthio and 3-alkylthio substituted products **26** in good yields (46-86%, Scheme 5.5).[9a]



X = Br, I, OTf, R^1= Ph, Me, $C_5H_{11,}$ R^2 = H, Me, R^3 = Me, Et

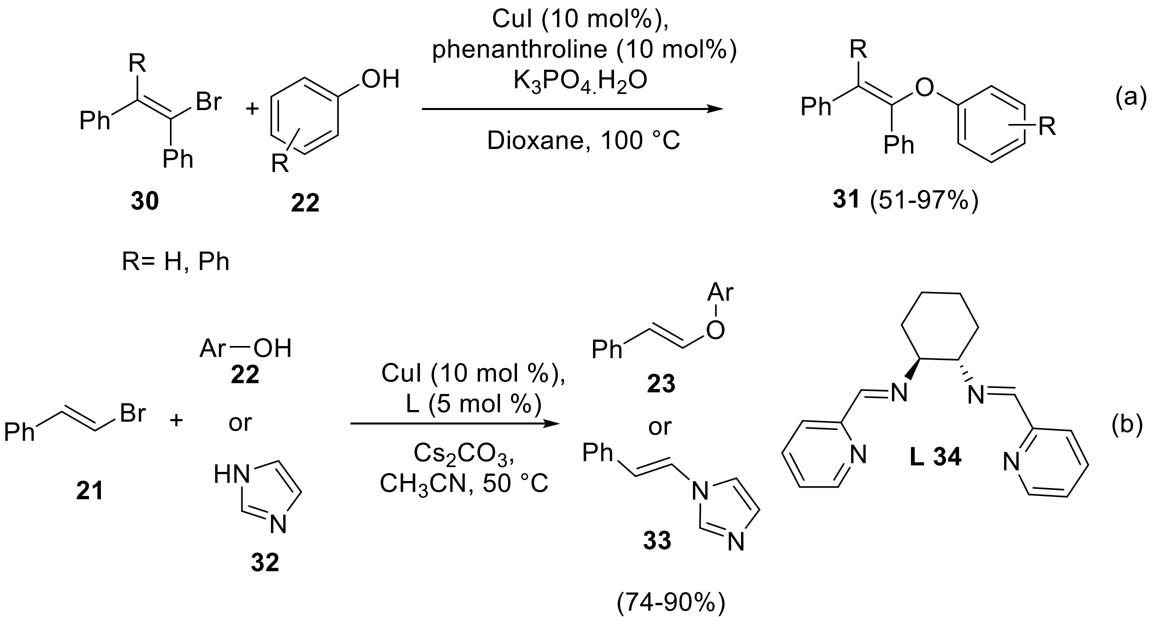
Scheme 5.5 Palladium catalyzed synthesis of enol ethers

Willis et al. reported a palladium catalyzed synthesis of aryl enol ethers **28** starting from vinyl triflates.[9b] The treatment of vinyl triflates **27** with phenol derivatives **22** in presence of $Pd_2(dba)_3$/phosphine ligand [1,1'-biphenyl]-2-yldi-tert-butylphosphane **29** afforded the corresponding aryl enol ethers **28** in modest to good yields (34-85%) (**Scheme 5.6**).



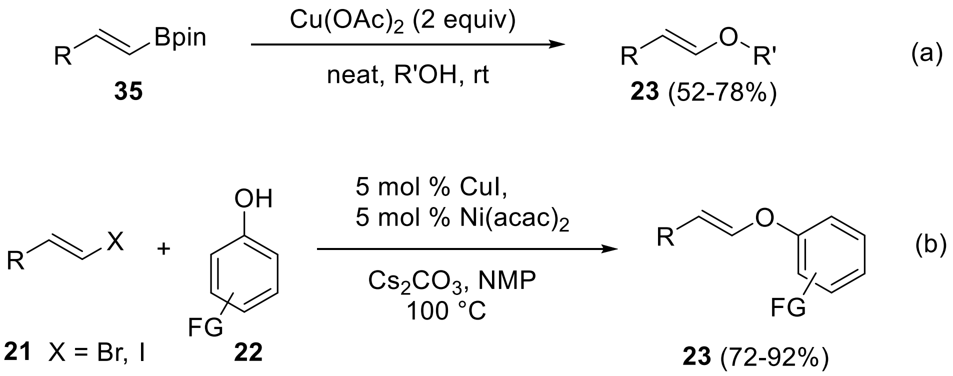
Scheme 5.6 Palladium catalyzed aryl enol ether synthesis from vinyl triflates

Limbarger et al. described a copper catalyzed coupling reaction of (*E*)-bromostilbene **30** with phenols **22** in presence of CuI (10 mol%) and phenanthroline ligand (10 mol%) to afford the corresponding enol ethers **31** in excellent yields (up to 97 %) (Scheme 5.7a).[9g] Similarly, Spindler and co-workers reported a copper catalyzed vinylation of azoles **32**/phenols **22** with vinyl bromides **21** to synthesize styrylazole **33** and enol ethers **23** respectively in good yields (Scheme 5.7b).[9e] This transformation was effectively achieved using copper iodide (10 mol%) and (1*E*,1'*E*)-*N*,*N'*-((1*S*,2*S*)-cyclohexane-1,2-diyl)bis(1-(pyridin-2-yl)methanimine) **34** as ligand (5 mol%) under basic conditions.



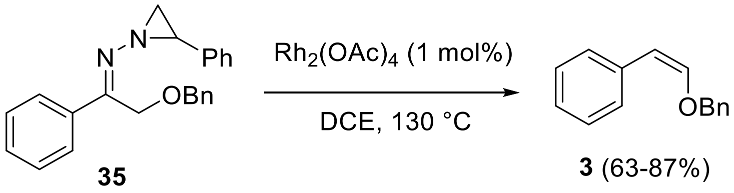
Scheme 5.7 Copper catalyzed coupling of vinyl bromides with phenols

Shade et al. reported a copper promoted coupling of vinyl boronates **35** and alcohols for the synthesis of allyl vinyl ethers **23** in good yields (Scheme 5.8a).[9i] Kundu et al. described a copper assisted nickel catalyzed ligand free cross coupling of vinyl halides **21** and phenol derivatives **22** to synthesize aryl vinyl ethers **23** in very good yields (Scheme 5.8b).[9d]



Scheme 5.8 Synthesis of enol ethers

Stoltz and co-workers effectively utilized rhodium to catalyze the Bamford-Stevens reaction to access aryl vinyl ethers **23** starting from Eschenmoser hydrazone **36** under relatively high temperature conditions in good yields (Scheme 5.9).[10]



Scheme 5.9 Rhodium catalyzed Bamford-Stevens reaction

However, most of the methods in the literature rely on the use of transition metals and some of them use expensive palladium and rhodium catalysts which is not cost effective for the large scale industrial applications.[9a-b,10] On the other hand less expensive metals such as copper, nickel require supporting ligands for the transformation.[9c-h] Most of the transition metals are toxic to different extents, and it is very expensive and challenging to remove the trace amounts of transition metal residues from desired products.[11] Also some of the transition metals are sensitive to oxygen and some require the assistance of co-catalysts or additives.[12] Traditional methods for the synthesis of vinyl/styrenyl ethers rely on double bond isomerization or carbonyl olefination like Wittig reaction and strong base mediated elimination of halides as well as alcohols.[8a,d] Transition-metal-free protocols are gaining a great importance for the last few years. It would be really useful to develop a protocol that does not rely on transition metals, ligands and strong bases for the large scale practical applications. Sulfonylhydrazones have been proved to be excellent and versatile synthetic intermediates for the in situ generation of diazo compounds in organic synthesis.[13] The role of sulfonylhydrazones to access olefins via Bamford-Stevens reaction is well established.[14]

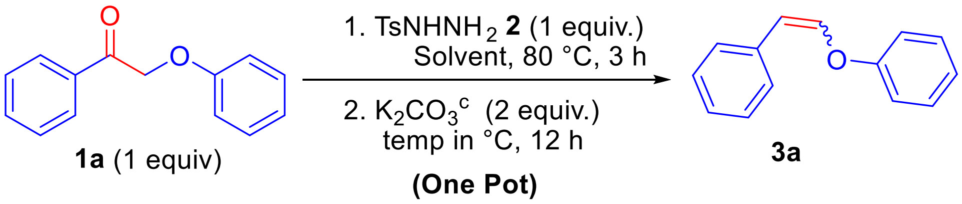
However, the synthesis of functionalized olefin derivatives has not been explored till date via Bamford-Stevens reaction under transition-metal-free conditions. Likewise, the reliable access to *Z*-olefins is an extremely challenging task. Hence alternative transition-metal-free pathways to synthesize styrenyl ethers are highly appealing and demanding. Herein, in this chapter for the first time we describe transition-metal-free application of sulfonyl hydrazones to access aryl vinyl ethers via Bamford-Stevens reaction. Aryl vinyl ethers have been synthesized starting from 2-aryloxy and alkoxy acetophenones and tosyl hydrazide using K_2CO_3 as a base under mild reaction conditions.

5.3 Result and discussion

5.3.1 Optimization studies

In order to access aryl vinyl ethers under transition-metal-free conditions, a model one pot reaction was carried out by heating phenyloxy acetophenone (2- phenoxy-1-

Table 5.1. Optimization of the reaction conditions[a-c]



Entry	Solvent	Temp Step-1 (°C)	Temp step-2 (°C)	Time (h)	Yield (%)[b]
1	DCE	80	80	12	34
2	THF	80	80	12	Trace
3	1,4-dioxane	80	80	12	52
4	DMF	80	80	12	45
5	DMSO	80	80	12	41
6	DCE	80	90	12	37
7	1,4-dioxane	80	100	12	73
8	DMF	80	100	12	61
9	DMSO	80	100	12	57
10	**1,4-dioxane**	**80**	**110**	**12**	**84**
11	1,4-dioxane	80	130	12	80

[a]Reaction conditions: Step-1: 2-phenoxy-1-phenylethan-1-one **1a** (1 equiv.), 4-methylbenzenesulfonohydrazide **2** (1 equiv.), solvent (2 mL) in pressure tube at 80 °C for 3 h, Step-2: potassium carbonate (2 equiv.), heated for 12 h, [b]Isolated yield after purification by column chromatography. [c]Reaction with bases such as LiO^tBu, Cs_2CO_3 afforded the desired product in lower yield and selectivity.

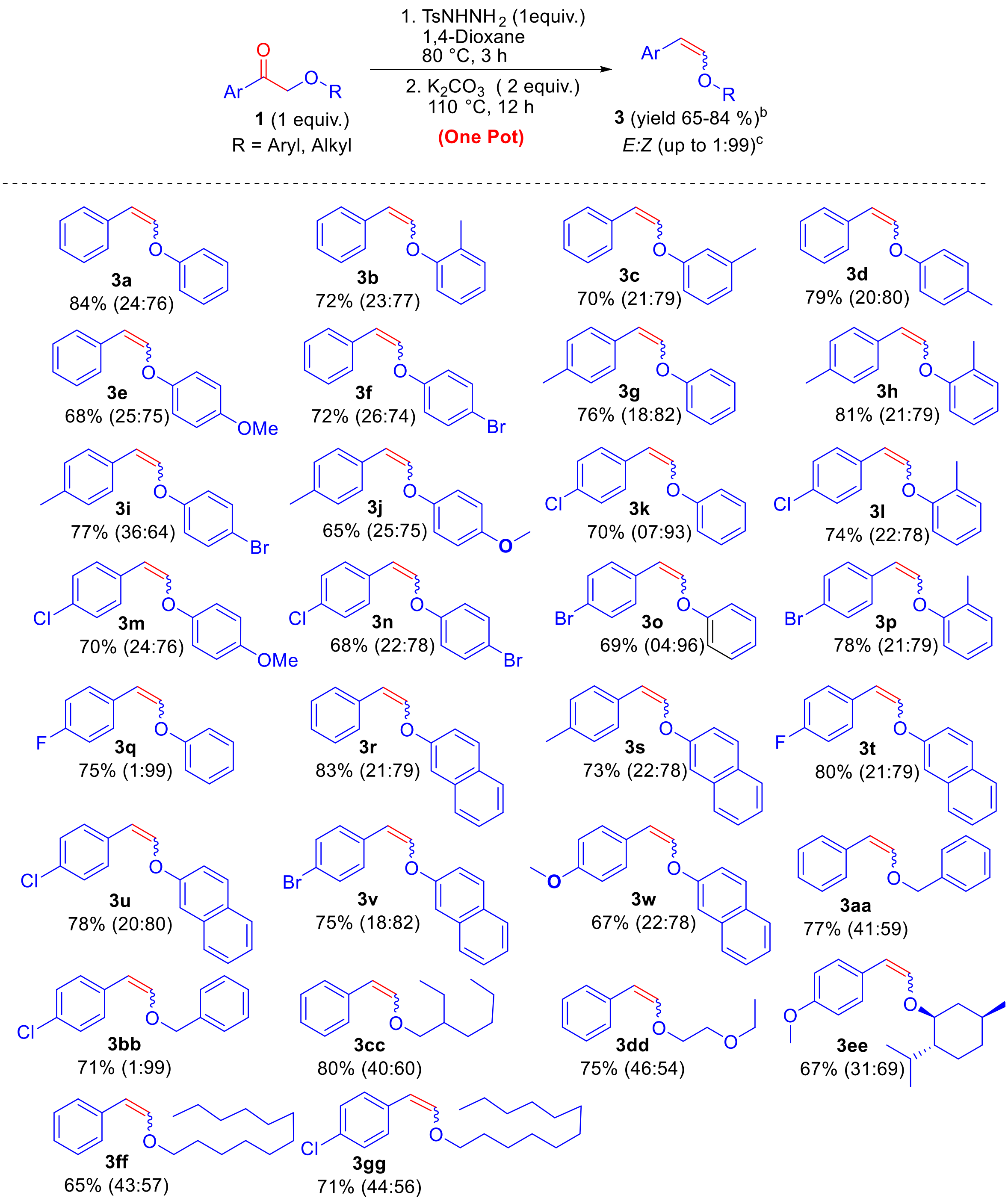
phenylethan-1-one) **1a** and tosylhydrazide **2** in DCE at 80 °C for 3 h followed by the addition of K_2CO_3 (2 equiv.) (Table 5.1). The reaction was continued for 12 h while maintaining the temperature. Gratifyingly, we observed that the desired product (2-phenoxyvinyl)benzene **3a** was obtained in 34% yield (entry 1, Table 5.1).

Encouraged by the initial result, we screened several solvents and varied the reaction temperature for achieving the optimum yield of **3a**. Using THF as a solvent, we observed the formation of only trace amount of product **3a** (entry 2, Table 5.1). Among all the solvents screened, 1,4-dioxane was found to be optimum at 80 ^{o}C thus affording the desired product **3a** in moderate yield (entry 3, Table 5.1). Further increase in the reaction temperature (110 °C) afforded the corresponding product **3a** in 84% yield (entry 10, Table 5.1). Thereafter increase in reaction temperature (130 °C) did not have any significant effect on the yield of the product **3a** (entry 11, Table 5.1). After screening several solvents at different temperatures, we found that heating substrate **1a** and tosyl hydrazide **2** (1 equiv.) in 1,4-dioxane at 80 °C for 3 h followed by the addition of K_2CO_3 (2 equiv.) at 110 °C for 12 h was found to be the optimum reaction condition (entry 10, Table 5.1).

5.3.2 Synthesis of styrenyl ethers

With this initial success and having an optimized reaction condition in hand, we planned to explore the wider substrate scope for the generality of the method. In this regard various aryloxy acetophenones (**1a-1w**) were synthesized starting from different phenacyl bromides and phenol derivatives. Similarly alkoxy acetophenones (**1aa-1gg**) were synthesized starting from different *α*-diazoacetophenone derivatives and alcohols (see Experimental Section). Various aromatic substrates containing phenyl, methyl, methoxy, bromo, chloro, fluoro substituents worked smoothly under the optimized reaction conditions to afford the corresponding desired products (**3a-3q)** in moderate to very good yields (see Table 5.2, up to 84% yield). Likewise, ketoethers bearing naphthyl functionality adjacent to oxygen also worked smoothly affording the desired products (**3r-3w**) in moderate to very good yields (67-83%) (Table 5.2). Further we turned our attention towards the synthesis of aliphatic keto ether substrates. Gratifyingly variety of substrates (**1aa-1gg**) worked nicely under optimized reaction conditions to afford the corresponding products **3aa-3gg** (see Table 5.2). Benzyl ketoethers under the optimized reaction condition afforded the corresponding products (**3aa**, **3bb**) in good yields. The branched as

Table 5.2. Synthesis of aryl/alkyl styrenyl ethers[a-c]



[a] Reaction conditions: Step-1: 2-aryloxy/alkoxy acetophenone derivative **1** (1 equiv.,), 4-methylbenzenesulfonohydrazide **2** (1 equiv.), 1,4-dioxane (2 mL) in pressure tube at 80 °C for 3 h, Step-2 potassium carbonate (2 equiv.), heated for 12 h, [b] Isolated yield after purification by column chromatography. [c] diastereomeric ratio was determined by ^{1}H NMR.

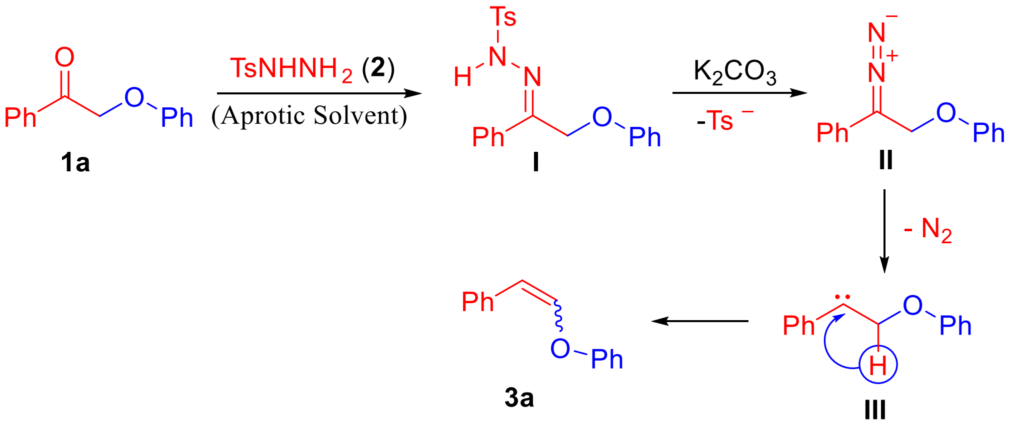
well as long chain ketoethers also reacted smoothly to afford the corresponding styrenyl ethers (**3cc**, **3ff** and **3gg**) in moderate to good yields (up to 80%). Chiral ketoether derived from (+)-menthol worked efficiently to give the corresponding product **3ee** in moderate yield 67%.

A variety of electron-donating and -withdrawing substituents on either phenyl rings tolerated the reaction conditions to afford the desired products and the results are summarized in Table 5.2. However, these functional groups did not have any significant effect on the reaction rate and yields. We observed that styrenyl ethers derived from aryloxy acetophenones were highly *Z*-selective (up to *E:Z* = 1:99)[15] while the products derived from alkoxy acetophenones (**3aa**, **3cc-3gg**) were found to be relatively less selective (up to *E:Z* = 31:69). The styrenyl ether **3bb** derived from benzyloxy acetophenone **1bb** was found to be highly *Z*-selective (*E:Z* = 01:99). It is very interesting to note that unlike the previous report[10] we did not observe any side products or multiple decomposition products during the reaction of any substrates. Likewise, the reaction worked smoothly without the assistance of any metal.

In order to make this approach more practical and for the wider applicability, we demonstrated the synthesis of **3a** on a gram scale starting from the corresponding 2-phenoxy-1-phenylethan-1-one **1a** under optimum reaction conditions (86% yield).

5.4 Proposed reaction mechanism

Based on our investigations and previous literature reports,[14,16,17] we propose that tosyl hydrazide **2** reacts with 2-phenoxy-1-phenylethan-1-one **1a** to form tosyl hydrazone **I**, which then reacts with base K_2CO_3 to form diazo intermediate **II**. This further undergoes thermal decomposition to form carbene intermediate **III** that subsequently leads to 1, 2-hydride shift followed by the formation of double bond. The *syn* hydride shift is believed to be the major reason for the *Z*-selectivity of the olefin (Scheme 5.10).



Scheme 5.10 Plausible mechanism

5.5 Conclusions

In conclusion, a transition-metal-free one-pot two step method has been developed for the synthesis of styrenyl ethers starting from 2-aryloxy/alkoxy acetophenones. The method works smoothly on both aromatic and aliphatic substrates. Protocol employs mild, commercially available and less expensive K_2CO_3 as base and the desired products were obtained in good to excellent yields. Moreover a wide range of functional groups was well tolerated the reaction conditions. The Bamford-Stevens reaction has been explored for the first time for the synthesis of functionalized olefins under transition-metal-free conditions. Experimental conditions are simple and the method proved to be scalable for the wider application.

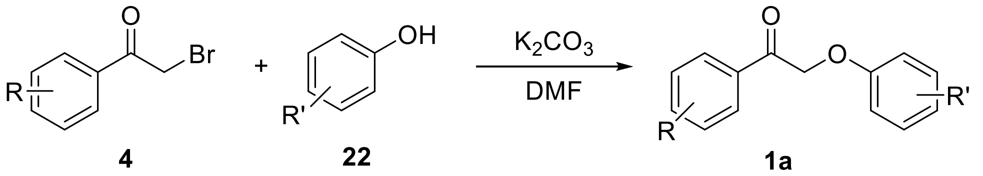
5.6 Experimental Section

5.6.1 General

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR data are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of Chloroform-d. ^{13}C-NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF (+ve, ⁻ve ion mode). IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. All reactions were carried out in dried glassware. All purchased chemicals were used without further purification. Column chromatography was carried out using silica gel.

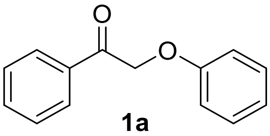
5.6.2 General procedure-A for the preparation of 2-aryloxy acetophenones 1

The compound **1a** to **1w** were synthesized according to a literature procedure.[18]



An oven-dried round bottomed flask was charged with K_2CO_3 (1.04 g, 7.54 mmol), 2-bromoacetophenone (1 g, 5.02 mmol), phenol (709 mg, 7.54 mmol) and DMF (10 mL) and stirred at rt under argon atmosphere for 24 h. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). Combined organic layers was dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow solid. The crude compound was purified by column chromatography using pet ether/ethyl acetate (97:3) to furnish pure compound **1a** as white solid (916 mg, 82% yield).

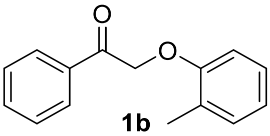
2-phenoxy-1-phenylethan-1-one (1a)



1a

m.p.: 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.64 – 7.59 (m, 1H), 7.52 – 7.48 (m, 2H), 7.31 – 7.25 (m, 2H), 7.01 – 6.93 (m, 3H), 5.27 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.67, 158.1, 134.7, 134.0, 129.7, 129.0, 128.3, 121.8, 114.9, 70.9.

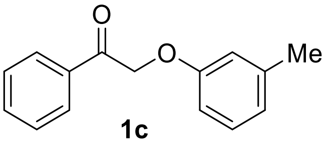
1-phenyl-2-(o-tolyloxy)ethan-1-one (1b)



1b

The compound **1b** was synthesized following the general procedure **A**; The compound **1b** was obtained as a white solid (757 mg, 67% yield). m.p.: 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dt, J = 8.4, 1.6 Hz, 2H), 7.64 – 7.60 (m, 1H), 7.50 (dd, J = 10.9, 4.7 Hz, 2H), 7.18 – 7.11 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 5.27 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 195.1, 156.3, 134.8, 133.9, 131.2, 128.9, 128.4, 127.3, 126.9, 121.5, 111.4, 71.2, 16.4.

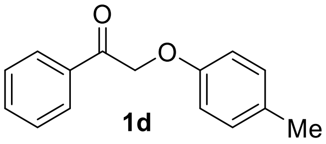
1-phenyl-2-(*m*-tolyloxy)ethan-1-one (1c)



1c

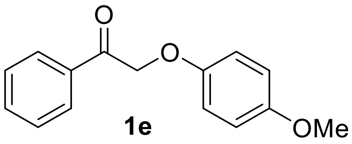
The compound **1c** was synthesized following the general procedure **A**; The compound **1c** was obtained as a white solid (684 mg, 60% yield). m.p.: 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.99 (m, 2H), 7.63 – 7.59 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.16 (t, J = 7.8 Hz, 1H), 6.81– 6.71 (m, 2H), 6.74 (dd, J = 8.2, 2.5 Hz, 1H), 5.25 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 158.1, 139.8, 134.7, 134.0, 129.4, 128.9, 128.3, 122.6, 115.8, 111.7, 70.6, 21.6.

1-phenyl-2-(*p*-tolyloxy)ethan-1-one (1d)


1d

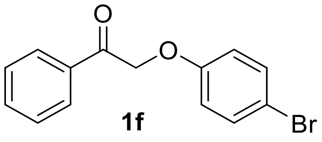
The compound **1d** was synthesized following the general procedure **A**; The compound **1d** was obtained as a yellow solid. (832 mg, 73%yield). m.p.: 61–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.63 – 7.60 (m, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.88 – 6.85 (m, 2H), 5.24 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 156.0, 134.7, 133.9, 131.0, 130.1, 128.9, 128.2, 114.8, 71.1, 20.6.

2-(4-methoxyphenoxy)-1-phenylethan-1-one (1e)


1e

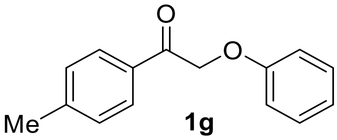
The compound **1e** was synthesized following the general procedure **A**; The compound **1e** was obtained as a white solid (915 mg, 75% yield). m.p.: 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.98 (m, 2H), 7.63 – 7.59 (m, 1H), 7.51 – 7.47 (m, 2H), 6.92 – 6.88 (m, 2H), 6.84 – 6.80 (m, 2H), 5.22 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 154.6, 152.4, 134.8, 133.9, 128.9, 128.3, 116.1, 114.8, 71.9, 55.8.

2-(4-bromophenoxy)-1-phenylethan-1-one (1f)


1f

The compound **1f** was synthesized following the general procedure **A**; The compound **1f** was obtained as a yellow solid (1.02 g, 70% yield). m.p.: 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 2H), 7.65 – 7.61 (m, 1H), 7.52 – 7.49 (m, 2H), 7.39 – 7.36 (m, 2H), 6.884 – 6.80 (m, 2H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 157.3, 134.5, 134.2, 132.5, 129.0, 128.2, 116.6, 114.0, 71.0.

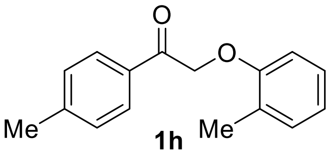
2-phenoxy-1-(*p*-tolyl)ethan-1-one (1g)



1g

The compound **1g** was synthesized following the general procedure **A**; The compound **1g** was obtained as a white solid (901 mg, 85% yield). m.p.: 79–81 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.31 – 7.26 (m, 4H), 7.00 – 6.93 (m, 3H), 5.25 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.3, 158.2, 145.0, 132.3, 129.7, 129.6, 128.4, 121.7, 115.0, 70.9, 21.9.

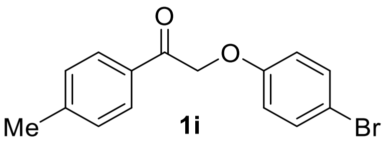
1-(*p*-tolyl)-2-(o-tolyloxy)ethan-1-one(1h)



1h

The compound **1h** was synthesized following the general procedure **A**; The compound **1h** was obtained as a white solid (757 mg, 67% yield). m.p.: 85–87 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.16 – 7.09 (m, 2H), 6.89 (t, J = 7.3 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.23 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.7, 156.4, 144.9, 132.4, 131.1, 129.6, 128.5, 127.3, 126.9, 121.4, 111.5, 71.2, 21.9, 16.5.

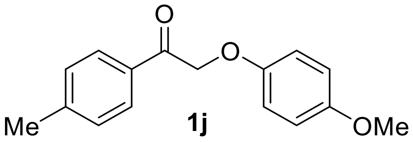
2-(4-bromophenoxy)-1-(p-tolyl)ethan-1-one (1i)



1i

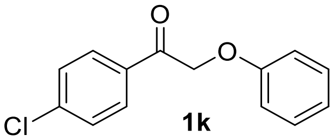
The compound **1i** was synthesized following the general procedure **A**; The compound **1i** was obtained as a white solid (915 mg, 61% yield). m.p.: 120–122 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.30 (d, J = 7.9 Hz, 2H), 6.84 – 6.80 (m, 2H), 5.23 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.8, 157.3, 145.2, 132.5, 132.0, 129.7, 128.3, 116.8, 114.0, 70.9, 21.9.

2-(4-methoxyphenoxy)-1-(*p*-tolyl)ethan-1-one (1j)



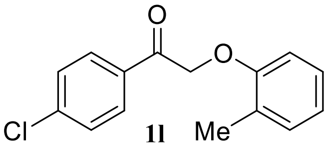
The compound **1j** was synthesized following the general procedure **A**; The compound **1j** was obtained as a white solid (744 mg, 62% yield). m.p.: 90–92 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.91– 6.87 (m, 2H), 6.84 – 6.79 (m, 2H), 5.19 (s, 2H), 3.75 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.6, 154.5, 152.4, 144.9, 132.3, 129.6, 128.3, 116.1, 114.8, 71.8, 55.8, 21.9.

1-(4-chlorophenyl)-2-phenoxyethan-1-one (1k)



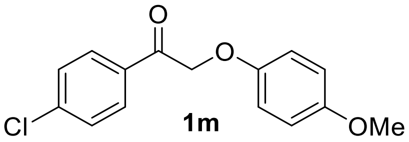
The compound **1k** was synthesized following the general procedure **A**; The compound **1k** was obtained as a yellow solid (848 mg, 80% yield). m.p.: 93–95 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 – 7.94 (m, 2H), 7.47 – 7.45 (m, 2H), 7.30 – 7.25 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.94 – 6.91 (m, 2H), 5.20 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.9, 157.9, 140.5, 133.0, 129.8, 129.7, 129.3, 127.7, 121.9, 114.9, 71.0.

1-(4-chlorophenyl)-2-(*o*-tolyloxy)ethan-1-one (1l)



The compound **1l** was synthesized following the general procedure **A**; The compound **1l** was obtained as a yellow solid (907 mg, 81% yield). m.p.: 66–68 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 – 7.95 (m, 2H), 7.48 – 7.44 (m, 2H), 7.17 – 7.10 (m, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.19 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.3, 156.1, 140.4, 133.1, 131.2, 129.9, 129.2, 127.3, 127.0, 121.6, 111.3, 71.3, 16.4.

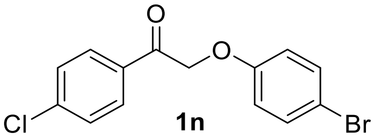
1-(4-chlorophenyl)-2-(4-methoxyphenoxy)ethan-1-one (1m)



1m

The compound **1m** was synthesized following the general procedure **A**; The compound **1m** was obtained as a yellow solid (654 mg, 55% yield). m.p.: 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.46 – 7.43 (m, 2H), 6.88 – 6.85 (m, 2H), 6.83 – 6.80 (m, 2H), 5.15 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 154.6, 152.1, 140.4, 133.0, 129.8, 129.2, 116.0, 114.8, 71.9, 55.6.

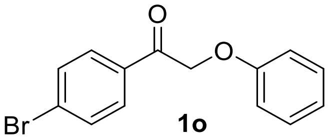
.2-(4-bromophenoxy)-1-(4-chlorophenyl)ethan-1-one (1n)



1n

The compound **1n** was synthesized following the general procedure **A**; The compound **1n**was obtained as a white solid (1.06 g, 76% yield). m.p.: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.49 – 7.46 (m, 2H), 7.39 – 7.35 (m, 2H), 6.83 – 6.79 (m, 2H), 5.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 157.1, 140.7, 132.8,132.6, 129.7, 129.4, 116.7, 114.2, 71.0.

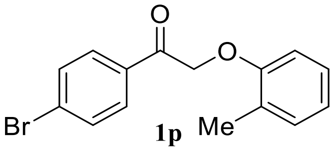
1-(4-bromophenyl)-2-phenoxyethan-1-one (1o)



1o

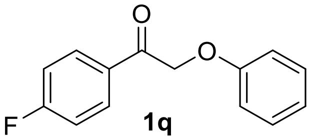
The compound **1o** was synthesized following the general procedure **A**; The compound **1o** was obtained as a yellow solid (630 mg, 60% yield). m.p.: 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.64 – 7.61 (m, 2H), 7.30 – 7.25 (m, 2H), 6.98 (t, *J* = 8 Hz, 1H), 6.93 – 6.90(m, 2H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.0, 133.4, 132.3, 130.5, 129.9 ,129.3, 122.0, 114.9, 71.0.

1-(4-bromophenyl)-2-(o-tolyloxy)ethan-1-one (1p)


1p

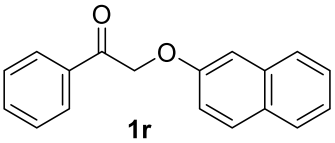
The compound **1p** was synthesized following the general procedure **A**; The compound **1p** was obtained as a yellowish solid (759 mg, 69% yield). m.p.: 80–82 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 – 7.87 (m, 2H), 7.65 – 7.61 (m, 2H), 7.17 – 7.10 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 5.19 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.53, 156.13, 133.53, 132.21, 131.23, 130.01, 129.18, 127.27, 126.94, 121.63, 111.32, 71.30, 16.45.

1-(4-fluorophenyl)-2-phenoxyethan-1-one (1q)


1q

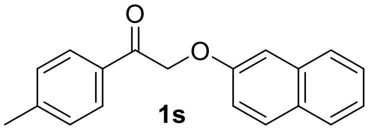
The compound **1q** was synthesized following the general procedure **A**; The compound **1q** was obtained as a white solid (720 mg, 68% yield). m. p.: 93–95 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 – 8.04 (m, 2H), 7.31 – 7.26 (m, 2H), 7.19 – 7.15 (m, 2H), 7.01 – 6.93 (m, 3H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.5, 167.6, 165.0, 158.0, 131.19 (d, J = 9.3 Hz), 129.8, 121.9, 116.3, 116.1, 114.9, 71.0.

2-(naphthalen-2-yloxy)-1-phenylethan-1-one (1r)


1r

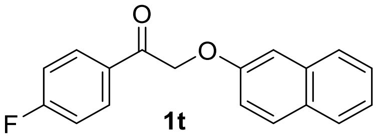
The compound **1r** was synthesized following the general procedure **A**; The compound **1r** was obtained as a white solid (1.1 g, 82% yield). m.p.: 105–107 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 – 8.00 (m, 2H), 7.74 (d, J = 8.9 Hz, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.50 – 7.46 (m, 2H), 7.43 – 7.39 (m, 1H), 7.35 – 7.31 (m, 1H), 7.25 (dd, J = 9.0, 2.6 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 156.0, 134.7, 134.4, 134.0, 129.8, 129.4, 128.9, 128.2, 127.6, 127.0, 126.6, 124.1, 118.8, 107.4, 70.8.

2-(naphthalen-2-yloxy)-1-(*p*-tolyl)ethan-1-one (1s)


1s

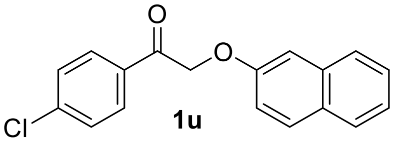
The compound **1s** was synthesized following the general procedure **A**; The compound **1s** was obtained as a brown solid (975 mg, 75% yield). m.p.: 82–84°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.34 – 7.30(m, 1H), 7.28 – 7.24 (m, 3H), 7.10 (d, J = 2.5 Hz, 1H), 5.32 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 156.1, 145.0, 134.4, 132.2, 129.8, 129.6, 129.4, 128.4, 127.7, 126.9, 126.6, 124.1, 118.8, 107.4, 70.8, 21.9.

1-(4-fluorophenyl)-2-(naphthalen-2-yloxy)ethan-1-one (1t)


1t

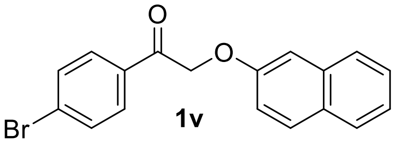
The compound **1t** was synthesized following the general procedure **A**; The compound **1t** was obtained as a white solid (838 mg, 65% yield). m.p.: 99–101°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11– 8.07 (m, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.2 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.37– 7.33 (m, 1H), 7.25 (dd, J = 9.1, 2.4 Hz, 1H), 7.21 – 7.15(m, 2H), 7.12 (d, J = 2.5 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 167.6, 165.0, 156.0, 134.4, 131.21 (d, J = 9.4 Hz), 130.0, 129.5, 127.8, 127.0, 126.7, 124.3, 118.7, 116.3, 116.1, 107.4, 71.0.

1-(4-chlorophenyl)-2-(naphthalen-2-yloxy)ethan-1-one (1u)


1u

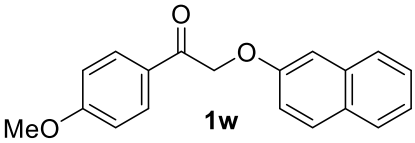
The compound **1u** was synthesized following the general procedure **A**; The compound **1u** was obtained as a yellowish solid (863 mg, 68% yield). m.p.:110–112°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 2H), 7.76 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.37 – 7.33 (m, 1H), 7.23 (dd, J = 9.0, 2.6 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 155.9, 140.5, 134.3, 133.0, 130.0, 129.9, 129.5, 129.3, 127.8, 127.0, 126.7, 124.3, 118.7, 107.4, 71.0.

1-(4-bromophenyl)-2-(naphthalen-2-yloxy)ethan-1-one (1v)



The compound **1v** was synthesized following the general procedure **A**; The compound **1v** was obtained as a yellow solid (947 mg, 77% yield). m.p.:120–122°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 – 7.88 (m, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.45 – 7.41 (m, 1H), 7.36 – 7.32 (m, 1H), 7.25 – 7.21 (m, 1H), 7.10 (d, J = 2.5 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.0, 155.9, 134.4, 133.4, 132.3, 123.0, 129.9, 129.5, 129.3, 127.8, 127.0, 126.7, 124.3, 118.7, 107.4, 71.0.

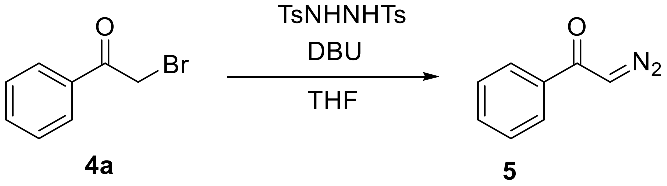
1-(4-methoxyphenyl)-2-(naphthalen-2-yloxy)ethan-1-one (1w)



The compound **1w** was synthesized following the general procedure **A**; The compound **1w** was obtained as a white solid (793 mg, 62% yield). m.p.: 96–98°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.72 (dd, J = 24.2, 8.5 Hz, 3H), 7.44 – 7.24 (m, 3H), 7.11 (d, J = 2.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 5.30 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.0, 164.2, 156.1, 134.4, 130.7, 129.8, 129.4, 127.8, 127.0, 126.6, 124.1, 118.8, 114.1, 107.4, 70.8, 55.6.

5.6.3 General procedure-B for the synthesis of α-diazoacetophenones (5)

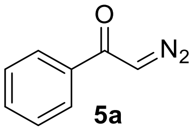
The compound 5a to 5c were synthesized according to a literature procedure.[19]



α-Bromoacetophenone **4a** (1 g, 5.02 mmol) and *N,N'*-ditosylhydrazine (3.42 mg, 10.05 mmol) were dissolved in THF (20 mL) and cooled to 0 °C. DBU (3.82 mL, 25.12 mmol) was added dropwise and the reaction was stirred at the same temperature for 10 minutes.

Upon completion of the reaction (monitored by TLC), it was quenched by the addition of saturated $NaHCO_3$ solution, and the solution was extracted with ethyl acetate three times (3 x 30 mL). The organic phase was washed with brine, dried over $MgSO_4$ and evaporated to give the crude α-diazoacetophenone **5a**. The crude compound was purified by column chromatography using pet ether/ethyl acetate to furnish *α*-diazoacetophenone **5a** (611 mg, 83% yield) as a yellow solid.

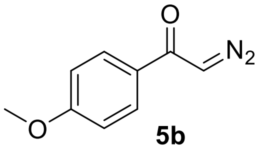
α-diazoacetophenone (5a)



5a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.3 Hz, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 136.5, 132.6, 128.5, 126.5, 54.1.

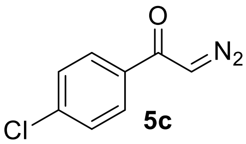
2-diazo-1-(4-methoxyphenyl)ethan-1-one (5b)



5b

The compound **5b** was synthesized starting from **4b** following the general procedure **B** described for **5a**; The compound **5b** was obtained as a yellow solid (630 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 5.85 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 163.4, 129.6, 128.9, 113.9, 55.6, 53.6.

1-(4-chlorophenyl)-2-diazoethan-1-one (5c)



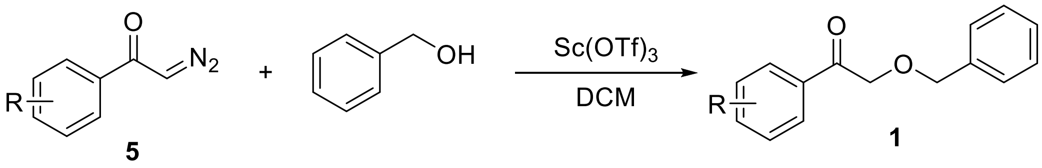
5c

The compound **5c** was synthesized starting from **4c** following the general procedure **B** described for **5a**; The compound **5c** was obtained as a yellow solid (687 mg, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 5.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 139.2, 135.1, 129.1, 128.2, 54.5.

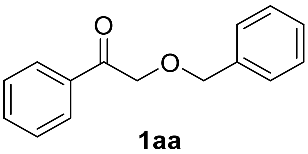
5.6.4 General procedure-C for the preparation of 2-alkoxy acetophenones 1

The compound **1aa** to **1gg** were synthesized according to a literature procedure.[20]



To a solution of the α-diazoacetophenoneone **5a** (300 mg, 2.05 mmol) in dichloromethane, benzyl alcohol (0.427 ml, 4.11 mmol) was added followed by $Sc(OTf)_3$ (101 mg, 0.2 mmol). The mixture was stirred at ambient temperature till completion of the reaction (monitored by TLC). Additional solvent was added and the solution was washed with water and concentrated to give the crude product which was purified by column chromatography on silica gel to afford 2-(benzyloxy)-1-phenylethan-1-one **1aa** as a white solid (319 mg, 68% yield).

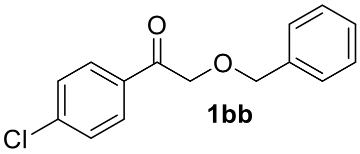
2-(benzyloxy)-1-phenylethan-1-one (1aa)



1aa

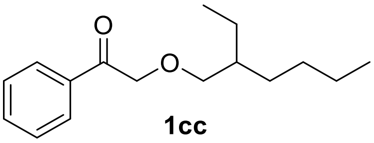
m.p.: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.90 (m, 2H), 7.59 – 7.54 (m, 1H), 7.47 – 7.42 (m, 2H), 7.40 – 7.28(m, 5H), 4.75 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 137.4, 135.0, 133.6, 128.8, 128.6, 128.2, 128.1, 128.0, 73.5, 72.6.

2-(benzyloxy)-1-(4-chlorophenyl)ethan-1-one (1bb)


1bb

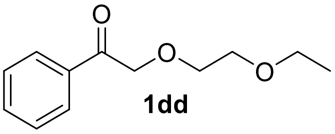
The compound **1bb** was synthesized following the general procedure **C**; The compound **1bb** was obtained as a yellow solid (351 mg, 81% yield). m.p.: 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89 – 7.85 (m, 2H), 7.44 – 7.41(m, 2H), 7.39 – 7.29 (m, 5H), 4.70 (s, 2H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 195.4, 140.1, 137.2, 133.3, 129.6, 129.1, 128.7, 128.2, 128.2, 73.6, 72.8.

2-((2-ethylhexyl)oxy)-1-phenylethan-1-one (1cc)


1cc

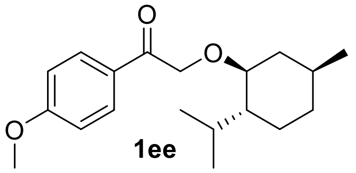
The compound **1cc** was synthesized following the general procedure **C**; The compound **1cc** was obtained as a pale yellow liquid (301 mg, 60 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.97 – 7.95 (m, 2H), 7.60 – 7.55 (m, 1H), 7.49 – 7.44 (m, 2H), 4.69 (s, 2H), 3.44 (d, *J* = 5.9 Hz, 2H), 7.61 – 7.53 (m,1H), 1.47 – 1.20 (m, 8H), 0.92 – 0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.3, 135.2, 133.5, 128.7, 128.2, 74.8, 74.4, 39.8, 30.5, 29.2, 23.8, 23.2, 14.2, 11.1.

2-(2-ethoxyethoxy)-1-phenylethan-1-one (1dd)


1dd

The compound **1dd** was synthesized following the general procedure **C**; The compound **1dd** was obtained as a colorless liquid (325 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.95 – 7.93 (m, 2H), 7.60 – 7.56 (m, 1H), 7.49 – 7.44 (m, 2H), 4.85 (s, 2H), 3.79 – 3.77 (m, 2H), 3.68 – 3.65 (m, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 196.5, 135.0, 133.5, 128.7, 128.0, 74.3, 71.0, 70.1, 66.7, 15.2.

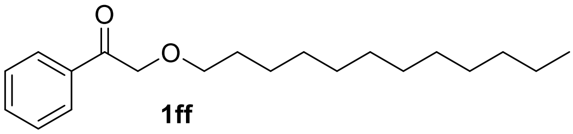
2-(((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)-1-(4-methoxyphenyl)ethan-1-one (1ee)



1ee

The compound **1ee** was synthesized following the general procedure **C**; The compound **1ee** was obtained as a colorless liquid (364 mg, 70% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 4.76 (d, *J* = 15.8 Hz, 1H), 4.60 (d, *J* = 15.8 Hz, 1H), 3.21 (td, *J* = 10.6, 4.2 Hz, 1H), 2.27 – 2.19 (m, 1H), 2.14– 2.09(m, 1H), 1.68 – 1.61 (m, 2H), 1.38 – 1.26 (m, 2H), 1.02 – 0.80 (m, 9H), 0.72 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.00, 139.85, 133.63, 129.89, 128.99, 80.41, 71.70, 48.28, 40.09, 34.51, 31.66, 25.59, 23.33, 22.40, 21.09, 16.24.

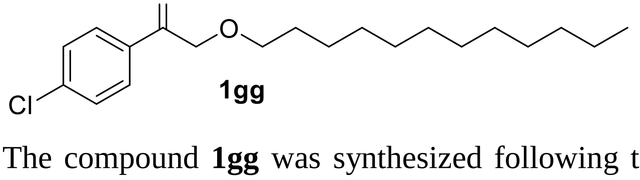
2-(dodecyloxy)-1-phenylethan-1-one (1ff)



1ff

The compound **1ff** was synthesized following the general procedure **C**; The compound **1ff** was obtained as a pale yellow solid (386 mg, 56% yield). m.p.: 45–47°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 – 7.94 (m, 6H), 7.60 – 7.56 (m, 3H), 7.48 – 7.44 (m, 6H), 4.72 (s, 6H), 3.56 (t, *J* = 6.7 Hz, 6H), 1.69 – 1.62 (m, 7H), 1.37 – 1.26 (m, 57H), 0.88 (t, *J* = 6.9 Hz, 10H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.9, 135.2, 133.6, 128.8, 128.1, 74.0, 72.2, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 26.2, 22.8, 14.2.

1-(4-chlorophenyl)-2-(dodecyloxy)ethan-1-one (1gg)



1gg

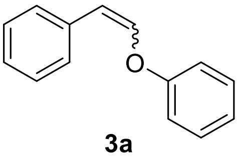
The compound **1gg** was synthesized following the general procedure **C**; The compound **1gg** was obtained as a pale yellow solid (342 mg, 61% yield). m.p.: 45–47°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 4.66 (s, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.36 – 1.25 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 196.0, 140.0, 133.5, 129.7, 129.1, 74.2, 72.2, 32.1, 29.8, 29.8, 29.7, 29.7, 29.7, 29.5, 29.5, 26.1, 22.9, 14.3.

5.6.5 General procedure-D for the preparation of styrenyl ethers (3) from 2-aryloxy acetophenones (1)

In an oven dried pressure tube containing a mixture of 2-phenoxy-1-phenylethan-1-one **1a** (200 mg, 0.94 mmol) and 4-methylbenzenesulfonohydrazide **2** (175 mg, 0.94 mmol), 1,4-dioxane (2 mL) was added. Then the reaction mixture was heated at 80 °C for 3 h with a screw cap closed and then K_2CO_3 (260 mg, 1.88 mmol) was added in one lot. The reaction mixture was heated again at 110°C for12 h with a screw cap closed. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to furnish the compound (2-phenoxyvinyl)benzene **3a** as colorless liquid (78 mg, 84% yield).

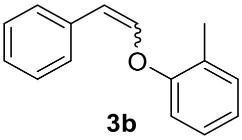
(2-phenoxyvinyl)benzene (3a)



3a

(*E*:*Z* = 24:76), IR (neat) cm^{-1}: 3047, 2921, 2855,1653,1591,1488; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H, *Z*), 7.48 – 7.40 (m, 6H, *E* and *Z*), 7.34– 7.29 (m, 1.74H , *E* and *Z*), 7.26 – 7.18 (m, 4H, *E* and *Z*), 6.71 (d, *J* = 6.9 Hz, 1H, *Z*), 6.45 (d, *J* = 12.4 Hz, 0.36H, *E*), 5.72 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 157.4, 157.3, 143.6, 141.8, 135.3, 135.1, 129.9, 128.8, 128.5, 126.8, 125.8, 123.5, 123.4, 117.1, 117.0, 113.8, 110.6; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{12}O$ $[M - H]^+$, 195.0810 found 195.0804.

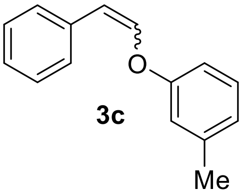
1-methyl-2-(styryloxy)benzene (3b)



3b

The compound **3b** was synthesized starting from **1b** following the general procedure **D** described for **3a**; The compound **3b** was obtained as a colorless liquid (67 mg, 72% yield). (*E*:*Z* = 23:77), IR (neat) cm^{-1}: 3027, 2922, 2853, 1650, 1586, 1489; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.28 (m, 3.32H, *E* and *Z*), 7.24 – 7.14 (m, 4.36H, *E* and *Z*), 7.04 – 6.99 (m, 2.54H, *E* and *Z*), 6.58 (d, *J* = 6.9 Hz, 1H, *Z*), 6.24 (d, *J* = 12.5 Hz, 0.30H, *E*), 5.60 (d, *J* = 6.9 Hz, 1H, *E* and *Z*), 2.38 (s, 3H, *Z*), 2.30 (s, 1H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.84, 144.51, 142.40, 135.48, 135.24, 131.4, 131.3, 128.8, 128.7, 128.46, 128.06, 127.2, 127.1, 126.7, 126.6, 125.66, 123.6, 123.5 , 116.67, 115.74, 112.60, 109.94, 16.47, 16.22; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{14}O$ $[M + H]^+$, 211.1123 found 211.1135.

1-methyl-3-(styryloxy)benzene (3c)

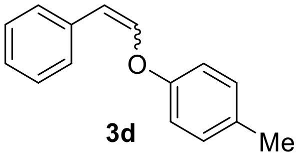


3c

The compound **3c** was synthesized starting from **1c** following the general procedure **D** described for **3a**; The compound **3c** was obtained as a pale yellow liquid (65 mg, 70% yield).

(*E*:*Z* = 21:79), IR (neat) cm^{-1}: 3031, 2922, 1653, 1590, 1488; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.67 (m, 2H, *Z*), 7.34 – 7.29 (m, 3.17H, *E* and *Z*), 7.23 – 7.18 (m, 2.35H, *E* and *Z*), 7.16 (d, *J* = 12.4 Hz, 0.27H, *E*), 6.95 – 6.86 (m, 3.74H, *E* and *Z*), 6.60 (d, *J* = 6.9 Hz, 1H, *Z*), 6.33 (d, *J* = 12.4 Hz, 0.27H, *E*), 5.60 (d, *J* = 6.9 Hz, 1H, *Z*), 2.36 (s, 3H, *Z*), 2.35 (s, 0.8H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 157.4, 157.3, 143.7, 142.0, 140.1, 135.4, 135.1, 129.6, 128.8, 128.5, 126.7, 125.8, 124.3, 124.2, 117.8, 117.7 , 114.1, 113.9, 113.5, 110.4, 21.6; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{14}O$ $[M - H]^+$, 209.0966 found 209.0973.

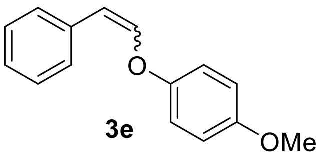
1-methyl-4-(styryloxy)benzene (3d)



3d

The compound **3d** was synthesized starting from **1d** following the general procedure **D** described for **3a**; The compound **3d** was obtained as a yellowish liquid. (74 mg, 79%yield) (*E*:*Z* = 20:80), IR (neat) cm^{-1}: 3029, 2923, 2859, 1653, 1605, 1504; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H, *E* and *Z*), 7.36 – 7.30 (m, 3H, *E* and *Z*), 7.23 – 7.15 (m, 4H, *E* and *Z*), 7.05 – 7.01 (m, 2H, *Z*), 7.99– 6.95 (m, 0.5H, *E*), 6.59 (d, *J* = 6.9 Hz, 1H, *Z*), 6.31 (d, *J* = 12.4 Hz, 0.25H, *E*), 5.59 (d, *J* = 6.9 Hz, 1H, *Z*), 2.34 (s, 4H, *E* and *Z*); ^{13}C NMR (100MHz, $CDCl_3$) δ 155.4, 155.2, 144.2, 142.4, 135.4, 135.2, 133.0, 132.9, 130.3, 130.3, 128.8, 128.7, 128.5, 126.7, 125.7, 117.1, 117.0, 113.2, 110.0, 20.8; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{14}O$ $[M - H]^+$, 209.0966 found 209.0973 .

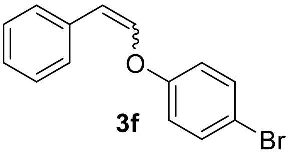
1-methoxy-4-(styryloxy)benzene (3e)



3e

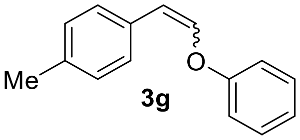
The compound **3e** was synthesized starting from **1e** following the general procedure **D** described for **3a**; The compound **3e** was obtained as a yellow oil (64 mg, 68% yield) (*E*:*Z* = 25:75), IR (neat) cm^{-1}: 3051, 2921, 2845, 1651, 1500, 1448; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H, *Z*), 7.36 – 7.29 (m, 3.6H, *E* and *Z*), 7.23 – 7.17 (m, 1.38H, *E* and *Z*), 7.13 (d, *J* = 12.5 Hz, 0.44H, *E*), 7.09 – 7.05 (m, 2H, *Z*), 7.03 – 7.00 (m, 0.72H, *E*), 6.92 – 6.88 (m, 2.72H, *E* and *Z*), 6.55 (d, *J* = 6.9 Hz, 1H, *Z*), 6.26 (d, *J* = 12.5 Hz, 0.33H, *E*), 5.56 (d, *J* = 6.9 Hz, 1H, *Z*), 3.81 (s, 4H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.9, 151.6, 151.1, 145.0, 143.1, 135.5, 135.2, 128.8, 128.7, 128.5, 126.6, 126.5, 125.7, 118.6, 118.3, 114.9, 114.8, 112.5, 109.6, 55.9; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{14}O_2$ $[M - H]^+$, 225.0916 found 225.0922.

1-bromo-4-(styryloxy)benzene (3f)


3f

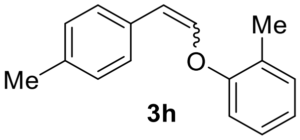
The compound **3f** was synthesized starting from **1f** following the general procedure **D** described for **3a**; The compound **3f** was obtained as a colorless liquid (68 mg, 72% yield). (*E*:*Z* = 26:74), IR (neat) cm^{-1}: 3059, 2923, 1653, 1584, 1483; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.65 (m, 2H, *Z*), 7.49– 7.44 (m, 2.69H, *E* and *Z*), 7.36 – 7.31 (m, 3.45H, *E* and *Z*), 7.25 – 7.21 (m, 1.29H, *E* and *Z*), 7.10 (d, *J* = 12.4 Hz, 0.39H, *E*), 7.04 – 7.00 (m, 2H, *Z*), 6.97 – 6.94 (m, 0.68H, *E*), 6.55 (d, *J* = 6.9 Hz, 1H, *Z*), 6.37 (d, *J* = 12.4 Hz, 0.34H, *E*), 5.67 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 156.4,146.3, 143.0, 141.2, 134.9, 134.7, 132.8, 128.9, 128.5, 127.0, 125.9, 118.8, 118.7, 116.0, 115.8, 114.6, 111.4; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{11}BrO$ [M - H]$^+$, 272.9915 found 272.9913.

1-methyl-4-(2-phenoxyvinyl)benzene (3g)


3g

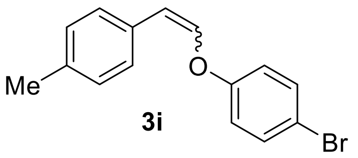
The compound **3g** was synthesized starting from **1g** following the general procedure **D** described for **3a**; The compound **3g** was obtained as a colorless liquid (71 mg, 76% yield) (*E*:*Z* = 18:82), IR (neat) cm^{-1}: 3034, 2921, 2858, 1656, 1593, 1489; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H, *Z*), 7.40 – 7.33 (m, 2.54H, *E* and *Z*), 7.22 (d, *J* = 12.4 Hz, 0.52H, *E*), 7.16 – 7.06 (m, 6.28H, *E* and *Z*), 6.58 (d, *J* = 6.9 Hz, 1H, *Z*), 6.34 (d, *J* = 12.4 Hz,0.22H, *E*), 5.61 (d, *J* = 6.9 Hz, 1H, *Z*), 2.35 (s, 3.70H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 157.5, 157.4, 142.8, 141.1, 136.5, 132.3, 132.1, 129.8, 129.5, 129.2, 128.7, 125.7, 123.4, 123.3, 117.0, 113.8, 110.6, 21.4; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{14}O$ [M + H]$^+$ 211.1123, found 211.1119.

1-methyl-2-((4-methylstyryl)oxy)benzene (3h)


3h

The compound **3h** was synthesized starting from **1h** following the general procedure described **D** for **3a**; The compound **3h** was obtained as a light colorless liquid (76 mg, 81% yield). (*E*:*Z* = 21:79), IR (neat) cm^{-1}: 3026, 2921, 2857, 1653, 1586, 1489; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H, *Z*), 7.24 – 7.11 (m, 6H, *E* and *Z*), 7.05 – 7.00 (m, 2.5H, *E* and *Z*), 6.56 (d, *J* = 6.9 Hz, 1H, *Z*), 6.25 (d, *J* = 12.5 Hz, 0.27H, *E*), 5.60 (d, *J* = 6.9 Hz, 1H, *Z*), 2.39 (s, 3H, *Z*), 2.36 (s, 3H, *Z*), 2.34 (s, 0.8H, *E*), 2.32 (s, 0.8H, *E*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 155.9, 155.4, 143.8, 141.7, 136.4, 132.5, 132.4, 131.3, 131.2, 129.5, 129.2, 128.7, 128.3, 128.0, 127.2, 127.1, 125.6, 123.4, 123.3, 116.5, 115.6, 112.7, 110.0, 21.4, 21.3, 16.5, 16.2; HRMS (ESI TOF) *m/z* calcd for $C_{16}H_6O$ [M - H]$^+$, 223.1123 found 223.1131.

1-bromo-4-((4-methylstyryl)oxy)benzene (3i)

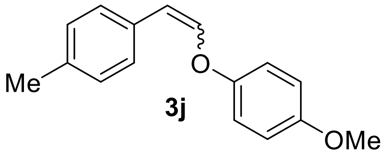


3i

The compound **3i** was synthesized starting from **1i** following the general procedure **D** described for **3a**; The compound **3i** was obtained as a pale yellow solid (73 mg, 77% yield).

(*E*:*Z* = 36:64), m.p.: 70–73 °C; IR (neat) cm^{-1}: 3028, 2917, 2859, 1655, 1586, 1483; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H, *Z*), 7.48 – 7.42 (m, 3H, *E* and *Z*), 7.22 – 7.11 (m, 4.48H, *E* and *Z*), 7.06 (d, *J* = 12.4 Hz, 0.64H, *E*), 7.02 – 6.99 (m, 2H, *Z*), 6.96 – 6.92 (m, 1H, *E*), 6.50 (d, *J* = 6.8 Hz, 1H, *Z*), 6.34 (d, *J* = 12.4 Hz, 0.56H, *E*), 5.64 (d, *J* = 6.8 Hz, 1H, *Z*), 2.34 (s, 4.77H, *E* and *Z*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 156.5, 156.5, 142.2, 140.5, 136.7, 136.8, 132.8, 131.9, 131.8, 129.6, 129.2, 128.8, 125.8, 118.7, 115.8, 115.7, 114.7, 111.5, 21.4, 21.3; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{13}BrO$ [M - H]$^+$, 287.0072 found 287.0066.

1-methoxy-4-((4-methylstyryl)oxy)benzene (3j)

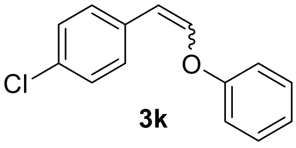


3j

The compound **3j** was synthesized starting from **1j** following the general procedure **D** described for **3a**; The compound **3j** was obtained as a yellow solid (61 mg, 65% yield). (*E*:*Z* = 25:75), m.p.: 60–62°C; IR (neat) cm^{-1}: 3004, 2922, 2839, 1654, 1504, 1456; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 – 7.56 (m, 2H, *Z*), 7.20 – 7.09 (m, 3.63H, *E* and *Z*), 7.08

– 7.04 (m, 2H, *Z*), 7.02– 6.98 (m, 0.70H, *E*), 6.91– 6.86 (m, 2.63H, *E* and *Z*), 6.49 (d, *J* = 6.9 Hz, 1H, *Z*), 6.24 (d, *J* = 12.5 Hz, 0.33H, *E*), 5.53 (d, *J* = 6.9 Hz, 1H, *Z*), 3.80 (s, 4H, *E* and *Z*), 2.34 (s, 3H, *Z*), 2.33(s, 1H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.8, 151.7, 144.2, 142.4, 136.4, 132.5, 132.3, 132.2, 130.0, 129.5, 129.2, 128.6, 125.6, 118.5, 118.2, 114.8, 112.5, 109.6, 55.8, 21.34, 21.3; HRMS (ESI TOF) *m/z* calcd for $C_{16}H_{16}O_2$ $[M + H]^+$, 241.1228 found 241.1223.

1-chloro-4-(2-phenoxyvinyl)benzene (3k)

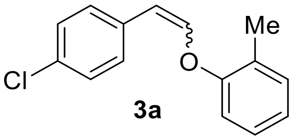


3k

The compound **3k** was synthesized starting from **1k** following the general procedure described **D** for **3a**; The compound **3k** was obtained as a yellowish liquid (66 mg, 70% yield).

(*E*:*Z* = 7:93), IR (neat) cm^{-1}: 3053, 2922, 1655, 1593, 1489; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H, *Z*), 7.33 – 7.27 (m, 2.40H, *E* and *Z*), 7.24– 7.14 (m, 2.57H, *E* and *Z*), 7.10 – 6.98 (m, 2.43H, *E* and *Z*), 6.56 (d, *J* = 6.9 Hz, 1H, *Z*), 6.21 (d, *J* = 12.4 Hz, 0.08H, *E*), 5.50 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 157.3, 144.1, 142.4,133.5, 132.2, 130.0, 129.9, 128.7, 128.6, 126.9, 123.7, 117.1, 109.3; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{11}ClO$ $[M - H]^+$, 229.0420 found 229.0423.

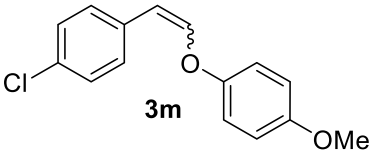
1-((4-chlorostyryl)oxy)-2-methylbenzene (3l)



3a

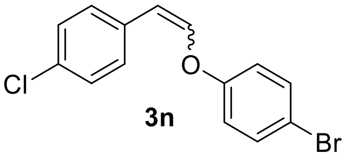
The compound **3l** was synthesized starting from **1l** following the general procedure described **D** for **3a**; The compound **3l** was obtained as a colorless liquid (70 mg, 74% yield). (*E*:*Z* = 22:78), IR (neat) cm^{-1}: 3032, 2923, 2856, 1652, 1587, 1489; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.62 (m, 2H, *Z*), 7.31 – 7.27 (m, 2H, *E* and *Z*), 7.26 – 7.17 (m, 3.94H, *E* and *Z*), 7.14 (d, *J* = 12.4 Hz, 0.33H, *E*), 7.06 – 6.97 (m, 2.47H, *E* and *Z*), 6.59 (d, *J* = 6.9 Hz, 1H, *Z*), 6.17 (d, *J* = 12.5 Hz, 0.28H, *E*), 5.55 (d, *J* = 6.9 Hz, 1H, *Z*), 2.36 (s, 3H, *Z*), 2.29 (s, 0.84H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.7, 145.1, 143.0, 134.0, 133.7, 132.0, 131.4, 131.4, 129.9, 128.9, 128.6, 128.1, 127.3, 127.2, 126.8, 123.8, 123.7, 116.8, 115.9, 111.3, 108.7, 16.4, 16.2; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{13}ClO$ $[M - H]^+$, 243.0577 found 243.0582.

1-chloro-4-(2-(4-methoxyphenoxy)vinyl)benzene (3m)


3m

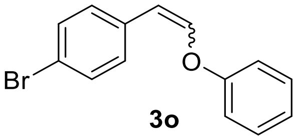
The compound **3m** was synthesized starting from **1m** following the general procedure **D** described for **3a**; The compound **3m** was obtained as a yellow solid (66 mg, 70% yield). (*E*:*Z* = 24:76), m.p.: 76–78°C; IR (neat) cm^{-1}: 3043, 3004, 2951, 1651, 1498, 1407; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H, *Z*), 7.30 – 7.23 (m, 3H, *Z*), 7.21 – 7.18 (m, 0.66H, *E*), 7.09 (d, *J* = 12.5 Hz, 0.4H, *E*), 7.06 – 7.02 (m, 2H, *Z*), 7.01 – 6.97 (m, 0.67H, *E*), 6.90 – 6.85(m, 2.62H, *E* and *Z*), 6.54 (d, *J* = 6.9 Hz, 1H, *Z*), 6.18 (d, *J* = 12.5 Hz, 0.31H, *E*), 5.49 (d, *J* = 6.9 Hz, 1H, *Z*), 3.79 (s, 4H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 156.1, 151.4, 150.9, 145.5, 143.6, 134.1, 133.7, 132.0, 129.9, 128.9, 128.6, 126.8, 118.7, 118.3, 114.9, 111.2, 108.3, 55.8, 55.8; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{13}ClO_2$ [M - H] +, 259.0526 found 259.0527.

1-bromo-4-((4-chlorostyryl)oxy)benzene (3n)


3n

The compound **3n** was synthesized starting from **1n** following the general procedure described **D** for **3a**; The compound **3n** was obtained as a pale yellow liquid (65 mg, 68% yield). (*E*:*Z* = 22:78); IR (neat) cm^{-1}: 2924,2865, 1655, 1586, 1483; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.56(m, 2H, *Z*), 7.49 – 7.44 (m, 2.60H, *E* and *Z*), 7.31 – 7.27 (m, 2H, *Z*), 7.23 – 7.21 (m, 0.52H, *E*), 7.08 (d, *J* = 12.4 Hz, 0.34H, *E*), 7.02 – 6.98 (m, 2H, *Z*), 6.96 – 6.92 (m, 0.54H, *E*), 6.55 (d, *J* = 6.9 Hz, 1H, *Z*), 6.30 (d, *J* = 12.4 Hz, 0.28H, *E*), 5.60 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 156.3, 143.5, 141.7, 133.2, 132.9, 132.9, 132.5, 130.1, 129.1, 128.7, 127.0, 118.9, 118.8, 116.3, 113.4, 110.1; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{10}BrClO$ $[M - H]^+$, 306.9526 found 306.9529.

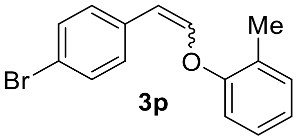
1-bromo-4-(2-phenoxyvinyl)benzene (3o)



3o

The compound **3o** was synthesized starting from **1o** following the general procedure **D** described for **3a**; The compound **3o** was obtained as a white solid (65 mg, 69% yield). (*E*:*Z* = 4:96), m.p.: 64–66°C; IR (neat) cm^{-1}: 3066, 2925, 2856, 1654, 1595, 1491; ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*- Isomer) δ 7.57 – 7.53 (m, 2H), 7.46 – 7.42 (m, 2H), 7.39 – 7.35 (m, 2H), 7.16 – 7.09 (m, 3H), 6.64 (d, *J* = 6.9 Hz, 1H), 5.56 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*- Isomer) δ 157.3, 142.6, 134.0, 131.6, 130.4, 130.0, 123.8, 120.4, 117.1, 109.3; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{11}BrO$ [M + H]$^+$ 137.0602, found 137.0607.

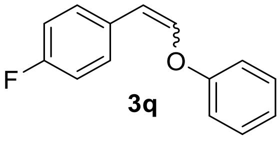
1-((4-bromostyryl)oxy)-2-methylbenzene (3p)



3p

The compound **3p** was synthesized starting from **1p** following the general procedure **D** described for **3a**; The compound **3p** was obtained as a white solid (74 mg, 78% yield). (*E*:*Z* = 21:79), m.p.: 53–56°C; IR (neat) cm^{-1}: 3029, 2924, 2855, 1653, 1589, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 2H, *Z*), 7.47 – 7.39 (m, 2.44H, *E* and *Z*), 7.24 – 7.14 (m, 3.30H, *E* and *Z*), 7.06 – 6.98 (m, 2.46H, *E* and *Z*), 6.61 (d, *J* = 6.9 Hz, 1H, *Z*), 6.16 (d, *J* = 12.5 Hz, 0.28H, *E*), 5.54 (d, *J* = 6.9 Hz, 1H, *Z*), 2.36 (s, 3H, *Z*), 2.29 (s, 0.78H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.7, 155.1, 145.2, 143.1, 134.2, 131.9, 131.5, 131.4, 131.4, 130.2, 128.2, 127.3, 127.2, 127.2, 123.9, 123.7, 120.2, 116.8, 115.9, 111.3, 108.7, 16.4, 16.2; HRMS (ESI TOF) *m/z* calcd for $C_{15}H_{13}BrO$ [M - H]$^+$, 287.0072 found 287.0072.

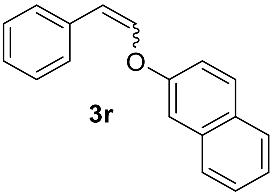
1-fluoro-4-(2-phenoxyvinyl)benzene (3q)



3q

The compound **3q** was synthesized starting from **1q** following the general procedure described **D** for **3a**; The compound **3q** was obtained as a pale yellowish liquid (70 mg, 75% yield).(E:Z = 1:99), IR (neat) cm^{-1}: 3047, 2923, 2855, 1658, 1593, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) (Z- Isomer)δ 7.68 – 7.64 (m, 2H), 7.39 – 7.35 (m, 2H), 7.15 – 7.11 (m, 3H), 7.05 – 6.99 (m, 2H), 6.60 (d, J = 6.9 Hz, 1H), 5.59 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (Z- Isomer) δ 161.6 (d, J = 246.4 Hz), 157.3, 141.4, 131.2, 131.2, 130.5 (d, J = 7.7 Hz), 129.9, 123.6, 117.0, 115.32 (d, J = 21.3 Hz), 109.5; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{11}FO$ [M - H]$^+$, 213.0716 found 213.0713.

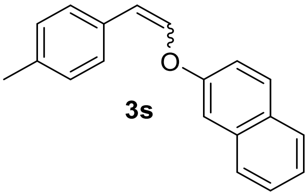
2-(styryloxy)naphthalene (3r)



3r

The compound **3r** was synthesized starting from **1r** following the general procedure **D** described for **3a**; The compound **3r** was obtained as a white solid (78 mg, 83% yield). (E:Z = 21:79), m.p.: 92–94°C; IR (neat) cm^{-1}: 3055, 2923, 2855, 1627, 1589, 1503, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.71 (m, 5.73H, E and Z), 7.50 – 7.21 (m, 10H, E and Z), 6.75 (d, J = 6.9 Hz, 1H, Z), 6.43 (d, J = 12.4 Hz, 0.27H, E), 5.71 (d, J = 6.9 Hz, 1H, Z); ^{13}C NMR (100 MHz, $CDCl_3$) (E and Z) δ 155.2, 143.4, 141.7, 135.2, 135.0, 134.4, 130.3, 130.0, 128.9, 128.5, 127.9, 127.3, 126.9, 126.8,125.9, 124.8, 118.9, 118.0, 114.4, 111.5, 111.1; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{14}O$ [M - H]$^+$, 245.0966 found 0952.

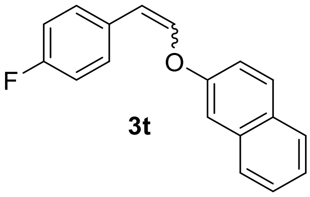
2-((4-methylstyryl)oxy)naphthalene (3s)



3s

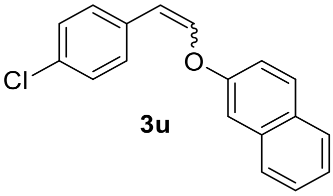
The compound **3s** was synthesized starting from **1s** following the general procedure **D** described for **3a**; The compound **3s** was obtained as a brown solid (69 mg, 73% yield). (E:Z = 22:78), m.p.: 92–94°C; IR (neat) cm^{-1}: 3019, 2918, 2857, 1629, 1597, 1509, 1465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 3.91H, E and Z), 7.61 (d, J = 8.2 Hz, 2H, Z), 7.48 – 7.33 (m, 4.87H, E and Z), 7.29 – 7.24 (m, 1.73H, E and Z), 7.16 – 7.13 (m, 2.69H, E and Z), 6.71 (d, J = 6.8 Hz, 1H, Z), 6.41 (d, J = 12.4 Hz, 0.27H, E), 5.69 (d, J = 6.9 Hz, 1H, Z), 2.35 (s, 4H, E and Z); ^{13}C NMR (100 MHz, $CDCl_3$) (E and Z) δ 155.2, 142.6, 140.9, 136.7, 134.4, 132.1, 130.3, 130.0, 129.6, 129.2, 128.8, 127.9, 127.3, 126.8, 125.8, 124.8, 118.8, 114.4, 111.4, 111.2, 21.4; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O$ $[M - H]^+$, 259.1123 found 259.1131.

2-((4-fluorostyryl)oxy)naphthalene (3t)


3t

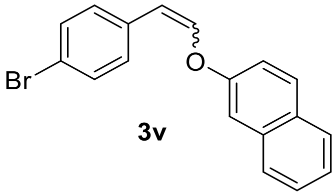
The compound **3t** was synthesized starting from **1t** following the general procedure **D** described for **3a**; The compound **3t** was obtained as a white solid (76 mg, 80% yield). (*E*:*Z* = 21:79), m.p.: 91–93°C; IR (neat) cm^{-1}: 3060, 2923, 2854, 1630, 1594, 1505, 1464, 1401; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 3.94H, *E* and *Z*), 7.72 – 7.67 (m, 1.91H, *E* and *Z*), 7.50 – 7.25 (m, 6H, *E* and *Z*), 7.22 (d, *J* = 12.4 Hz, 0.29H, *E*), 7.06 – 7.00 (m, 2.46H, *E* and *Z*), 6.73 (d, *J* = 6.9 Hz, 1H, *Z*), 6.39 (d, *J* = 12.4 Hz, 0.27H, *E*), 5.67 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (101 MHz, $CDCl_3$) (*E* and *Z*) δ 161.6 (d, *J* = 246.5 Hz), 155.1, 143.1, 143.1, 141.3 (d, *J* = 2.4 Hz), 134.3, 131.2, 131.1, 130.47 (d, *J* = 7.8 Hz), 130.1, 127.9, 127.4, 127.3, 127.3, 127.2, 126.9, 126.9, 124.9, 124.9, 118.9, 118.7, 115.79 (d, *J* = 21.6 Hz), 115.37 (d, *J* = 21.3 Hz), 113.3, 111.6, 111.5, 110.0; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{13}FO$ $[M - H]^+$, 263.0872 found 263.0891.

2-((4-chlorostyryl)oxy)naphthalene (3u)


3u

The compound **3u** was synthesized starting from **1u** following the general procedure **D** described for **3a**; The compound **3u** was obtained as a brownish solid (74 mg, 78% yield). (*E*:*Z* = 20:80), m.p.: 99–101°C; IR (neat) cm^{-1}: 3062, 2924, 2854, 1649, 1594, 1505, 1464; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86– 7.76 (m, 4H, *E* and *Z*), 7.67 – 7.63 (m, 2H, *E* and *Z*), 7.51 – 7.37 (m, 4H, *E* and *Z*), 7.35 – 7.25 (m, 5H, *E* and *Z*), 6.76 (d, *J* = 6.9 Hz, 1H, *E* ad *Z*), 6.36 (d, *J* = 12.4 Hz, 0.26H, *E*), 5.64 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 155.0, 143.9, 142.2, 134.3, 133.5, 132.3, 130.4, 130.1, 129.0, 127.9, 127.3, 127.1, 126.9, 125.0, 118.9, 118.7, 113.0, 111.7, 109.8; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{13}ClO$ $[M + H]^+$, 279.0577 found 279.0571.

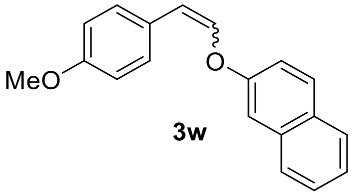
2-((4-bromostyryl)oxy)naphthalene (3v)



3v

The compound **3v** was synthesized starting from **1v** following the general procedure **D** described for **3a**; The compound **3v** was obtained as a white solid (72 mg, 75% yield). (*E*:*Z* = 18:82), m.p.: 102–104°C; IR (neat) cm^{-1}: 3061, 2924, 2854, 1644, 1592, 1507, 1471; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 – 7.76 (m, 3.77H, *E* and *Z*), 7.61 – 7.57 (m, 2H, *E* and *Z*), 7.51 – 7.37 (m, 6.16H, *E* and *Z*), 7.35 – 7.32 (m, 1H, *E* and *Z*), 7.29 – 7.20 (m, 1.37H, *E* and *Z*), 6.78 (d, *J* = 6.9 Hz, 1H, *Z*), 6.34 (d, *J* = 12.4 Hz, 0.23H, *E*), 5.64 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 155.0, 144.0, 142.4, 134.3, 133.9, 131.9, 131.6, 130.4, 130.1, 127.9, 127.4, 127.3, 127.2, 127.0, 125.0, 120.5, 118.8, 118.7, 113.0, 111.7, 109.8; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{13}BrO$ [M - H]$^+$, 323.0072 found 323.0078.

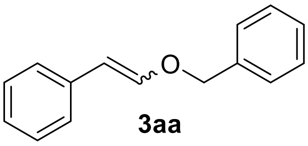
2-((4-methoxystyryl)oxy)naphthalene (3w)



3w

The compound **3w** was synthesized starting from **1w** following the general procedure **D** described for **3a**; The compound **3w** was obtained as a brown solid (63 mg, 67% yield). (*E*:*Z* = 22:78), m.p.: 92–94°C; IR (neat) cm^{-1}: 3057, 2923, 2846, 1602, 1509, 1462; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 – 7.74 (m, 4H, *E* and *Z*) 7.69 – 7.64 (m, 2H, *E* and *Z*), 7.47 – 7.25 (m, 7H, *E* and *Z*), 7.18 (d, *J* = 12.4 Hz, 0.29H, *E*), 6.90 – 6.86 (m, 2.61H, *E* and *Z*), 6.67 (d, *J* = 6.8 Hz, 1H, *Z*), 6.39 (d, *J* = 12.4 Hz, 0.28H, *E*), 5.66 (d, *J* = 6.8 Hz, 1H, *Z*), 3.81 (s, 3.72H, *E* and *Z*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 158.5, 155.2, 141.8, 140.0, 134.4, 130.2, 130.2, 127.9, 127.8, 127.2, 127.2, 127.1, 126.8, 124.7, 124.7, 118.9, 118.8, 114.4, 114.2, 114.0, 111.3, 111.2, 110.9, 55.5, 55.4; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ [M]$^+$, 276.1150 found 276.1158.

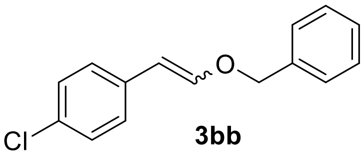
(2-(benzyloxy)vinyl)benzene (3aa)



3aa

The compound **3aa** was synthesized starting from **1aa** following the general procedure **D** described for **3a**; The compound **3aa** was obtained as a pale yellow liquid (72 mg, 77% yield). (*E*:*Z* = 41:59), IR (neat) cm^{-1}: 3031, 2922, 1720, 1647, 1494, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.62 (m, 2H, *Z*), 7.39 – 7.37 (m, 5.77H, *E* and *Z*), 7.35 – 7.23 (m, 7.52H, *E* and *Z*), 7.17 – 7.12 (m, 1.66H, *E* and *Z*), 7.08 (d, *J* = 12.9 Hz, 0.72H, *E*), 6.28 (d, *J* = 7.0 Hz, 1H, *Z*), 5.96 (d, *J* = 12.9 Hz, 0.70H, *E*), 5.27 (d, *J* = 7.0 Hz, 1H, *Z*), 4.99 (s, 2H, *Z*), 4.90 (s, 1.50H, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 147.8, 146.4, 137.4, 136.8, 136.4, 136.0, 128.7, 128.4, 128.4, 128.3, 128.2, 127.8, 127.4, 125.9, 125.3, 107.0, 106.4, 75.1, 72.0; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ [M - H]$^+$, 209.0966 found 209.0970.

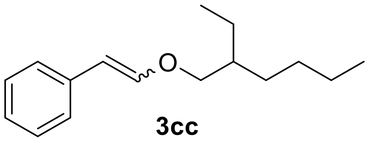
1-(2-(benzyloxy)vinyl)-4-chlorobenzene (3bb)



3bb

The compound **3bb** was synthesized starting from **1bb** following the general procedure **D** described for **3a**; The compound **3bb**was obtained as a colorless liquid (144 mg, 86% yield). (*Z* isomer) IR (neat) cm^{-1}: 3034, 2925, 1414, 1650, 1594, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 2H), 7.40 – 7.30 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 7.0 Hz, 1H), 5.22 (d, *J* = 7.0 Hz, 1H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 137.1, 134.5, 131.2, 129.7, 128.8, 128.4, 128.3, 127.4, 105.4, 75.2; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ [M - H]$^+$, 243.0577 found 243.0582.

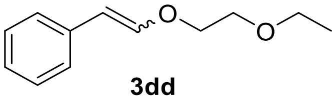
(2-((2-ethylhexyl)oxy)vinyl)benzene (3cc)



3cc

The compound **3cc** was synthesized starting from **1cc** following the general procedure **D** described for **3a**; The compound **3cc** was obtained as a colorless liquid (75 mg, 80% yield). (*E*:*Z* = 40:60) IR (neat) cm^{-1}: 3031, 2955, 2867, 1722, 1605, 1458; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 2H, *Z*), 7.29 – 7.20 (m, 4.75H, *E* and *Z*), 7.14 – 7.05(m, 1.65H, *E* and *Z*), 7.01 (d, *J* = 13.0 Hz, 0.67H, *E*), 6.19 (d, *J* = 7.0 Hz, 1H, *Z*), 5.83 (d, *J* = 12.9 Hz, 0.64H, *E*), 5.18 (d, *J* = 7.0 Hz, 1H, *Z*), 3.83 (d, *J* = 5.8 Hz, 2H, *Z*), 3.72 (d, *J* = 5.8 Hz, 1.28H, *E*), 1.68 – 1.60 (m, 1.76H, *E* and *Z*), 1.51 – 1.25 (m, 15H, *E* and *Z*), 0.94 – 0.88 (m, 10H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 148.6, 147.4, 136.8, 136.4, 128.7, 128.3, 128.2, 125.6, 125.1, 105.6, 105.2, 76.6, 72.6, 40.1, 39.6, 30.6, 30.5, 29.2, 29.1, 23.9, 23.8, 23.2, 23.2, 14.2, 14.2, 11.2, 11.2; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ $[M - H]^+$, 231.1749 found 231.1756.

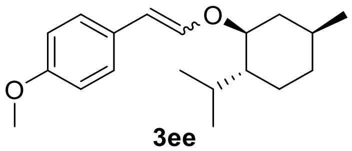
(2-(2-ethoxyethoxy)vinyl)benzene (3dd)



3dd

The compound **3dd** was synthesized starting from **1dd** following the general procedure **D** described for **3a**; The compound **3dd** was obtained as a pale yellow liquid (70 mg, 75% yield). (*E*:*Z* = 46:54) IR (neat) cm^{-1}: 3028, 2970, 2923, 2869, 1721, 1645, 1600, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60– 7.58(m, 2H, *Z*), 7.29 – 7.20(m, 5.87H, *E* and *Z*), 7.15 – 7.05 (m, 1.89H, *E* and *Z*), 7.03 (d, *J* = 13.0 Hz, 0.91H, *E*), 6.24 (d, *J* = 7.0 Hz, 1H, *Z*), 5.86 (d, *J* = 13.0 Hz, 0.89H, *E*), 5.23 (d, *J* = 7.0 Hz, 1H, *Z*), 4.07 – 3.04 (m, 2H, *Z*), 3.99 – 3.97 (m, 1.89H, *E*), 3.72 – 3.69 (m, 4H, *Z*), 3.60 – 3.54 (m, 3.86H, *E*), 1.26 –1.20 (m, 6H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 148.1, 147.0, 136.5, 136.1, 128.7, 128.4, 128.3, 125.8, 125.8, 125.23, 106.3, 106.0, 72.9, 69.7, 69.3, 69.1, 67.0, 67.0, 15.3, 15.3; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ $[M - H]^+$, 191.1072 found 191.1067.

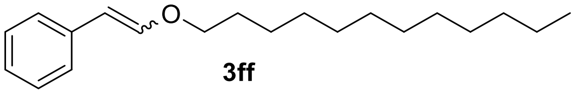
1-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)vinyl)-4-methoxybenzene (3ee)



3ee

The compound **3ee** was synthesized starting from **1ee** following the general procedure **D** described for **3a**; The compound **3ee** was obtained as a yellow liquid (144 mg, 86% yield). (*E*:*Z* = 31:69) IR (neat) cm^{-1}: 2949, 2921, 2866, 1721, 1609, 1512, 1456; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.52 (m, 2H, *Z*), 7.15 – 7.12 (m, 1H, *Z*), 6.85 – 6.79 (m, 2.94H, *E* and *Z*), 6.77 (d, *J* = 12.6 Hz, 0.48H, *E*), 6.17 (d, *J* = 7.0 Hz, 1H, *Z*), 5.89 (d, *J* = 12.6 Hz, 0.44H, *E*), 5.12 (d, *J* = 7.0 Hz, 1H, *Z*), 3.79 (s, 3H, *Z*), 3.78 (s, 1.40H, *E*), 3.61 – 3.49 (m, 1.58H, *E* and *Z*), 2.25 – 2.14 (m, 1.55H, *E* and *Z*), 2.12 – 2.05 (m, 1.63H, *E* and *Z*), 1.71 – 1.65 (m, 3.26H, *E* and *Z*), 1.51 – 1.34 (m, 3.34H, *E* and *Z*), 1.16 – 0.98 (m, 3.45H, *E* and *Z*), 0.94 – 0.91 (m, 10H, *E* and *Z*), 0.80 (d, *J* = 6.9 Hz, 4.44H, *E* and *Z*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 157.8, 157.4, 146.2, 144.8, 129.5, 129.4, 129.3, 126.1, 114.2, 113.7, 106.8, 104.4, 83.6, 81.5, 55.4, 55.4, 48.1, 48.0, 42.1, 41.5, 34.5, 31.8, 31.7, 26.1, 26.0, 23.6, 22.3, 21.0, 20.9, 16.6, 16.5; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ [M]$^+$, 288.2089 found 288.2086

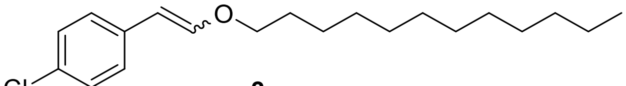
(2-(dodecyloxy)vinyl)benzene (3ff)



3ff

The compound **3ff** was synthesized starting from **1ff** following the general procedure **D** described for **3a**; The compound **3ff** was obtained as a colorless liquid (144 mg, 86% yield). (*E*:*Z* = 43:57) IR (neat) cm^{-1}: 2921, 2854, 1727, 1654, 1459; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 – 7.57 (m, 2H, *Z*), 7.30 – 7.20 (m, 5H, *E* and *Z*), 7.15 – 7.09 (m, 1.85H, *E* and *Z*), 6.99 (d, *J* = 13.0 Hz, 0.73H, *E*), 6.20 (d, *J* = 7.0 Hz, 1H, *Z*), 5.83 (d, *J* = 12.9 Hz, 0.75H, *E*), 5.20 (d, *J* = 7.0 Hz, 1H, *Z*), 3.91 (t, *J* = 6.6 Hz, 2H, *Z*), 3.82 (t, *J* = 6.6 Hz, 1.53H, *E*), 1.75 – 1.66 (m, 3.85H, *E* and *Z*), 1.44 – 1.26 (m, 34H, *E* and *Z*), 0.88 (t, *J* = 6.9 Hz, 5H, *E* and *Z*); ^{13}C NMR (100 MHz, CDCl$_3$) (*E* and *Z*) δ 148.3, 147.1, 136.8, 136.3, 128.7, 128.3, 128.2, 125.7, 125.2, 105.9, 105.4, 73.9, 70.2, 32.1, 30.0, 29.8, 29.8, 29.7, 29.7, 29.7, 29.7, 29.5, 29.5, 29.5, 29.5, 26.1, 26.0, 22.8, 14.3; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ $[M - H]^+$, 287.2375 found 247.2371.

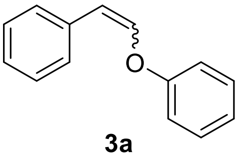
1-chloro-4-(2-(dodecyloxy)vinyl)benzene (3gg)



3gg

The compound **3gg** was synthesized starting from **1gg** following the general procedure **D** described for **3a**; The compound **3gg** was obtained as a yellow liquid (144 mg, 86% yield). (*E*:*Z* = 44:56) IR (neat) cm^{-1}: 2923, 2855, 1726, 1646, 1488, 1463; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 2H, *Z*), 7.26 – 7.19 (m, 3.92H, *E* and *Z*), 7.14 – 7.09 (m, 1.74H, *E* and *Z*), 6.96 (d, *J* = 13.0 Hz, 0.80H, *E*), 6.21 (d, *J* = 7.0 Hz, 1H, *Z*), 5.77 (d, *J* = 12.9 Hz, 0.80H, *E*), 5.15 (d, *J* = 7.0 Hz, 1H, *Z*), 3.91 (t, *J* = 6.6 Hz, 2H, *Z*), 3.81 (t, *J* = 6.6 Hz, 1.67H, *E*), 1.75 – 1.65 (m, 3.82H, *E* and *Z*), 1.43 – 1.26 (m, 36H, *E* and *Z*), 0.88 (t, *J* = 6.9 Hz, 5.80H, *E* and *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 148.8, 147.5, 135.3, 134.8, 131.0, 131.0, 129.4, 1288, 128.4, 1263, 104.8, 104.3, 74.1, 704, 32.01, 30.0, 29.8, 29.8, 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 26.1, 26.0, 22.8, 14.3; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{16}O_2$ $[M - H]^+$, 321.1985 found 321.1988.

Gram scale synthesis of (2-phenoxyvinyl)benzene (3a)



3a

The compound **3a** was synthesized on gram scale starting from **1a** (1g, 4.71 mmol), tosyl hydrazone **2** (877 mg, 4.71 mmol) and K_2CO_3 (1.30g 9.42mmol) following the general procedure **D**; The compound **3a** was obtained as a yellow liquid (802 mg, 86% yield). (*E*:*Z* = 24:76), ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H, *Z*), 7.48 – 7.40 (m, 6H, *E* and *Z*), 7.34 – 7.29 (m, 1.74H , *E* and *Z*), 7.26 – 7.18 (m, 4H, *E* and *Z*), 6.71 (d, *J* = 6.9 Hz, 1H, *Z*), 6.45 (d, *J* = 12.4 Hz, 0.36H, *E*), 5.72 (d, *J* = 6.9 Hz, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) (*E* and *Z*) δ 157.4, 157.3, 143.6, 141.8, 135.3, 135.1, 129.9, 128.8, 128.5, 126.8, 125.8, 123.5, 123.4, 117.1, 117.0, 113.8, 110.6; HRMS (ESI TOF) *m/z* calcd for $C_{14}H_{12}O$ $[M - H]^+$, 195.0810 found 195.0804.

5.7Appendix IV: ^{1}H, ^{13}C spectral data of representative compounds

Compound No.	**Figure AII.X**	**Data**	**Page No.**
3a	Figure V.1 and V.2	^{1}H and ^{13}C	182
3b	Figure V.3 and V.4	^{1}H and ^{13}C	183
3bb	Figure V.5 and V.6	^{1}H and ^{13}C	184
3cc	Figure V.7 and V.8	^{1}H and ^{13}C	185

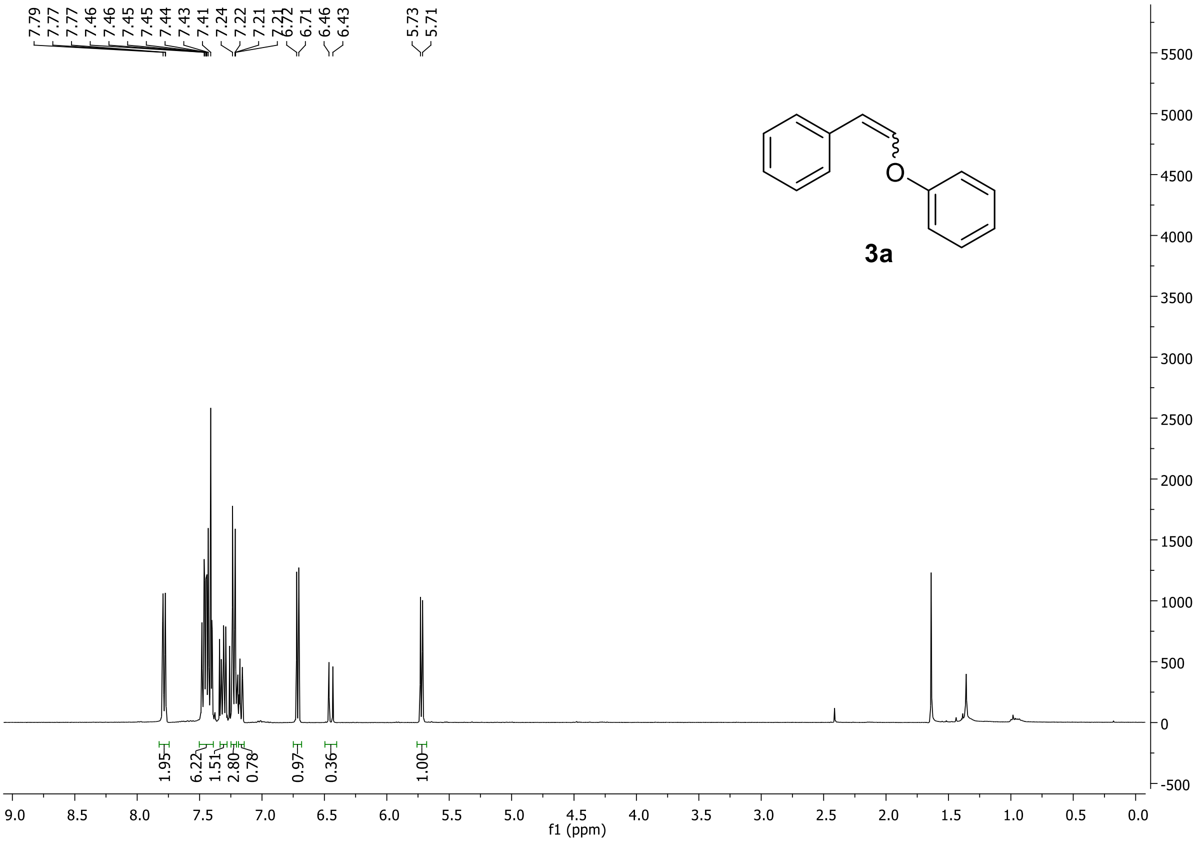


Figure V.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

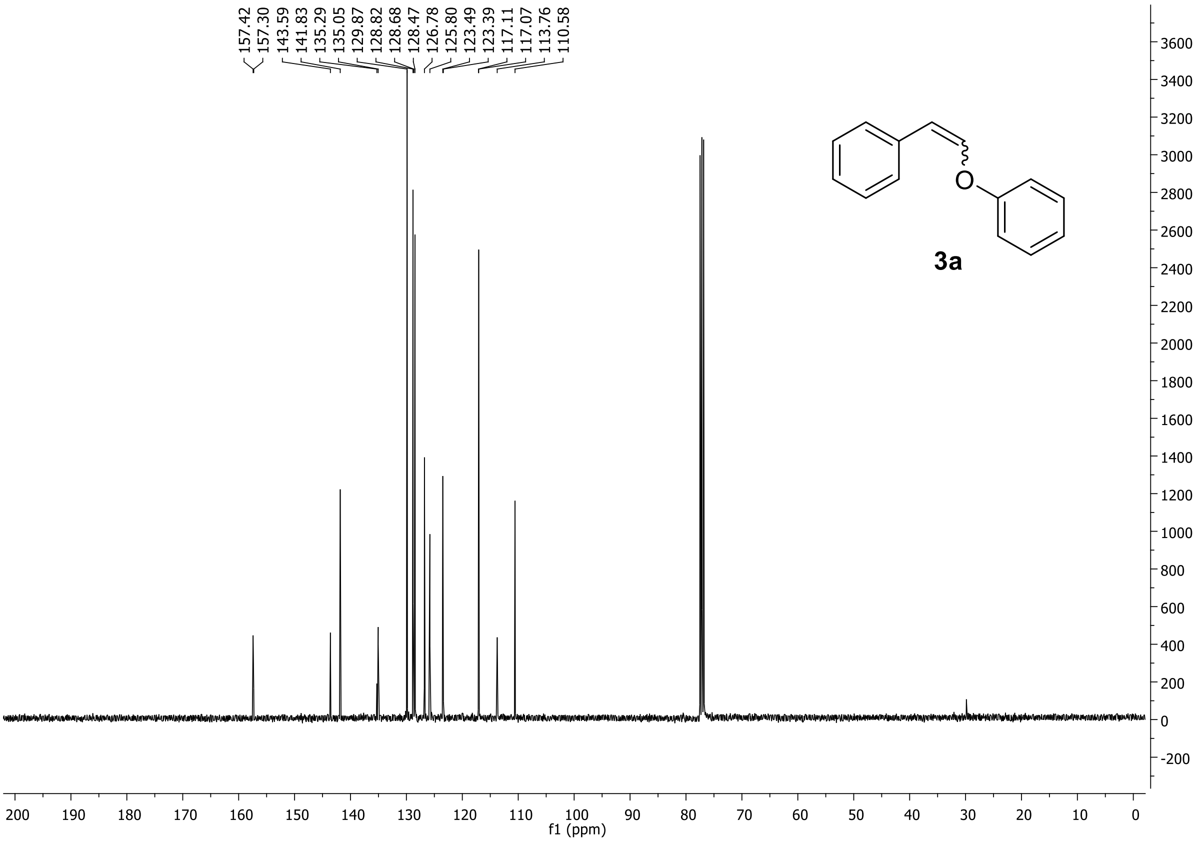


Figure V.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

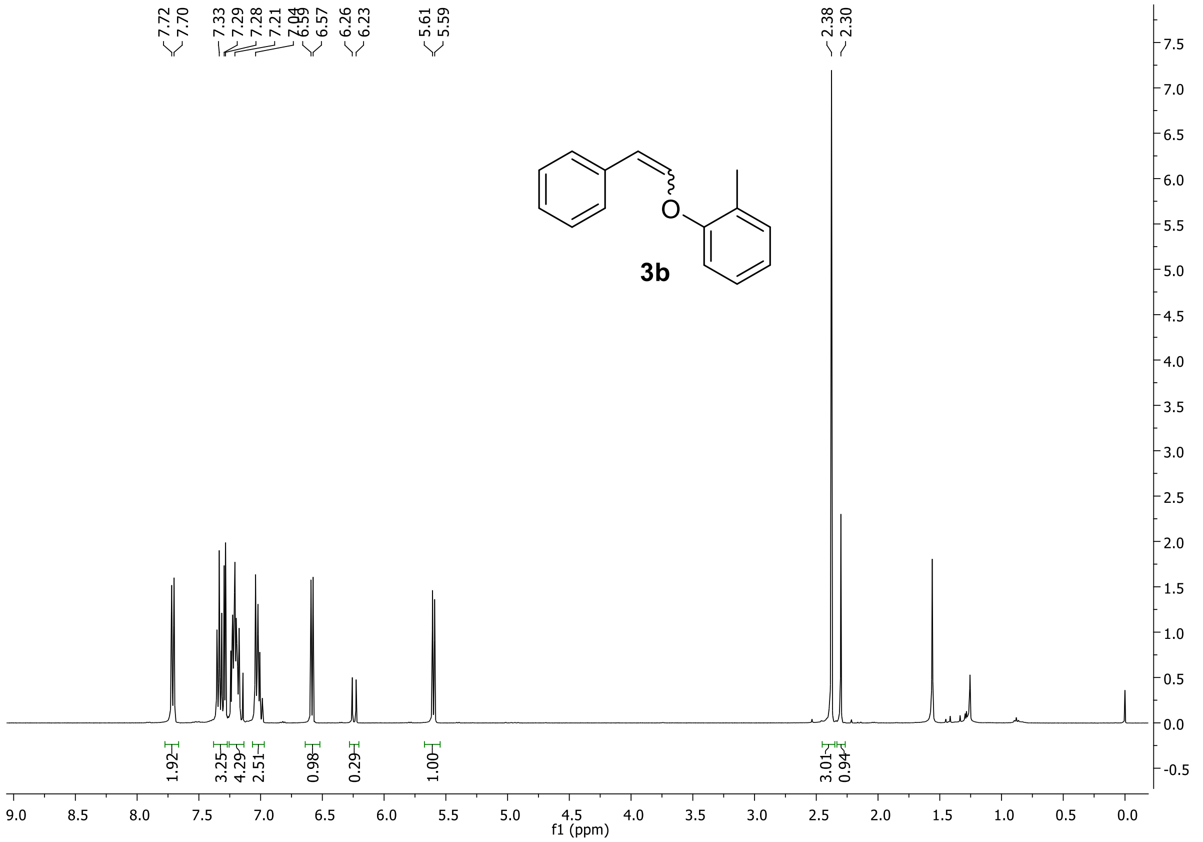


Figure V.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3b**

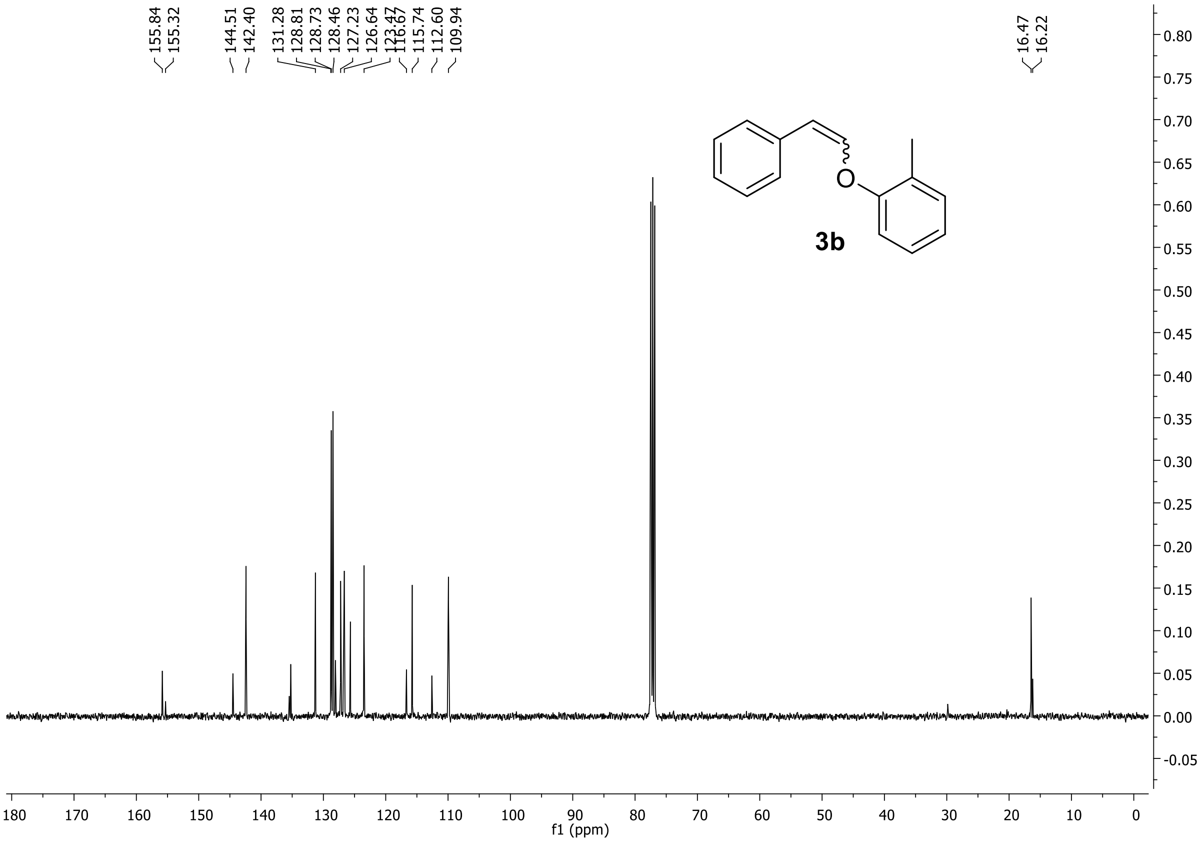


Figure V.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3b**

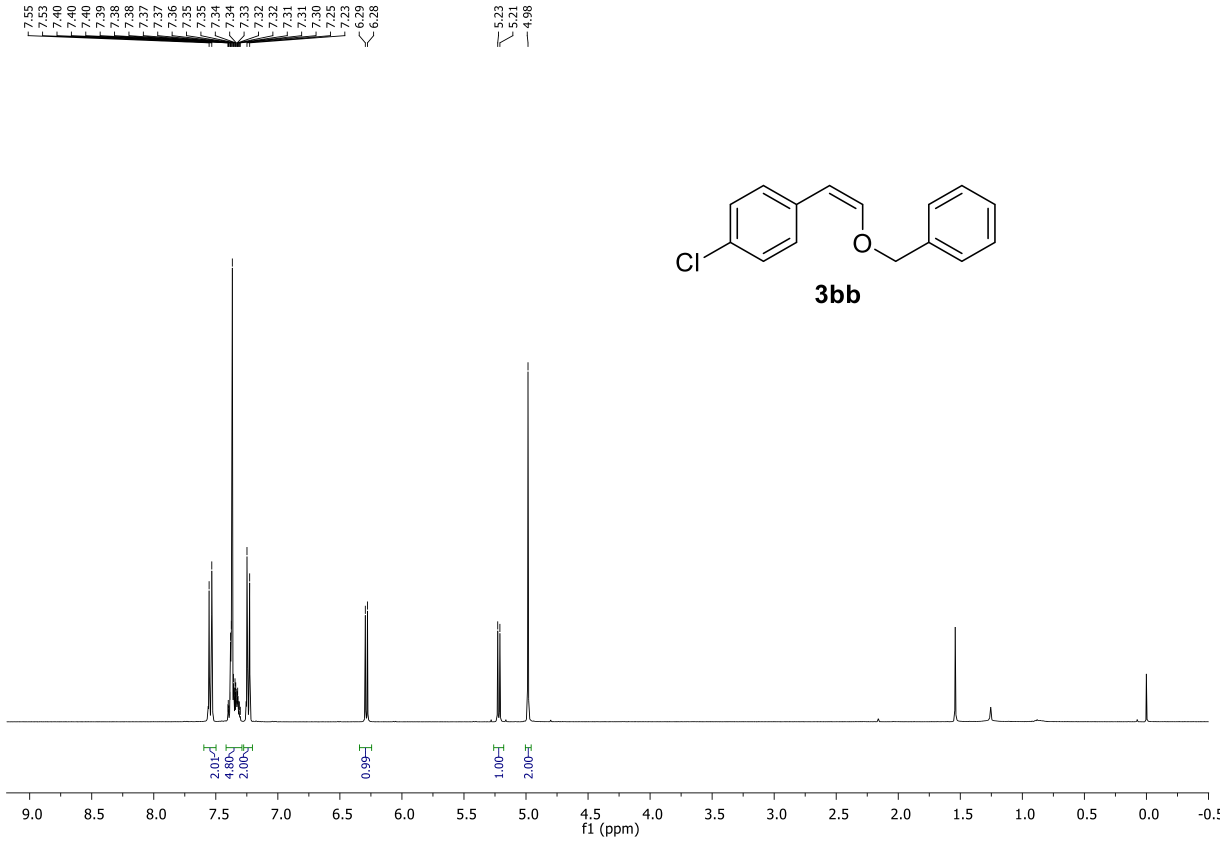


Figure V.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3bb**

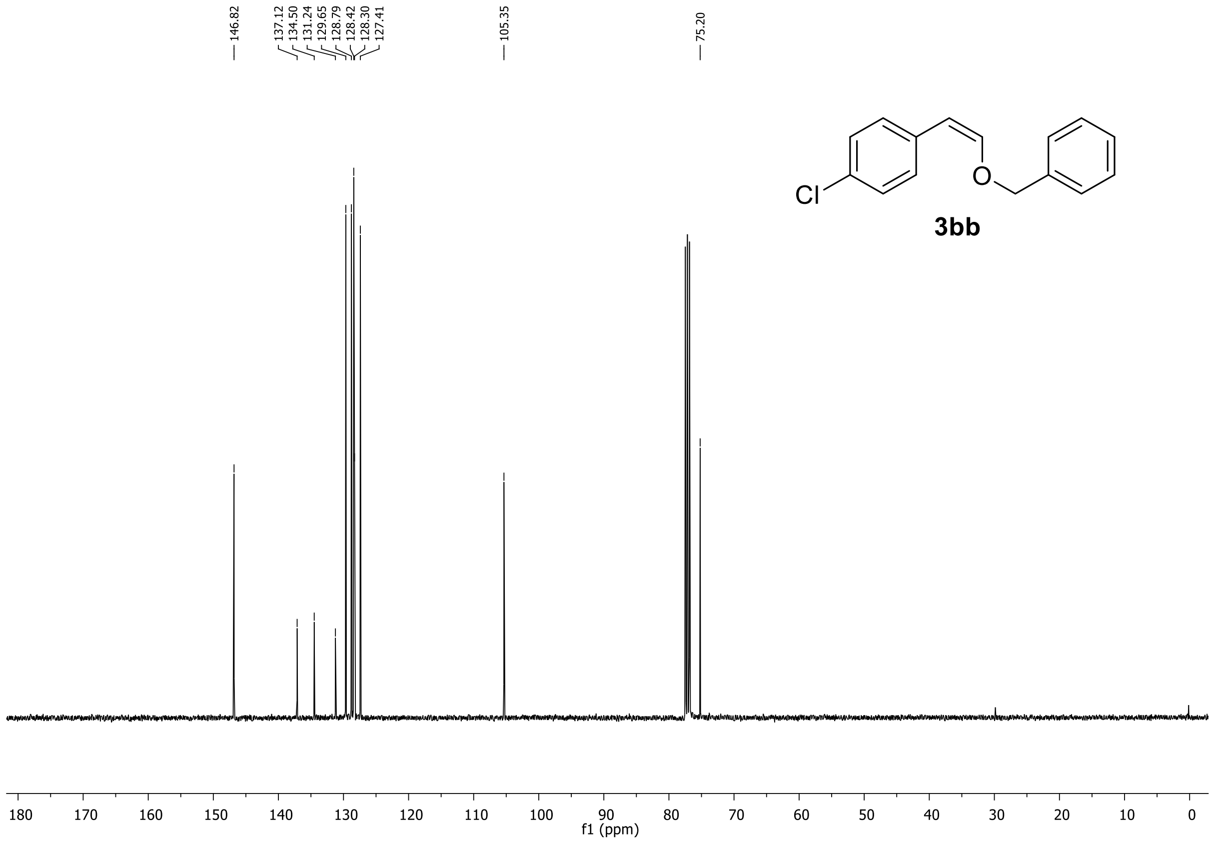


Figure V.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3bb**

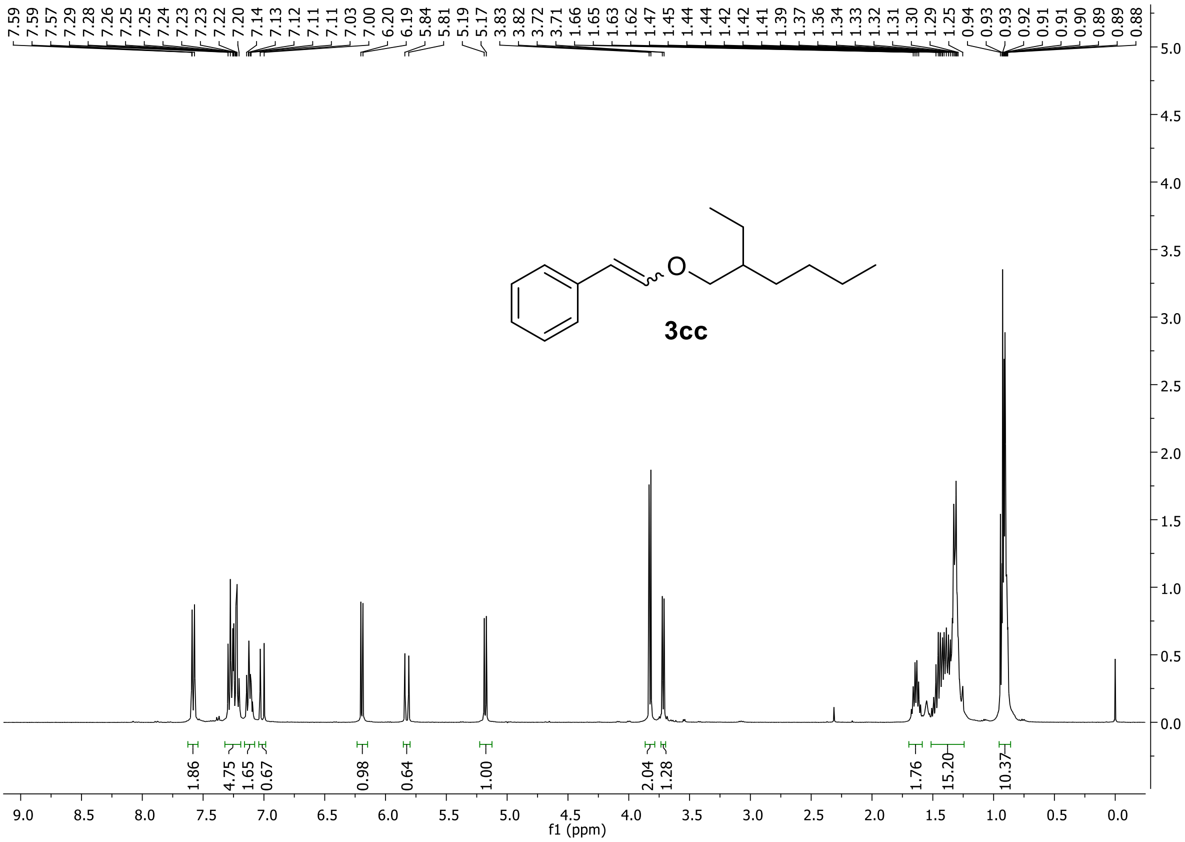


Figure V.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3cc**

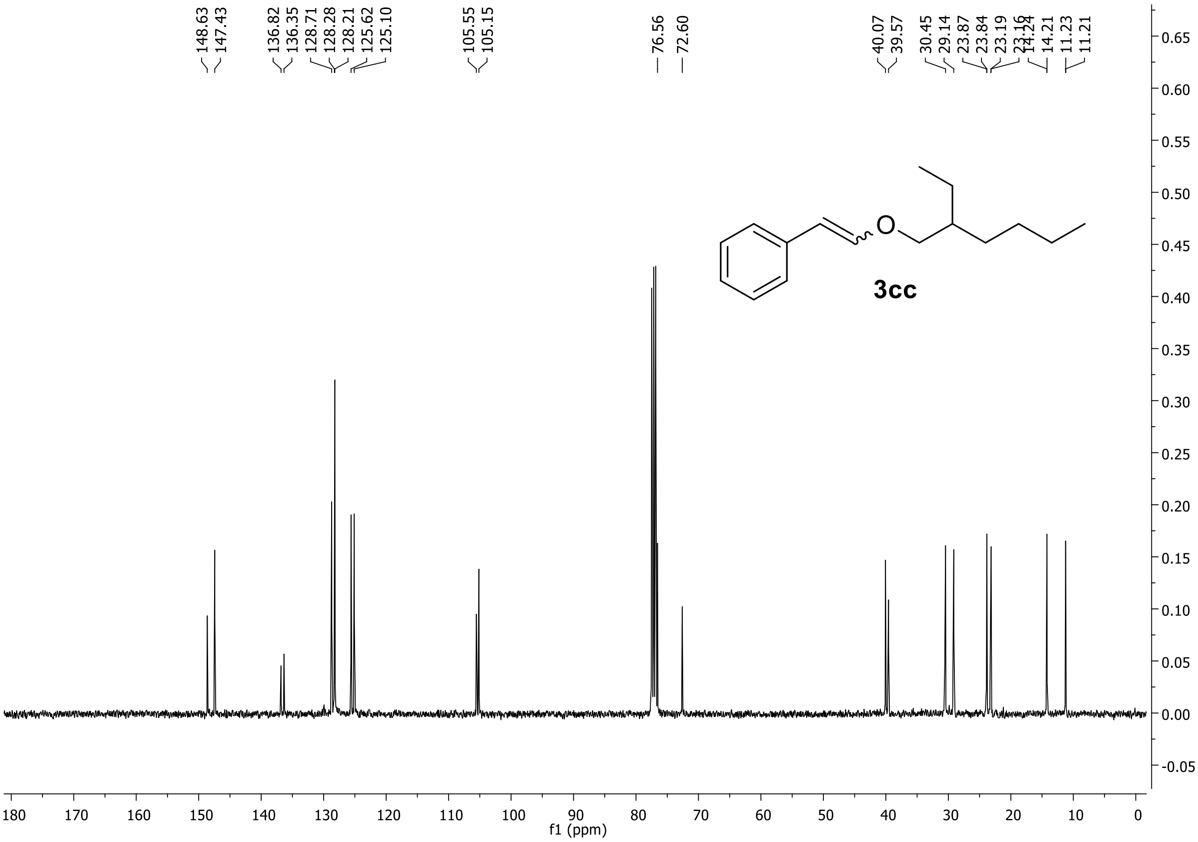


Figure V.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3cc**

5.7 References and notes

1. (a) El-Nabi HAA. *Tetrahedron* 1997;53:1813;
   (b) Firl J, Sommer S. *Tetrahedron Lett*. 1970;1929;
   (c) Boger DA, Robarge KD. *J Org Chem.* 1988;53: 3373.
2. Kitazawa E, Imamura T, Saigo K, Mukaiyama T. *Chem Lett.* 1975;569.
3. Maligres PE, Waters MM, Lee J, Reamer RA, Askin D. *J Org Chem.* 2002;67;1093.
4. Fujimura O, Fu GC, Grubbs RH. *J Org Chem*. 1994;59:4029.
5. Baldwin JE, Höfle GA, Lever Jr OW. *J Org Chem.* 1974;96:7125
6. (a) Ouali A, Laurent R, Caminade A-M, Majoral J-P, Taillefer M. *J Am Chem Soc.* 2006;128:15990;
   (b) Taillefer M, Ouali A, Renard B, Spindler J-F. *Chem Eur J.* 2006;12:5301;
   (c) Bao W, Xin Lv YL. *Synthesis* 2008;12:1911;
   (d) Kaddouri H, Vicente V, Ouali A, Ouazzani F, Taillefer M. *Angew Chem, Int Ed.* 2009;48:333.
7. (a) Green TW, Wuts PGM. *Protecting groups*, 3rd ed.; Wiley: New York, 1991;619;
   (b) Chen YL, Hedberg KG, Guarino KJ. *Tetrahedron Lett*. 1989;30:1067.
8. (a) Ying J, Bauld NL. *J Org Chem*. 1999;64:9251;
   (b) Okimoto Y, Sakaguchi S, Ishii Y*J. Am Chem Soc*. 2002;124:1590;
   (c) Suprenant S, Chan WY, Berthelette C. *Org Lett.* 2003;5:4851;
   (d) Winternheimer DJ, Shade RE, Merlic CA. *Synthesis* 2010;2497.
9. (a) Rossi R, Bellina F, Mannina L. *Tetrahedron* 1997;53:1025;
   (b) Willis MC, Taylor D, Gillmore AT. *Chem Commun*. 2003;2222.
   (c) Wan Z, Jones CD, Koenig TM, Pu YJ, Mitchell D. *Tetrahedron Lett*. 2003;44: 8257;
   (d) Kundu D, Maity P, Ranu BC. *Org. Lett*. 2014;16:1040;
   (e) Taillefer M, Ouali A, Renard B, Spindler J-F. *Chem Eur J*. 2006;12:5301;
   (f) Kabir MS, Lorenz M, Namjoshi OA, Cook JM. *Org Lett*. 2010;12:464;
   (g) Limberger J, Leal BC, Back DF, Dupont J, Monterio AL. *Adv Synth Catal.* 2012;354:1429;
   (h) Jouvin K, Bayle A, Legrand F, Evano G. *Org Lett.* 2012;14:1652;
   (i) Shade RE, Hyde AM, Olsen J-C, Merlic CA. *J Am Chem Soc*. 2010;132:1202.
10. May JA, Stoltz BM. *J Am Chem Soc.* 2002;124:12426.

11. (a) Nair D, Scarpello J, White L, Freista dos Santos L, Vankelecom I, Livingston A. *Tetrahedron Lett.* 2001;42:8219;

    (b) Garett C, Prasad K. *Adv Synth Catal.* 2004;346:889;

    (c) Rivera-Utrilla J, Bautista-Toledo I, Ferro-Garcia M, Moreno-Catilla C*J. Hazard Mater.* 2003;41:323.

12. (a) Gansauer A, Bluhm H. *Chem Rev*. 2000:100:2771;

    (b) *Multimetallic Catalysts in Organic Synthesis*; Shibasaki M, Yamamoto Y, Eds.; Wiley-VCH: Weinheim, 2004;

    (c) Wang C, Xi Z. *Chem Soc Rev.* 2007;36:1395;

    (d) Oxgaard J, Tenn WJ, III, Nielsen RJ, Periana RA, Goddard WA, III. *Organometallics* 2007;26:1565;

    (e) Ackermann L. *Chem Rev*. 2011;111:1315;

    (f) Boutadla Y, Davies DL, Macgregor SA, Poblador-Bahamonde AI. *Dalton Trans.* 2009;5820;

    (g) Lapointe D, Fagnou K. *Chem Lett*. 2010;39:118.

13. (a) Aggarwal VK., de Vicente J, Bonnert RV. *Org Lett*. 2001;3:2785;

    (b) Aggarwal VK, Alonso E, Fang G, Ferrara M, Hynd G, Porcelloni M. *Angew Chem Int Ed.* 2001;40:1433;

    (c) Fulton JR, Aggarwal VK, de Vicente J. *Eur J Org Chem.* 2005;1479;

    (d) Aggarwal VK, Alonso E, Hynd G, Lydon KM, Palmer MJ, Porcelloni M, Studley JR. *Angew Chem Int Ed.* 2001;40:1430;

    (e) Cheung W-H, Zheng S.-L, Yu W-Y, Guo-Chuan Zhou G-C, Che C-M. *Org Lett*. 2003;5:2535.

14. Bamford WR, Stevens TS. *J Chem Soc*. 1952;4735.

15. Time dependent ^{1}H NMR study revealed that chemoselectivity did not change with the reaction time (see ESI)

16. Taber DF, Herr RJ, Pack SK, Geremia JM. *J Org Chem.* 1996;61:2908.

17. It is known in the literature use of aprotic solvents for Bamford Stevens reaction favors the *Z*-selectivity via carbene intermediate followed *syn*-1, 2-hydride shift. Whereas, protic solvents leads to mixture of *E* and *Z* olefins via ionic intermediate.

18. Huang K, Ortiz-Marciales M, Correa W, Pomales E, Lo XY. *J Org Chem.* 2009;74:4195–4202.

19. Toma T, Shimokawa J, Fukuyama T. *Org Lett*. 2007;9:3195− 3197.

20. Pansare SV, Jain RP, Bhattacharyya A. *Tetrahedron Lett*. 1999;40:5255-5258.

SUMMARY

Oxidative C-H functionalization to form new C-C, C-N, and C-S bonds has emerged as an elegant and robust synthetic method for accessing useful products, featuring atom economy and straightforwardness. However, many of these methods are based on transition metal catalysis, which is usually associated with drawbacks such as cost, toxicity and need for non-commercial ligands. As an alternative, transition-metal-free versions have become very important for avoiding more expensive transition metal reagents and to tackle the environmental issues. Potassium persulfate ($K_2S_2O_8$) has emerged as one of the powerful transition-metal-free reagents in organic synthesis. It is relatively cheap, environmentally friendly powerful oxidant and frequently used for the degradation of environmental and soil carbon pollutants. It has also been widely used as a radical initiator in a number of industrial applications. In this regard, we have focused our attention to explore the strength of $K_2S_2O_8$ for the novel transition-metal-free protocols.

We have developed an expedient and direct transition-metal-free regioselective thiocyanation of phenols, anilines and heterocycles using NH_4SCN and $K_2S_2O_8$. The transformation is realized via the direct C-H functionalization under transition-metal-free conditions at an ambient temperature in excellent yields. Similarly, we demonstrated a one-pot protocol for the direct and clean transformation of aryl acetic acids to aldehydes and ketones in water using less expensive $K_2S_2O_8$ as a reagent. The protocol relies on the direct decarboxylation of sp^3-hybridized carbon in water without any over oxidation into carboxylic acids with minimal waste. Further, we have developed a transition-metal-free carbamoylation of heterocycles using formamides/NMF/DMF and $K_2S_2O_8$. The transformation is realized via direct dehydrogenative aminocarbonylation of heterocyclic compounds. The method proved to be practical and a series of primary to tertiary carboxamides were synthesized without any side products. We also developed a novel one-pot transition-metal-free synthesis of styrenyl ethers from 2-aryloxy/alkoxy acetophenones via Bamford-Stevens reaction for the first time. The novel methodology described here is practical and scalable. We have developed transition-metal-free protocols for the direct access of aryl thiocyanates, aldehydes and ketones, azaheterocyclic carboxamides and styrenyl ethers for the thesis work.

Tetrahedron Letters 58 (2017) 415–418

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transition-metal-free regioselective thiocyanation of phenols, anilines and heterocycles

Trimbak B. Mete, Tushar M. Khopade, Ramakrishna G. Bhat *

Department of Chemistry, Indian Institute of Science Education and Research (IISER), Pune 411008, Maharashtra, India

ARTICLE INFO

Article history:
Received 15 November 2016
Revised 16 December 2016
Accepted 18 December 2016
Available online 20 December 2016

Keywords:
Thiocyanation
Transition-metal-free
Persulphate
Radical cation
Radical scavenger

ABSTRACT

An expedient direct and regioselective thiocyanation of phenols, anilines and heterocycles is described. Transformation is realized via the direct C—H functionalization under transition metal free conditions at ambient temperature in excellent yields. Method proved to be monoselective and variety of functional groups tolerated the reaction conditions. The practicality of the protocol is demonstrated in gram scale synthesis of a precursor of PPAR δ agonist in excellent yield.

Introduction

Organosulfur derivatives are very important class of compounds with biological importance. Hence, efforts have been devoted to synthesize organosulfur compounds by directly introducing the sulfur moieties into the organic scaffolds. Among these, direct thiocyanation of aromatic and heteroaromatics is one of the most important and convenient methods for carbon-sulfur bond formation. Many aryl thiocyanates exhibit potent biological and pharmacological activities and they are the building blocks of many biologically active heterocycles and agrochemicals.[1] Moreover, aryl thiocyantes are versatile precursors for making various useful organosulfur compounds such as thiols,[2] thioethers,[3] thioesters,[4] thiocarbamates,[5] disulfides,[6] sulfur containing heterocycles[7] and many pharamceuticals.[1a] Owing to the importance, efforts were made to access the thiocyanates by different methods.[8] Usually, thiocyanates are obtained by direct electrophilic thiocyanation of arenes or nucleophilic substitution reaction of the corresponding organic molecules. Even though some of these traditional methods contributed to the various synthetic transformations, however, use of toxic transition metal reagents, corrosive molecular halogen and halogen based reagents, harsher reaction conditions impede their wide utility. Certainly, these are the limiting factors for the successful and wider applications. Some of the reagents that have been explored for the thiocyanation under various conditions are antimony (V) chloride/lead (II) thiocyanate,[9] arylthallium bistrifluoroacetate/potassium thiocyanate,[10] Zn(SCN)$_2$/Cl$_2$,[11] ceric ammonium nitrate (CAN)/ammonium thiocyante,[8c] Mn(OAc)$_3$,[12] Cu(SCN)$_2$/Cl$_2$,[13] NaSCN/Br$_2$.[14] These methods greatly rely either on the use of heavy and toxic transition metals, or on corrosive halogen and stronger oxidants. Use of these stoichiometric reagents, oxidants and in turn generation of a large amount of heavy metal waste is the real drawback of these methods. Most of these thiocyanation methods were focused on limited substrates, mostly on electron rich indoles and closely related *N*-bearing heterocycles which are of high reactivity. Some of these methods are also accompanied by low regio- and chemo-selectivity. In the recent years, efforts have been made to improvise these classic protocols using specialized reagents. Some of these methods are thiocyanation of aryl organometallic compounds,[15] copper promoted thiocyanation of aryl iodides,[16] direct cyanation of organosulfur compounds[17] thiocyanation of arylboronic acids.[18] However, these methods are not devoid of the use of transition metals or harsh reaction conditions and they generate metal waste in the process. Efforts have also been focused on the metal free and visible light promoted thiocyanation in an elegant way.[8g,19] However, most of the protocols of thiocyanation available in the literature are executed on indoles, imidazoheterocycles and nitrogen containing activated heterocycles.[8a–g,12,19] Also, thiocyanation of aromatic amines and nitrogen heterocycles are reported to be facile. On the other hand, interestingly thiocyanation of phenols are less explored[20] and not studied extensively possibly due to its intrinsic electronic nature. Practical use of

---

* Corresponding author.
E-mail address: rgb@iiserpune.ac.in (R.G. Bhat).

http://dx.doi.org/10.1016/j.tetlet.2016.12.043
0040-4039/

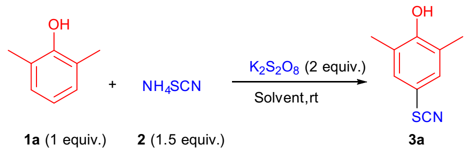
some of these available methods are seriously limited due to the use of toxic $Pb(SCN)_2$, molecular halogen, and formation of side products. Thiocyanation of phenols are not facile especially with electron withdrawing groups and have limited substrate scope. Practical, efficient and highly selective transition metal free transformations are gaining great importance for the last few years.[21] Synthetic organic chemists have been focusing on the approaches that are transition metal free in nature and they are increasingly becoming popular. Hence, efforts are being made for the transition metal free direct C-H functionalization of organic molecules. Phenol and heterocycle scaffolds are core to many bioactive molecules and pharmaceuticals. In this regard, development of transition metal free, more efficient and practical protocol for the direct thiocyanation of diverse phenol, aniline and heterocycle derivatives is highly desirable. Herein, we report novel, practical and direct transition metal free regioselective thiocyanation of phenols, aromatic amines and heterocycles with inexpensive NH_4SCN under mild conditions. This method has several advantages such as broad substrate scope and transition metal free reaction condition.

Results and discussions

At the outset of our investigation, we selected 2,6-dimethyl phenol **1a** and ammonium thiocyanate **2** as model substrates. In order to optimize the reaction conditions different oxidants, solvents, and conditions were explored. In presence of 2 equiv. of oxone in DCE at room temperature, reaction afforded trace amount of the expected product. Several solvents such as CH_3CN, THF, DCM were screened; however, reaction did not afford the expected product. Later, the reaction of **1a** and **2** in presence of $K_2S_2O_8$ in acetic acid at room temperature afforded the thiocyanated product **3a** in 70% yield (entry 4, Table 1).

Reaction proceeded in acetonitrile affording **3a** in 85% yield. Gratifyingly, when solvent DCM was used, the reaction proceeded smoothly by affording **3a** in excellent yield (95%) in 4 h at room temperature (see Table 1).

Table 1
Optimization of the reaction conditions.[a]



Entry	Oxidant	S Solvent	Time (h)	Yield[b] (%)
1	Oxone	DCM	12	Trace
2	TBHP	DCM	12	NR
3	O_2	DCM	12	NR
4	$K_2S_2O_8$	Acetic acid	12	70
5	$K_2S_2O_8$	Acetonitrile	12	85
6	**$K_2S_2O_8$**	**DCM**	**4**	**95**
7	$K_2S_2O_8$	DCE	4	93
8	$K_2S_2O_8$	THF	12	50
9	$K_2S_2O_8$	Water	6	68
10	$K_2S_2O_8$	Methanol	12	73
11	$K_2S_2O_8$	1,4-dioxane	12	60
12	$K_2S_2O_8$	DMF	12	Trace
13	$(NH_4)_2S_2O_8$	DCM	4	94
14	$Na_2S_2O_8$	DCM	4	93
15	No Reagent	DCM	12	NR
15	No Reagent	DCM	12	NR

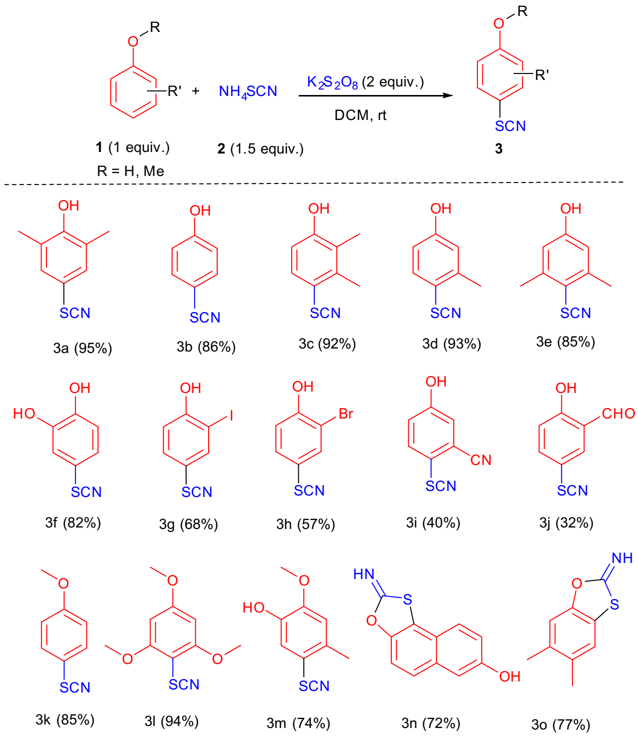
[a] Reaction conditions: **1a** (0.1 g), **2** (1.5 equiv), Oxidant (2 equiv, 1.64 mmol), solvent (2 mL), rt (24 °C), 4 h.

[b] Isolated yield.

Notably, the reaction also proceeded in water yielding **3a** in 68%. DCM was found to be the best solvent after screening the reaction in few other solvents. Based on further investigation, we observed that both $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ were effective for the direct thiocyanation of the **1a**. Further studies revealed that 2 equivalents of $K_2S_2O_8$ were crucial for the transformation and for the higher yield. However, we observed the incomplete conversion, when the amount of $K_2S_2O_8$ was reduced to 1–1.5 equivalents. Importantly, reaction did not work in the absence of oxidant $K_2S_2O_8$ (entry 15, Table 1). The oxidants such as molecular oxygen and TBHP did not facilitate the reaction. With the optimized reaction conditions in hand, to generalize the methodology, the substrate scope of this metal free direct thiocyanation was investigated (Table 2).

To our delight, various substrates underwent a facile direct and regioselective thiocyanation under optimized reaction conditions by affording the desired products in good to excellent yields.[22] Various phenol and anisole derivatives with electron donating and withdrawing groups reacted efficiently under the optimized reaction conditions to afford the corresponding desired products (entry **3a–3m,** Table 2). It is noteworthy that direct thiocyanation exclusively occurred at the *para* position. The reaction found to be facile, monoselective and did not form any disubstituted products. Phenols bearing electron withdrawing groups such as iodo, bromo, cyano, aldehyde resulted in relatively lower yields of the corresponding products (**3g–3j**). However, cyano and aldehyde functional groups tolerated the reaction conditions. While the *o*-nitrophenol did not react under the optimized reaction condition. The thiocyanate functional group was confirmed by the characteristic IR absorption peak (~2160 cm^{-1}) and ^{13}C NMR data. We did not observe the formation of any isothiocyanates. Reactions of

Table 2
Direct regioselective thiocyanation of phenol derivatives.[a]



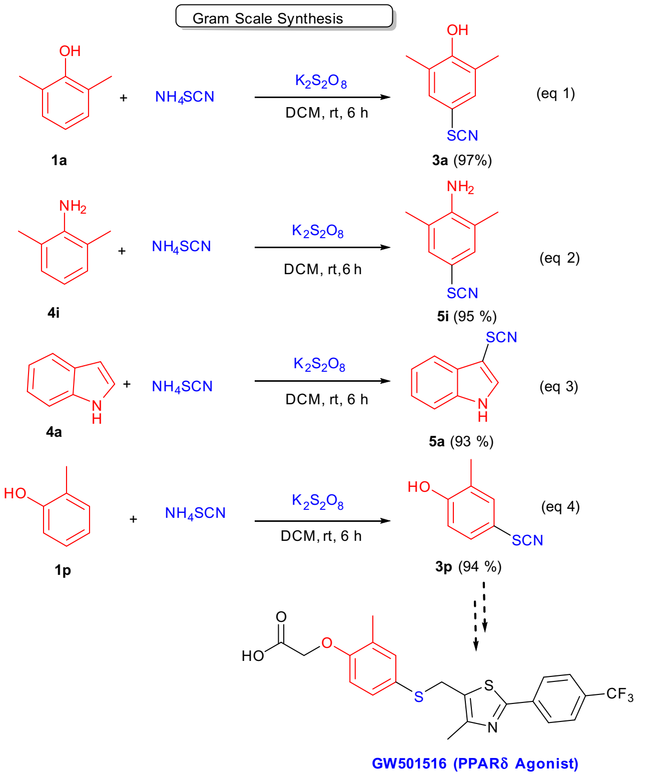
[a] Reaction conditions: Substituted phenols and Anisoles (0.1 mg). NH_4SCN (1.5 equiv), DCM, (2 mL), reaction time (4 h), Isolated yields after column chromatography given in brackets. rt (24 °C).

naphthalene derivative (**1n**) and 3,4-dimethyl phenol (**1o**) under the reaction conditions resulted in the corresponding stable oxathioimines (**3n**, **3o**).

Encouraged by the success, we turned our attention towards the relatively more reactive anilines and heterocycles. Different indole derivatives (**4a–4g**) under the optimized conditions underwent direct C-3 thiocyanation easily in excellent yields (**5a–5g**, Table 3). Indoles bearing —CN, —NO_2, —Br groups reacted regioselectively to afford the corresponding thiocyanted products (**5c–5e**) in good to excellent yields. Notably, 2,2′-bithiophene (**4h**) reacted with ease to afford the C-2 mono thiocyanated product **5h** in excellent yield. Later, we explored the reactivity of various aniline derivatives. All the aniline derivatives under the reaction conditions afforded thiocyanted products (**5i–5n**) in good to excellent yields.

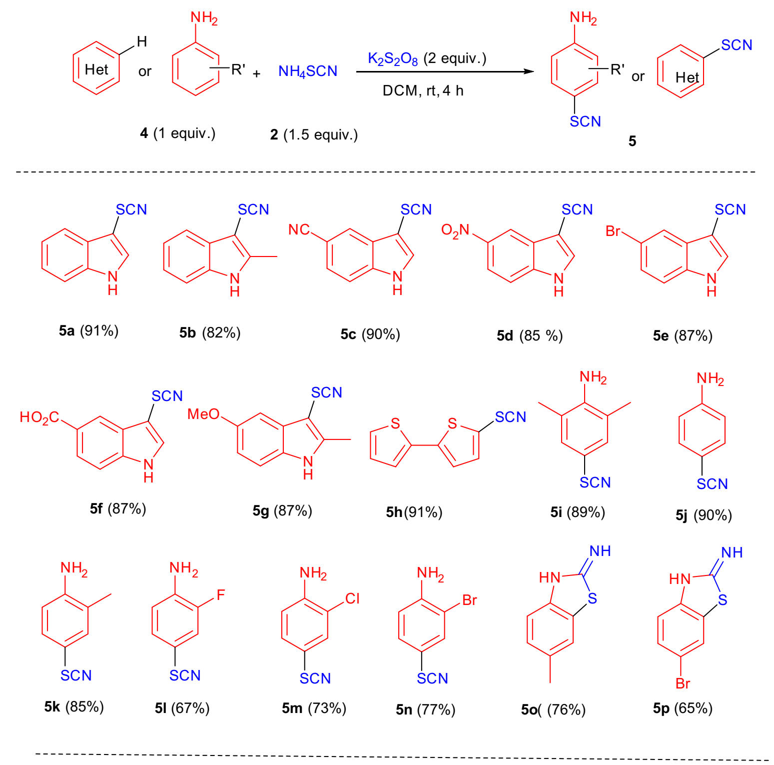
It is very important to note that direct thiocyanation was highly regioselective and occurred at *para* position. Substrates bearing electron withdrawing groups afforded the thiocyanated products in excellent yields. However, *para* substituted anilines resulted in the formation of the corresponding stable azathioimines (**5o, 5p**) via *ortho* thiocyanation.

In order to make this approach more practical and for the future development, we extended this method on gram scale (Scheme 1). 2,6-Dimethyl phenol **1a**, 2,6-dimethyl aniline **4i** and indole **4a** afforded the corresponding thiocyanated products (**3a, 5i, 5a**, Eqs. (1)–(3)) in excellent yields. GW501516 is a well known, most potent and selective peroxisome proliferator-activated receptor δ (PPARδ) agonist. Compound **3p** (Scheme 1), precursor of GW501516 was earlier synthesized using NaSCN and molecular bromine.[2] Using our protocol we synthesized compound **3p** under optimized reaction condition on a 3g scale in excellent yield (94%, Eq. (4)). Easy, practical and metal free reaction conditions demon-



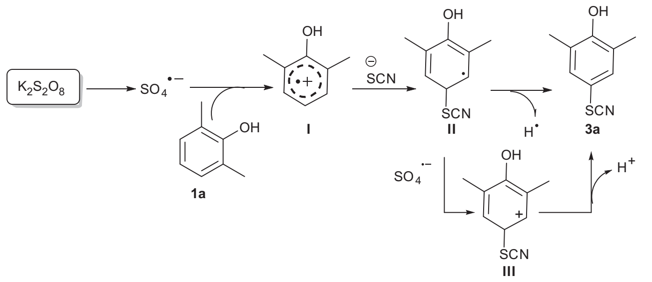
Scheme 1. Thiocyanation on a gram scale. (Reaction conditions: Phenol, Aniline and Indole (2 g), $K_2S_2O_8$ (2 equiv), DCM (20 mL), rt (24 °C), time (6 h), 2-methyl phenol, **1p** (3 g, 30 mL).)

Table 3
Direct and regioselective thiocyanation of anilines and heterocycles.[a]



---

[a] Reaction conditions: Substituted Aromatic amines and Heterocycles (0.1 g). NH_4SCN (1.5 equiv), DCM, (2 mL), reaction time (4 h), rt (24 °C), Isolated yields after column chromatography given in brackets.



Scheme 2. Proposed mechanism for the direct thiocyanation.

strated the practical utility of this method for the direct thiocyanation.

In order to gain further insight into the mechanism, we treated the reaction mixture with the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The thiocyanation reaction did not proceed even after prolonged reaction time and this indicated that most likely free radical pathway might have been involved during the course of the reaction. $K_2S_2O_8$ is known to generate a strong, short-lived oxidant-sulphate radical anion ($SO_4^{\bullet-}$) easily. The sulphate radical anion ($E^o = 2.6$ V) is known to generate radical cation on interaction with the low ionization potential aromatics.[23]

In order to investigate further the formation of a radical cation intermediate, we carried out UV–Vis spectroscopy studies. We observed an intense UV absorption band in the visible region between 400 and 500 nm during the reaction of phenol **1a** with $K_2S_2O_8$ at rt (see supporting Information). This study strongly favours the formation of radical cation intermediate during the reaction and is in accordance with the previous literature findings.[24]

Based on these investigations and previous literature, the plausible mechanism is proposed (Scheme 2). Potassium persulphate would decompose to generate very strong oxidant sulphate radical anion ($SO_4^{\bullet-}$), which in turn oxidizes the aromatic compound to form radical cation intermediate **I**. Simultaneous nucleophilic addition of thiocyanate anion to the cation intermediate would lead to the formation of radical intermediate **II**. Ultimately the loss of hydrogen radical from **II** would afford the desired compound **3a**. Alternatively, further oxidation of the intermediate **II** will lead to the formation of cation intermediate **III**. Finally, the elimination of H$^+$ from this intermediate would afford the desired product **3a**.

Conclusions

In conclusion, we have demonstrated the transition-metal-free regioselective and monoselective direct thiocyantion of phenols, anilines and other aromatics under mild conditions. The use of commercially available and inexpensive $K_2S_2O_8$ has been explored for the thiocyantion in an efficient manner. Most importantly, this protocol proved to be scalable on a multi gram quantity. The desired products were obtained in good to excellent yields and a wide range of functional groups were tolerated. Initial understandings suggested that reaction proceeded via radical cation intermediate. This protocol presents a new and viable path to access thiocyanated aromatics and precursors of bioactive molecules.

Acknowledgments

T. B. M. and T. M. K thank CSIR, New Delhi, India for the fellowship. Financial support from Indian Institute of Science Education and Research (IISER), Pune, India is gratefully acknowledged by the authors to carry out this research work.

A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.12.043.

References

1. (a) Guy RG. In: Patai S, ed. *The Chemistry Cyanates and their Thioderivatives, Part 2*. New York: John Wiley and Sons; 1977:819 [chapter 18];
   (b) Owens RG. In: Torgeson DC, ed. *In Fungicide: An Advanced Treatise*. New York: Academic Press; 1967:147 [chapter 5];
   (c) Houmam A, Hamed EM, Still IWJ. *J Am Chem Soc*. 2003;125:7258;
   (d) Mackinnon DL, Farrell AP. *Environ Toxicol Chem*. 1992;11:1541.
2. Wei ZL, Kozikowski AP. *J Org Chem*. 2003;68:9116.
3. Verkruijsse HD, Brandsma L. *Synthesis*. 1991;818.
4. (a) Kitagawa I, Ueda Y, Kawasaki T, Mosettig E. *J Org Chem*. 1963;46:3335;
   (b) Toste FD, LaRaronde F, Still IWJ. *Tetrahedron Lett*. 1995;36:2949.
5. (a) Riemschneider R, Wojahn F, Orlick G. *J Am Chem Soc*. 1951;73:5905;
   (b) Riemschneider R. *J Am Chem Soc*. 1956;78:844.
6. Prabhu KR, Ramesha AR, Chandrasekaran S. *J Org Chem*. 1995;60:7142.
7. (a) Wood JL. *Organic Reactions*, Vol 3. New York: Wiley; 1967. 240;
   (b) Kelly TR, Kim MH, Certis ADM. *J Org Chem*. 1993;58:5855.
8. (a) Grant MS, Snyder HR. *J Am Chem Soc*. 1960;82:2742;
   (b) Nair V, Nair LG. *Tetrahedron Lett*. 1998;39:4585;
   (c) Nair V, George TG, Nair LG, Panicker SB. *Tetrahedron Lett*. 1999;40:1195;
   (d) Yadav JS, Reddy BVS, Murali Krishna BB. *Synthesis*. 2008;2008:3779;
   (e) Toste FD, De Stefano V, Still IWJ. *Synth Commun*. 1995;25:1277;
   (f) Nikoofar K. *Chem Sci Trans*. 2013;2:691;
   (g) Fan W, Yang Q, Xu F, Li P. *J Org Chem*. 2014;79:10588;
   (h) Zhu D, Chang D, Shi L. *Chem Commun*. 2015;51:7180;
   (i) Khazaei A, Zolfigol MA, Mokhlesi M, Pirveysian M. *Can J Chem*. 2012;90:427;
   (j) Wu G, Liu Q, Shen Y, Wu W, Wu L. *Tetrahedron Lett*. 2005;46:5831.
9. Uemura S, Onoe A, Okazaki H, Okano M. *Bull Chem Soc Jpn*. 1975;48:619.
10. Taylor EC, Kienzle F. *Synthesis*. 1972;38.
11. Bacon RGR, Guy RG. *J Chem Soc*. 1960;318.
12. Pan X-Q, Lei M-Y, Zou J-P, Zhang W. *Tetrahedron Lett*. 2009;50:347.
13. Kaufmann HP, Kulchler KA. *Eur J Inorg Chem*. 1934;67:944.
14. Kaufmann HP, Oehring W. *Eur J Inorg Chem*. 1926;59:187.
15. Takagi K, Takachi H, Sasaki K. *J Org Chem*. 1995;60:6552.
16. Yang YF, Zhou Y, Wang JR, Liu L, Guo QX. *Chin Chem Lett*. 2006;17:1283.
17. Still IWJ, Watson IDJ. *Synth Commun*. 2001;31:1355.
18. Sun N, Che L, Mo W, Hu B, Shen Z, Hu X. *Org Biomol Chem*. 2015;13:691.
19. Mitra S, Ghosh M, Mishra S, Hajra A. *J Org Chem*. 2015;80:8275.
20. (a) Kaufmann HP, Oehring W. *Ber*. 1926;59B:187;
    (b) Likhosherstov MV, Petrov AA. *J Gen Chem (USSR)*. 1933;3:183;
    (c) Kaufmann HP, Kulchler KA. *Ber*. 1934;67B:944;
    (d) Kita Y, Takeda Y, Okuno T, et al. *Chem Pharm Bull*. 1887;1997:45;
    (e) Prakash O, Kaur H, Pundeer R, Dhillon RS, Singh SP. *Synth Commun*. 2003;33:4037.
21. (a) Wang H, Guo L-N, Duan X-H. *Org Lett*. 2013;15:5254;
    (b) Lin J-P, Zhang F-H, Long Y-Q. *Org Lett*. 2014;16:2822;
    (c) Siddaraju Y, Lamani M, Prabhu KR. *J Org Chem*. 2014;79:3856;
    (d) Shichao L, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336;
    (e) Yang H, Duan X-H, Zhao J-F, Guo L-N. *Org Lett*. 1998;2015:17;
    (f) Gesu A, Pozzoli C, Torre E, Aprile S, Pirali T. *Org Lett*. 1992;2016:18;
    (g) Yang D, Yan K, Wei W, et al. *J Org Chem*. 2015;80:11073.
22. **General Procedure for the synthesis of Thiocyanatophenols, Thiocyanatoindoles and Thiocyanatoanilines:** In an oven dried round bottom flask containing a mixture of 2,6-dimethyl phenol **1a** (100 mg, 0.82 mmol), ammonium thiocyanate **2** (94 mg, 1.23 mmol) and potassium persulphate (443 mg, 1.64 mmol) in DCM (2 mL) were stirred for 4 h. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered through sintered funnel containing silica and sodium sulphate. The Filtrate was concentrated under reduced pressure to afford the crude product **3a**. This was purified by column chromatography (EtOAc:Hexane) to furnish the pure compound **3a** as a white solid (139 mg, 95% yield). Similar procedure was used for the thiocyanation of anisoles, anilines and heterocycles.
23. (a) Minisci F, Citterio A. *Acc Chem Res*. 1983;16:27;
    (b) Hey DH, Jones GH, Perkins MJ. *J C S Perkin I*. 1972;118.
24. (a) Kita Y, Tohma H, Hatanaka K, et al. *J Am Chem Soc*. 1994;116:3684;
    (b) Sankararaman S, Haney WA, Kochi JK. *J Am Chem Soc*. 1987;109:7824.

Tetrahedron Letters 58 (2017) 2822–2825

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Oxidative decarboxylation of arylacetic acids in water: One-pot transition-metal-free synthesis of aldehydes and ketones

Trimbak B. Mete, Tushar M. Khopade, Ramakrishna G. Bhat *

Department of Chemistry, Indian Institute of Science Education & Research (IISER), Pune 411008, Maharashtra, India

ARTICLE INFO

Article history:
Received 13 May 2017
Accepted 4 June 2017
Available online 14 June 2017

Keywords:
Transition-metal-free
Water
Persulfate
One-pot synthesis
Decarboxylation

ABSTRACT

One-pot transition-metal-free synthesis of aromatic aldehydes and ketones via oxidative decarboxylation of arylacetic acids in water is developed. Protocol relies on the direct decarboxylation of sp^3-hybridized carbon in water without any over oxidation into carboxylic acids with minimal waste. Reaction mechanism is investigated and application of this protocol is demonstrated on a gram scale.

Introduction

Aldehydes and ketones are very important class of compounds and they have been used extensively in wide areas of chemical synthesis.[1] Evidently, the effort towards the quick and short synthesis of aldehydes and ketones always has been desirable. Traditional synthesis of aldehydes and ketones rely on activating the carboxylic acid into a Weinreb amide[2] or into an acyl halide[3] with subsequent nucleophilic attack with hydrides or organometallic species. One-step synthesis of ketones starting from carboxylic acids can be achieved using excess of organolithium reagents; however formation of tertiary alcohols is unavoidable.[4] These harsh conditions can lead to the erosion of stereochemical purity thus leading to partial racemization.[5] Nevertheless, efforts have been made to improvise the existing methods. Cyanocuprates have been explored to convert the carboxylic acids directly into ketones.[6] Quick and efficient cleavage of carbon-carbon bond is one of the most important challenges in organic synthesis.[7] The selective cleavage of C—C σ bond has greatly attracted the attention of researchers in the recent times due to its inert nature. Undoubtedly, development of an efficient protocol for the selective cleavage of C—C σ bond is a great challenge and still much to be explored. Transition metal catalyzed decarboxylation via C—C bond cleavage has been gaining a great importance due its significant role in decaboxylative reactions.[8] Elegant and valuable protocols are developed in this area for making carbon-carbon and carbon-heteroatom bonds starting from carboxylic acids and by cleaving the C—C bond to carboxylate group.[9] Also, decarboxylation reaction procedures are usually done at neutral reaction conditions and importantly carbon dioxide liberated as a sole non-toxic by-product. Transition metal catalyzed decarboxylation at sp^2-hybridized carbon is mostly explored in the literature and more strikingly, decarboxylation at sp^3-hybridized carbon to introduce a functional group is relatively rare and challenging.[10] Transition metal catalyzed synthesis of aldehydes, ketones and amides via oxidative decarboxylation has been explored very recently.[11,12] Reactivity of cuprous salt was explored for the novel synthesis of aldehydes from methyl ketones in presence of oxygen.[13] Recently, Song and co-workers demonstrated the ability of cupric salts for the aerobic oxidative decarboxylation at sp^3-hybridized carbon to afford aldehydes, ketones[11] and amides[12] at high temperatures. Decarboxylative non-aerobic oxidation of phenyl acetic acid to benzaldehyde was described by using cupric salts at high temperature and pressure thus mimicking the geochemically relevant conditions.[14] All of these protocols rely on transition metal, viz. copper for catalyzing the transformation.[15] However, there are only countable protocols for the oxidative decarboxylation of aryl carboxylic acids under transition-metal-free conditions. Earlier, decarboxylation of carboxylic acids to aldehydes and ketones were achieved by using tetrabutylammonium periodate in 1,4-dioxane under refluxing condition, combination of iron(III)/manganese(III) tetraphenylprorphyrins and tetrabutylammonium periodate, and (diacetoxyiodo)benzene/NaN_3.[16,17] Thus development of more easier, practical and non-hazardous protocol for the synthesis of aldehydes and ketones via oxidative decarboxylation under

---

* Corresponding author.
E-mail address: rgb@iiserpune.ac.in (R.G. Bhat).

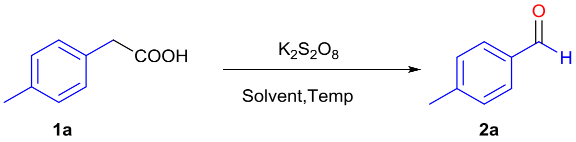
http://dx.doi.org/10.1016/j.tetlet.2017.06.013

transition-metal-free conditions is highly desirable. There are ambiguities in defining a true 'green method'. However, some of the most accepted guiding principles such as minimal waste, higher mass productivity lower E-factor, non-toxicity etc define the greener methods. Practical, efficient and highly selective transition-metal-free transformations using environmentally benign, less expensive and readily available reagents are gaining a great importance for the last few years.[18] As a part of our ongoing efforts to develop transition metal free protocols,[19] we herein, report an oxidative decarboxylative strategy for the direct and clean synthesis of aldehydes and ketones without over oxidation into carboxylic acids in water with a minimal waste and lower E-factor. This simple protocol uses potassium persulfate as a reagent and makes the novel use of it for the synthesis of aldehydes and ketones starting from arylacetic acids.

We commenced our initial work with 4-methyl phenylacetic acid **1a** with $K_2S_2O_8$ as a model reaction (Table 1). Attempted reaction of **1a** with $K_2S_2O_8$ (2 equiv.) in CH_3CN/H_2O (1:1) at room temperature (both in air and inert condition) did not work even after prolonged reaction condition (entry 1, Table 1). Interestingly, when the reaction was carried at elevated temperature (80 °C), to our delight, the desired product, 4-methylbenzaldehyde **2a** was formed in 75% isolated yield (Table 1, entry 2) in 12 h. With this result in hand, further the reaction was screened in different solvent conditions. However, the reaction was sluggish in CH_3CN and DCE (entries 4, 6) and afforded only trace amount of desired product **2a**. However, the reaction in DCE/H_2O at 80 °C afforded the desired product in 60% yield (entry 7). Interestingly, the model reaction worked efficiently only in water at 80 °C affording the desired product 4-methyl benzaldehyde **2a** in 75% yield (entry 8). Gratifyingly, with the elevated temperature (90 °C) under aerial condition reaction afforded the compound **2a** in excellent yield of 85% (entry 9). PIDA, PIFA and Oxone were found to be ineffective reagents for the desired transformation (entries 10–12). Attempts to lower the reaction temperature resulted in lower yield with incomplete conversion of the starting material (entry 13). Reactions under oxygen or open air atmosphere did not change the course of the reaction and also did not have any significant effect on yield or reaction time (entries 9, 14). Reaction did not work in the absence of potassium persulfate (entry 15). After extensive screening of solvents and temperature optimum reaction condition was emerged as 4-methylphenyl acetic acid **1a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 90 °C in water under aerial atmosphere (entry 9, Table 1) in 12 h. It is also important to note that persulfates are very popular for their ability to oxidize variety of contaminants in ground water via 'in situ chemical oxidation' (ISCO).[20] Persulfates are known to be benign, eco-friendly or green and low cost reagent.[21]

Encouraged by the initial success and with an optimized reaction condition in hand; we explored the substrate scope of the method. Under optimal reaction conditions arylacetic acids (**1a**–**1o**) possessing the electron-donating group as well as electron withdrawing groups reacted smoothly by affording the corresponding aldehydes (**2a**–**2o**) in moderate to good yields (Scheme 1). 1-Naphthylacetic acid **1p** reacted smoothly and gave the corresponding naphthaldehyde **2p** in 80% yield. Similarly, the heteroaromatic acid such as 2-thienyl acetic acid **1q** under reaction conditions afforded the 2-thienyl carboxylaldehyde (**2q**). α-Substituted phenyl acetic acids (**1r**–**1w**) under optimal reaction conditions afforded the corresponding ketones (**2r**–**2w**) in excellent yields (86–92%). The anti-inflammatory drug, ibuprofen **1u** afforded the corresponding ketone[22] **2u** in excellent yield as well. Interestingly, the amino acid phenyl glycine **1x** afforded benzaldehyde **2d** instead of anticipated amide. Probably, imine might have formed during the course of reaction, which upon hydrolysis resulted in **2d**. The position of the substituents on the ring had no significant and noticeable effect on reaction rate and yields. Functional group such as hydroxyl, chloro, bromo, methoxy and nitro were well tolerated. However, unfortunately, attempted reac-

Table 1
Optimization of the reaction conditions.[a]



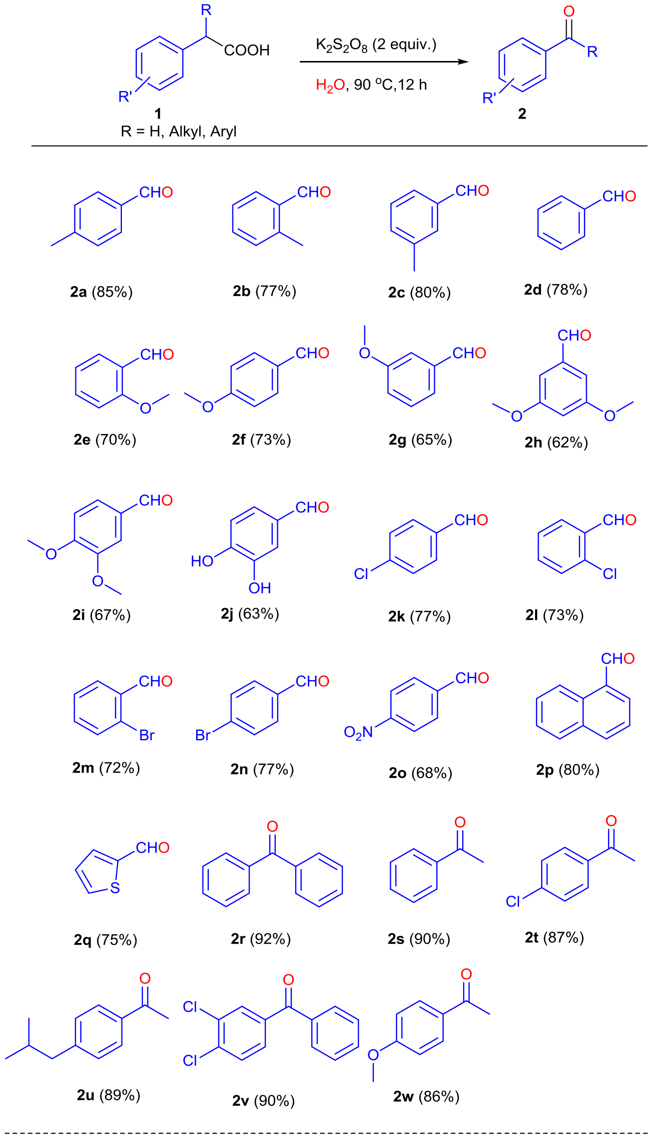
Entry	Reagent	Solvent	Temp (°C)	Atm	Yield[b] (%)
1	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	rt	Air	NR
2	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	80	Air	75
3	$K_2S_2O_8$	CH_3CN	Reflux	Air	Trace
4	$K_2S_2O_8$	CH_3CN	Reflux	O_2	12
5	$K_2S_2O_8$	MeOH	Reflux	Air	NR
6	$K_2S_2O_8$	DCE	90	O_2	Trace
7	$K_2S_2O_8$	DCE/ H_2O (1:1)	80	Air	60
8	$K_2S_2O_8$	H_2O	80	Air	75
9	$K_2S_2O_8$	**H_2O**	**90**	**Air**	**85**
10	PIDA	H_2O	90[c]	Air	27
11	PIFA	H_2O	90[c]	Air	21
12	Oxone	H_2O	90[c]	Air	15
13	$K_2S_2O_8$	H_2O	50	Air	20
14	$K_2S_2O_8$	H_2O	90	O_2	83
15	–	H_2O	90	Air	–

Bold values correspond to the optimum reaction conditions.

[a] Reaction conditions: 4-methylphenyl acetic acid **1a** (1 equiv.), potassium persulfate (2 equiv.), solvent (2 mL) under corresponding atmosphere for 12 h.

[b] Isolated yield after purification by column chromatography.

[c] Reactions did not work at rt.

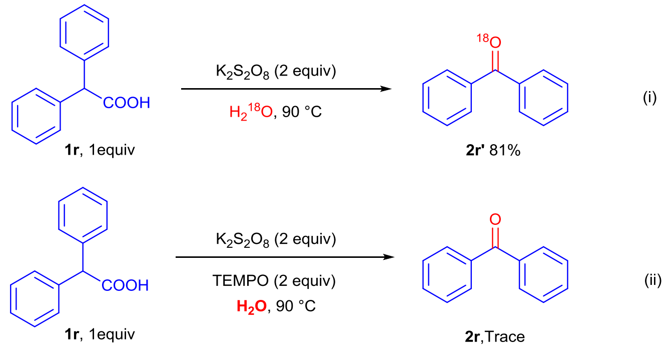


Scheme 1. Oxidative decarboxylation of arylacetic acids to aldehydes and ketones. [a]Reaction conditions: arylacetic acid 1 (1 equiv.), potassium persulfate (2 equiv.), water (2 mL) open atmosphere; reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography.

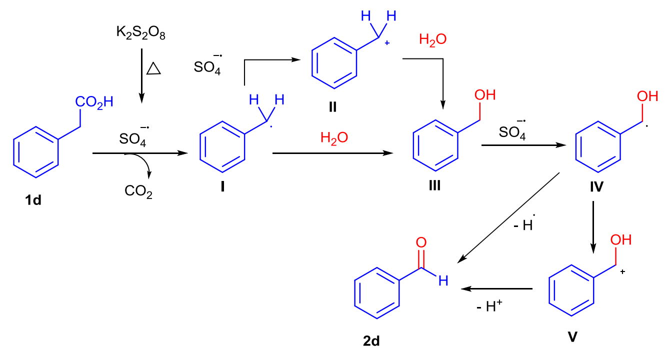
tions of aliphatic acids such as 3-butenoic acid, *tert*-butyl acetic acid and valeric acid did not afford the desired products.

To make the protocol more general and for the wider applicability we demonstrated the synthesis of benzaldehyde **2d** (83%) and benzophenone **2r** (93%) on a gram scale starting from the corresponding arylacetic acids **1d** and **1r** respectively under optimum conditions. During the optimization we observed that reaction worked efficiently in water under atmosphere of air as well as oxygen. Effective minimization of reagents in this protocol led to a minimal waste (free from halogen and transition metal), thus producing only 3.5 g of waste for every 1 g of the product formed. It is also gratifying to note that this one pot reaction with E (environmental) factor of 3.49[23] and mass productivity of 23% (mass intensity 4.5)[23] satisfies the defined metrics[24] for the cleaner and greener chemical processes.

In order to investigate and elucidate the reaction mechanism few control experiments were carried out. Compound **1a** when treated with $K_2S_2O_8$ (2 equiv.) in water under inert conditions afforded the corresponding aldehyde **2a** in good yield (80%). This experiment indicates that oxygen did not have any role in the reaction mechanism. Interestingly, reaction did not work in the absence of water. To validate the role of water in the reaction, compound **1r** was treated with $K_2S_2O_8$ (2 equiv.) in labeled water ($H_2^{18}O$, 97%) under inert condition for 12 h. To our delight we isolated the corresponding **2r**′ in excellent yield (81%, eq. i, Scheme 2). Presence of ^{18}O was confirmed by the HRMS and GC-mass spectrometry (^{18}O content 96.3%, see ESI). It is very significant to note that this protocol gives a direct access to prepare ^{18}O-labeled aldehydes and ketones quantitatively without resorting to an exchange experiment. Later, to gain further insight into the mechanism, diphenyl acetic acid **1r** was treated with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard optimal conditions. The result showed that reaction did not proceed even after prolonged reaction time indicating that TEMPO inhibited the radical pathway (eq. ii, Scheme 2).



Scheme 2. Control experiments for understanding the mechanism.



Scheme 3. Plausible mechanism for the formation of aldehyde and ketones.

Based on our investigations and previous literature[25] we propose that sulfate radical anion ($SO_4^{\cdot -}$) (produced by the decomposition of potassium persulfate) upon reaction with phenyl acetic acid **1d** generates benzyl radical **I** by extrusion of carbon dioxide. $SO_4^{\cdot -}$ further oxidizes the benzyl radical to the corresponding benzyl carbocation **II** via one electron oxidation. This reactive species reacts with water to form the corresponding benzyl alcohol **III**. Persulfate further oxidizes benzyl alcohol to the corresponding intermediates **IV** and **V**. Ultimately, the loss of proton from **V** would afford the desired product, benzaldehyde **2d**. Alternatively, intermediate **IV** would directly afford benzaldehyde **2d** by the loss of hydrogen radical (Scheme 3).

Conclusions

In conclusion, we have demonstrated a one-pot protocol for the direct and clean transformation of arylacetic acids to aldehydes and ketones in water with minimal waste. Protocol employs environmentally friendly and less expensive $K_2S_2O_8$ as reagent, and commercially available arylacetic acids without any over oxidation. Method also demonstrated the direct access to ^{18}O-labeled aldehydes and ketones without relying on exchange experiment. Experimental conditions are simple and above all reaction is carried out only in water and it has been demonstrated on a gram scale for wider application.

Acknowledgments

R.G.B. thanks DST-SERB (EMR/2015/000909), Govt. of India for the generous research grant. Authors also thank Indian Institute of Science Education and Research (IISER), Pune for the financial support. T.B.M. and T.M.K thank CSIR, New Delhi, India for the fellowship.

A. Supplementary data

Supplementary data (experimental details and ^1H, ^{13}C NMR spectra of compounds **2a–2w**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.013.

References

1. (a) Larock RC. *Comprehensive Organic Transformations*. New York: Wiley-VCH; 1989;
   (b) Otera J, ed. *Modern Carbonyl Chemistry*. Weinheim: Wiley-VCH; 2000;
   (c) Wilkinson MC. *Org Lett*. 2011;13:2232–2235;
   (d) Nicholson JW, Wilson AD. *J Chem Educ*. 2004;81:1362–1366;
   (e) Park A, Park K, Kim Y, Lee S. *Org Lett*. 2011;13:944–947.
2. (a) Qu B, Collum DB. *J Org Chem*. 2006;71:7117–7119;
   (b) Nahm S, Weinreb SM. *Tetrahedron Lett*. 1981;22:3815–3818;
   (c) Kanagani CO, Kelley DE, Day BW. *Tetrahedron Lett*. 2006;47:6289–6292.
3. (a) Posner GH, Whitten CE, McFarland PE. *J Am Chem Soc*. 1972;94:5106–5108;
   (b) Dieter RK. *Tetrahedron Lett*. 1999;55:4177–4236;
   (c) Wang X, Zhang L, Sun X, Xu Y, Krishnamurthy D, Senanayake CH. *Org Lett*. 2005;7:5593–5595;
   (d) Ryu I, Ikebe M, Sonoda N, Yamato S, Yamamura G, Komatsu M. *Tetrahedron Lett*. 2002;43:1257–1259.
4. (a) Gilman H, van Ess PR. *J Am Chem Soc*. 1933;55:1258–1261;
   (b) Tegner C. *Acta Chem Scand*. 1952;6:782–790;
   (c) Jorgenson MJ. *Org Synth*. 1973;5:775–779;
   (d) Lubell WD, Rapoport H. *J Am Chem Soc*. 1988;110:7447–7455;
   (e) Alonso F, Lorenzo E, Yus M. *J Org Chem*. 1996;61:6058–6059.
5. Mislow K, Brenner J. *J Am Chem Soc*. 1953;75:2318–2322.
6. Genna DT, Posner GH. *Org Lett*. 2011;13:5358–5361.
7. (a) Crabtree RH. *Chem Rev*. 1985;85:245–269;
   (b) Jun C-H. *Chem Soc Rev*. 2004;33:610–618;
   (c) Tobisu M, Chatani N. *Chem Soc Rev*. 2008;37:300–307;
   (d) Masarwa A, Marek I. *Chem Eur J*. 2010;16:9712–9721;
   (e) Murakami M, Matsuda T. *Chem Commun*. 2011;47:1100–1105.
8. (a) Song Q, Feng Q, Zhou M. *Org Lett*. 2013;15:5990–5993;
   (b) Mai S, Zhaoa Y, Song Q. *Org Biomol Chem*. 2016;14:8685–8690.
9. (a) Tanaka D, Romeril SP, Myers AG. *J Am Chem Soc*. 2005;127:10323–10333;
   (b) Myers AG, Tanaka D, Mannion MR. *J Am Chem Soc*. 2002;124:11250–11251;
   (c) Goossen LJ, Rodríguez N, Goossen K. *Angew Chem Int Ed*. 2008;47:3100–3120;
   (d) Goossen LJ, Rodríguez N, Melzer B, Linder C, Deng G, Levy LM. *J Am Chem Soc*. 2007;129:4824–4833;
   (e) Forgione P, Brochu M-C, St-Onge M, Thesen KH, Bailey MD, Bilodeau F. *J Am Chem Soc*. 2006;128:11350–11351;
   (f) Bilodeau F, Brochu M-C, Guimond N, Thesen KH, Forgione P. *J Org Chem*. 2010;75:1550–1560.
10. (a) Torregrosa RRP, Ariyarathna Y, Chattopadhyay K, Tunge JA. *J Am Chem Soc*. 2010;132:9280–9282;
    (b) Zhang C, Seidel D. *J Am Chem Soc*. 2010;132:1798–1799;
    (c) Shang R, Ji D-S, Chu L, Fu Y, Liu L. *Angew Chem Int Ed*. 2011;50:4470–4474;
    (d) Shang R, Yang Z-W, Wang Y, Zhang S-L, Liu L. *J Am Chem Soc*. 2010;132:14391–14393.
11. Feng Q, Song Q. *J Org Chem*. 2014;79:1867–1871.
12. Song Q, Feng Q, Yang K. *Org Lett*. 2014;16:624–627.
13. Zhang L, Bi X, Guan X, et al. *Angew Chem Int Ed*. 2013;52:11303–11307.
14. Yang Z, Hartnett HE, Shock EL, Gould IR. *J Org Chem*. 2015;80:12159–12165.
15. Even though it is assumed that salts of copper and nickel can be green and sustainable alternatives, a recent report suggests that they do possess significant toxicities: Egorova KS, Ananikov VP. *Angew Chem Int Ed*. 2016;55:12150–12162.
16. Tangestaninejad S, Mirkhani V. *J Chem Res*. 1998;820–821.
17. Telvekar VN, Sasane KA. *Synlett*. 2010;2778–2779.
18. (a) Wang H, Guo L-N, Wang S, Duan X-H. *Org Lett*. 2015;17:3054–3057;
    (b) Yuan M, Chen L, Wang J, et al. *Org Lett*. 2015;17:346–349;
    (c) Lu S, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336–9352;
    (d) Mi X, Wang C, Huang M, Wu Y, Wu Y. *J Org Chem*. 2015;80:148–155;
    (e) Wei W, Wen J, Yang D, et al. *J Org Chem*. 2014;79:4225–4230;
    (f) Jiang Q, Shenga W, Guo C. *Green Chem*. 2013;15:2175–2179;
    (g) Kim SM, Kim DW, Yang JW. *Org Lett*. 2014;16:2876–2879.
19. Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:415–418.
20. (a) Tsitonaki A, Petri B, Crimi M, Mosbaek H, Siegrist RL, Bjerg PL. *Environ Sci Technol*. 2010;40:55–91 (In Situ Chemical Oxidation of Contaminated Soil and Groundwater Using Persulfate);
    (b) Sra KS, Thomson NR, Barker JF. *Environ Sci Technol*. 2010;44:3098–3104;
    (c) Liu H, Bruton TA, Li W, et al. *Environ Sci Technol*. 2016;50:890–898.
21. Syed S. *Hydrometallurgy*. 2006;82:48–53.
22. Interestingly, this ketone is also a natural metabolite of Ibuprofen drug following the similar oxidative decarboxylation pathway during drug metabolism: Komuro M, Nagatsu Y, Higuchi T, Hirobe M. *Tetrahedron Lett*. 1992;33:4949–4952.
23. Calculation of E (environmental) factor, mass productivity and mass intensity of representative examples are given in Supporting information.
24. (a) Sheldon RA. *Chem Commun*. 2008;3352–3365;
    (b) Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*. New York: Oxford University Press; 1998. 30.
25. Tanner DD, Osman SA. *J Org Chem*. 1987;52:4689–4693.

Tetrahedron Letters 58 (2017) 4709–4712

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transition-metal-free synthesis of primary to tertiary carboxamides: A quick access to prodrug-pyrazinecarboxamide

Trimbak B. Mete, Ankit Singh, Ramakrishna G. Bhat *

Department of Chemistry, Indian Institute of Science Education & Research (IISER), Pune 411008, Maharashtra, India

ARTICLE INFO

Article history:
Received 13 September 2017
Revised 2 November 2017
Accepted 5 November 2017
Available online 6 November 2017

Keywords:
Transition-metal-free
Caboxamide
Carbamoylation
Potassium persulfate
Heteroaromatic

ABSTRACT

One-pot expedient and direct carbamoylation of heterocyclics is described. The transformation is realized via direct dehydrogenative aminocarbonylation of heterocyclic compounds under transition-metal-free conditions. This method is regioselective and the protocol is proved to be scalable on a gram scale. Further, the therapeutically useful antitubercular agent pyrazinecarboxamide is successfully synthesized by employing this protocol.

Introduction

Carboxamide is a very important and useful functional group and heterocyclic carboxamides are significant structural scaffolds in many materials, natural products and bioactive compounds.[1] They are also useful synthetic building blocks for many pharmaceuticals and agrochemicals.[2] Along with traditional or conventional condensation reactions of carboxylic acids/carboxylic acid derivatives and amines under harsher basic conditions or using coupling reagents, many alternative strategies have been developed for the synthesis of carboxamides in the recent years. Some of various strategies including cross-dehydrogenative coupling, amine dehydrogenation or oxidation reactions, transamidation reactions, aldehyde-amine coupling reactions, and C—N coupling reactions have been developed for carboxamide synthesis in recent years.[2] Alternatively, transition metal (Pd, Co, Ag, Ti) catalyzed protocols such as aminocarbonylation of aromatic and heteroaromatic halides, direct carbamoylation of pyridines, and hydration of nitriles have been developed in pursuit of achieving newer methods.[3] However, these methods rely on transition metal salts and some of these methods require the use of toxic and corrosive gases such as carbon monoxide and ammonia or alternatively ammonia equivalents such as aqueous ammonia, ammonium carbamate and other amine bases. All these methods require the use of transition metals and most of them need preactivated aryl/heteroaryl halides. The limitation of some of these methods is that they are confined to primary carboxamides only with limited scope on pyridines and found to be not suitable for the synthesis of secondary and tertiary carboxamides. Likewise, methods did not work on quinoline and other heteroaromatics. Although aminocarbonylation via direct activation of *N*-protected formamide is known[4] yet the transition-metal-free carbamoylation of heteroaromatics via direct activation of formamide and *N*, *N*-dimethylformamide has not been much successful till date. Some of the examples of direct aminocarbonylation suffer from lower yields and afford the mixture of aminocarbonylated and domintating α-amidoalkylated side products. Methods are also limited to fewer substrate scopes (mostly with pyridines and formamide) with lower chemoselectivity and moreover these have not been studied in a great detail.[5]

Practical and expedient transition-metal-free protocols are gaining great importance[6] and are promising alternatives to the traditional methods as the contamination due to the residual transition metals can be avoided at lower costs. Thus it is more desirable to develop sustainable transition-metal-free practical protocol for the direct access of primary to tertiary carboxamides of different heteroaromatics. We have shown considerable interest in developing transition-metal-free protocols[7] and our ongoing research activities prompted us to evaluate the method for the direct aminocarbonylation using formamide, *N*-methylformamide and *N*, *N*-dimethylformamide by functionalizing the C—H bond. Based on the earlier literature,[8] it is known that persulfate is an efficient oxidant and a very good radical initiator and it could be

---

* Corresponding author.
E-mail address: rgb@iiserpune.ac.in (R.G. Bhat).

https://doi.org/10.1016/j.tetlet.2017.11.006

explored for the homolytic cleavage of formamide. Interestingly, persulfates are known to be mild and benign and eco-friendly low cost reagents.[9]

As a part of our ongoing research programme on transition-metal-free protocols, we herein, report the direct aminocarbonylation of heteroaromatics via cross-dehydrogenative coupling approach. This simple and user friendly protocol for aminocarbonylation uses potassium persulfate and formamide/*N*-methylformamide (NMF)/DMF as reagents to access primary to tertiary carboxamides with high selectivity.

Result and discussion

We commenced our initial work with pyridine **1a** and formamide **2a** as model substrates (Table 1). The initial reaction of **1a** and formamide **2a** in presence of $K_2S_2O_8$ (2 equiv.) in DCE at room temperature (both in air and inert condition) did not work even after prolonged reaction condition (entry 1, Table 1). However, at 50 °C trace amount of product **3aa** formed (entry 2, Table 1). While, heating the reaction mixture at 70 °C afforded modest yield of the desired product **3aa** (entry 3, Table 1). Interestingly, when formamide **2a** was used as solvent as well as substrate the reaction proceeded smoothly at elevated temperature (70 °C), to afford the desired product **3aa** in 79% isolated yield (Table 1, entry 6) in 12 h.

While, solvents such as water, THF and acetonitrile were found to be not good solvents for the desired transformation. After screening several solvents and temperature conditions optimum reaction condition was emerged as pyridine **1a** (1 equiv.), $K_2S_2O_8$ (2 equiv.) at 70 °C and formamide (20 equiv, solvent as well as reagent) under aerial atmosphere (entry 6, Table 1) in 12 h. With this optimized result in hand, we explored the substrate scope of the method with different substrates and primary to tertiary amides.

Under optimal reaction conditions, substrates (**1a**–**1m**) possessing the electron-donating as well as electron withdrawing groups reacted smoothly with formamide **2a** to afford the corresponding carboxamides (**3aa**–**3ma**) in moderate to good yields (Table 2). Encouraged by this success we planned to explore the generality of the protocol by exploring various substrates with secondary and tertiary formamides. Under the standardized reaction conditions, substrates (**1a–b**, **1e–f**) reacted smoothly with the *N*-methyl formamide (NMF) **2b** to afford the corresponding secondary carboxamides (**3ab, 3bb, 3eb, 3fb**) in very good yields (see Table 2).

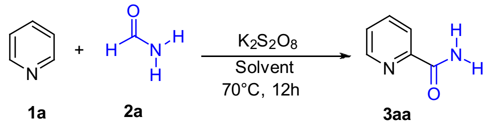
Further, the protocol was explored on quinoline and its derivative, and pyrazine (**1l**, **1m**, **1n**) with NMF **2b** under the reaction conditions to afford the secondary carboxamides (**3lb, 3mb, 3nb**) in very good yields (up to 85% yield). Further, the strength of the protocol was explored for the access of tertiary carboxamides using DMF. Earlier, in the literature it was observed that DMF is relatively unreactive towards the aminocarbonylation and known to give side products emanating from α-amidoalkylation as major products. Different substrates **1a, 1e–g, 1l–1m, 1o–p** (pyridine, quinoline, bipyridyl derivatives) were treated with the DMF **2c** under optimal reaction conditions to afford the corresponding tertiary carboxamides (**3ac, 3ec, 3fc, 3gc, 3lc, 3mc, 3oc, 3pc**) in moderate yields. It is very important to note that we did not observe any α-amidoalkylation side products. The position of the substituents on the ring had no significant and noticeable effect on the reaction rate and yields. Different functional group such as bromo, chloro, methoxy and cyano were well tolerated under the reaction conditions. Method proved to be regio- and chemoselective for the α-aminocarbonylation only and we did not observe any γ-carboxamides and α-amidoalkylated side products.

It is very significant to note that protocol gave access to primary to tertiary carboxamides on various substrates including DMF and quinolines. Pyrazine carboxamide is known as Rifater or Tebrazid and is a prescribed prodrug for the tuberculosis worldwide. In order to make this protocol practical and for the wider applicability we demonstrated the synthesis of pyrazine carboxamide **3na** (86% yield) starting from **1n** and formamide **2a** using optimal reaction conditions. Further, we synthesized pyrazine carboxamide **3na** in a gram scale and the method proved to be scalable. The method is simple and straightforward unlike the conventional methods such as coupling of pyrazine carboxylic acid and formamide via the activation either by acid chloride or by coupling agents such as DCC/EDC·HCl.

In order to understand and to gain further insight into the mechanism, pyridine **1a** and formamide **2a** were treated with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) under standard optimal conditions. We observed that reaction did not proceed even after prolonged reaction time thus indicating that the

Table 1

Condition screening and Optimization of aminocarbonylation of pyridine[a].



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	DCE	rt	12	NR[d]
2	DCE	50	12	trace
3	DCE	70	12	40
4	Formamide[b]	rt	12	NR
5	Formamide[b]	50	12	50
6	Formamide[b]	70	12	79
7	H_2O	70	12	30
8	THF	70	6	24
9	CH_3CN	70	12	45
10	Formamide	100	12	Decomposed

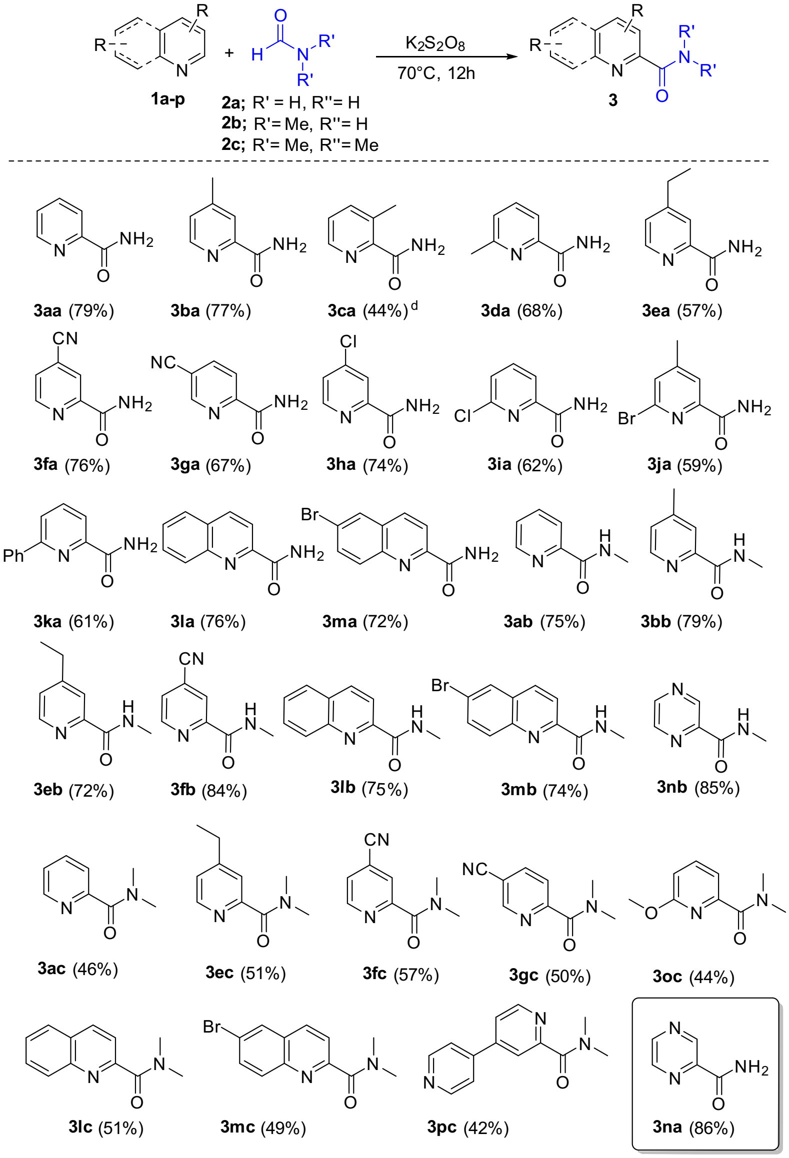
[a] Reaction Conditions: Pyridine **1a** (1 equiv.), Formamide (10 equiv.) potassium persulfate (2 equiv.), solvent (2 mL) under aerial atmosphere for 12 h.

[b] Formamide was used as substrate as well as solvent (20 equiv.).

[c] Isolated yield after purification by column chromatography.

[d] Reactions did not work at rt.

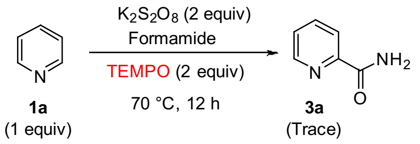
Table 2
Synthesis of primary to tertiary heteroaryl caboxamides.[a–d]



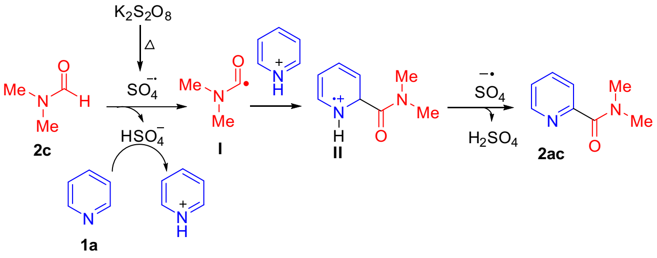
[a]Reaction Conditions: Pyridine **1a** (1 equiv.), Formamide or NMF or DMF (20 equiv.) potassium persulfate (2 equiv.) under aerial atmosphere for 12 h, [b]Formamide/NMF/DMF were used as substrate as well as solvent (20 equiv.), [c]Isolated yield after purification by column chromatography. [d]**3ca**'(5-methylpicolinamide) was obtained as regioisomer along with **3ca** (**3ca**:**3ca'** 58:42).

possible radical pathway was inhibited by the TEMPO (Scheme 1).

Based on the literature precedents[10] and on our experimental observation we propose that sulfate radical anion ($SO_4^{\cdot-}$) (produced in situ by the decomposition of potassium persulfate under the reaction conditions) reacts with the amide such as DMF **2c** to generate the carbamoyl radical **I** thus forming bisulphate anion. In turn alkaline pyridine is protonated and further undergoes the radical reaction with carbomyl species **I** to generate the intermediate **II**. This reactive species further gets aromatized by reacting with the sulfate radical anion to afford the desired product **2ac** (see Scheme 2).



Scheme 1. Control experiment to understand the mechanistic pathway.



Scheme 2. Plausible mechanism for the formation of carboxamide.

Conclusions

In summary, we have developed a transition metal free one-pot protocol that enables the direct aminocarbonylation of few heterocycles. Straightforward and simple protocol gives a direct access to primary to tertiary carboxamides employing user friendly and less expensive $K_2S_2O_8$ as reagent. Protocol works well with usually unreactive substrates such as NMF, DMF and quinoline and other heterocycles. Moreover, the protocol is clean and did not give any side products emanating from competing α-amidoalkylation. Pyrazinecarboxamide a prescribed drug has been synthesized using this protocol and the practicality of the protocol was demonstrated on a gram scale for the wider application.

Acknowledgments

R. G. B. thanks DST-SERB (EMR/2015/000909), Govt. of India for the generous research grant. Authors also thank Indian Institute of Science Education and Research (IISER), Pune for the financial support. T. B. M. thank CSIR, New Delhi, India and A. S. thank IISER-P for the fellowship.

A. Supplementary data

Supplementary data (experimental details and ^1H, ^{13}C NMR spectra of compounds **3**) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.11.006.

References

1. (a) Johansson I, ed. *Kirk-Othmer Encyclopedia of Chemical Technology*, 2. New York: John Wiley & Sons; 2004:442–463;
   (b) Abicky J, ed. *The Chemistry of Amides*. New York: WileyInterscience; 1970;
   (c) Greenberg A, Breneman CM, Liebman JF, eds. *The Amide inkage: Structural Significance in Chemistry, Biochemistry and Materials Science*. New York: John Wiley & Sons; 2000;
   (d) Haynes C, Kirkwood RC. *Pestic Sci*. 1992;35:161–165;
   (e) Constable DJC, Dunn PJ, Hayler JD, et al. *Green Chem*. 2007;9:411–420;
   (f) Regitano JB, Koskinen WC. *J Agric Food Chem*. 2008;56:5801–5805.
2. (a) *Metabolic Pathways of Agrochemicals: Part 2: Insecticides and Fungicides* (Ed.: Roberts TR., Hutson DH), Royal Society of Chemistry.;
   (b) Arthur G. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*. Wiley-Interscience; 2000;
   (c) Pattabiraman VR, Bode JW. *Nature*. 2011;480:471–479;
   (d) Roy S, Roy S, Gribble W. *Tetrahedron*. 2012;68:9867–9923;
   (e) Carey JS, Laffan D, Thomson C, Williams MT. *Org Biomol Chem*. 2006;4:2337–2347;
   (f) Allen CL, Williams JMJ. *Chem Soc Rev*. 2011;40:3405–3415;
   (g) Chen C, Hong SH. *Org Biomol Chem*. 2011;9:20–26;
   (h) Ekoue-Kovi K, Wolf C. *Chem Eur J*. 2008;14:6302–6315;
   (i) Izumi Y, Ichihashi H, Shimazu Y, Kitamura M, Sato H. *Bull Chem Soc Jpn*. 2007;80:1280–1287;
   (j) Gunanathan C, Ben-David Y, Milstein D. *Science*. 2007;317:790–792;
   (k) Crochet P, Cadierno V. *Chem Commun*. 2015;51:2495–2505.
3. (a) Alsabeh PG, Stradiotto M, Neumann H, Beller M. *Adv Synth Catal*. 2012;354:3065–3070;
   (b) Gadge ST, Bhanage BM. *Synlett*. 2014;25:85–88;
   (c) Suresh AS, Baburajan P, Ahmed M. *Tetrahedron Lett*. 2015;56:4864–4867;
   (d) Nielsen DU, Tanning RH, Lindhardt AT, Gogsig TM, Skrydstrup T. *Org Lett*. 2011;13:4454–4457;
   (e) Han W, Jin F, Zhao Q, Du H, Yao L. *Synlett*. 2016;27:1854–1859;
   (f) Kukushkin VY, Pombeiro AJL. *Chem Rev*. 2002;102:1771–1802;
   (g) Caronna T, Gambarotti C, Palmisano L, Punta C, Recupero F. *Chem Commun*. 2003;18:2350–2351;
   (h) Cunico RF, Maity BC. *Org Lett*. 2002;4:4357–4359.
4. (a) Ding ST, Jiao N. *Angew Chem Int Ed*. 2012;51:9226–9237;
   (b) Muzart J. *Tetrahedron*. 2009;65:8313–8323.
5. (a) Minisci F, Gardini GP, Galli R, Bertini F. *Tetrahedron Lett*. 1970;11:15–16;
   (b) Minisci F, Recupero F, Punta C, et al. *Chem Commun*. 2002;2496–2497;
   (c) Amrollahi Biyouki MA, Smith RAJ, Bedford JJ, Leader JP. *Synth Commun*. 1998;28:3817–3825;
   (d) Zhang Y, Teuscher KB, Ji H. *Chem Sci*. 2016;7:2111–2118.
6. (a) Jiang Q, Shenga W, Guo C. *Green Chem*. 2013;15:2175–2179;
   (b) Mi X, Wang C, Huang M, Wu Y, Wu Y. *J Org Chem*. 2015;80:148–155;
   (c) Yuan M, Chen L, Wang J, et al. *Org Lett*. 2015;17:346–349;
   (d) Kim SM, Kim DW, Yang JW. *Org Lett*. 2014;16:2876–2879;
   (e) Lu S, Gong Y, Zhou D. *J Org Chem*. 2015;80:9336–9352;
   (f) Wei W, Wen J, Yang D, et al. *J Org Chem*. 2014;79:4225–4230;
   (g) Wang H, Guo L-N, Wang S, Duan X-H. *Org Lett*. 2015;17:3054–3057.
7. (a) Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:415–418;
   (b) Mete TB, Khopade TM, Bhat RG. *Tetrahedron Lett*. 2017;58:2822–2825.
8. (a) Tanaka T. *Sci Am*. 1981;244:124–136;
   (b) Xia R, Xie M-S, Niu H-Y, Qu G-R, Guo H-M. *Org. Lett*. 2014;16:444–447;
   (c) Guo X, Qiu K, Feng X. *Chin J Polym Sci*. 1989;7:165–173.
9. Tanner DD, Osman SA. *J Org Chem*. 1987;52:4689–4693.
10. (a) Gardini GP, Minisci F, Palla G, Arnone A, Galli R. *Tetrahedron Lett*. 1971;59–62;
    (b) Minisci F. *Synthesis*. 1973;1973:1–24;
    (c) Tauber J, Imbri D, Opatz T. *Molecules*. 2014;19:16190–16222.