Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents

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2022

"Dedicated

To

My Beloved Parents,

Brothers & Sisters"

CERTIFICATE

This is to certify that the thesis titled **"Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents"** submitted by **Mr. Puneet Kumar** is an original research work and has not been previously submitted in part or full for the award of any other degree or diploma to this or any other university.

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DECLARATION

I, Puneet Kumar declare that the thesis titled "**Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents**" submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me under the supervision of **Dr. Jawahar Lal Jat**, Assistant Professor, Department of Chemistry, School of Physical & Decision Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow, U.P., India. I further confirm that said work has not been submitted anywhere else for the award of any degree, diploma, fellowship, etc. either in this or any other University or other institution of higher learning. I, further declare that the material obtained from other sources has been duly acknowledged in the thesis. I also declare that the thesis is essentially free from all kinds of plagiarism.

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(**Puneet Kumar**)

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List of Abbreviation

Ac	acetyl
aq.	aqueous
Ar	aromatic
ASA	aluminium sulfuric acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BKR	Beckmann rearrangement
Boc	t-butyloxycarbonyl
br	broad (NMR and IR spectroscopy)
Bu	butyl
d	doublet (NMR Spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethylsulfoxide
DPH	2,4-dinitrophenylhydroxylamine
DPPH	*O*-(diphenylphosphinyl)hydroxylamine
equiv.	equivalent
EtOAc	ethylacetate
HFIP	Hexafluro-2-propanol
HOSA	Hydroxylamine-*O*-sulfonic acid
Hz	Hertz
J	coupling constants
m	multiplet (NMR spectroscopy)
m.p.	melting point
Me	methyl
MSH	*O*-mesitylenesulfonyl hydroxylamine
n	primary
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
p	*para*
PEG	poly(ethylene glycol)s

Ph	phenyl
ppm	part(s) per million
PTSA	p-Toluenesulfonic acid
q	quartet
R	alkyl group
rt	room temperature
s	singlet (NMR spectroscopy)
sec	secondary
t	triplet
t	tertiary
TFA	trifluoroacetic acid
TFE	2,2,2-trifluroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl(4-methylphenylsulfonyl)
TsONHBoc	*N*-Boc-*O*-tosylhydroxylamine
TsONHMe	*N*-methyl-*O*-tosyl-hydroxylamine

Abstract

The thesis entitled "**Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents**" consists of four chapters. Nitrogen is the most occurred element in nature and also in a major class of biologically active natural and pharmaceutical products. In addition, the key presence of nitrogen in 84% of marketed drugs has a successful impact on the medicinal field and living health. Secondary amides, anilines, and nitriles are important functional groups, and they exist in many natural products and biologically active molecules, and approved drugs. Furthermore, they can be used as versatile building blocks in the synthesis of natural products, Pharmaceuticals, agrochemicals, dyes, and several value-added products. Therefore, the development of efficient synthetic methodologies for the preparation of these groups has attracted intense interest from synthetic chemists. Traditional methods for preparing these compounds generally involve tedious procedures, harsh reaction conditions, metal waste, toxic reagents, or byproducts. In recent decades, many groups have reported modifications of the reaction conditions that allow the transformation to proceed under milder reaction conditions. However, these developed methodologies suffer from limited substrate scope, complicated procedures, multi-step syntheses, elevated temperatures, the requirement of additives, and low functional group tolerance. Additionally, many of the reagents and catalysts used could plausibly take part in side reactions, thus restricting their applications in industries. Therefore the practical and direct synthesis of these nitrogen-containing functional groups from readily available starting materials under mild and environmentally benign conditions with a high scope is still a synthetic challenge. Furthermore, the selection of nitrogen sources is crucial to these transformations.

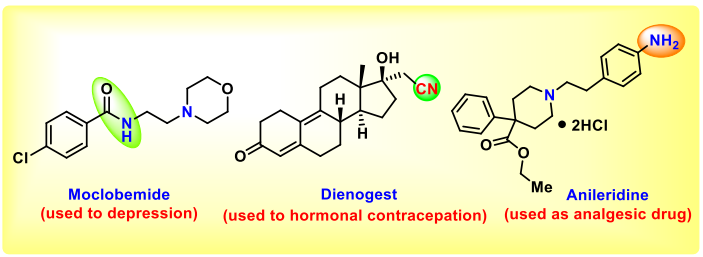
Recently, *O*-(substituted)hydroxylamine reagents have emerged as powerful nitrogen transfer reagents in various synthetic reactions such as amination, amidation, and aziridination etc. These reagents bring in several advantages over the other traditionally used reagents. Some of the special features of these reagents include generation of water-soluble by-products, commercially available reagents or ease of synthesis from cheaper raw materials, non-toxic nature, stability at ambient temperature, and ease of

handling etc made them popular among the scientific community for further applications.

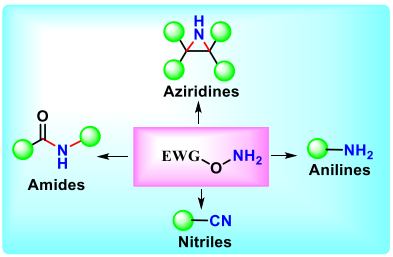
In this context, we have developed highly efficient, one-pot, environmentally benign, mild, and operationally simple methods for the synthesis of secondary amides, anilines, and nitriles from easily available starting materials using *O*-*(*sulfonyl)hydroxylamines as the aminating agents.

Chapter 1: **A General overview of nitrogen-containing compounds and *O*-(substituted)hydroxylamines: Introduction and motivation of present work**

This chapter starts with a brief introduction to nitrogen-containing organic compounds, particularly secondary amides, aryl amines, and nitriles. Their general methods of synthesis, important applications, and transformation have been briefly described. The general overview of *O*-(sulfonyl)hydroxylamine reagents also have been briefly described in this chapter.



Applications of nitrogen containing compounds



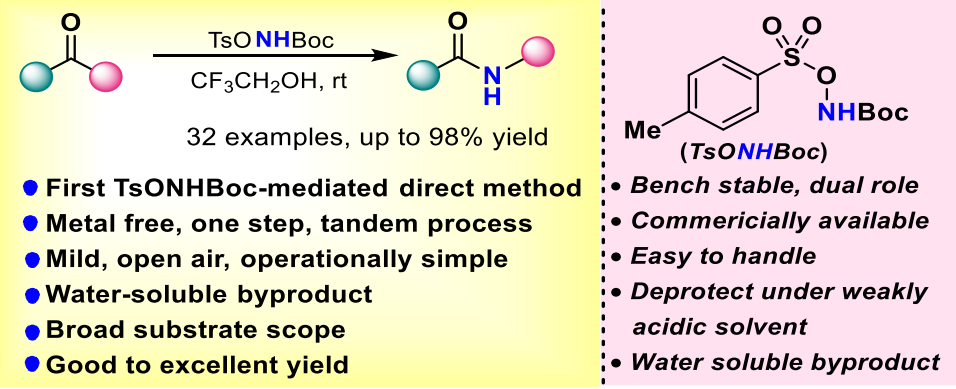
Reactions of *O*-(Substitutedl)hydroxylamine reagents

The experimental investigations and findings are described in the subsequent chapters (Chapters 2-4). Each chapter is individually discussed, and distributed in the introduction, literature review, results and discussions, experimental section, and references.

Chapter 2: Direct and metal-free transformation of ketones into *sec*- amides using TsONH-Boc aminating reagent

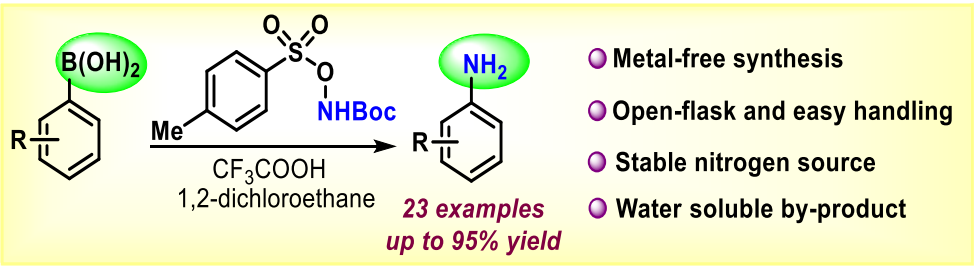
This chapter describes the first methodology for the conversion of ketones directly into the *sec*-amides *via* Beckmann rearrangement using TsONHBoc as the nitrogen source. It is anticipated that this reagent played dual roles: first, it promoted the generation of the activated oxime intermediate, and then the facile formation of amides. The additive

and metal-free direct method works in weakly acidic solvent and generated water soluble byproduct (TsOH).



Chapter 3: **Direct and metal-free transformation of aryl boronic acid into aromatic amines using *N*-Boc-*O*-tosylhydroxylamine reagent**

This chapter describes the direct and metal-free method for the synthesis of aromatic amines from aromatic boronic acids and esters by using the TsONHBoc as an aminating reagent.

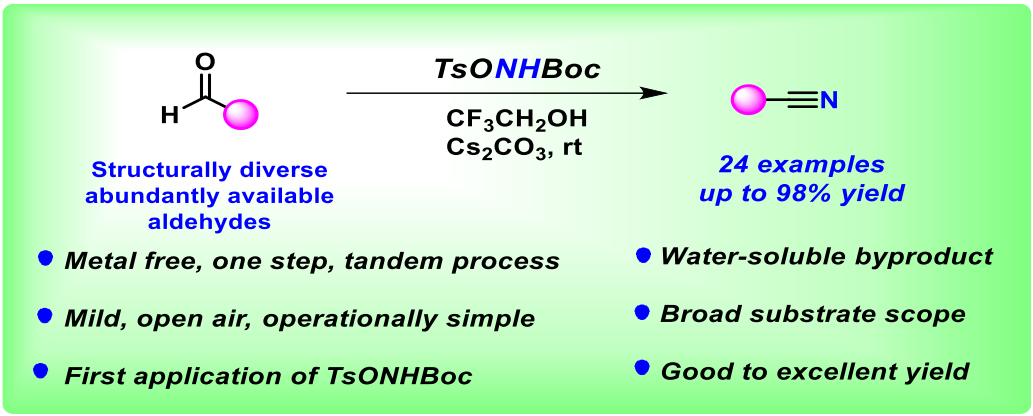


This reagent is extremely stable, easy to use, and produces a non-interfering by-product (*i.e.* TsOH) that is easily removed by an aqueous workup. Under acidic conditions, the method applies to boronic acids having electron-withdrawing as well as electron-donating groups to provide corresponding anilines in good to excellent yields. The existing method could be utilized to obtain aromatic primary amines at the gram scale.

Chapter 4: **Metal-free transformation of aldehydes into nitriles using TsONHBoc reagent**

This chapter describes the economical and practical approach of nitriles from readily available aldehydes using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as an aminating agent. This direct and metal-free synthesis of nitriles with high yields tolerates a wide range of substrates such as aromatic, aliphatic, allylic, heteroaryl, and α,β-unsaturated

aldehydes. Shelf stability, low cost, and ease-handling of TsONHBoc introduces an additional advantage.



Chapter 1

A general overview on nitrogen-containing compounds (secondary amides, anilines, and nitriles) and *O*-(substituted)hydroxylamines: Introduction and motivation of present work

Secondary amides, anilines, and nitriles moieties are present in various naturally occurring bioactive compounds. They are also used as a versatile synthetic intermediate in organic chemistry. *O*-(substituted)hydroxylamines serve as a useful aminating reagent. Recently, these reagents have been used in amination, aziridination, amidation, cyanation etc. In this chapter, we have described the importance and general synthetic routes and applications of secondary amides, anilines, and nitriles followed by emerging synthetic applications of *O*-(substituted)hydroxylamine reagents.

1.1 Introduction

Nitrogen is a widespread element in heterocyclic and acyclic active pharmacological compounds. Urea is the first nitrogen-containing compound, synthesized in 1828 by Friedrich Wöhler from silver cyanate (AgOCN) and ammonium chloride (NH_4Cl). Bioactive chemical libraries are dominated by amines, imines, nitriles, amides, and carbamates, while 910 FDA-approved drugs contain at least one nitrogen atom in their molecular framework (84% among 1035 unique small-molecule drugs).[1]

The nearly 97,400 articles on nitrogen heterocycles that have been published between 2009 and early 2020, of which 12,615 publications have been recorded in the year 2019,[2] provided evidence of their significance in the synthesis of nitrogen heterocycles. Numerous *N*-heterocyclic compounds, which are widely present in nature and have physiological and pharmacological effects, are the building blocks of several biologically significant molecules, such as many vitamins, nucleic acids, medicines, antibiotics, dyes, and agrochemicals (Fig. 1.1-1.3).[3-7]

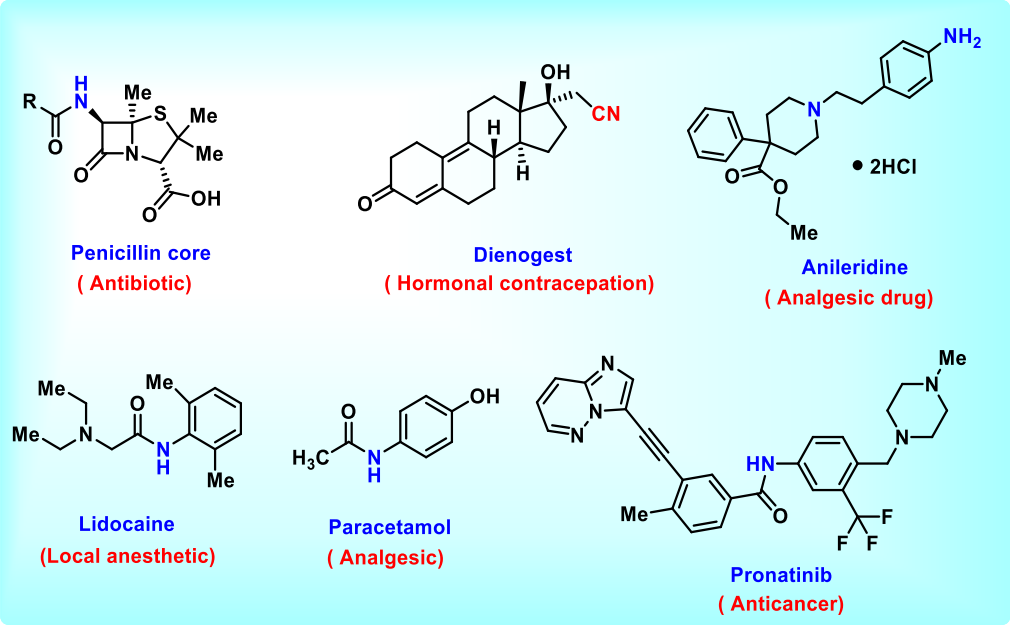


Figure 1.1. Selected nitrogen containing drug molecules[3b]

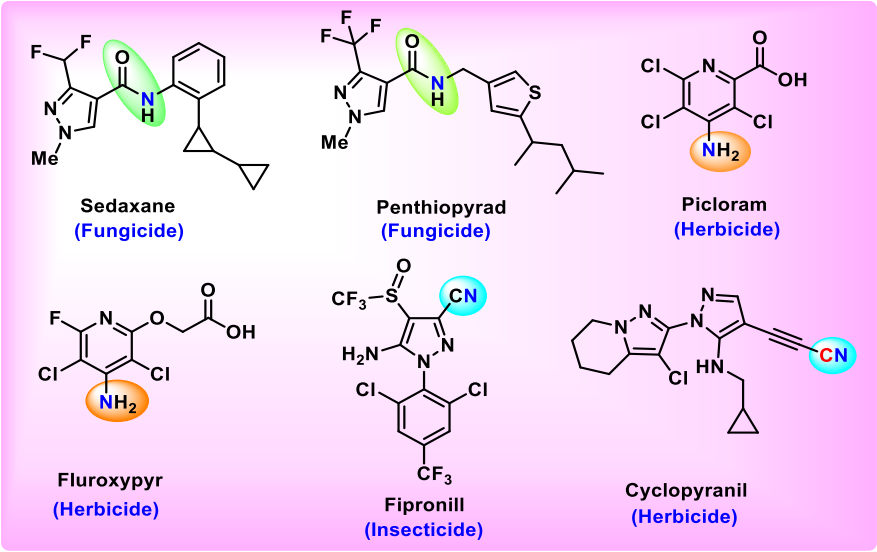


Figure 1.2. Selected nitrogen containing agrochemicals[3c]

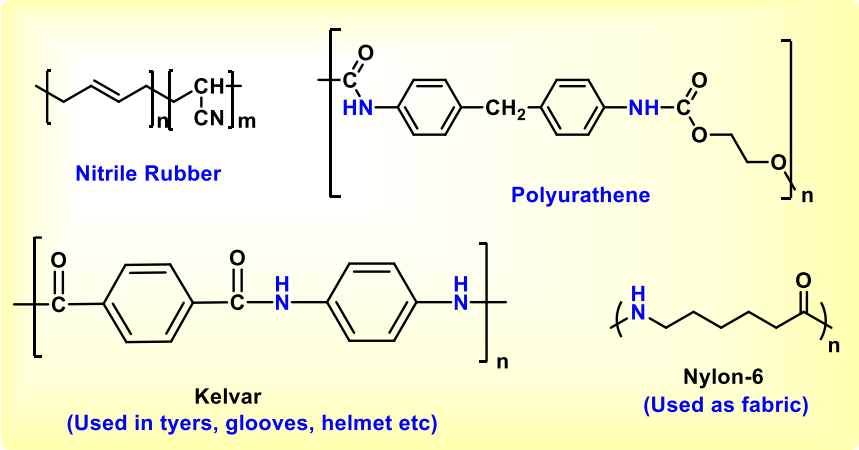


Figure 1.3. Selected nitrogen-containing polymers[3d]

Over the last two-three decades, the scientific community have contributed well for the development of the efficient synthetic methods of nitrogenous compounds.[8-12] A constant increase in pharmaceutical and medicinal field as well as in synthetic organic chemistry, have taken notice of these nitrogen-containing compounds with distinctive properties and applications[13-15.] Numerous heterocyclic compounds containing nitrogen are known to possess a variety of pharmacological properties, such as anticancer, anti-HIV, antimalaria, anti-tubercular, anti-microbial, and diabetic properties.[16-22] A large portion of research in the medical field is focused on the development of novel molecules and composites,

rendering nitrogen-based heterocyclic chemistry a prominent and distinctive class. Among all the nitrogen-containing compounds, secondary amides, nitriles, and anilines are widely used in the fields of agrochemicals, pharmaceuticals, and polymer industries. Their brief applications in various fields and general synthetic approaches have been described below:

1.2 Secondary amides: A general overview

Nitrogen containing heterocyclic and acyclic compounds are widely distributed in nature and are essential to life. Among all the nitrogen containing compounds discovered so far, secondary amides are the most important class of compounds in the pharmaceutical, polymer, and agrochemical industries. *Sec*-amide group having the representation RCONHR shows its wide occurrence in natural products and pharmaceutical field.[23] Also, their presence in the peptide bonds and numerous marketed drugs ares of great importance for life.[24]

i) Importance of secondary amides in the pharmaceutical industry

The secondary amide group is of crucial importance in natural products, such as peptides, proteins, and bioactive molecules.[25] In the pharmaceutical field, the synthesis of the amide bond is the most frequent reaction performed due to the larger occupancy of the amide bond in the marketed drugs (Fig. 1.4).[26]

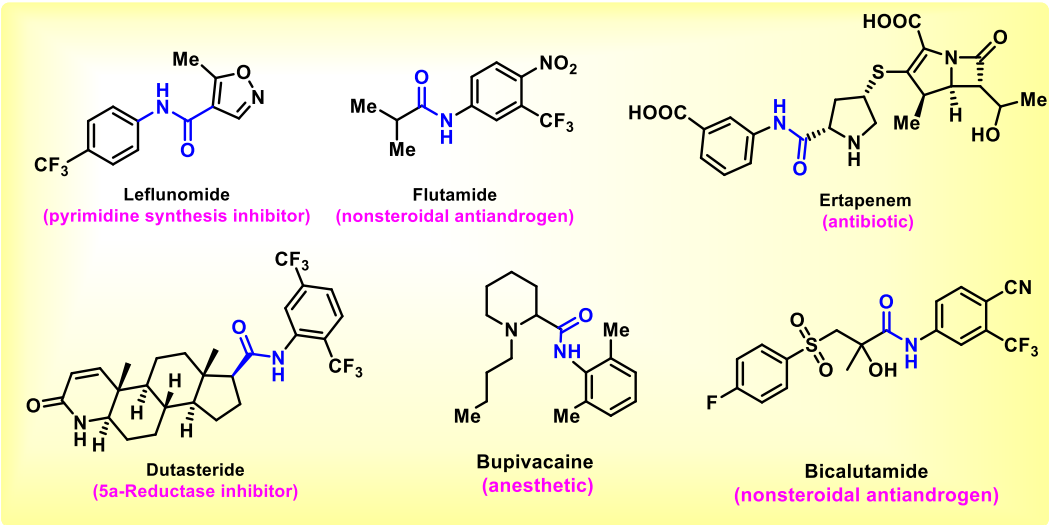


Figure 1.4. Selected secondary amide containing drug molecules

ii) Importance of secondary amides in the agriculture industry

Secondary amides also have widespread applications in numerous agrochemical products such as anthranilic diamides[27], are an important class of insecticides, diflufenican[28] acts as residual and foliar herbicide, and thifluzamide[29] is used as foliarly or as a seed treatment in various crops for the control of basidomycete diseases (Fig. 1.5).

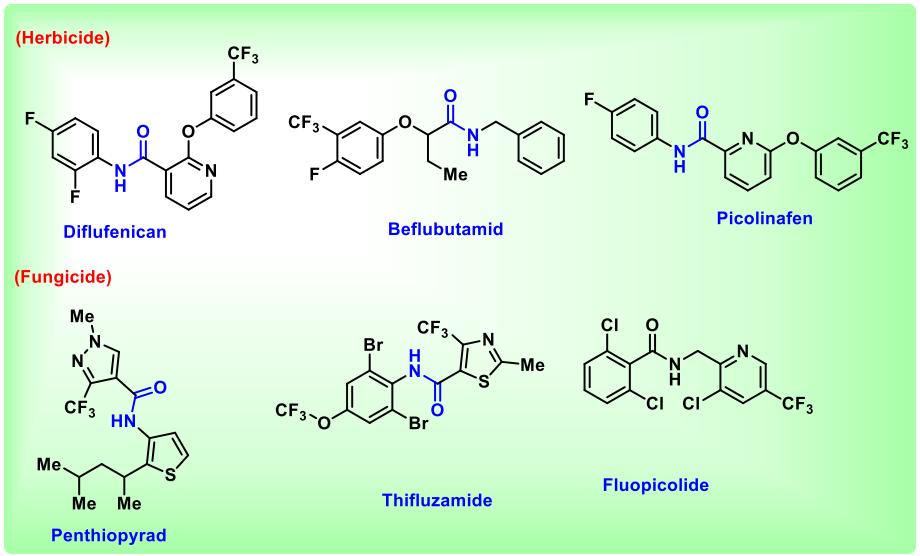


Figure 1.5. Selected secondary amide containing agrochemicals

iii) Importance of secondary amides in the polymer industry and others

Polymers with a repeated unit of sec-amide, -CO-NH-, are known as polyamides which are a backbone of naturally occurring polyamides, for example; proteins. However, significant progress has been achieved for artificial polyamides such as NYLON 6,6 (*poly(hexamethylene adipamide)* which was first carried out by Wallace Carothers in 1935[30], *meta*-aramid fiber, marketed under the name Nomex[31], and *para*-aramid fiber, (trade name Kevlar) as shown in fig. 1.6.[32] In addition, the sec-amide bond has a wide presence in useful surfactants.[33]

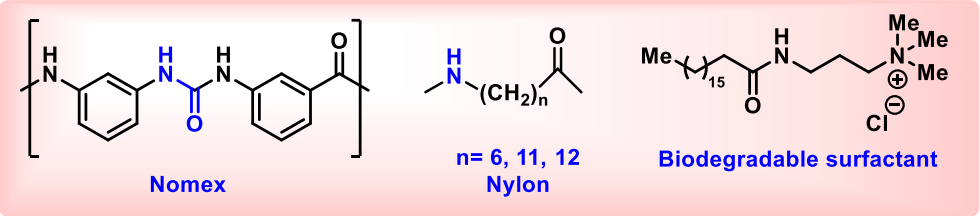


Figure 1.6. Selected secondary amide-containing polymers

The broad presence of secondary amides in various fields inspires scientists to develop diverse synthetic routes for their synthesis. In this direction, several achievements have been made in the last 20 decades.

Conventionally, the most popular method for its synthesis was the coupling of carboxylic acid and an amine. Later, in the same way, the other approaches were disclosed such as; oxidative amide synthesis followed by coupling of alcohols, aldehydes, with amine surrogates using a stoichiometric number of oxidants or catalysts.[34] Although these methods were widely applied for the sec-amide synthesis, they require high reaction temperature and strong acids which is not compatible with other functional groups. Next, this amide bond was synthesized from ketoxime intermediate in presence of an acid, known as Beckmann rearrangement. This reaction was applied on an industrial level for the synthesis of caprolactam. However, the presence of strong acid limits its milder applications. Afterward, several improvements were incorporated for the mild access of the versatile amide bond (Fig. 1.7).[35] The literature review on the synthesis of secondary amides has been discussed in chapter 2 of this thesis.

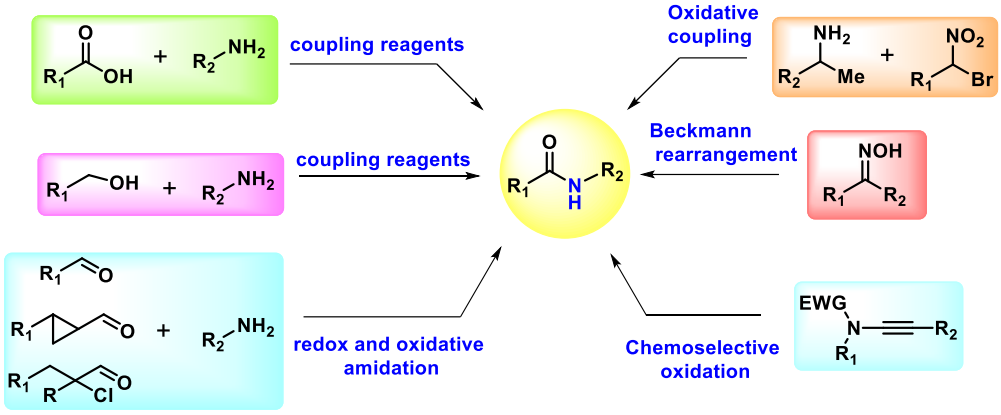


Figure 1.7. Various synthetic routes for the synthesis of *sec*-amide from different sources

Another category of nitrogen containing compounds is aryl amines which are widely distributed in agrochemicals, pharmaceuticals, and polymer industries. Their vast exploration is briefly discussed in section 1.3

1.3 Primary arylamines: A general overview

Anilines and their derivatives are used in the synthesis of polymers, rubber, agricultural chemicals, dyes & pigments, pharmaceuticals, and photographic chemicals. They are generally prepared *via* hydrogenation of their nitro aromatic precursors. Aniline and its derivatives are a noteworthy class of chemicals that are found in a wide range of natural products as well as they are used as versatile synthetic intermediates. Aniline derivatives are widely used in the production of polyurethane, which is essential to manufacture plastics for medical industries. They are used in the manufacturing of several types of medical devices. Hence they are highly required in the medical industry. Aniline derivative, N-acetyl-*p*-aminophenol i.e. Paracetamol is widely used as an antipyretic and analgesic drug.[36] Traditionally the synthesis of aniline derivatives involves the introduction of nitro group on the aromatic ring using a concentrated nitrating mixture (H_2SO_4 and HNO_3) followed by reduction of the nitro group *via* metallic or catalytic hydrogenation process. Some other methods like direct substitution of aryl halides with ammonia at high temperature, and transition metal-catalyzed amination of aryl halides with ammonia or its surrogates are also available for aniline synthesis.[37] The brief general overview of aniline derivatives has been discussed below.

1.3.1 Importance of aniline derivatives in pharmaceuticals:

Many natural and pharmaceutical compounds contain primary aniline motifs in their structural skeleton (Figure 1.8). For example, Anileridine is used as an analgesic drug. Sulfadoxine is used to treat malaria. Butamben is used as a local anesthetic. It is the ester of 4-aminobenzoic acid and butanol. Nomifensine is an antidepressant that contains aniline moiety. Procainamide is a type I antiarrhythmic agent prescribed for irregular heartbeat.[38]

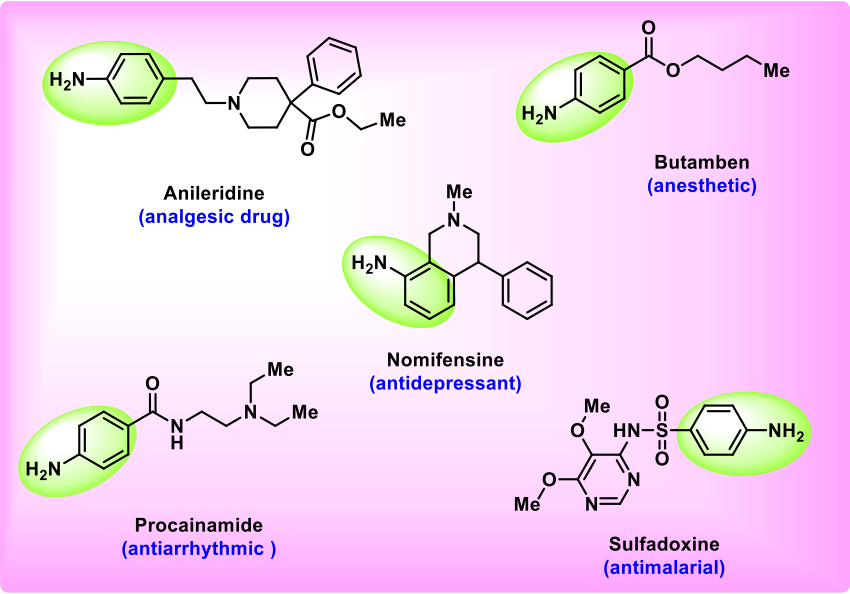


Figure 1.8. Selected drug molecules containing aniline moiety

1.3.2 Presence of aniline moiety in agrochemicals:

Agrochemicals are essential for crop protection and also fulfill the criteria for environmentally friendly products. The aniline moiety is also widely present in agrochemical products (Figure 1.9). For example, Trifluralin, Pendimethlin, Diflufenican, Flufenacet are used as herbicides that contain the aniline moiety in their structure. Triflumizole and Thifluzamide is used as fungicide, Triflumuron is used as insecticide[39] and these agrochemicals are derived from aniline derivatives.

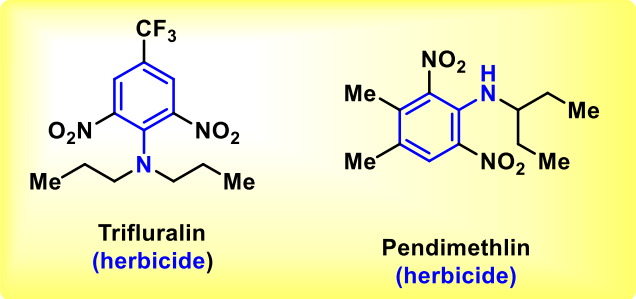


Figure 1.9. Selected agrochemicals containing aniline moiety

1.3.3 Presence of aniline moiety in polymers and dyes:

Polyanilines are among the most important representatives of the class of electrically conductive polymers and organic semiconductors of the semi-flexible rod polymer family.[40] They provide a broad range of application areas, including microwave absorption, gas separation membrane, chemical sensor, rechargeable battery, photovoltaic cell, electromagnetic interference shielding, and more. During the polymerization of aniline monomer, polyanilines is found in one of three idealized oxidation states: (a) leucoemeraldine (white/clear), (b) emeraldine (salt-green/baseblue), and (c) pernigraniline (blue/violet). Fully oxidized polyaniline is known as pernigraniline base. Half of the oxidized polyaniline is called emerald base, and completely reduced is known as lecomeraldine base (Fig. 1.10).[41]

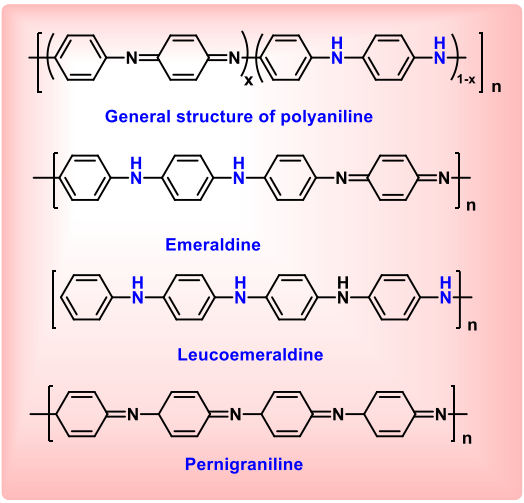


Figure 1.10. General structure of polyaniline and its types

On the other hand, anilines are also used in the synthesis of dyes. Azo dyes are present in about 70% of all organic dyes produced in the world. Anilines are the main precursors for the formation of the azo dyes and aniline derivatives are also found in many other dyes (Fig. 1.11).[42]

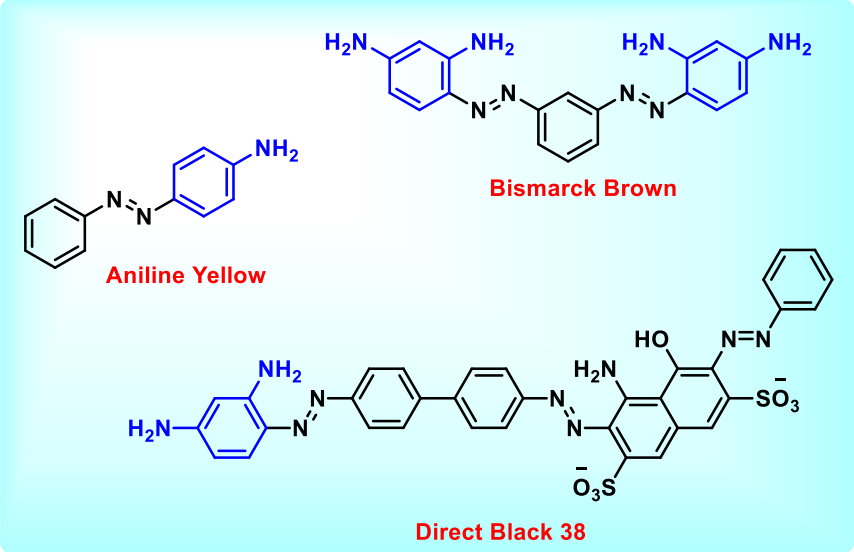


Figure 1.11. Selected examples of azo dyes containing anilines

1.3.4 Synthetic application of primary arylamines

Aniline is used as a versatile synthetic intermediate. It is converted into diazonium salt via diazotization reaction and synthesized diazonium salt can be transformed into several useful products under various conditions such as benzene, chloro benzene, bromo benzene, cyano benzene, phenol, biphenyl, and hydrazine etc. These transformed compounds are widely present in the field of pharmaceutical, agrochemical and polymer industries. They also serve as synthetic intermediates (Fig. 1.12).

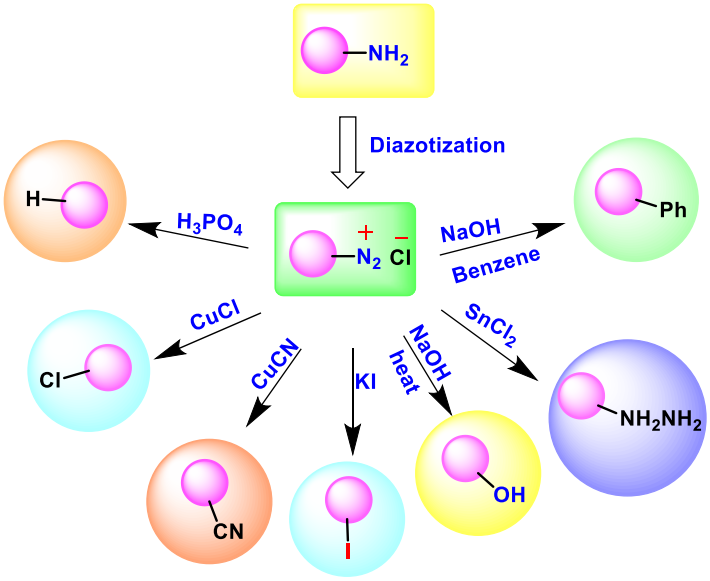


Figure 1.12. Synthetic application of anilines

Arylamines are also used in the synthesis of amino acids, proteins, peptides, and several bioactive heterocyclic compounds. They are also used in the preparation of explosives as well as in photographic chemicals and electronics (Fig. 1.13).

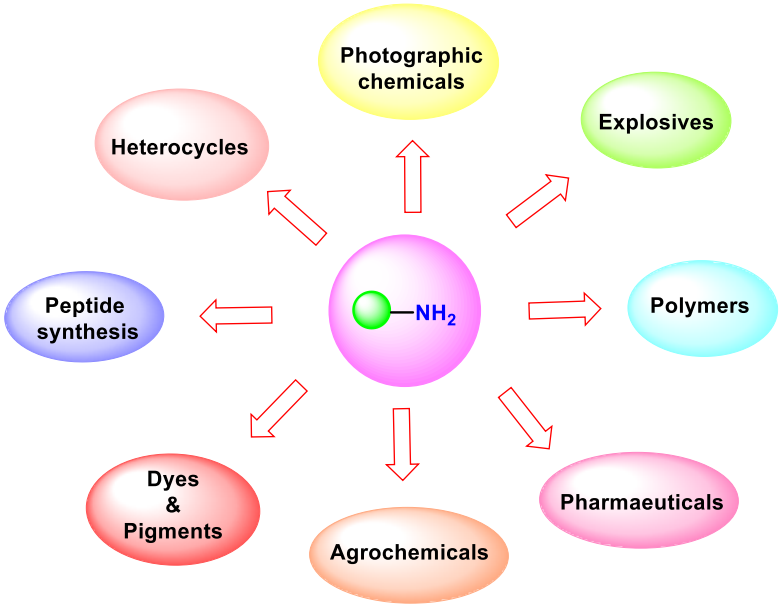


Figure 1.13. Various application of anilines in the different fields

The broad utility of arylamines in various fields inspires scientists to develop diverse synthetic routes for their synthesis. In this direction, several achievements have been made in the last two to three decades. The selected advancements are described below.

Significant progress has been achieved over the past ten years in the field of copper-catalyzed oxidative amination of aryl boronic acids (e.g., Chan-Lam coupling).[43] Further the electrophilic amination of several organometallic reagents [44] (such as Li, Zn, and B) using transition metals (Pd, Ni, or Cu) as well as the direct C-H amination of aromatic rings[45] have attracted significant attention for the production of N,N-dialkyl anilines. Remarkably, it has shown to be much more demanding[46] to synthesize primary arylamines from arylboronic acids and its derivatives. Fu and colleagues reported cross-coupling of arylboronic acids with aqueous ammonia using copper(I) oxide as a catalyst.[46a] The transition metals are used as a catalyst in all of the above-reported protoclos. Metal free procedures are much favored from a practical perspective, especially in the pharmaceutical industry where the cost of removing unwanted metal impurity can be enormous.[47] Hence recent, research on the synthesis of primary anilines under mild, metal-free, efficient, and environmentally benign conditions has attracted the attention of researchers and scientists (Fig. 1.14). The literature review on the synthesis of primary anilines has been discussed in chapter 3 of this thesis.

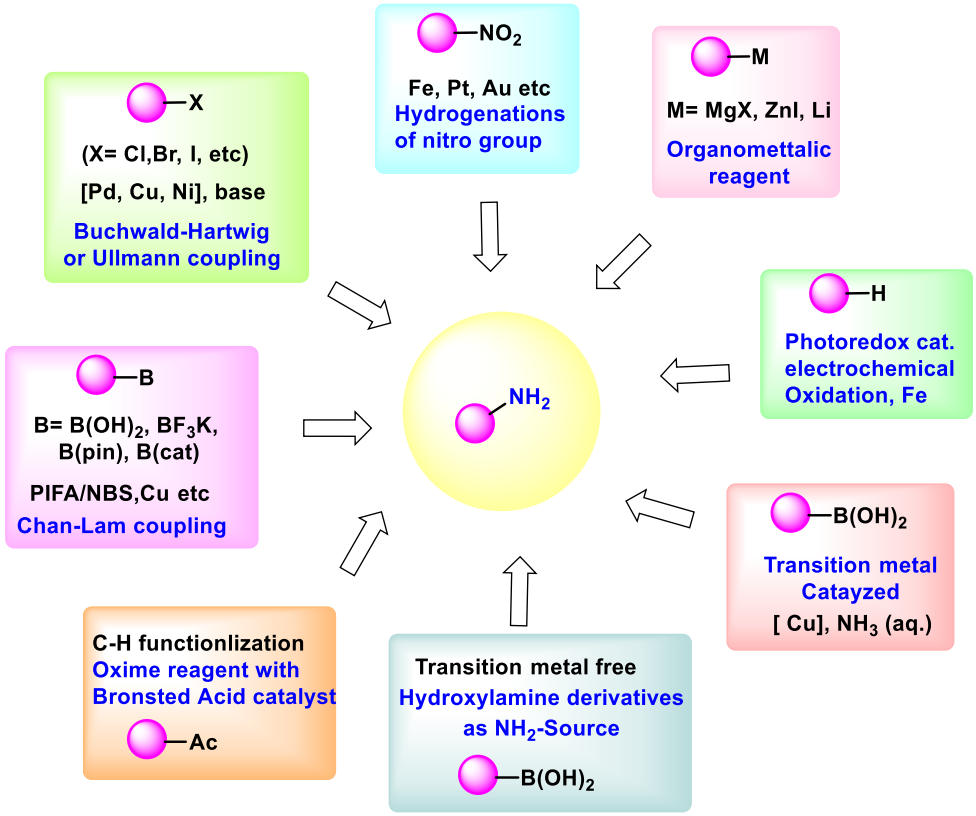


Figure 1.14. Synthesis of primary anilines from different routes[48]

Nitriles are another important class of nitrogen-containing functional groups. They are widely present in bioactive natural products, drug molecules, polymeric materials, and chemicals used in agriculture.

1.4 Nitriles: A general overview

Among all the nitrogen containing compounds discovered so far nitriles are extensively employed to synthesize amides, amines, esters, carboxylic acids, and other compounds. They have been used as intermediates in the generation of agricultural chemicals, dyes, and pharmaceuticals[49]. Nitriles are those molecules which contain -C≡N functional group.[50] In industrial literature, the prefix cyano- is used in place of the word nitrile. High dipole moments are evidence that nitriles are polar. In 1782 Scheele generated the nitrile of formic acid, hydrogen cyanide, the first compound in the homolog row of nitriles [51-52] The importance of nitriles in various field have been described below.

i) Importance of nitriles in the pharmaceutical industry

There are more than 30 drugs incorporating nitrile that are recommended for a wide range of medical conditions, and there are more than 20 additional nitrile-containing drugs that are currently undergoing clinical trials. Primacor (milrinone) is a phosphodiesterase inhibitor used to treat heart failure,[53] especially when treatment with vasodilators and diuretics has failed. Cromakalim is an ATP channel opener that is potassium-dependent and used to treat hypertension.[54] The lack of selectivity in this "first generation" treatment prompted researchers to look for selective drugs with uncoupled anti-ischemic and vasorelaxant effects.[55] Rilpivirine is one of the several etravirine analogues is developed which being recognized as one of "the most effective anti-HIV agent(s) yet reported.[56] Zaleplon is a sedative that does not contain benzodiazepines and is prescribed for sleeplessness.[57] Gouty arthritis is cured with febuxostat, a non-purine xanthine oxidase inhibitor.[58] Anastrazole is the best drug having nitrile with the trade name arimidex, manufactured by Astra-Zeneca, is the preferred drug for estrogen-dependent breast cancer (Fig. 1.15).[59]

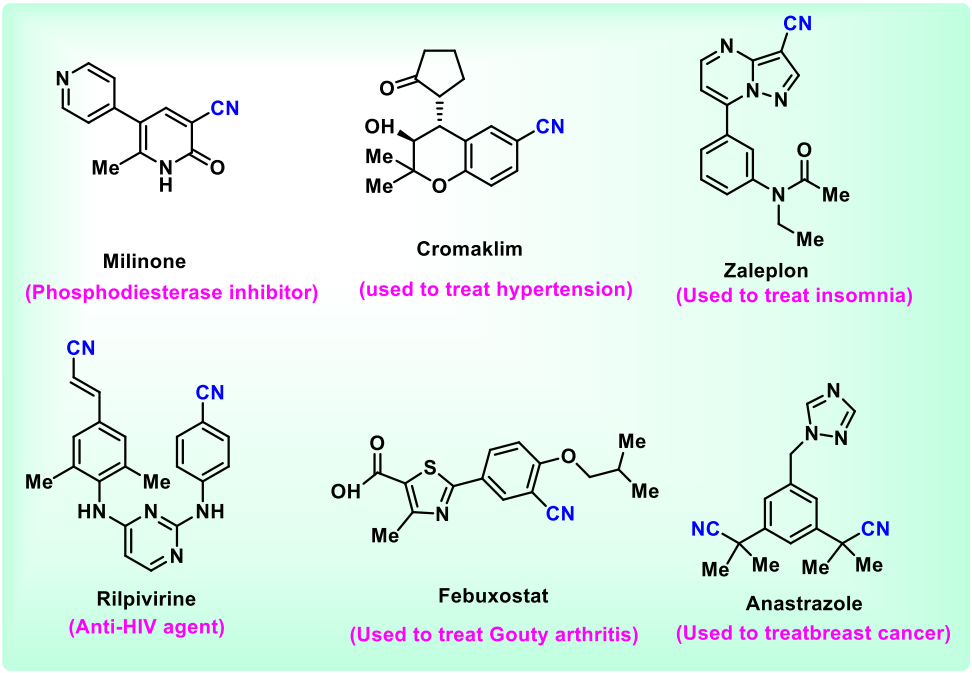


Figure 1.15. Selected nitrile-containing drugs

ii) Importance of nitriles in agrochemicals

Nitrile's have a profound impact on the biological activity of agrochemicals like herbicides, insecticides, fungicides, and plant growth regulators, it has earned a special place in the inventory of the agrochemical chemist. One of the most effective pesticides to be introduced in past decade is the N-phenylpyrazole insecticide (fipronil), which was produced in 1993 by Rhone-Poulenc[60] It is a powerful pesticide that works well against a variety of pest, insects that are harmful to humans, animals, and agricultural production. The chloride channel is blocked by fipronil through its action on the GABA (gamma-aminobutyric acid) receptor[61]. Trifluoromethylphenyl pyrethroid fluvalinate (Mavriks)[62] was first developed by Zoecon (later Zandos Ag) and eventually replaced by tau-fluvalinate, which contains two of the four fluvalinate isomers. A synthetic pyrethroid called tau-fluvalinate (Apistans) is applied topically to honeybees to protect them from the parasite mite Varroa jacobsoni. There are some evidence of mite resistance to tau-fluvalinate.[63] β-Methoxyacrylates a significant class of industrial fungicides is focused on the natural products strobilurins, which include strobilurin A and Oudemansin A. Azoxystrobin, one of the first members of this class of fungicide, was introduced in 1996 (Fig. 1.16).[64]

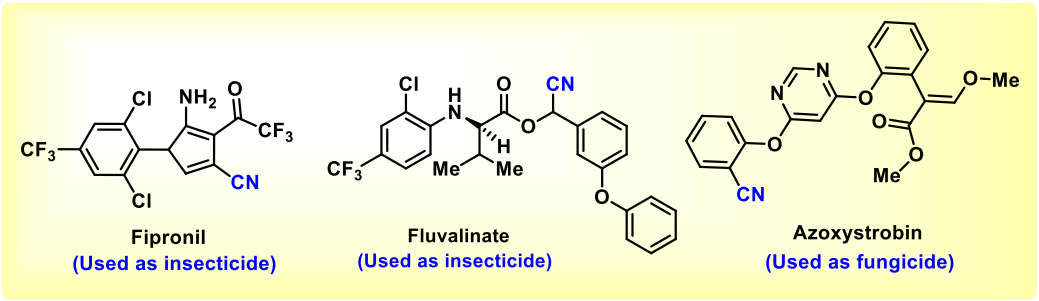


Figure 1.16. Selected nitrile containing agrochemicals

iii) Importance of nitriles in polymer indusrty

Numerous useful substances contain nitriles, such as methyl cyanoacrylate, which is used in super glue, nitrile rubber, and medical gloves. Since nitrile rubber resists fuels and lubricants, it is frequently utilized in automobiles and other seals. The field of advanced

polymer chemistry provides a diverse range of polymerization methodologies, providing the direct synthesis of innovative polymeric materials through the use of functionalized monomers in either solution or melt form. Polymerization reactions, copolymer formation, grafting, functionalization, synthesizing telechelic polymers, crosslinking, chain extension, site-selective functionalization, and so on, are all examples of common chemical modification processes used today. Nitrile-containing polymers, which include a highly reactive CN group, have been the target of a huge number of synthetic transformations in this field. The presence of active nitrile groups in the polymer enables it to build innovative macromolecules with superior characteristics and a broader range of potential applicability by introducing new functional groups into the molecule via modification reactions. Polymers such as Polyacrylonitrile (PAN), Poly (Styrene-co-Acrylonitrile), (SAN), Poly (Butadiene-co-Styrene-Acrylonitrile) (ABS) have been developed *via* chemical reaction involving nitrile group in homo or copolymers.

PAN was widely used in this context due to its versatility in designing the final carbon fibre structure along with the building of a more stable ladder structure through nitrile polymerization. NBR is derived from the radical copolymerization of acrylonitrile and butadiene copolymers. NBR does not crystallize under stress, but its tensile strength is limited. However, it has excellent resistance to non-polar solvents, fats, oils, and chemicals. NBR has seen widespread application in the sealing of tubes, equipment for oil transport, and other types of oil-resistant gear.The Acrylonitrile-butadiene-styrene (ABS) terpolymer, a category of engineered thermoplastics, has undergone several isolated cases of chemical transformation of the nitrile group. Copolymer plastics made from styrene and acrylonitrile are known as styrene acrylonitrile resin (SAN). A higher thermal resistance makes it a popular alternative to polystyrene. Styrene makes up around 70–80% of the chains, while acrylonitrile accounts for about 20-30% of the weight. It is used in manufacturing food containers, water bottles, kitchenware, computers, packaging, battery cases, optical fibres etc. Acrylonitrile butadiene styrene (ABS) is a thermoplastic polymer having 105 °C (221 °F) glass transition temperature. ABS is used to make recorders, clarinets, piano motions, and keyboard keycaps. Some other uses of ABS are in golf club heads (due to its shock absorption), automotive trim components, bumper bars, binoculars,

inhalers, monoculars, nebulizers, tendon prostheses, drug-delivery systems and pen toys etc (Fig. 1.17).[65-67]

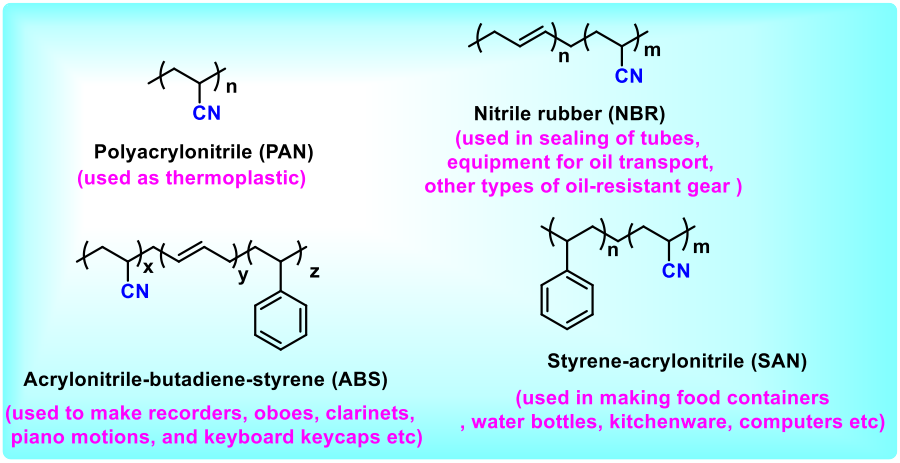


Figure 1.17. Selected nitrile containing polymers

iv) Synthetic application of nitriles

Nitriles are used as a versatile synthetic intermediate for the formation of amines, amides, esters, carboxylic acids, amidines, and aldehydes along with nitrogen-containing heterocyclic compounds (Fig. 1.18).[68]

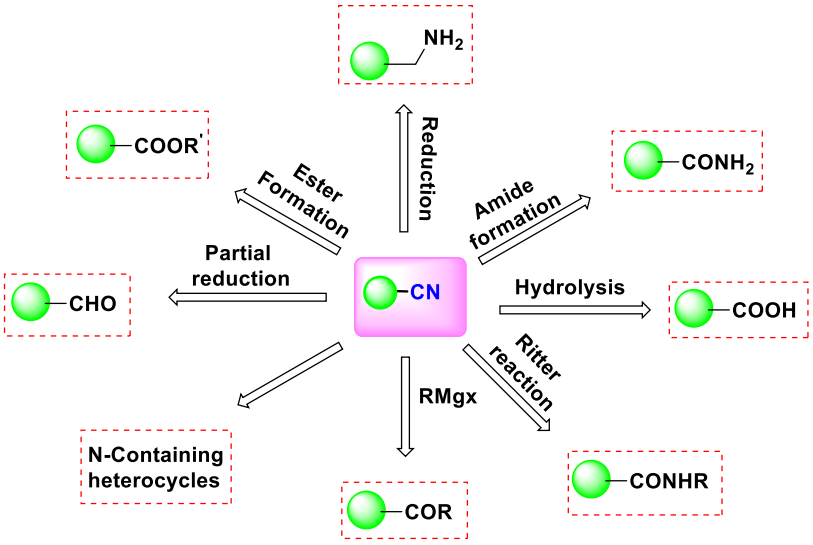


Figure 1.18. Synthetic applications of nitrile

The broad presence of nitriles in various fields inspires scientists to develop diverse synthetic routes for their synthesis. In this direction, several achievements have been made in the last 2-3 decades for the synthesis of nitriles via different synthetic modes.

Traditional nitrile preparation methods use hazardous or poisonous chemicals and generate a stoichiometric amount of metal waste. Recent advancements have made it possible to combine catalysts with nonmetallic cyano group sources.[69] However, these procedures frequently used aryl halides. Due to easy accessibility and low toxicity, alcohols and aldehydes provide suitable starting materials. Some aldehydes have been utilized in the preparation of nitriles, however, the employed reagents are not suitable for industrial-scale production. Schmidt reaction provides direct access to nitrile from aldehydes but uses highly toxic and explosive sodium azide as a nitrogen source[70]. The other nitrogen sources used for nitrile synthesis are hydroxylamine[71] and its derivatives[72] and trapped ammonia (Fig. 1.19-1.20).[73] The literature review on the nitriles synthesis has been discussed in chapter 4 of this thesis.

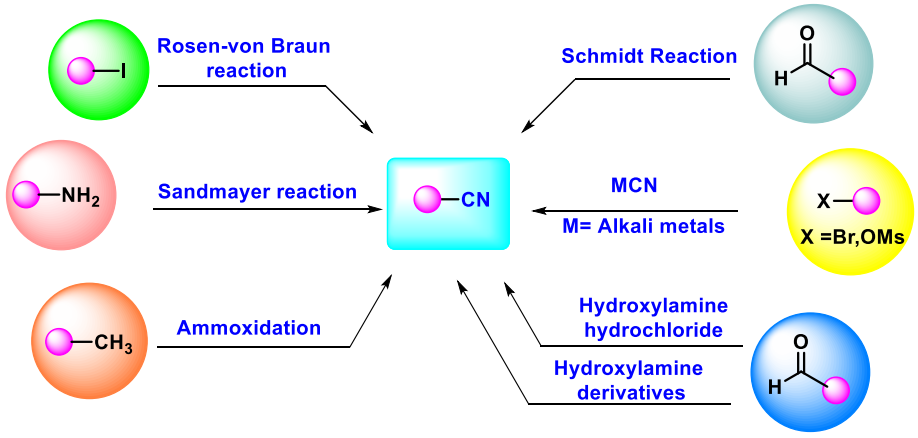


Figure 1.19. Advancements in the synthesis of nitriles[74]

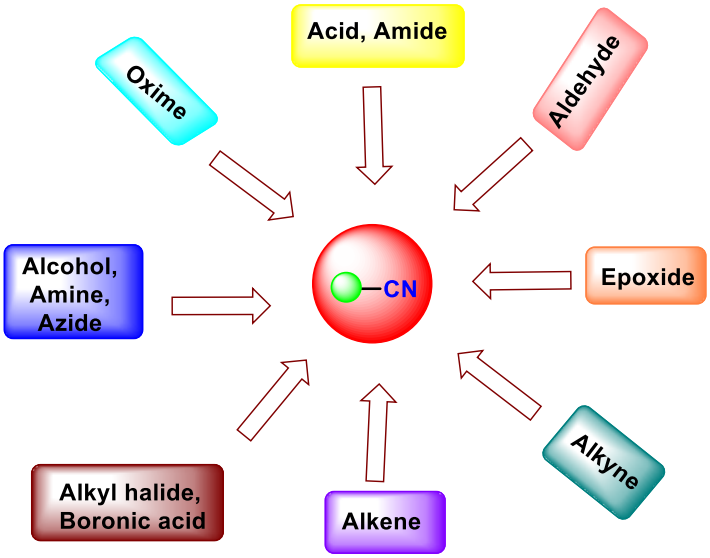


Figure 1.20 Various routes for the synthesis of nitriles[75]

1.5 General overview of *O*-(substituted)hydroxylamine reagents

Hydroxylamine is an oxygenated derivative of ammonia. Many *O*-substituted derivatives of hydroxylamine are commercially available and they can also be prepared easily from commercially available low-cost starting materials.[76a] Diverse *O*-substituted hydroxylamine reagents such as *O*-(diphenylphosphinyl)hydroxylamine (DPPH),[76b] *O*-(Mesitylsulfonyl)hydroxylamine (MSH)[76c], hydroxylamine-*O*-sulfonic acid (HOSA)[76d], 2,4-dinitrophenylhydroxylamine (DPH)[77] and other corresponding reagents in which oxygen is attached with good leaving groups, have a great potential in amination reaction. Some of the *O*-substituted derivatives of hydroxylamine reagents are shown in figure 1.21.

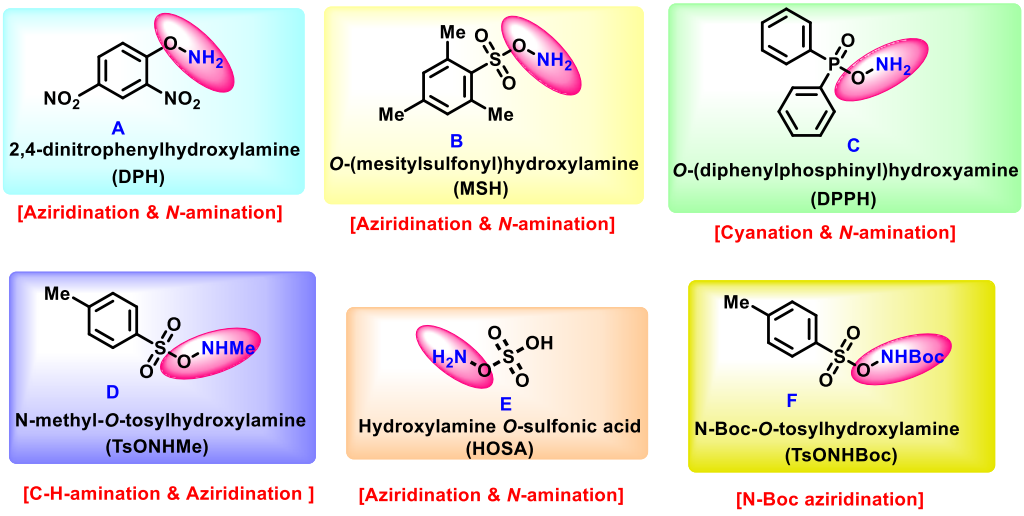


Figure 1.21. Some selected *O*-substituted hydroxylamine reagent

1.5.1 Synthetic application of *O*-substituted hydroxylamine reagent

O-substituted hydroxylamine reagents have great synthetic versatility. These reagents are widely used in different types of nucleophilic synthetic transformations including amination and reductive deamination reactions, nitrile from oxime formation and also to produce diazo and amide compounds. The broad category of heterocycles and their derivatives are synthesized by using *O*-substituted hydroxylamine reagents (Fig. 1.22).

Special features of *O*-substituted hydroxylamine reagents:

- ✓ Easily prepared from low-cost precursors.
- ✓ Have great synthetic versatility
- ✓ Generate non-toxic water-soluble by-products.
- ✓ Have great potential in amination reactions and -NH_2 insertion reactions.
- ✓ Act as both electrophilic and nucleophilic reagents depending on conditions.

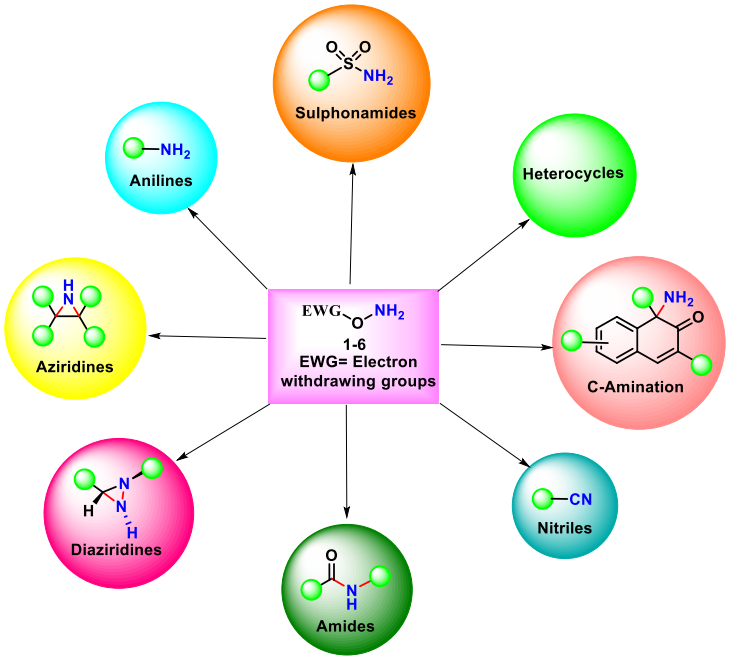
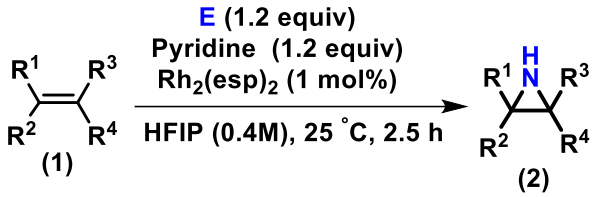


Figure 1.22. Synthetic application of *O*-substituted hydroxylamine reagent

O-substituted hydroxylamine reagent**s** have been mainly utilized in the following synthetic transformation:

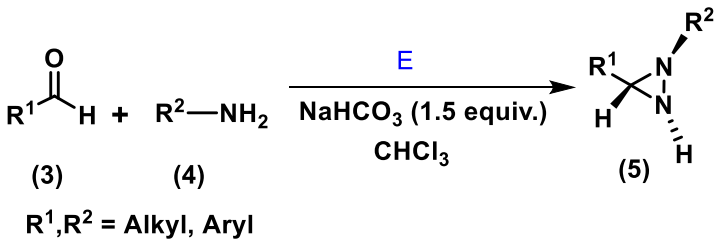
- ✓ **Aziridination**
- ✓ **Diaziridination**
- ✓ **Amination: C-amination, N-amination, S-NH_2, Boronic acid to amine**
- ✓ **Amidation and Cyanation**

In 2017, Zhiwei Ma and co-workers have developed an efficient protocol for stereospecific N-H and N-Alkyl aziridination of olefins using HOSA as the nitrogen source. Structurally varied alkenes **(1)** on treatment with HOSA **(E)** (1.2 eq.) in the presence of 1 mol% $Rh_2(esp)_2$ catalyst and 1.2 eq. pyridine in HFIP at 25 ^oC produced the corresponding aziridine **(2)** with high regio and stereoselectivities. (Scheme 1.1).[78]



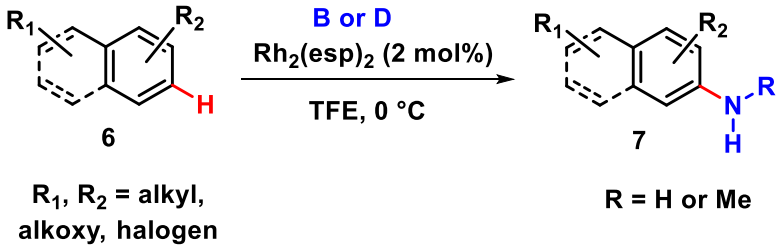
Scheme 1.1. *N*-H Aziridination of olefins using HOSA

Alexander *et. al.* developed an improved methodology to synthesize differently substituted diaziridines **(5)** by reacting different aldehydes **(3)** with amines **(4)** and HOSA **(5)** in the presence of an inorganic base such as $NaHCO_3$ or K_3PO_4 (Scheme 1.2).[79] The diaziridines **(5)** were obtained with a single diastereomer in excellent yield.



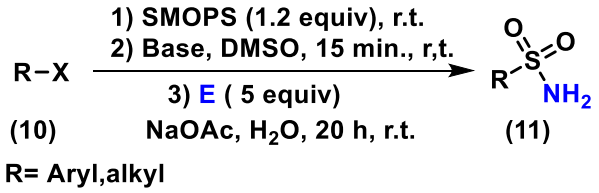
Scheme 1.2. Synthesis of diastereoselective diaziridines

Falck and co-workers reported direct C-H arene amination in the presence of $Rh_2(esp)_2$ (Du-Bois) catalyst in TFE solvent at 0 °C using *O*-(mesitylsulfonyl)hydroxylamine **B** and *N*-methyl-*O*-sulfonyl-hydroxylamine **D** as nitrogen source (Scheme 1.3).[80]



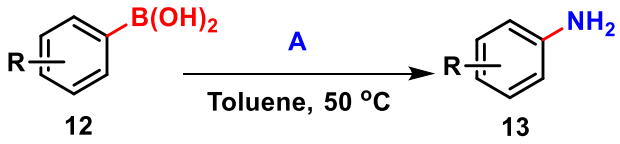
Scheme 1.3. C-H arene amination using MSH and TsONHMe reagents

Jeremy M. Baskin *et. al.* have reported a simple and efficient strategy on the synthesis of sulfinic acid salts and sulfonamides from various corresponding alkyl and aryl halides using SOMPS and HOSA in DMSO at room temperature (Scheme 1.4**)**.[81]



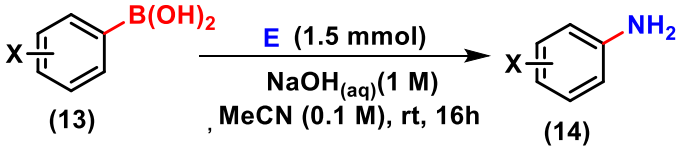
Scheme 1.4. Synthesis of alkyl sulfonamide using HOSA

A metal-free protocol for the synthesis of aryl amines from the corresponding aryl boronic acids was developed by Falck and Kürti. They developed an efficient protocol for the conversion of aryl boronic acids into aryl amines using DPH **(A**) as a nitrogen source in toluene solvent at 50 ^{o}C (Scheme 1.5).[82]



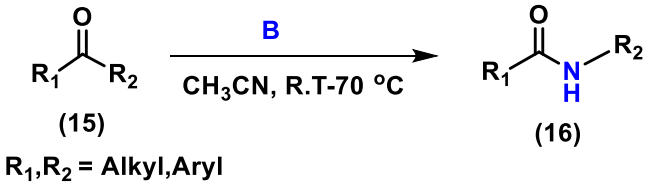
Scheme 1.5. Synthesis of primary anilines from aryl boronic acid using DPH

Voth and co-workers have introduced an efficient transition metal-free approach for the direct conversion of phenylboronic acid into primary anilines using HOSA. Boronic acid **(13)** was reacted with HOSA **(E)** in the presence of aq. NaOH in MeCN at room temperature and the corresponding aniline **(14)** was obtained in excellent yield (Scheme 1.6).[83]



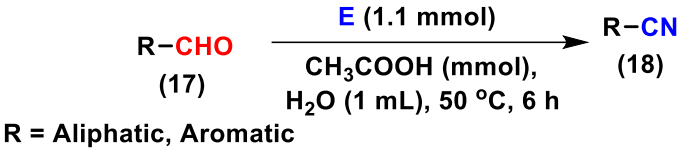
Scheme 1.6. Synthesis of primary anilines using HOSA as nitrogen source

Dinesh Chandra *et al.* accomplished a metal free operationally simple and highly effective Beckmann rearrangement for direct synthesis of secondary amides from ketones using *O*-(mesitylsulfonyl)hydroxylamine as nitrogen source in acetonitrile solvent (Scheme 1.7) [84]



Scheme 1.7. Metal-free direct synthesis of secondary amide from ketone.

Quinn *et. al.* developed an efficient approach to convert aldehydes into nitriles using HOSA. The aldehydes were heated with HOSA (**E)** (1.1 eq.) at 50 °C in acidic water to produce the desired nitriles in excellent yields (Scheme 1.8).[85]



Scheme 1.8. Direct synthesis of nitriles from aldehydes

1.6 Conclusion

Nitrogen containing compounds like secondary amides, anilines and nitriles are present in the numerous bioactive natural and value added compounds, synthetic and semi-synthetic products. In the literature survey, the methods for the synthesis of nitrogen containing compounds have several drawbacks like use of toxic metals, multi-step process, elevated temperature, use of additives etc. In this direction aminating agents, like *O*-(substituted)hydroxylamines, have been recently used to transfer nitrogen in various synthetic reactions (such as C-H amination, aziridination, Beckmann rearrangement etc). Some of the special features of *O*-(substituted)hydroxylamine reagent are generating water-soluble by-products makes the process environmentally benign, commercial availability, non-toxic nature etc makes them popular. In this context, the development of any direct mild and efficient method for amidation, cyanation and amination using *O*-(substituted)hydroxylamines reagents will be highly desirable.

1.7 Motivation of the present work

Various applications of nitrogen-containing compounds discussed above have positively motivated us to further develop mild, highly efficient, and benign methods with a broad range of applications and understandings in synthetic organic chemistry. Keeping in mind, our aim is to develop a one-pot, mild, simple, economical, and practical method for amidation, cyanation, and amination using TsONHBoc as the nitrogen source.To accomplish our task, we used TsONHBoc as an aminating reagent for the following reasons: (a) Its existence in non-zwitter ionic form (b) Stable and readily available and (c) Generation of a non-interfering and non-nucleophilic by-products that can be easily removed by using basic aqueous work-up.

1.8 References

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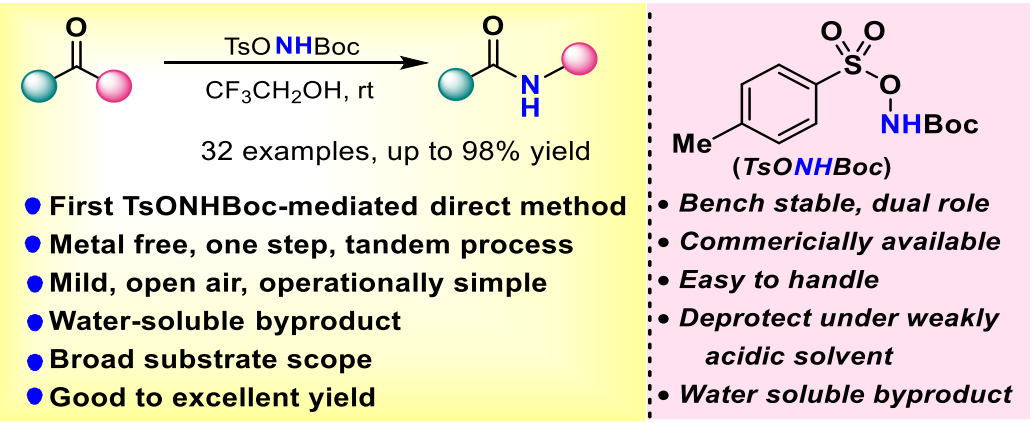
Chapter 2

Direct and metal-free transformation of ketones into *sec*-amides using TsONHBoc as a aminating reagent

This chapter describes the first methodology for the conversion of ketones directly into the *sec*-amides *via* Beckmann rearrangement using TsONHBoc as the nitrogen source. It is anticipated that this reagent played dual roles: first, it promotes the generation of the activated oxime intermediate and then facilitates the formation of amides. The additive and metal-free direct method works in weakly acidic solvent and generated a water-soluble byproduct (TsOH), which can be easily removed by basic aq. work-up.



New J. Chem. **2022**, *46*(31), pp. 14782-14785.

2.1 Introduction

Secondary amides are essential structural constituents of widespread medicines, biologically potent molecules, polymeric materials, dyes, and other multifunctional products, including adaptable building blocks for chemical reactions (Fig. 2.1- 2.4).[1] The synthesis of both drugs and alkaloids involves the conversion of amides into nitrogen-containing hetero-atomic molecules, which is a highly intriguing process.[2]

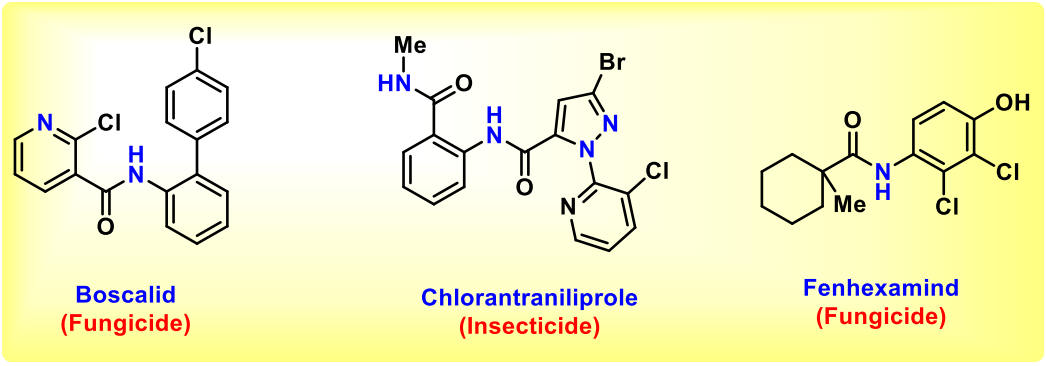


Figure 2.1. Selected examples of agrochemicals containing *sec*-amide linkage

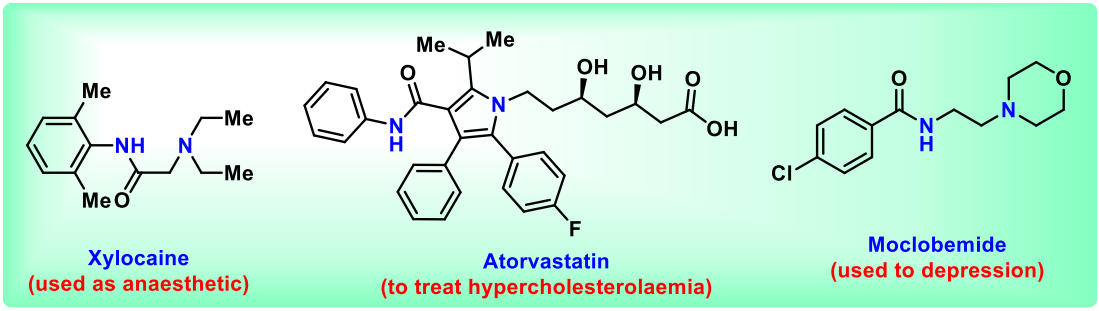


Figure 2.2. Selected examples of drug molecules containing *sec*-amide linkage

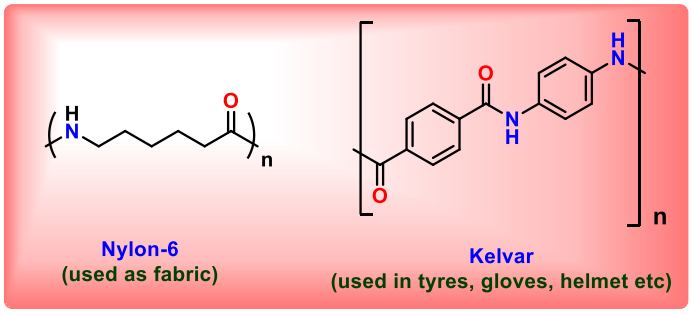


Figure 2.3. Selected examples of polymers containing *sec*-amide linkage

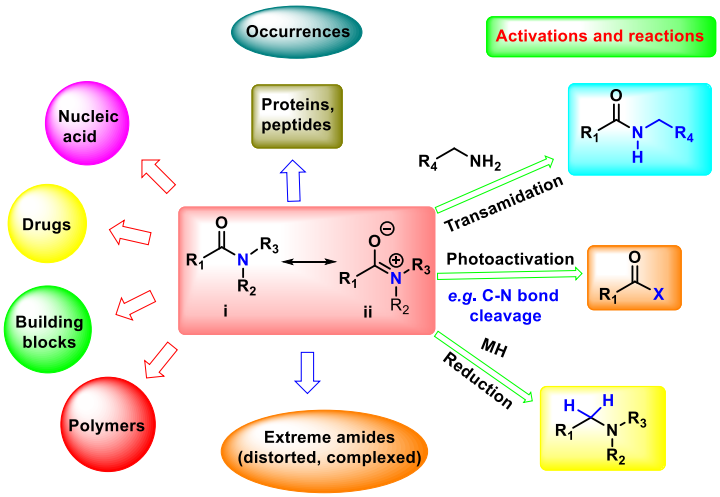
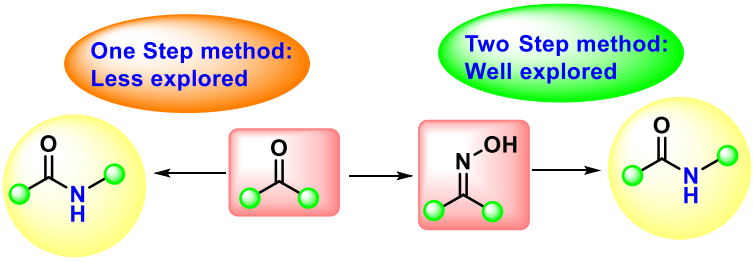


Figure 2.4. Synthetic transformations of amide

Conventionally, secondary amides were synthesized with the use of amines and carboxylic acid derivatives, but with insufficient atom economy.[3] Its use for industrial purposes was restricted by the unwanted waste that was excreted during these reactions. In 1886, Ernst Otto Beckmann reported the amide synthesis from oxime.[4] Due to the harsh reaction conditions (elevated temperature and use of strong acids), limit its applications for sensitive substrates. Significant progress has been made to address these issues, and several ketoxime-mediated methods have been developed. However, the methods for the synthesis of secondary amides directly from ketones are less explored (Scheme 2.1).



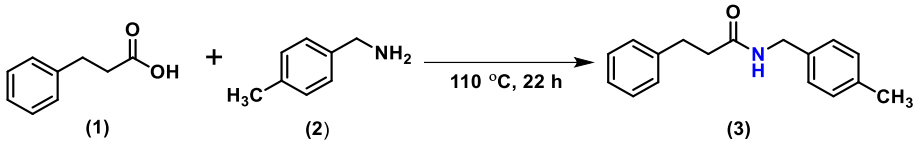
Scheme 2.1. Synthesis of *sec*-amides from ketones.

Herein, an up-to-date progress for the synthesis of *sec*-amides are described in section 2.2.

2.2 Synthesis of Secondary amides: Literature review

2.2.1 Synthesis of *sec*-amides *via* acid amine coupling

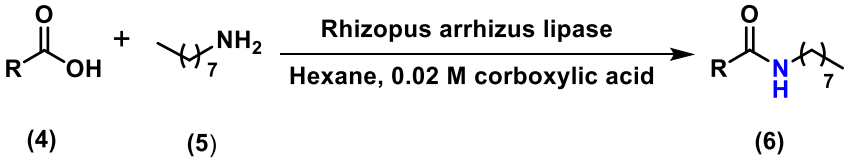
Conventionally, secondary amides were synthesized with the help of carboxylic acid derivatives and amines with poor atom economy. Amides can also be generated thermally *via* the coupling of a carboxylic acid and an amine without using a catalyst at >140 °C.[5] Recently, it was revealed that a substantial amount of amide can also be produced even at low temperatures by the azeotropic removal of water (Scheme 2.2).[6-8]



Scheme 2.2. Synthesis of *sec*-amides *via* acid amine coupling

2.2.2 Synthesis of secondary amides using biocatalyst

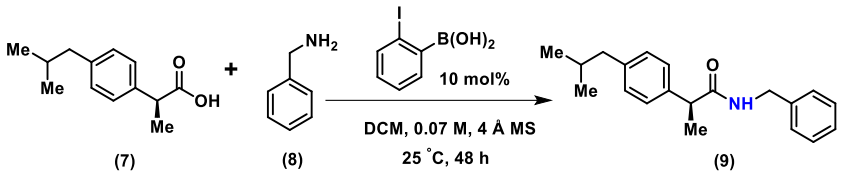
The first approach was proposed by Ulijn *et al.* for the amidation of carboxylic acids directly in the presence of protease as a biocatalyst.[9] The synthesis of protein chain in the presence of catalyst using pair of amino acids under a chemically favorable reaction was also described (Scheme 2.3).



Scheme 2.3. Amidation of carboxylic acids using Rhizopus arrhizus lipase biocatalyst

2.2.3 Synthesis of secondary amides using boron catalyst

Hall and coworkers reported that phenylboronic acid having a substitution at *ortho* position, especially phenylboronic acid containing iodo group at *ortho* position, were effective catalysts at r.t. for amidation reactions.[10] This method required 48 hours and more dilute concentration (0.07 M) than earlier methods and a variety of amides were generated at only 25 °C in THF or DCM with up to 90% yields (Scheme 2.4).



Scheme 2.4. Amidation of carboxylic acids using boron based catalyst

2.2.4 Metal catalyzed synthesis of Secondary amides *via* acid amine coupling

Talukdar *et al.* employed solvent-free microwave irradiated method for the synthesis of *N*-methylamides from carboxylic acids and *N*,*N*-dimethylurea using $ZrOCl_2.8H_2O$ as a catalyst.[11] A variety of amides were produced in short reaction durations with moderate to high yields (Scheme 2.5).

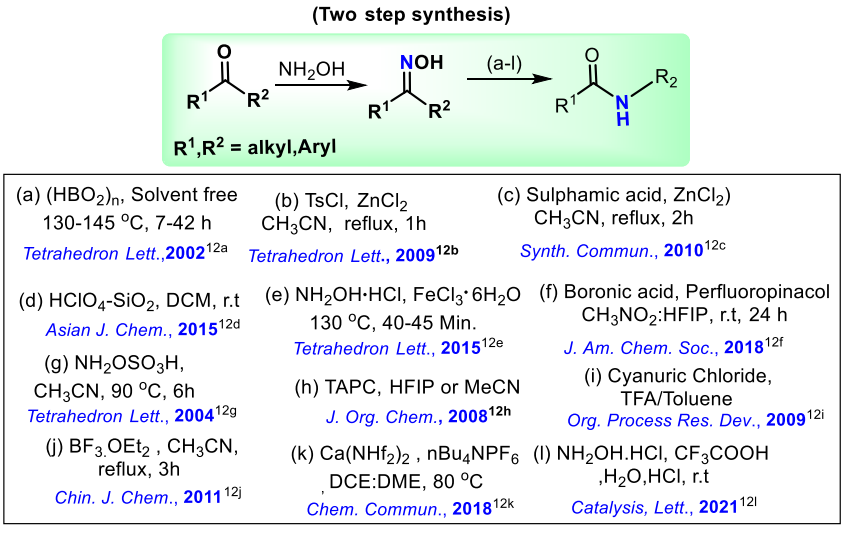
Scheme 2.5. Zr- catalyzed amidation of carboxylic acids

2.2.5 Acid catalysed synthesis of Secondary amides from oxime via Beckmann rearrangement (Two step synthesis of *sec*-amides)

Ketoximes were traditionally subjected to the Beckmann rearrangement (BKR) in the presence of Lewis or Brønsted acids, like phosphorous pentachloride in $(C_2H_5)_2O$ solvent, concentrated H_2SO_4, and HCl in $(Ac)_2O$, but these procedures have major problems, like corrosiveness, hazardous to the environment, and produces a high amount of byproducts. Therefore, to resolve these problems, several new mild protocols that were less harmful to the environment were developed.

Chandrasekhar *et al*. revealed metaboric acid catalyzed BKR for the synthesis of secondary amides from ketones.[12a] Jun and co-workers reported the Beckmann rearrangement to convert ketoximes into the amides using TsCl.[12b] Li *et al*. developed a high temperature-induced Beckmann rearrangement mediated by sulfamic acid and zinc chloride as a catalyst.[12c] Umanadh *et al.* developed a BKR protocol using silica adsorbed perchloric acid.[12d] Mahajan *et al.* reacted hydroxylamine hydrochloride with ketones in absence of

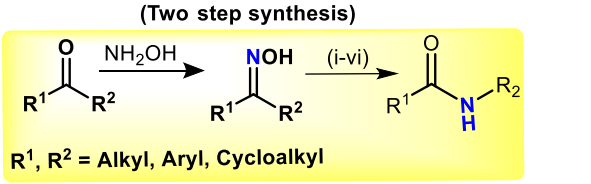
solvent to synthesize secondary amides through Beckmann rearrangement using hydrated ferric chloride as a catalyst with moderate to high yields.[12e] Mo *et al.* demonstrated ortho phenylcarbonyl phenyl boronic acid and *ortho* alkoxycarbonylbenzene boronic acid catalyzed BKR for the synthesis of secondary amides and produced a variety of amide derivatives.[12f] B. Wang and co-workers reported an efficient protocol, they treated ketoxime with hydroxylamine-*O*-sulfonic acid in dry acetonitrile for the production of the corresponding amide *via* Beckmann rearrangement.[12g] Hashimoto and co-workers synthesized secondary amides from ketoximes using TAPC in HFIP or acetonitrile solvent. Cyclohexanone oxime can readily be converted to the corresponding lactam under this condition.[12h] Hashimoto and his research group converted cyclohexanone oxime into corresponding ε-caprolactam utilizing phosphazene TAPC or cyanuric chloride.[12i] A cost-effective and efficient protocol was reported by An *et al*. using boron trifluoride etherate ($BF_3.OEt_2$), catalyzed Beckmann rearrangement in anhydrous acetonitrile.[12j] Kiely-Collins and co-workers reported mild calcium-catalyzed Beckmann rearrangement. This method provided high to good yield, well functional group tolerance and broad substrate scope.[12k] F. Manente and co-workers in 2021 reported organocatalytic trifluoroacetic acid (TFA) mediated Beckmann rearrangement to prepare cyclohexanone amide ε-caprolactam from cyclohexanone oxime using hydroxylamine hydrochloride and HCl in water (Scheme 2.6).[12l]



Scheme 2.6. Acid and metal-catalyzed Beckmann rearrangement (two-step synthesis)

2.2.6 Transition metal-catalyzed synthesis of *sec*-amides from oxime *via* Beckmann rearrangement

Arisawa *et al*. reported $[RhCl(cod)]_2$ catalyzed Beckmann rearrangement for conversion of ketoxime to amide using tris(*p*-tolyl) phosphine and CF_3SO_3H.[13a] Yadav and co-workers reported the Beckmann rearrangement using $Yb(OTf)_3$ as a catalyst for the synthesis of desired amides and lactams from respective ketoximes.[13b] De *et al*. disclosed the $Y(OTf)_3$ catalyzed Beckmann rearrangement of ketoxime to the corresponding amide.[13c] Ramalingan revealed the transformation of oximes to corresponding amides using Hg_2Cl_2.[13d] Mitsudome and co-workers have described the liquid-phase Beckmann rearrangement of a variety of ketoximes into the corresponding amides which are catalyzed by titanium cation-exchanged montmorillonite.[13e] Mandal and co-workers reported the synthesis of ε-caprolactam *via* Beckmann rearrangement. This reaction was found to be extremely effective when niobium was included in mesoporous silica (Nb-HMS-X) (Scheme 2.7).[13f]



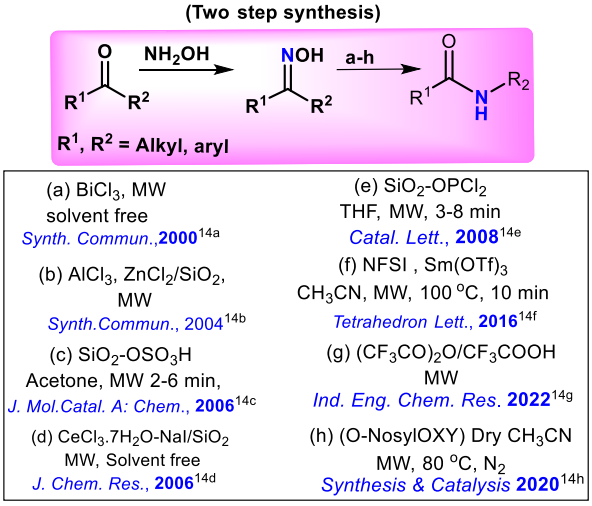
(i) $[RhCl(cod)]_2$, CF_3SO_3H, $(p\text{-tol})_3P$ $(ClCH_2)_2$, refluxing, 3h	*Org. Lett.*, **2001**[13a]
(ii) $Yb(OTf)_3$,Heat, CH_3CN	*J. Chem. Res. (S),* **2002**[13b]
(iii) $Y(OTf)_3$	*Org. Prep. and Proced. Inter.*, **2004**[13c]
(iv) $HgCl_2$, CH_3CN, 8 h	*J. Org. Chem.*, **2007**[13d]
(v) Ti-mont, Benzonitrile 90 °C, 7h, Ar	*Tetrahedron Lett.*,**2012**[13e]
(vi) Nb incorported Mesoporous silica catalyst Nb-HMS-X	*RSC Adv.*, **2014**[13f]

Scheme 2.7. Transition metal catalyzed Beckmann rearrangement

2.2.7 Microwave-assisted synthesis of *sec*-amides from oxime *via* Beckmann rearrangement

A. J. Thakur and coworkers reported the conversion of ketoximes into the corresponding amides using $BiCl_3$ under microwave irradiation.[14a] F. M. Moghaddam *et al.* reported the

transformation of ketoximes to respective amides using $AlCl_3$-$ZnCl_2/SiO_2$ under microwave irradiation.[14b] Z. Li and co-workers, developed silica sulphate catalyzed the transformation of ketoximes to corresponding amides in acetone using microwave radiation.[14c] Z. Li and co-workers reported solvent-free and microwave-assisted conversion of ketoximes to respective amides.[14d] Li and group revealed microwave-assisted and silica-supported phosphorus chloride catalyzed conversion of ketoximes to desired amides in THF solvent.[14e] *N*-fluorobenzenesulfonimide (NFSI) Lewis acid-catalyzed conversion of ketoximes to corresponding amides was reported by F. Xie and co-workers. Lewis acids have a great ability to promote the electrophilicity of NFSI using several easily accessible oximes substrates.[14f] Chencan Du *et al.* recently reported the microwave assistated organocatalytic Beckmann rearrangement to synthesize the desired lactam from cyclohexanone oxime using trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA).[14g] Dharm Dev *et al.* have reported a microwave assisted protocol utilizing 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate to convert oximes into amides in dry acetonitrile at 80 ^oC (Scheme 2.8).[14h]

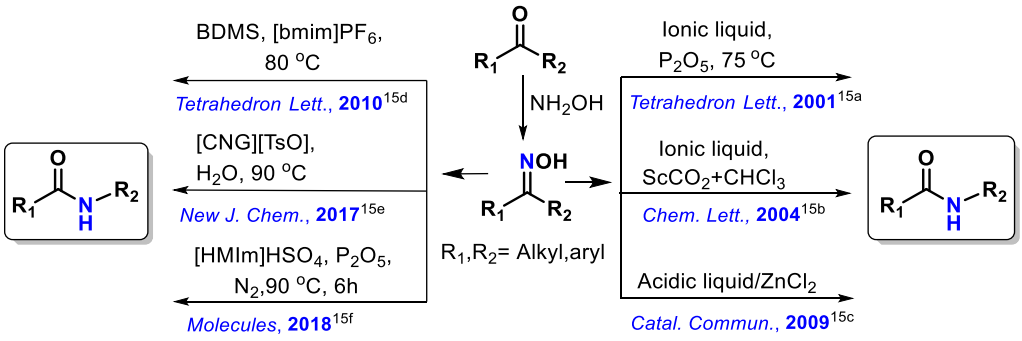


Scheme 2.8. Microwave assisted Beckmann rearrangement from ketoximes

2.2.8 Synthesis of *sec*-amides from oxime *via* Beckmann rearrangement in ionic liquids

R. X. Ren *et al.* reported the Beckmann rearrangement with P_2O_5 to generate caprolactam from cyclohexanone oxime using (1-n-butyl-3-methylimidazolium hexafluorophosphate)

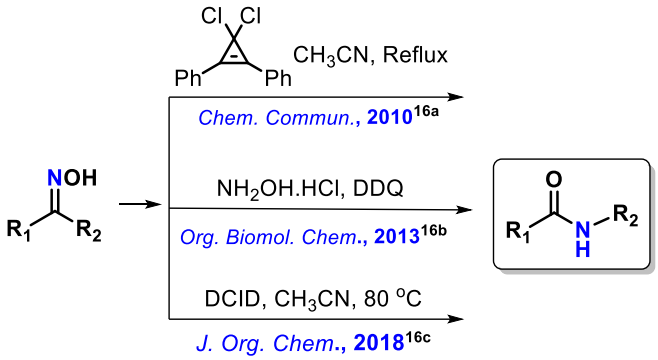
([bmim][PF6]) as ionic liquid solvent.[15a] K. Oiao *et al.* reported the synthesis of the desired lactam from cyclohexanone oxime utilizing supercritical carbon dioxide and chloroform as the extractant in presence of an acidic ionic liquid catalyst.[15b] Liu and co-workers used ionic liquid acidified with bronsted acid that contained a double -SO_3H cation and zinc chloride as catalyst.[15c] Yadav *et al.* reported BDMS (bromodimethylsulfonium bromide) catalyzed Beckmann rearrangement using [bmim]PF_6 which provided excellent yields of corresponding amides and lactams from their respective ketoximes. Additionally, the ionic liquid can be re-used three times.[15d] Production of the desired lactam from cyclohexanone oxime using new salt cyanoguanidinium tosylate (ionic liquid) was reported by Fernández-Stefanuto *et al.*[15e] Zhao *et al.* reported the acidic ionic liquid-*N*-methylimidazolium hydrosulfate catalyzed Beckmann rearrangement. The benzophenone oxime transformed into the desired amide with moderate yields at elevated temperature, however, addition of P_2O_5 yielded the desired amide with excellent yield (Scheme 2.9).[15f]



Scheme 2.9. Beckmann rearrangement in ionic liquids (Two step synthesis)

2.2.9 Miscellaneous methods

Srivastava *et al.* reported organocatalytic Beckmann rearrangement using the 1-Chloro-2,3-diphenylcyclopropenium ion as a highly efficient organocatalyst to synthesize desired amides from the different ketoximes.[16a] To generate the appropriate amides using sp3 C-H and C-C bond breaking, Qiu and co-workers reacted hydroxylamine hydrochloride with benzyl hydrocarbons in presence of DDQ as a promotor to synthesize ketoxime which further transformed into the corresponding amides.[16b] Dichloroimidazolidinediones (DCIDs) mediated Beckmann rearrangement was revealed by Gao and co-workers in acetonitrile solvent at 80 °C (Scheme 2.10).[16c]

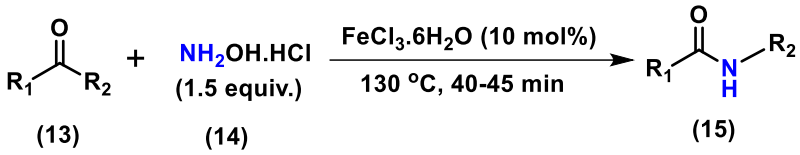


Scheme 2.10. Miscellaneous methods for the amide synthesis

2.2.10 Direct synthesis of Secondary amides from ketones *via* Beckmann rearrangement (one-step synthesis)

The direct methods for the synthesis of secondary amides from ketones are less explored and these are summarized below.

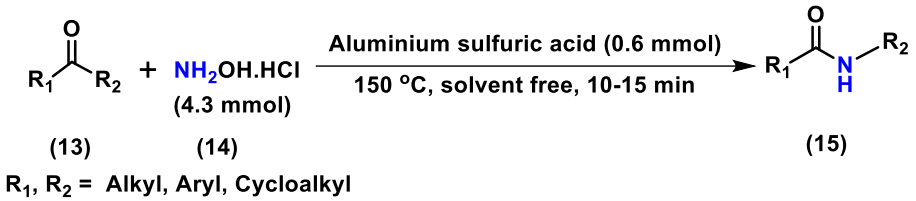
i) Mahajan *et al*. revealed ferric chloride catalyzed protocol of secondary amides directly from ketones using hydroxylamine hydrochloride under solvent-free conditions with excellent yields. *In-situ* generation of oxime took place under a solid phase process, where C-C bond cleavage and C-N bond formation occurred. Ferric chloride is stable, affordable, environmentally benign, and simple to use**.** This protocol has some limitations like the use of the additive, elavated temperature, poor functional group tolerance etc (Scheme 2.11).[17]



Scheme 2.11. $FeCl_3.6H_2O$ catalyzed direct synthesis of secondary amide from ketone

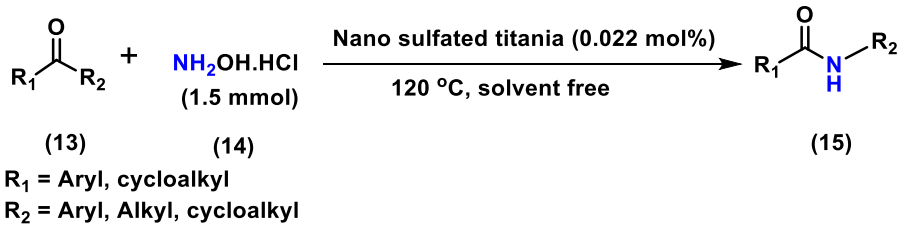
ii) M. Hosseini-Sarvari and H. Sharghi have developed a protocol for the direct preparation of secondary amides by reacting ketones with $NH_2OH.HCl$ and aluminium sulfuric acid (ASA) in the absence of solvent. Various Aliphatic and aromatic ketones were converted into the corresponding secondary amides selectively with one isomeric form. Cyclic ketones react slowly as compared to aromatic ketones to provide a good yield of

corresponding lactams. Although the method works well it has some drawbacks such as the utilization of strong acid, higher temperature leading to a narrow range of functional group tolerance, poor substrate scope and a slower rate of reaction in the case of aliphatic cyclic ketones etc. (Scheme 2.12).[18]



Scheme 2.12. Direct synthesis of secondary amides from ketones using ASA

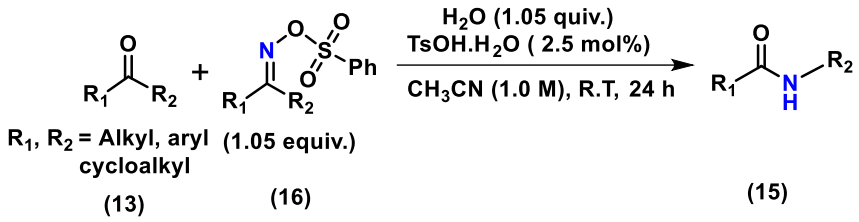
iii) Nano-catalyzed Beckmann rearrangement for direct synthesis of secondary amides from ketones was reported by Hosseini-Sarvari and co-workers using nano- TiO_2/SO_4^{-2} solid catalyst in the absence of solvent at elevated temperature. In this methodology cyclic ketones like cyclopentanone, cyclohexanone and cycloheptanone were converted into the corresponding lactams with excellent yields. Aromatic ketones were also provided the corresponding amides in excellent yields. Unfortunately, this methodology did not work with aliphatic acyclic ketones. It has some other limitations like poor substrate scope and it requires elevated temperature for the generation of corresponding amides (Scheme 2.13).[19]



Scheme 2.13. Nano catalyzed direct synthesis of secondary amides from ketones

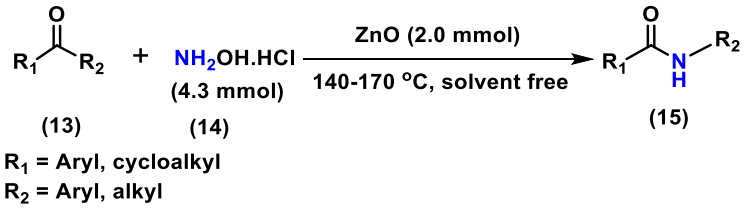
iv) K. Hyodo *et al.* reported Brønsted acid catalyzed mild and efficient Beckmann rearrangement for direct transformation of ketones into secondary amides through transoximation at room temperature in acetonitrile solvent. In this methodology, heterocyclic and electron-rich aromatic ketones reacted well and provided moderate to excellent yields of corresponding amides respectively at room temperature. However,

halogenated aromatic ketones reacted slowly and generated corresponding amides with excellent yields at 40 ^{o}C. Cyclic ketones transformed into the corresponding lactams with good to excellent yields at 40 ^{o}C. Ketones containing nitro and cyano groups generated the corresponding amides at higher temperatures. They reported that water is essential to accelerate the rate of reaction. This protocol required very low temperature (-10 ^{o}C) to produce the corresponding amide in case of acetophenones having cyclopropyl, cyclohexyl rings at the alpha position and 0 ^{o}C for acetophenone containing alpha-methyl group. Some substrates like tetralone produced an isomeric mixture of amides at reflux (Scheme 2.14). [20]



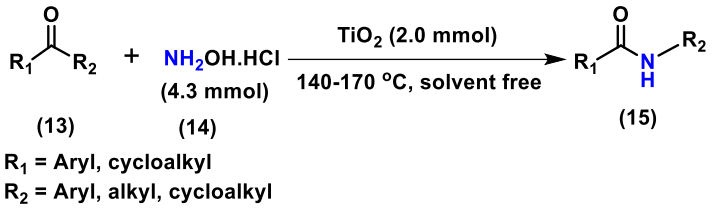
Scheme 2.14. Brønsted acid catalyzed direct synthesis of secondary amides

v) H. Sharghi and co-workers reported a solvent free efficient protocol for the synthesis of secondary amides from ketones using hydroxylamine hydrochloride and zinc oxide (ZnO). ZnO is easy to handle, non-toxic, and economical. The developed methodology worked very well with aromatic electron rich ketones and with halogenated aromatic ketones providing excellent to good yields of corresponding amides. Cyclic ketones also transformed into corresponding lactams with excellent yields. The major limitation of this methodology is that it did not work with aliphatic acyclic ketones and the use of elevated temperature limits its exploration of substrates having labile groups (Scheme 2.15).[21]



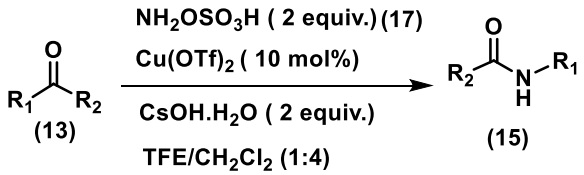
Scheme 2.15. ZnO catalyzed direct synthesis of secondary amide from ketone

vi) Same authors developed the methodology for the direct transformation of ketones into secondary amides, using hydroxylamine hydrochloride in the presence TiO_2 (2.0 mmol). Electron rich aromatic ketones provided excellent yields of corresponding amides. Cyclic ketones also reacted well and generated corresponding amides with good yields. The developed method has several advantages like solvent-free, environmentally benign, easy to handle, use of an easily accessible economic catalyst, and high yields. Although this method is good, it required a higher temperature for the generation of corresponding secondary amides (Scheme 2.16).[22]



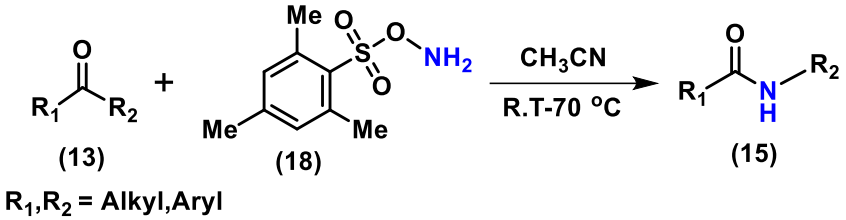
Scheme 2.16. TiO_2 catalyzed direct synthesis of secondary amides from ketones

vii) Munnuri *et al.* developed a mild and efficient $Cu(OTf)_2$ catalyzed protocol to convert ketones directly into secondary amides using HOSA as a nitrogen source. Ketones were treated with HOSA and base $CsOH.H_2O$ in TFE/CH_2Cl_2 to produce the corresponding amide. Substrates containing electron-donating groups provided excellent yields of the corresponding amides at r.t. However, substrates having electron-withdrawing groups afforded lower yields or require elevated temperature. Cyclic ketones produced corresponding lactams in good yields. Aliphatic ketones were heated to generate the amides in moderate yields. Different functional groups such as ether, ester, alcohol, allylic group, *t*-butyl group *etc*., were well tolerated under this condition. The major limitation of this protocol is the use of the stoichiometric amount of additives ($CsOH.H_2O$) (Scheme 2.17).[23]



Scheme 2.17. $Cu(OTf)_2$ catalyzed direct synthesis of secondary amides

viii) Dinesh Chandra *et al.* accomplished an operationally simple and highly effective Beckmann rearrangement for direct synthesis of secondary amides from ketones using *O*-(mesitylsulfonyl)hydroxylamine (MSH) as a nitrogen source in acetonitrile solvent without using metal. This method works very well with all types of aromatic ketones such as electron rich, electron deficient, heterocyclic, aliphatic cyclic and acyclic ketones provided good to excellent yields of corresponding secondary amides. This methodology has certain drawbacks such as a less stable aminating agent, which requires fresh preparation in every use (Scheme 2.18).[24]



Scheme 2.18. Metal free direct synthesis of secondary amide from ketone

In conclusion, although the above-developed methods have made significant advancements in the field of secondary amide synthesis, however, most of them still suffer from some limitations such as limited substrates scopes, tedious purification process, poor to average yield, longer reaction time, the requirement of additive, non-environmentally benign process and non-compatible with acid-sensitive group and the less exploration of amide from ketones in a single step. Therefore, the need for more research has seemed to be done towards the development of more efficient, mild, operationally simple and direct methods for the conversion of ketones into secondary amides. This encouraged us to ameliorate the synthetic strategy of amides toward a mild reaction condition with economical, practical, and environmentally favorable conditions.

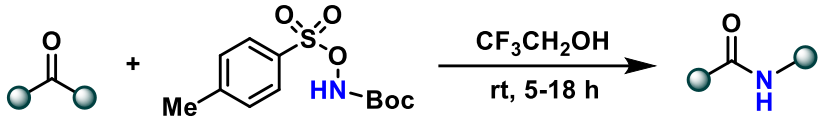
In this direction, *O*-substituted hydroxylamines[25] reagents have attracted our attention for its application in amidation reaction. However, the preparation of these compounds has some inherent disadvantages, such as the requirement of an additional step of *N*-Boc deprotection using strong acid (TFA), the explosive and highly unstable nature of the isolated product (e.g., $TsONH_2$), the requirement of a fresh preparation (MSH), storage at

0 ^{o}C or below, hygroscopic and zwitter ionic form (hydroxylamine-*O*-sulfonic acid).[26] The above limitations encourage us to develop a newer methodology that proceeds *via in situ* de-protection of *N*-Boc group that eliminates the additional de-protection and isolation of highly unstable *N*-free reagent.

2.3 Objective of the work

So, the objective of this chapter of the thesis was to develop a highly efficient metal free, one pot method for the synthesis of secondary amides from ketones under mild and additive-free condition.

Herein, we have used the TsONHBoc for the first time as the aminating agent for the direct synthesis of *sec*-amides from ketones (Scheme 2.19). The active amino reagent ($TsONH_2$) is produced *in situ* through TFE mediated *N*-Boc deprotection at room temperature.



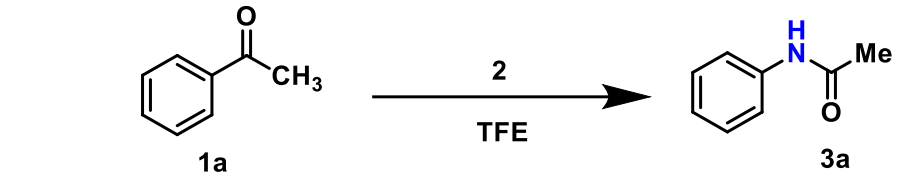
Scheme 2.19. Direct method for the synthesis of *sec*-amides from ketones

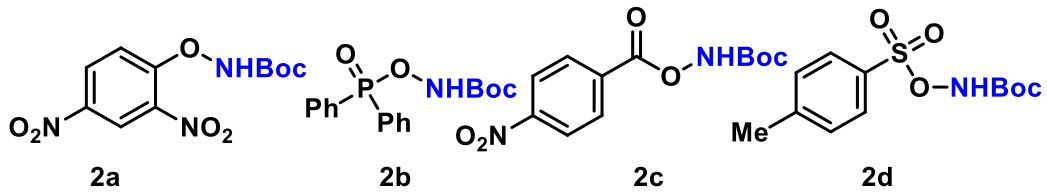
2.4 Result and discussion

2.4.1 Optimization of the reaction condition

We started the reaction optimization by investigating various aminating agents for the *in situ* cleavage of the *N*-Boc protecting group in weakly acidic solvent (TFE), (Table 2.1). Several *O*-substituted hydroxylamines **(2a-d)** were tried, and the *N*-Boc group was intact in the case of **2a-c** (entry **1-3**).

Table 2.1: Optimization of reaction condition[a]



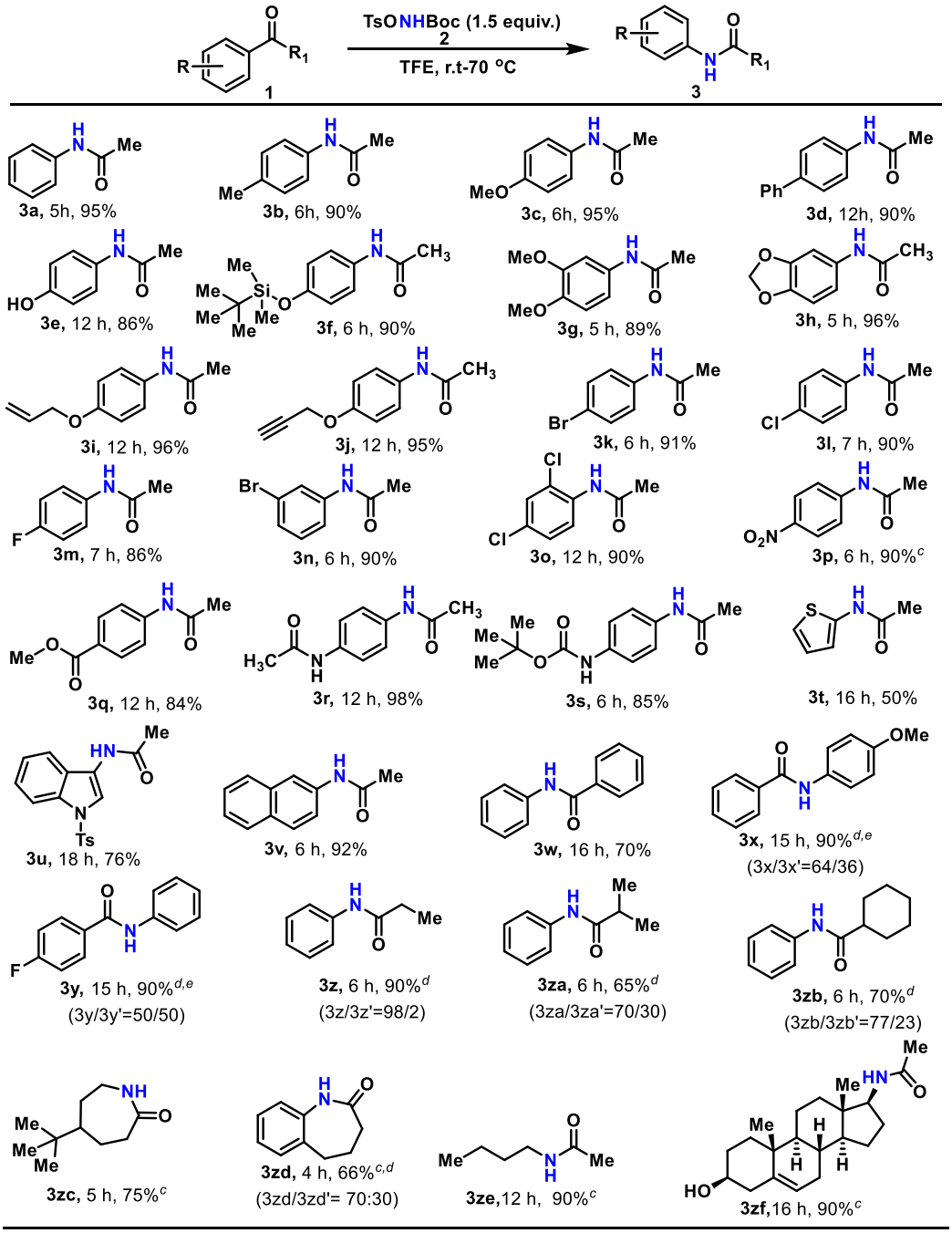


Entry	Aminating reagent	Yield (%)[b]
1	2a	0
2	2b	0
3	2c	0
4	2d	95
5[c]	2d	0

[a]Reaction condition: **1a** (0.5 mmol, 1.0 equiv.), aminating agent **2** (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt. [b]Isolated yield. [c]No reaction was observed in other solvents like MeOH, CH_3CN, CH_2Cl_2, THF, DMF

Subsequently, a similar reaction condition was applied to *N*-Boc-*O*-tosylhydroxylamine **2d**, and to our surprise, *N*-Boc was de-protected *in situ*, yielding the desired amide **3a** with a higher yield of 95% (entry 4). Other commonly used solvents such methanol, CH_3CN, CH_2Cl_2, THF, and *N*,*N*-dimethyl formamide were ineffective (entry 5).

2.4.2 Preparation of secondary amides[a,b]



[a]Reaction condition: **1** (0.5 mmol, 1.0 equiv.), TsONHBoc **2d** (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt, [b]Isolated yield. [c]Reaction performed at 80 °C [d]Regioisomers observed, ratio determined by ^{1}H NMR of the crude mixture and major isomer is shown here. [e]mixture of non-separable regioisomers.

Scheme 2.20. Preparation of *sec*-amides from ketones

Further to check the scope of this method, various ketones were examined under optimized reaction conditions (Scheme 2.20). Firstly, we tried acetophenones containing electron donating groups at para position. The para-substituted electron rich acetophenone, having methyl, methoxy, or phenyl groups, easily transformed into the corresponding amides with excellent yields (**3b**-**3d**). Acetophenone having a free hydroxyl group survived very well and provided excellent yields of corresponding amide (**3e**). Under the optimized reaction condition, a very labile TBS group was well tolerated (**3f**). Disubstituted acetophenones proved to be good substrates and readily produced desired product (**3g** and **3h**). The excellent yield of amides (**3i and 3j**) was obtained from ketones containing reactive functionalities like allyloxy and propargyloxy. On further exploration of substrate scope, we tried acetophenones having electron withdrawing group like halogens at different positions on aromatic ring, which provided excellent yields of corresponding amides (**3k-3o**). *p*-nitro acetophenone produced the desired product **3p** with a 90% yield at a higher temperature. This process tolerated many sensitive functional group like Boc, ester and amide (**3q-s**). Heteroarylic ketones transformed into desired amides (**3t** and **3u**) with 50% and 76% yields respectively. The naphthyl substituted ketones generated corresponding amide **3v** with 92% yield. Under optimized reaction conditions, diaryl ketones generated isomeric mixtures of the corresponding amides (**3x-3y**) because of the difference in the migratory aptitude of groups. Substrates **2za-2zb** produced the desired product (**3za-3zb**) in the form of an isomeric mixture. Substituted cyclohexanone transformed into desired lactam **3zc** with 75% yield at slightly elevated temperature. Aliphatic ketones were readily converted into corresponding amide **3ze** with an excellent yield. Complex substrate like pregnenolone provided excellent yields of the desired amide **3zf** under the similar reaction condition**.**

2.5 Conclusion

We have described the first application of TsONHBoc reagent for the direct synthesis of *sec*-amides from ketones. The benefit of this reagent is that it doesn't need strong acid (TFA) to de-protect Boc group as it gets easily cleaved under TFE and generates an active $TsONH_2$ reagent. We believe this method may find suitable applications in the industry.

2.6 Experimental section

2.6.1 General Information

Unless otherwise stated, all the reactions were carried out using oven dried glassware under an open atmosphere in a round bottom flask with magnetic stirring bar at room temperature. Ketones were used as received without further purification. The aminating reagents were also prepared by following reported literature. TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}) and the spots were visualized with UV light or by charring the plates dipped in PMA or Ninhydrin or DNP solution. The compounds were purified by flash column chromatography using silica gel (100-200 mesh) with distilled solvents (EtOAc:Hexane) as mobile phase otherwise mentioned. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz instruments respectively in $CDCl_3$ or DMSO-d_6 solvents. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, DMSO-d_6: δ H = 2.5 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br s = broad signal.

2.6.2 Preparation of aminating reagents

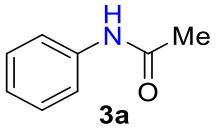
Aminating reagents **2a**[27]**, 2b**[28], **2c**[29] and **2d**[30] were synthesized in accordance with the methods described in the literature.

2.6.3 General procedure for preparation of *sec*-amides from ketones

In an open round bottom flask ketones (0.5 mmol, 1.0 equiv.) and aminating agent (0.75 mmol, 1.5 equiv.) were dissolved in TFE solvent (0.5 mL) at room temperature The solution was stirred until complete conversion, determined by TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the resulting mixture was diluted with ethyl acetate (10 mL) and extracted with a solution of EtOAc (3×5 mL). The organic layer was washed with brine solution (5 mL) and dried over anhydrous Na_2SO_4. The crude product was obtained after the removal of all volatiles in *vaccuo* and was washed with *n*-hexane to remove some minor non-polar impurities (for **3a-d**, **3g**, **3k-n** and **3r**) or passed through a plug of silica gel using ethyl acetate and hexane as eluent to get pure amides.

2.7 Characterization of the products

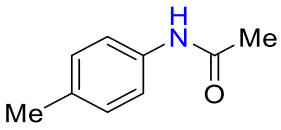
N-Phenylacetamide (3a): Prepared according to general procedure and titled amide was isolated as white solid (65 mg, 95% yield; m. p. 113-115 °C) whose spectral data was consistent with the literature values.[31]



3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.16 (s, 3H).

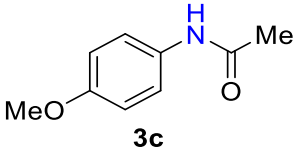
N-(p-Tolyl)acetamide (3b): Prepared according to general procedure and titled amide was isolated as white solid (67 mg, 90% yield; m. p. 151-152 °C) whose spectral data was consistent with the literature values.[31]



3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 2H), 7.20 (br s, 1H), 7.11 (d, J = 8.1 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H).

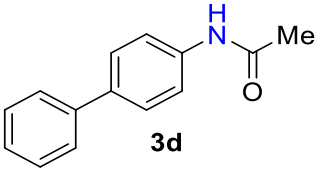
N-(4-Methoxyphenyl)acetamide (3c): Prepared according to general procedure and titled amide was isolated as white solid (79 mg, 95% yield; m. p. = 130-132°C) whose spectral data was consistent with the literature values.[31]



3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.48 (br s, 1H), 3.90 (s, 3H), 2.21 (s, 3H).

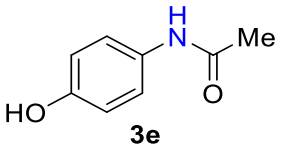
N-([1,1'-biphenyl]-4-yl)acetamide (3d): Prepared according to general procedure and titled amide was isolated as white solid (95 mg, 90% yield; m. p. = 170-172 °C) whose spectral data was consistent with the literature values.[32]



3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.65 – 7.49 (m, 6H), 7.42 (t, J = 7.3 Hz, 2H), 7.37 – 7.29 (m, 1H), 2.19 (s, 3H).

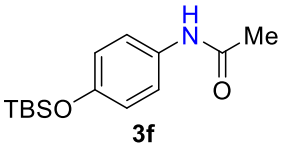
N-(4-Hydroxyphenyl)acetamide (3e): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 1:1, v/v) afforded the titled amide as brown solid (65 mg, 86% yield; m. p. 169-170 °C), whose spectral data was consistent with the literature values.[31]



3e

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.13 (s, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 1.97 (s, 3H).

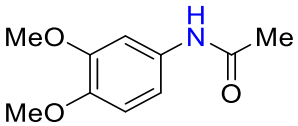
N-(4-((tert-butyldimethylsilyl)oxy)phenyl)acetamide (3f): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (120 mg, 90% yield; m. p. = 120-122 °C) whose spectral data was consistent with the literature values.[33]



3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.32 (d, J = 7.1 Hz, 2H), 6.75 (d, J = 7.1 Hz, 2H), 2.10 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H).

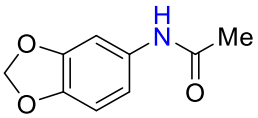
N-(3,4-Dimethoxyphenyl)acetamide (3g): Prepared according to general procedure and titled amide was isolated as white solid (87 mg, 89% yield; mp 125-128 °C) whose spectral data was consistent with the literature values.[34]



3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 1.9 Hz, 1H), 7.17 (br s, 1H), 6.88-6.76 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.16 (s, 3H).

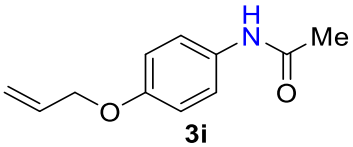
N-(benzo[d][1,3]dioxol-5-yl)acetamide (3h): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as white solid (86 mg, 96% yield; m. p. = 92-95 °C) whose spectral data was consistent with the literature values.[35]



3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.17 (d, J = 2.0 Hz, 1H), 6.80 – 6.67 (m, 2H), 5.92 (s, 2H), 2.11 (s, 3H).

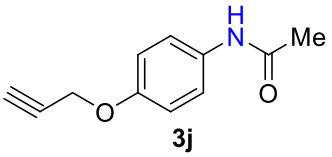
N-(4-(Allyloxy)phenyl)acetamide (3i): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (92 mg, 96% yield; m. p. = 92-95 °C) whose spectral data was consistent with the literature values.[36]



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 2H), 7.14 (br s, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.11-5.97 (m, 1H), 5.40 (d, J = 16.9 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 4.51 (d, J = 5.2 Hz, 2H), 2.15 (s, 3H).

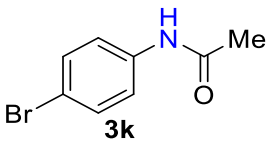
N-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (3j): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (90 mg, 95% yield; m. p. = 92-95 °C) whose spectral data was consistent with the literature values.[37]



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.65 (s, 2H), 2.51 (s, 1H), 2.12 (s, 3H).

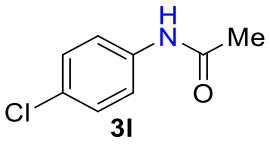
N-(4-Bromophenyl)acetamide (3k): Prepared according to general procedure and titled amide was isolated as white solid (97.4 mg, 91% yield; mp = 166-170 °C) whose spectral data was consistent with the literature values.[31]



3k

^{1}H NMR (400 MHz, CDCl3) δ 7.46-7.36 (m, 4H), 7.18 (br s, 1H), 2.17 (s, 3H).

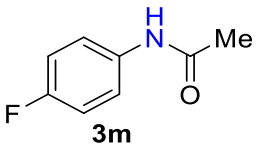
N-(4-Chlorophenyl)acetamide (3l): Prepared according to general procedure and titled amide was isolated as white solid (76 mg, 90% yield; m. p. = 176-179 °C) whose spectral data was consistent with the literature values.[38]



3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 2.17 (s, 3H).

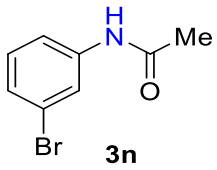
N-(4-Fluorophenyl)acetamide (3m): Prepared according to general procedure and titled amide was isolated as white solid (66 mg, 86% yield; m. p. = 155-158°C) whose spectral data was consistent with the literature values.[31]



3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.7, 4.8 Hz, 2H), 7.38 (br s, 1H), 7.00 (t, J = 8.6 Hz, 2H), 2.16 (s, 3H).

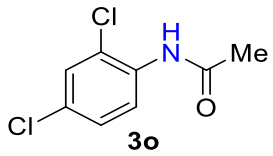
N-(3-Bromophenyl)acetamide (3n): Prepared according to general procedure and titled amide was isolated as white solid (97 mg, 90% yield; m. p. = 83-85 °C) whose spectral data was consistent with the literature values.[35]



3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.25-7.13 (m, 2H), 2.18 (s, 3H).

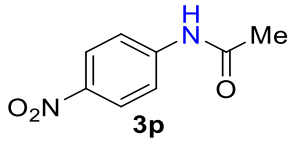
N-(2,4-Dichlorophenyl)acetamide (3o): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as brown solid (92 mg, 90% yield; m. p. = 142-144 °C) whose spectral data was consistent with the literature values.[39]



3o

^{1}H NMR (400 MHz, CDCl3) δ 8.33 (d, J = 8.8 Hz, 1H), 7.56 (br s, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.25-7.20 (m, 1H), 2.24 (s, 3H).

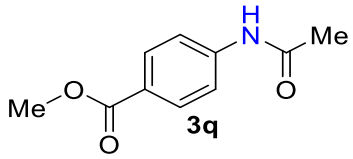
N-(4-Nitrophenyl)acetamide (3p): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as yellow solid (81 mg, 90% yield; m. p. = 210-212 °C) whose spectral data was consistent with the literature values.[40]



3p

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.46 (br s, 1H), 2.25 (s, 3H).

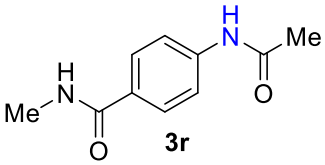
Methyl 4-acetamidobenzoate (3q): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as white solid (81 mg, 84% yield; m. p. = 112-115 °C) whose spectral data was consistent with the literature values.[31]



3q

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.48 (br s, 1H), 3.90 (s, 3H), 2.21 (s, 3H).

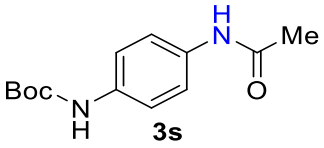
4-acetamido-N-methylbenzamide (3r): Prepared according to general procedure and titled amide was isolated as white solid (94 mg, 98% yield; m. p. = 183-185 °C) whose spectral data was consistent with the literature values.[41]



3r

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (br s, 2H), 7.48 (s, 4H), 2.00 (s, 6H).

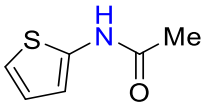
tert-Butyl (4-acetamidophenyl)carbamate (3s): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (106.4 mg, 85% yield; m. p. = 162-165 °C) whose spectral data was consistent with the literature values.[31]



3s

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.15 (br s, 1H), 6.45 (br s, 1H), 2.15 (s, 3H), 1.51 (s, 9H).

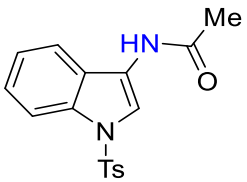
N-(Thiophen-2-yl)acetamide (3t): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled amide as brown solid (35 mg, 50% yield; m. p. = 158-160 °C) whose spectral data was consistent with the literature values.[31]



3t

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 6.91 – 6.80 (m, 2H), 6.68-6.62 (m, 1H), 2.20 (s, 3H).

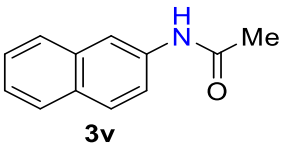
N-(1-Tosyl-1H-indol-3-yl)acetamide (3u): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as white solid (125 mg, 76% yield; m. p. 192-194 °C) whose spectral data was consistent with the literature values.[31]



3u

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.41-7.32 (m, 2H), 7.29 (br s, 1H), 7.25-7.21 (m, 1H), 7.18 (d, J = 8.1 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H).

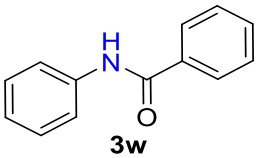
N-(Naphthalen-2-yl)acetamide (3v): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as brown solid (85.2 mg, 92% yield; m. p. = 134-136 °C) whose spectral data was consistent with the literature values.[42]



3v

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.78 (d, J = 7.8 Hz, 3H), 7.53-7.33 (m, 4H), 2.24 (s, 3H).

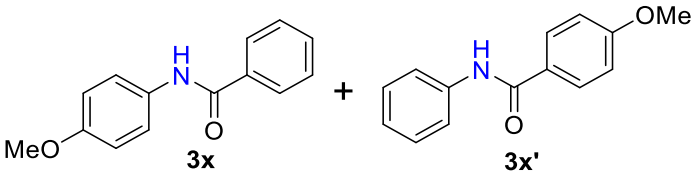
N-Phenylbenzamide (3w): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as white solid (69 mg, 70% yield; m. p. 168-170°C) whose spectral data was consistent with the literature values.[31]



3w

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.86 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H), 7.58-7.51 (m, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H).

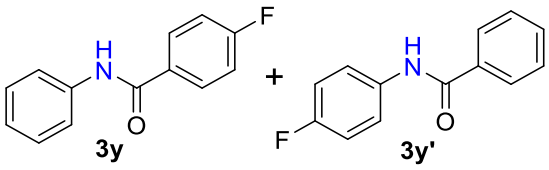
N-(4-Methoxyphenyl)benzamide (3x) and 4-methoxy-N-phenylbenzamide (3x'):[42] Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as white solid (102 mg, 90% yield; 64:36 isomeric mixture; m. p. = 110-115 °C) whose spectral data was consistent with the literature values.[43]



3x **3x'**

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 10.03 (s, 0.6H), 7.89 (t, J = 7.9 Hz, 3.2H), 7.71 (d, J = 8.1 Hz, 1.2H), 7.62 (d, J = 8.7 Hz, 2H), 7.54-7.38 (m, 3H), 7.27 (t, J = 7.7 Hz, 1.2H), 7.07-6.93 (m, 1.8H), 6.86 (d, J = 8.8 Hz, 2H), 3.76 (s, 1.8H), 3.67 (s, 3H).

4-fluoro-N-phenylbenzamide (3y) and N-(4-fluorophenyl)benzamide (3y'): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled amide as white solid (97 mg, 90% yield; 1:1 isomeric mixture; m. p. = 175-180 °C) whose spectral data was consistent with the literature values.[44]

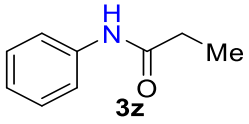


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 10.27 (s, 1H), 8.08-8.02 (m, 2H), 7.99-7.94 (m, 2H), 7.84-7.75 (m, 4H), 7.62-7.50 (m, 3H), 7.39-7.32 (m, 4H), 7.23-7.16 (m, 2H), 7.11 (t, J = 7.4 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 165.52, 165.33, 164.48, 162.86, 159.54, 157.15, 139.09, 135.56, 135.53, 134.85, 131.59, 131.44, 131.41, 130.44, 130.35, 128.62, 128.40, 127.64, 123.75, 122.28, 122.20, 120.47, 115.42, 115.28, 115.20, 115.06.

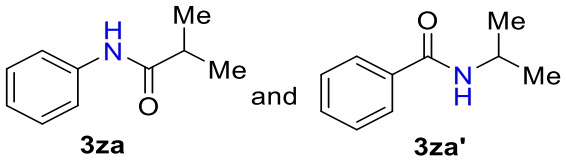
^{19}F NMR (376 MHz, DMSO-d_6) δ -108.77 (s, 1F), -118.83 (s, 1F).

N-Phenylpropionamide (3z): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled amide as white solid (67 mg, 90% yield; m. p. = 108-110°C) whose spectral data was consistent with the literature values.[45]



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.53 (d, J = 7.9 Hz, 2H), 7.26 (t, J = 7.7 Hz, 2H), 7.06 (t, J = 7.2 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H).

N-Phenylisobutyramide (3za) and N-isopropylbenzamide (3za'): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded 3za as white solid (53 mg, 65% yield; m. p. = 110-111°C) along with 3za' (19 mg, 24% yield) whose spectral data was consistent with the literature values.[31,46]



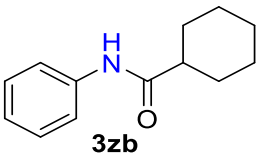
N-Phenylisobutyramide (3za):[31]

1H NMR (400 MHz, CDCl3) δ 7.53 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 2.59-2.43 (m, 1H), 1.26 (d, J = 6.8 Hz, 6H).

N-Isopropylbenzamide (3za'):[46]

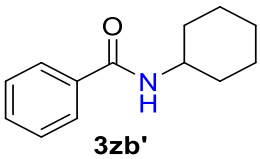
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.69 (m, 2H), 7.51 – 7.33 (m, 3H), 6.09 (s, 1H), 4.36-4.19 (m, 1H), 1.24 (d, J = 6.5 Hz, 6H).

***N-Phenylcyclohexanecarboxamide (3zb) and N-cyclohexylbenzamide (3zb')*:** Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled amide 3z as white solid (71 mg, 70% yield; mp 141-144 °C) along with 3zb' white solid (18 mg, 18% yield, m. p. = 141-144 °C) whose spectral data was consistent with the literature values.[31]



3zb

and



3zb'

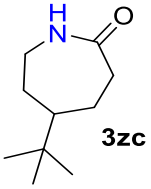
N-Phenylcyclohexanecarboxamide (3zb):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.9 Hz, 2H), 7.35-7.24 (m, 3H), 7.08 (t, J = 7.3 Hz, 1H), 2.27-2.18 (m, 1H), 1.95 (d, J = 12.6 Hz, 2H), 1.83 (d, J = 11.1 Hz, 2H), 1.73-1.66 (m, 1H), 1.60-1.49 (m, 2H), 1.38-1.25 (m, 3H).

N-cyclohexylbenzamide (3zb'):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 5.96 (br s, 1H), 4.07-3.89 (m, 1H), 2.09-1.96 (m, 2H), 1.80-1.71 (m, 2H), 1.70-1.65 (m, 1H), 1.48-1.37 (m, 2H), 1.30-1.17 (m, 3H).

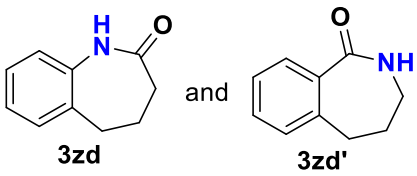
5-(tert-Butyl)azepan-2-one (3zc): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (64 mg, 75% yield; m. p. = 150-154 °C) whose spectral data was consistent with the literature values.[47]



3zc

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (br s, 1H), 3.28-3.14 (m, 2H), 2.57-2.28 (m, 2H), 2.02-1.89 (m, 2H), 1.32-1.14 (m, 3H), 0.86 (s, 9H).

1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (3zd) and 2,3,4,5-tetrahydro-1H-benzo[c]-azepin-1-one (3zd'): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled amide as white solid (53 mg, 66% yield; m. p. = 136-138 °C) along with **3zd'** as white solid (20 mg, 25% yield; m. p. = 100-103 °C) whose spectral data was consistent with the literature values.[43, 48]



3zd **3zd'**

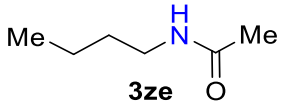
1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (3zd):[43]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (br s, 1H), 7.25-7.14 (m, 2H), 7.14-7.06 (m, 1H), 7.03 (d, J = 7.7 Hz, 1H), 2.80 (t, J = 7.2 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 2.29-2.15 (m, 2H).

2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (3zd'):[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.68 (dd, J = 7.5, 1.6 Hz, 1H), 7.37 (td, J = 7.4, 1.6 Hz, 1H), 7.31 (td, J = 7.5, 1.4 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 3.10 (q, J = 6.4 Hz, 2H), 2.83 (t, J = 7.1 Hz, 2H), 2.05 – 1.93 (m, 2H).

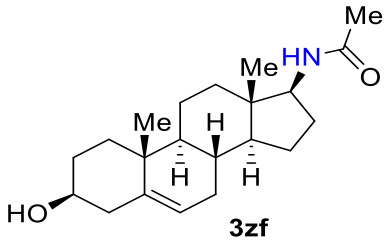
N-Butylacetamide (3ze): Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled amide as clear oil (52 mg, 90% yield) whose spectral data was consistent with the literature values.[34]



3ze

^{1}H NMR (400 MHz, CDCl3) δ 6.84 (br s, 3H), 3.22 (dd, J = 13.1, 7.0 Hz, 2H), 1.98 (s, 3H), 1.49 (dt, J = 14.9, 7.3 Hz, 2H), 1.43 – 1.28 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

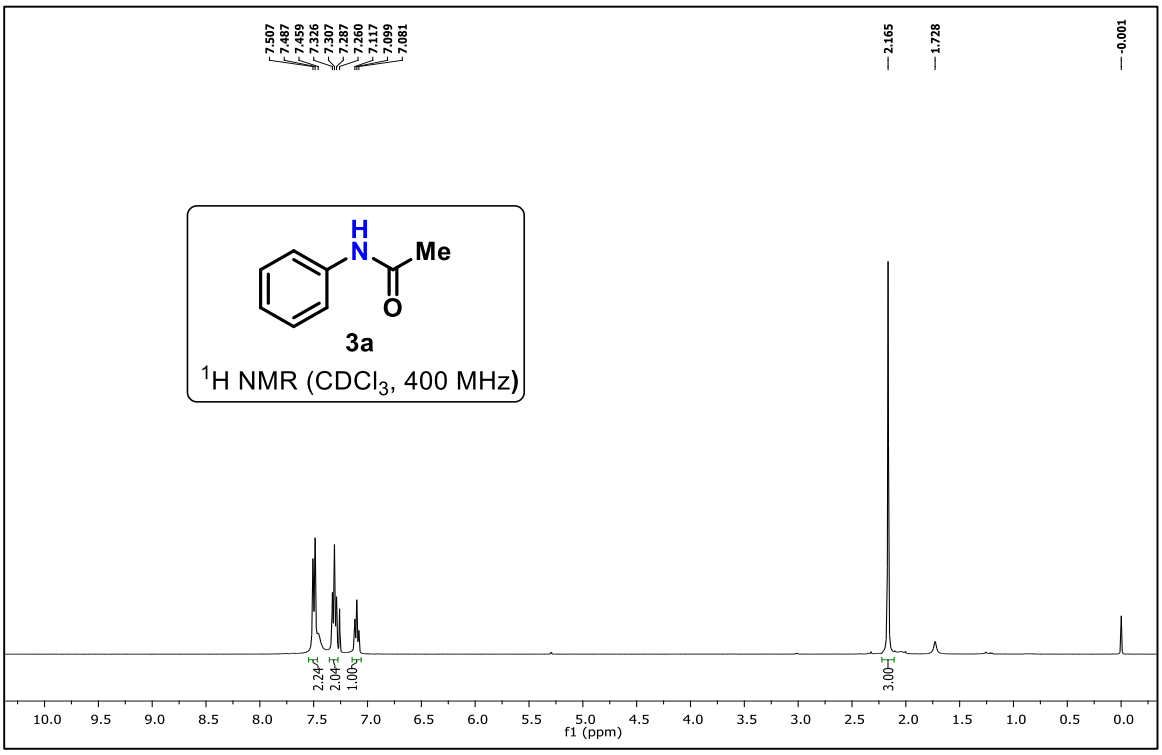
N-((3S,8R,9S,10R,13S,14S,17S)-3-Hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a] phen-anthren-17-yl)acetamide (3zf):[31] Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled amide as white solid (149 mg, 90% yield; m. p. = 234-236 °C) whose spectral data was consistent with the literature values.[31]

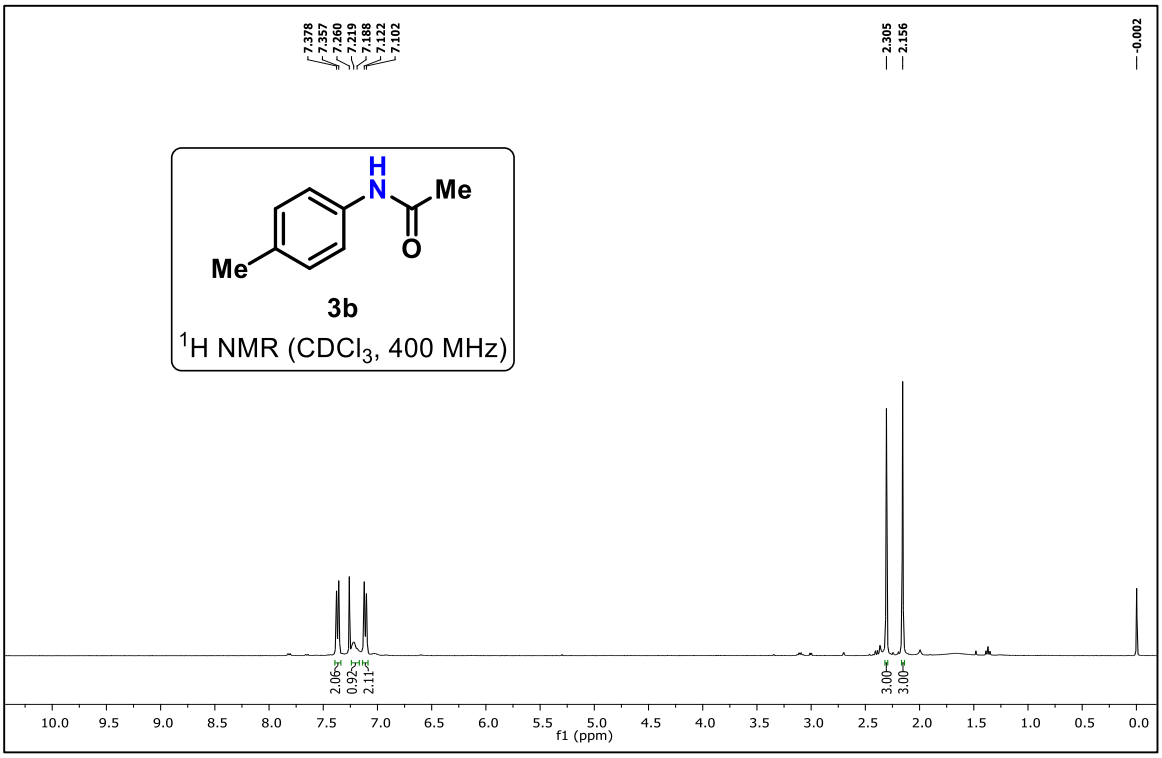


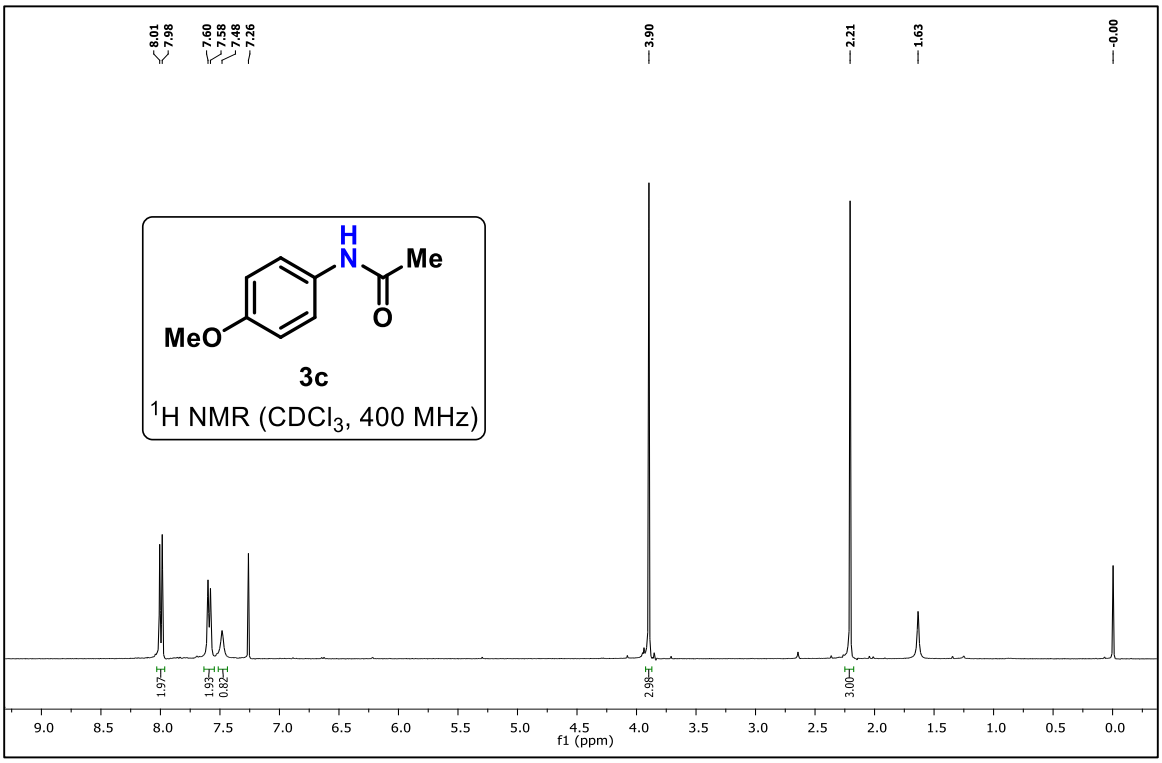
3zf

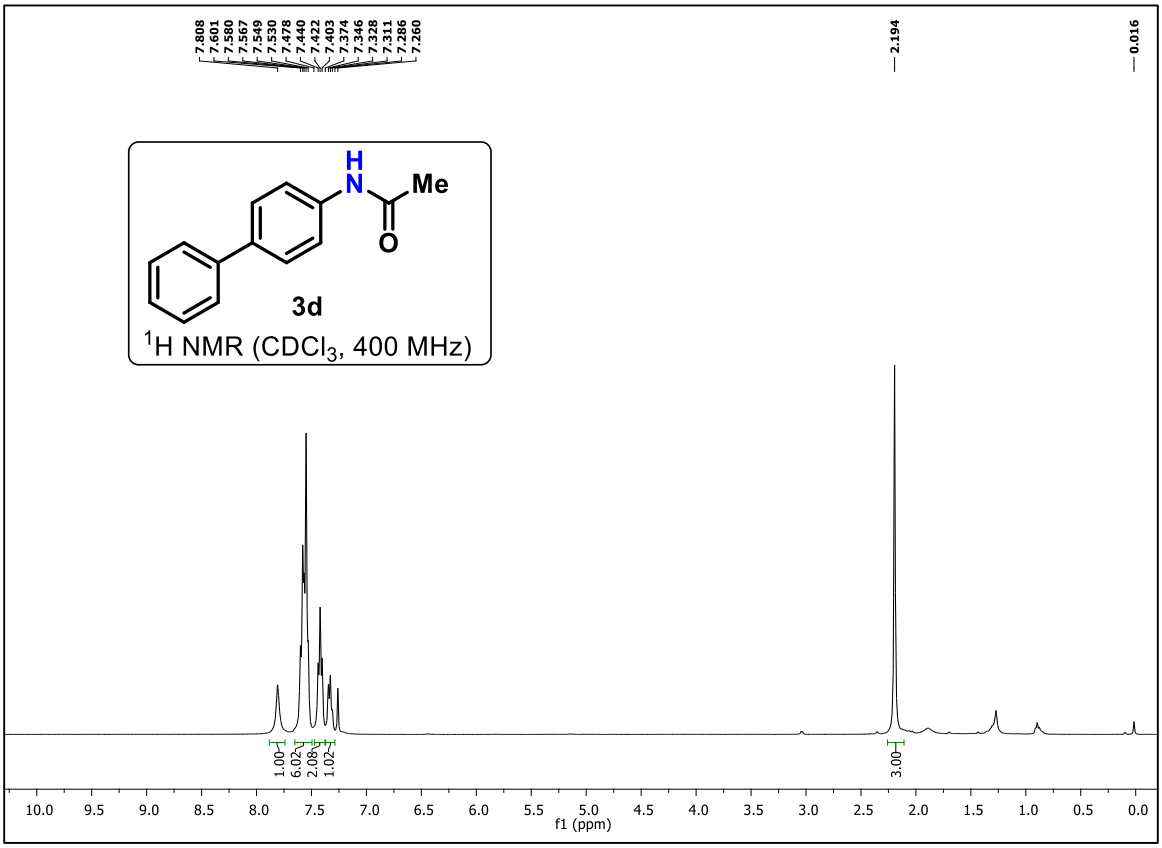
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37-5.32 (m, 1H), 5.31-5.23 (m, 1H), 3.89 (q, J = 9.0 Hz, 1H), 3.52 (td, J = 11.1, 5.5 Hz, 1H), 2.35-2.06 (m, 3H), 2.05 – 1.93 (m, 4H), 1.84 (d, J = 10.2 Hz, 2H), 1.69 (dd, J = 15.7, 11.8 Hz, 2H), 1.64-1.53 (m, 3H), 1.53-1.35 (m, 3H), 1.34-1.18 (m, 3H), 1.16-1.03 (m, 2H), 1.01 (s, 3H), 0.96 (dd, J = 11.5, 4.6 Hz, 1H), 0.70 (s, 3H).

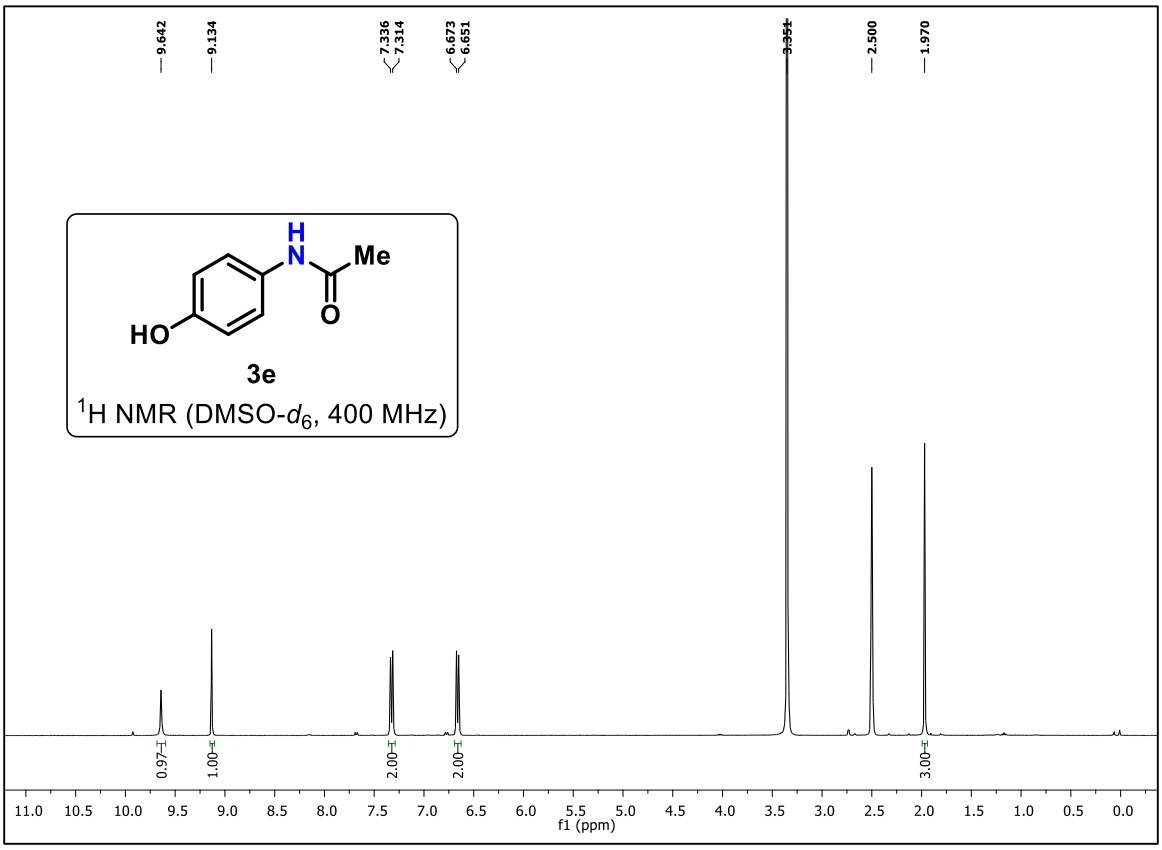
2.8 ^{1}H, ^{13}C and ^{19}F NMR Spectra of the products

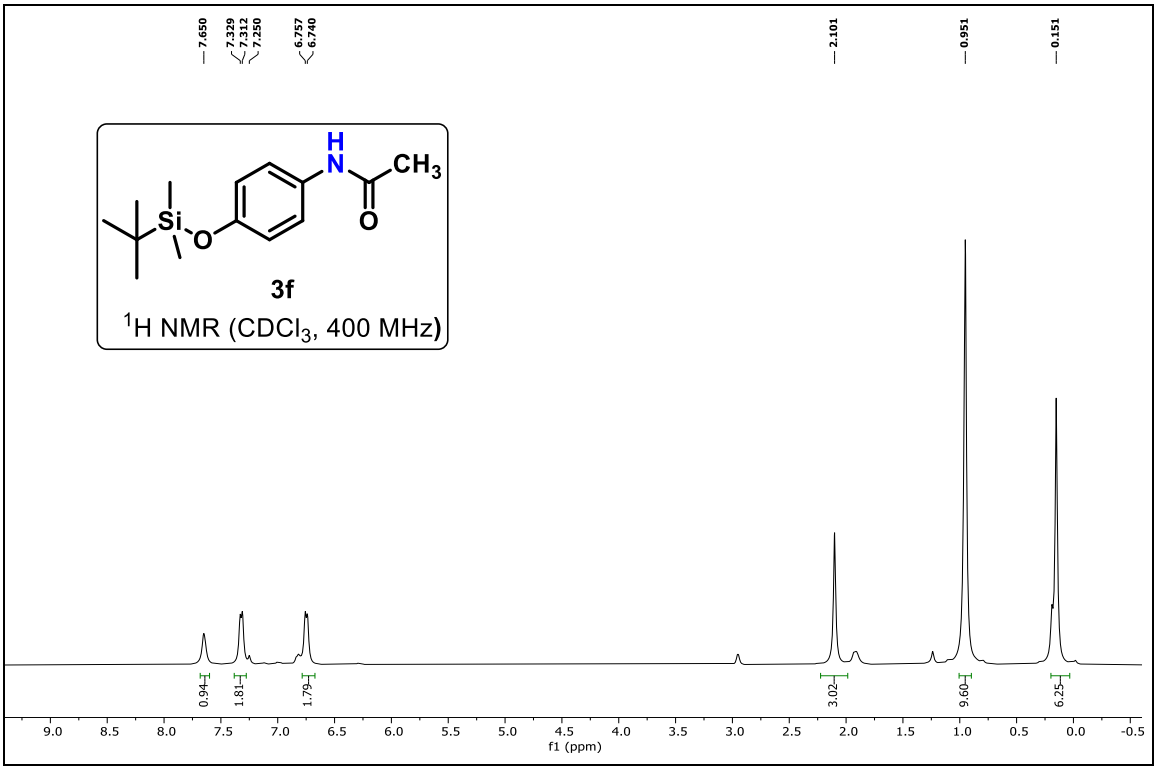


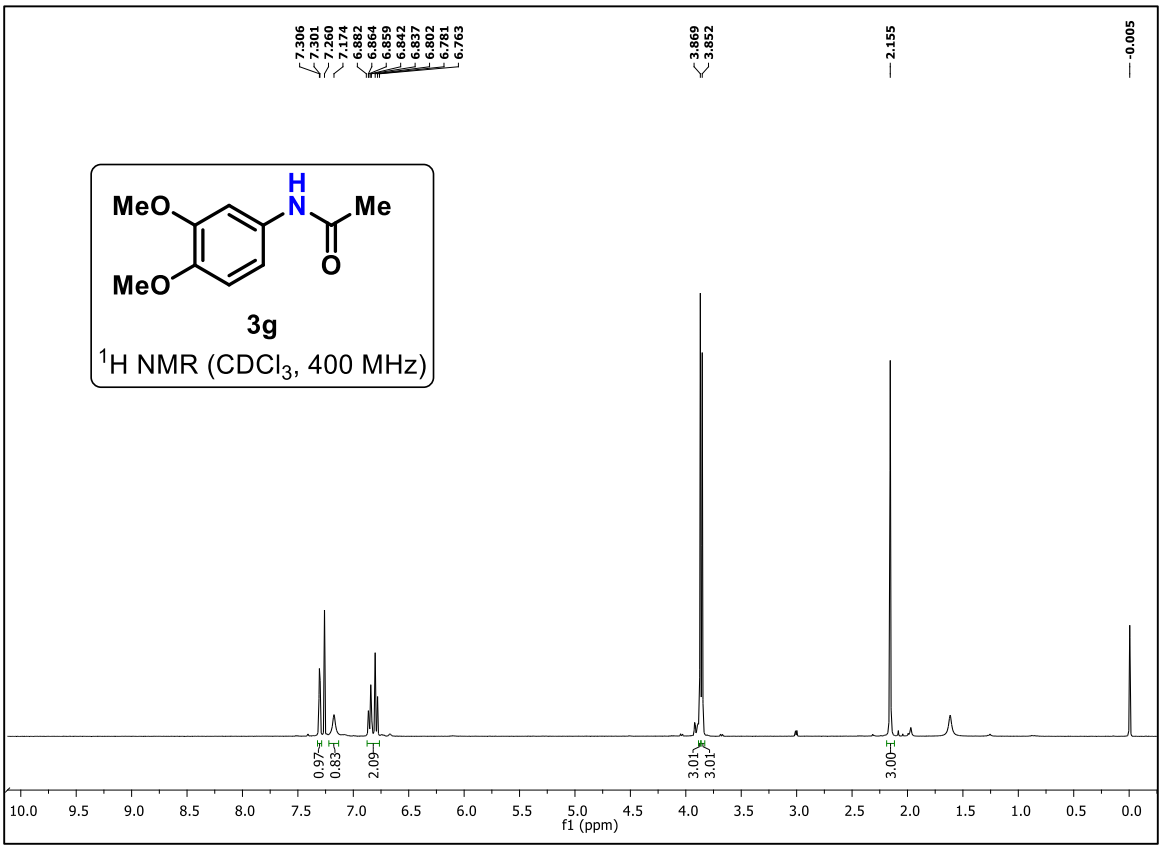


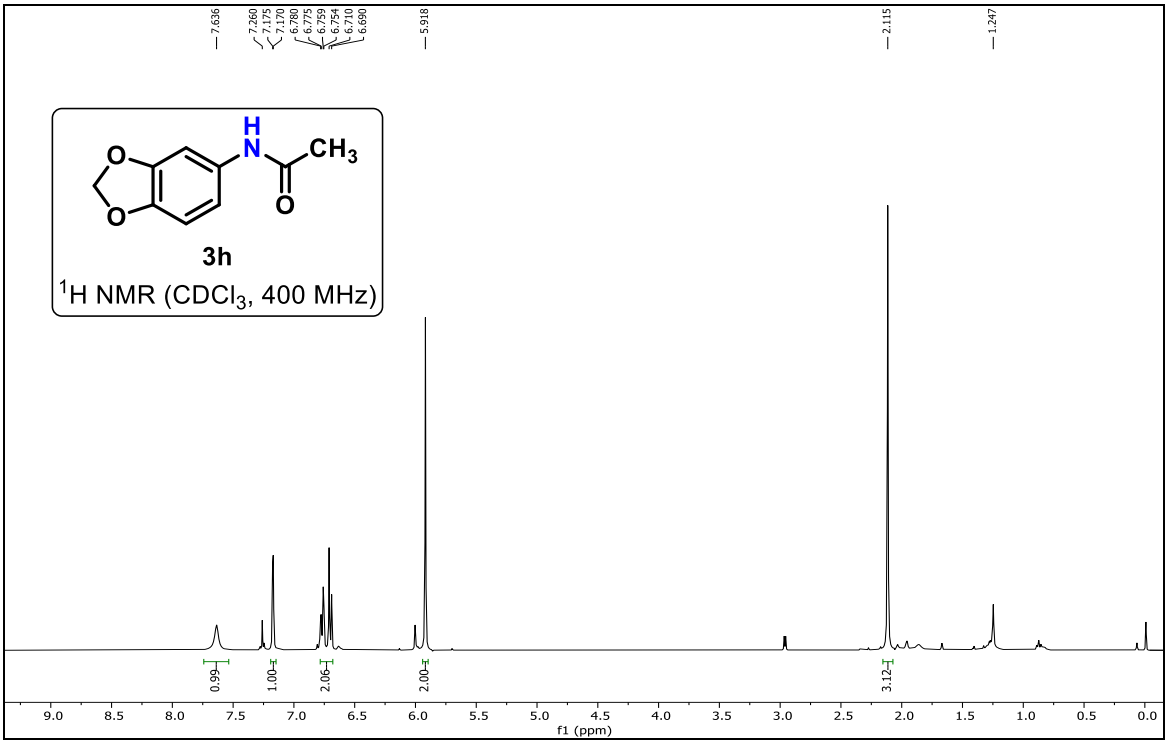

8.01
7.98
7.60
7.58
7.48
7.26
3.90
2.21
1.63
-0.00
H
N
Me
O
MeO
3c
^{1}H NMR (CDCl$_3$, 400 MHz)
1.97
1.93
0.82
2.98
3.00
f1 (ppm)

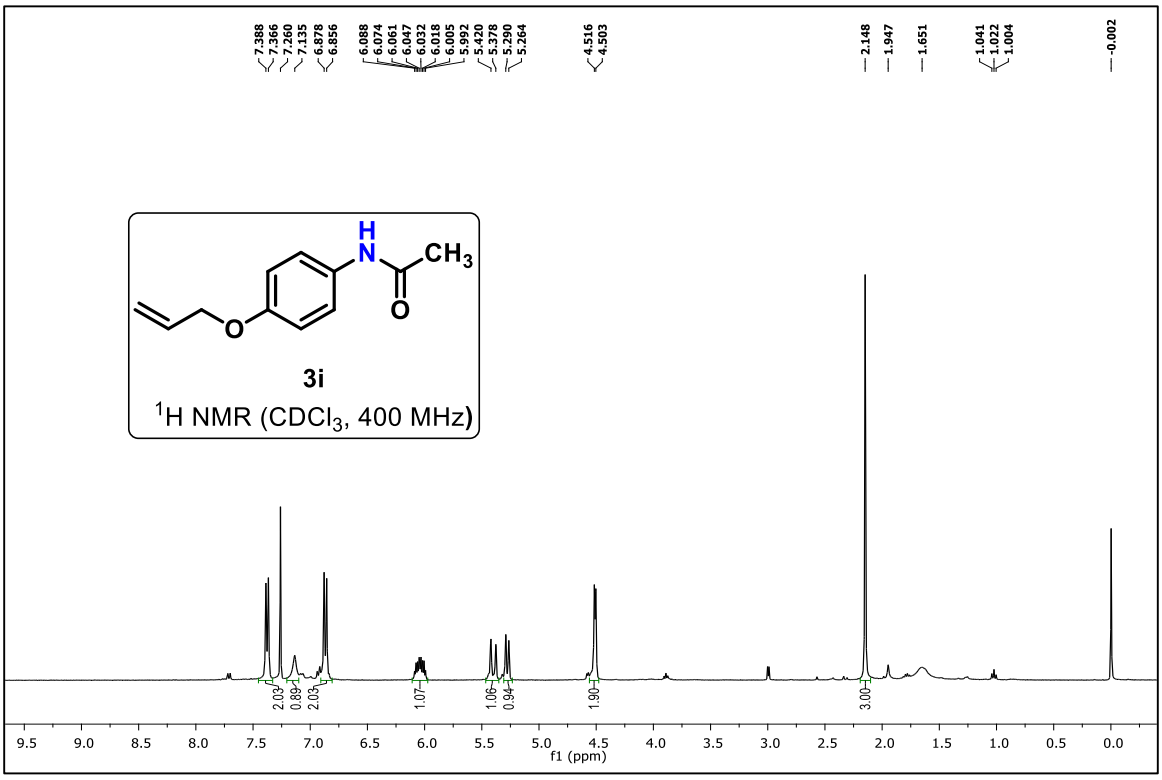

7.808
7.601
7.580
7.567
7.549
7.530
7.478
7.440
7.422
7.403
7.374
7.346
7.328
7.311
7.286
7.260
2.194
0.016
H
N
Me
O
3d
^{1}H NMR (CDCl$_3$, 400 MHz)
1.00
6.02
2.08
1.02
3.00
f1 (ppm)

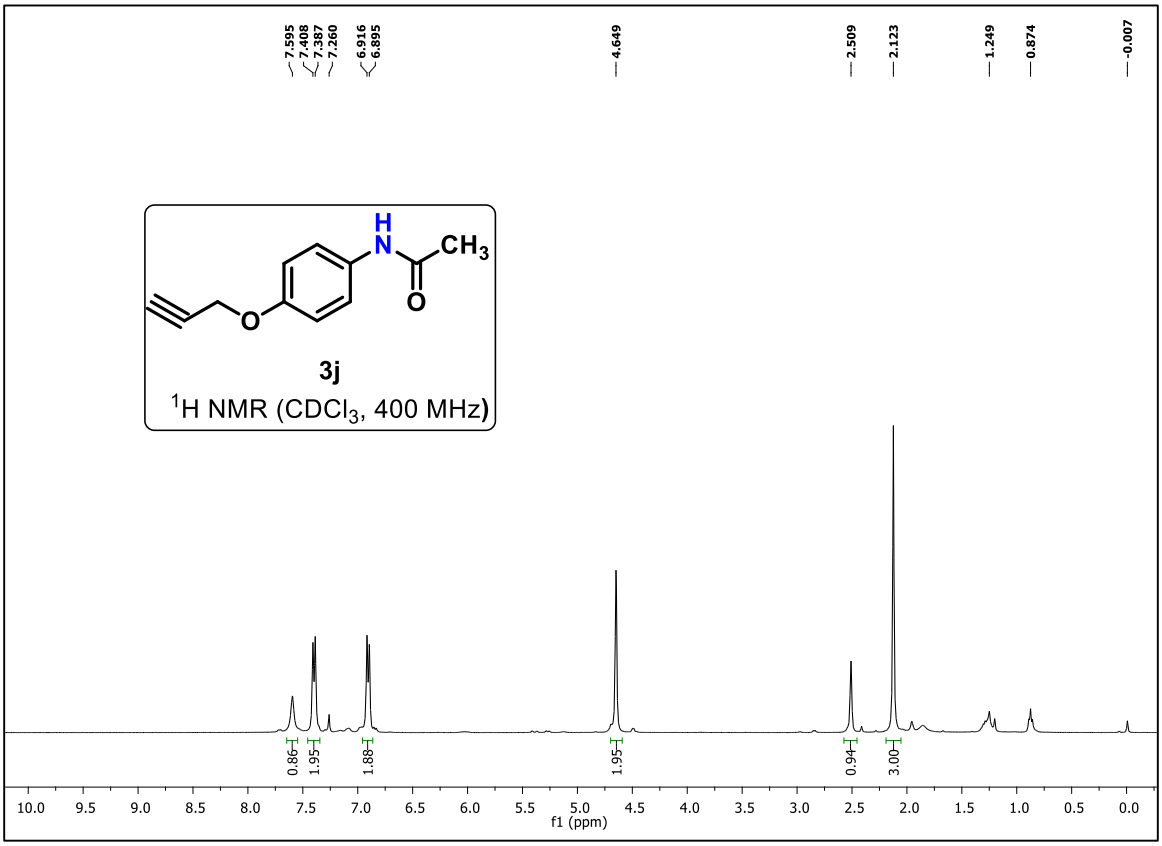

9.642
9.134
7.336
7.314
6.673
6.651
3.351
2.500
1.970
HO
N
H
Me
O
3e
^{1}H NMR (DMSO-d_6, 400 MHz)
0.97
1.00
2.00
2.00
3.00
f1 (ppm)

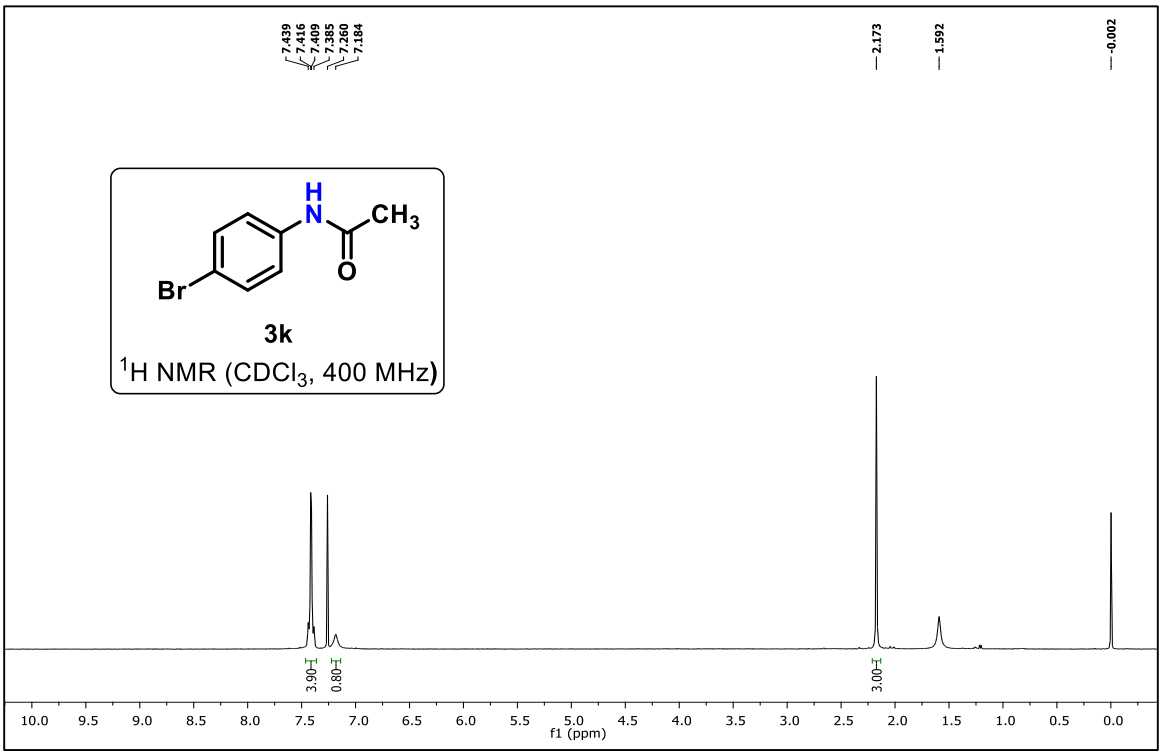

7.650
7.329
7.312
7.250
6.757
6.740
2.101
0.951
0.151
Si
O
N
H
CH3
O
3f
^{1}H NMR (CDCl$_3$, 400 MHz)
0.94
1.81
1.79
3.02
9.60
6.25
f1 (ppm)

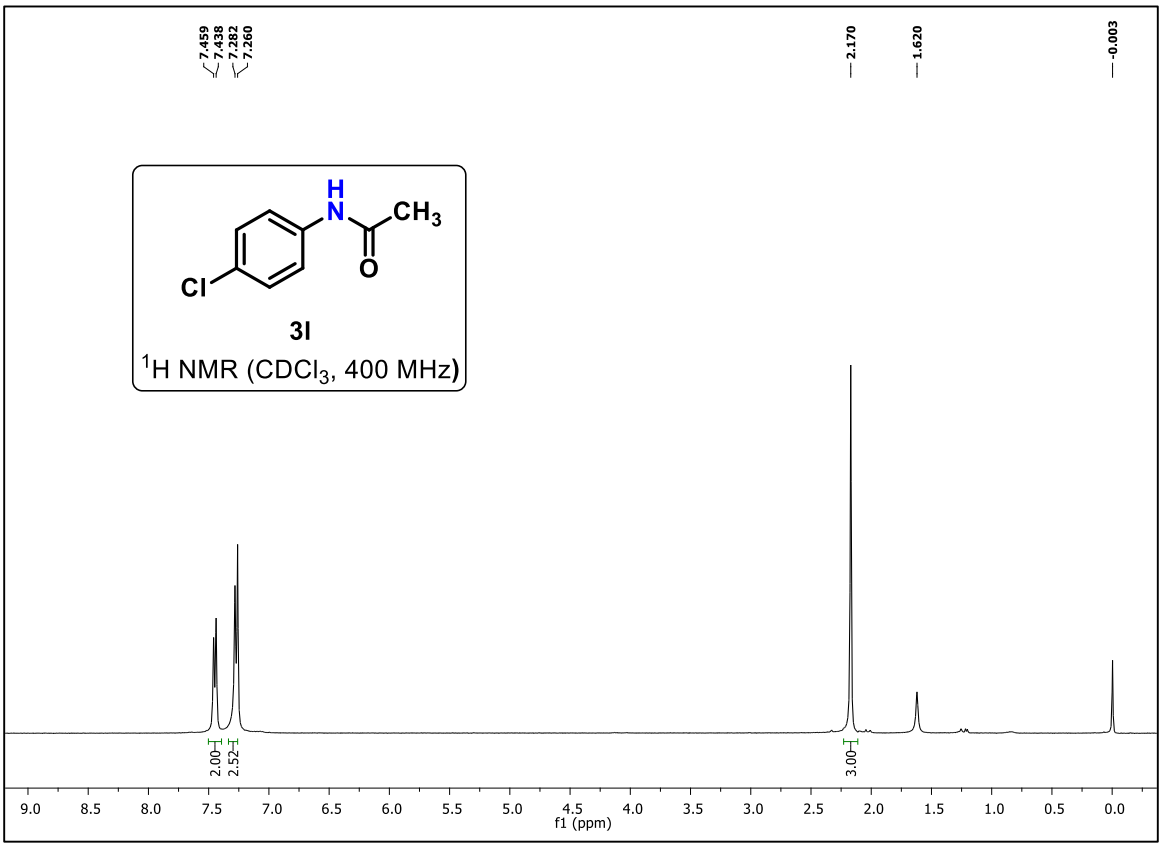

7.306
7.301
7.260
7.174
6.882
6.864
6.859
6.842
6.837
6.802
6.781
6.763
3.869
3.852
2.155
-0.005
MeO
MeO
H
N
Me
O
3g
^{1}H NMR (CDCl$_3$, 400 MHz)
0.97
0.83
2.09
3.01
3.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

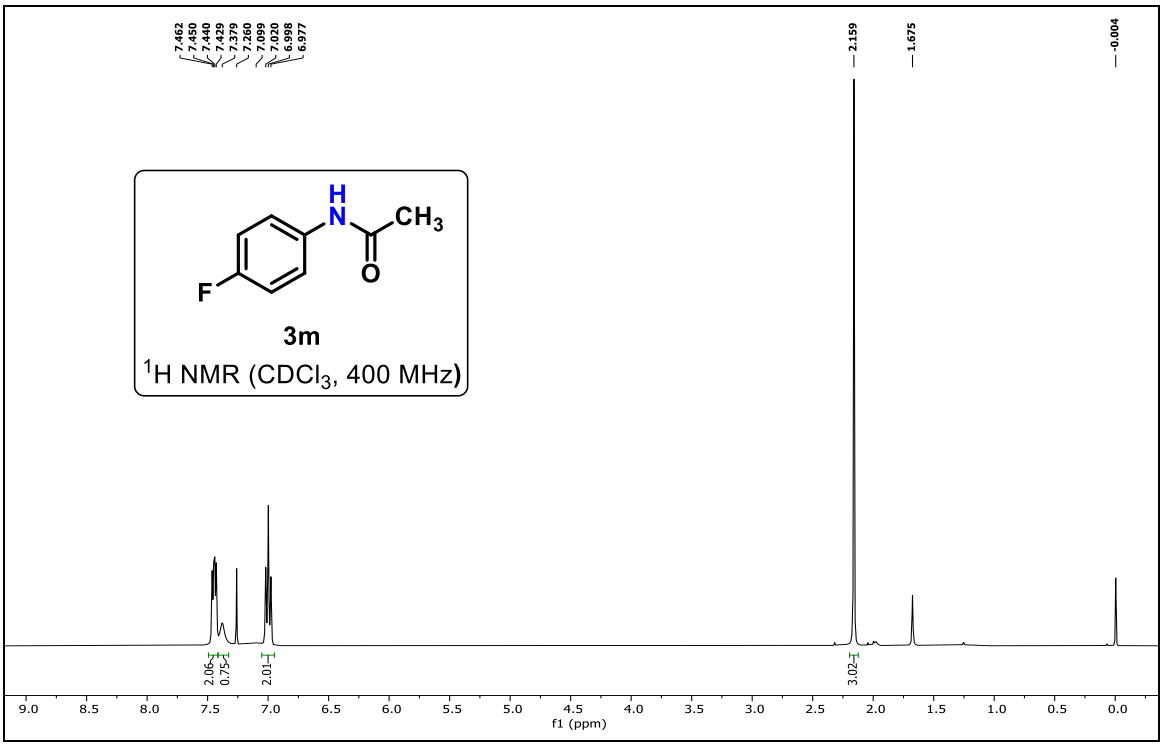

7.636
7.260
7.175
7.170
6.780
6.775
6.759
6.754
6.710
6.690
5.918
2.115
1.247
O
O
H
N
CH$_3$
O
3h
^{1}H NMR (CDCl$_3$, 400 MHz)
0.99
1.00
2.06
2.00
3.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

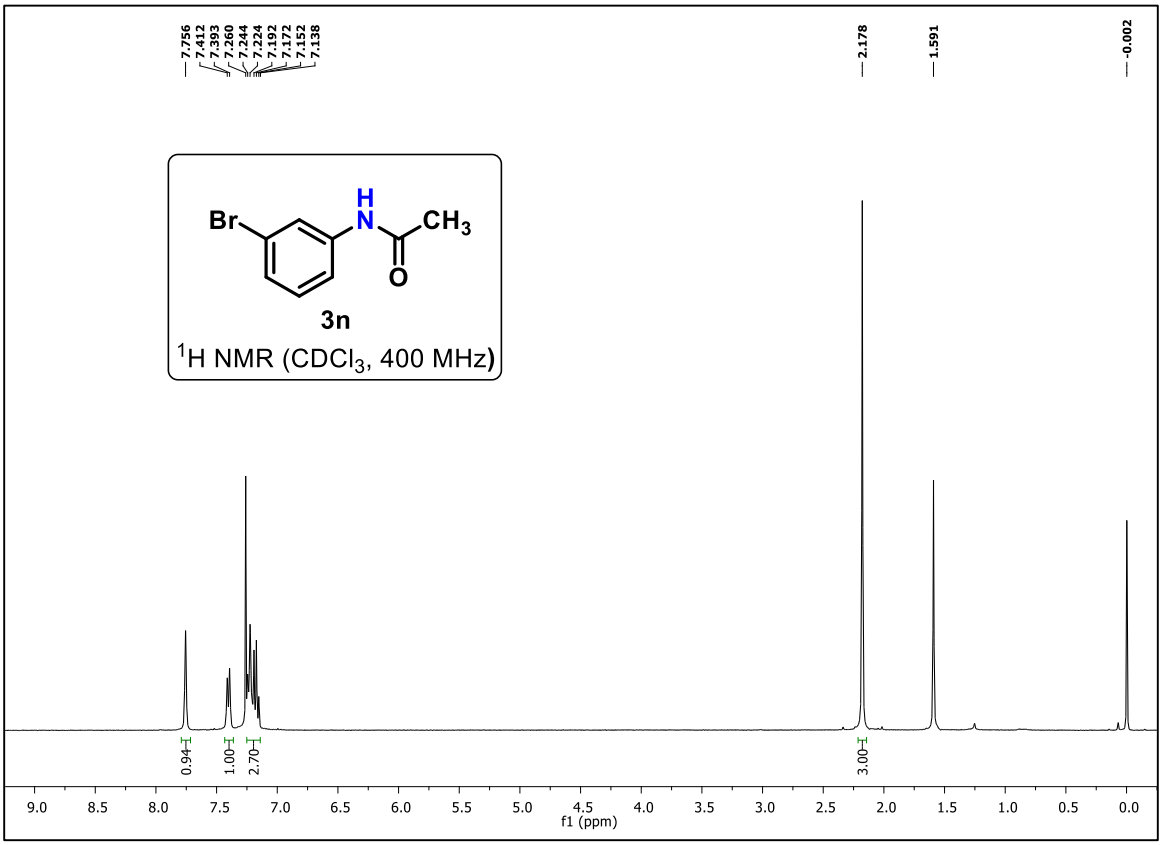

7.388
7.366
7.260
7.135
6.878
6.856
6.088
6.074
6.061
6.047
6.032
6.018
6.005
5.992
5.420
5.378
5.290
5.264
4.516
4.503
2.148
1.947
1.651
1.041
1.022
1.004
-0.002
H
N
CH3
O
O
3i
1H NMR (CDCl3, 400 MHz)
2.09
0.89
2.03
1.07
1.06
0.94
1.90
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

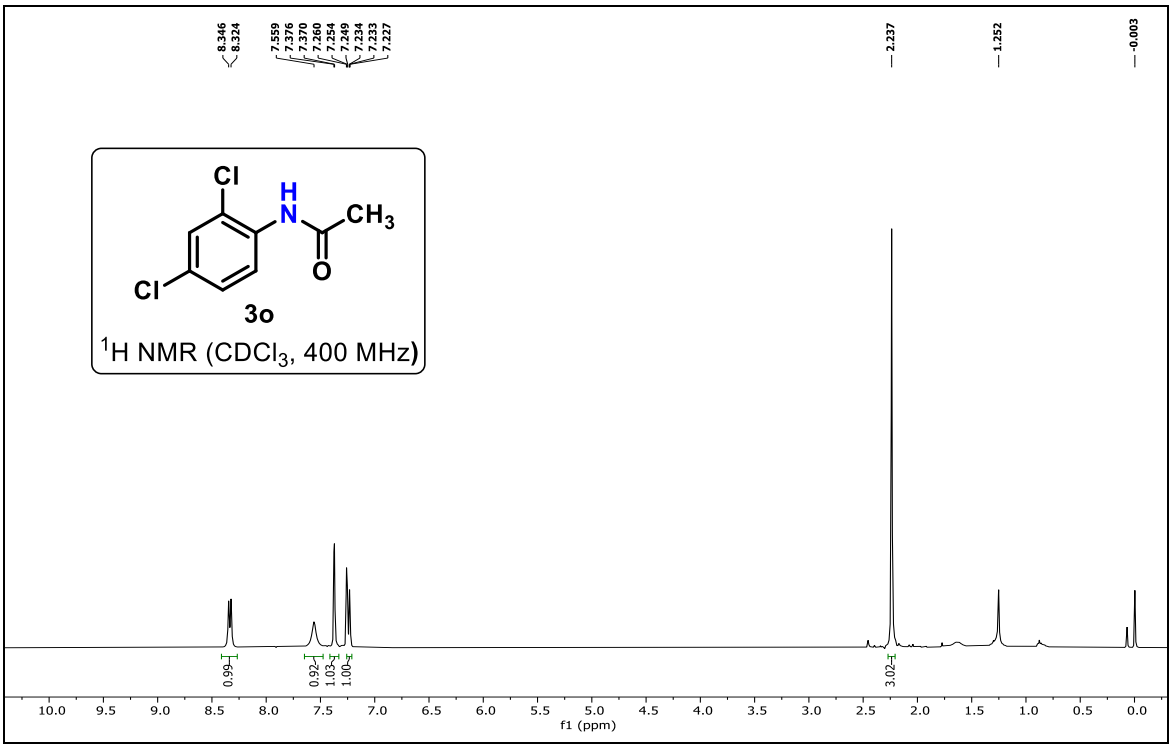

7.595
7.408
7.387
7.260
6.916
6.895
4.649
2.509
2.123
1.249
0.874
-0.007
H
N
CH3
O
O
3j
1H NMR (CDCl3, 400 MHz)
0.86
1.95
1.88
1.95
0.94
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

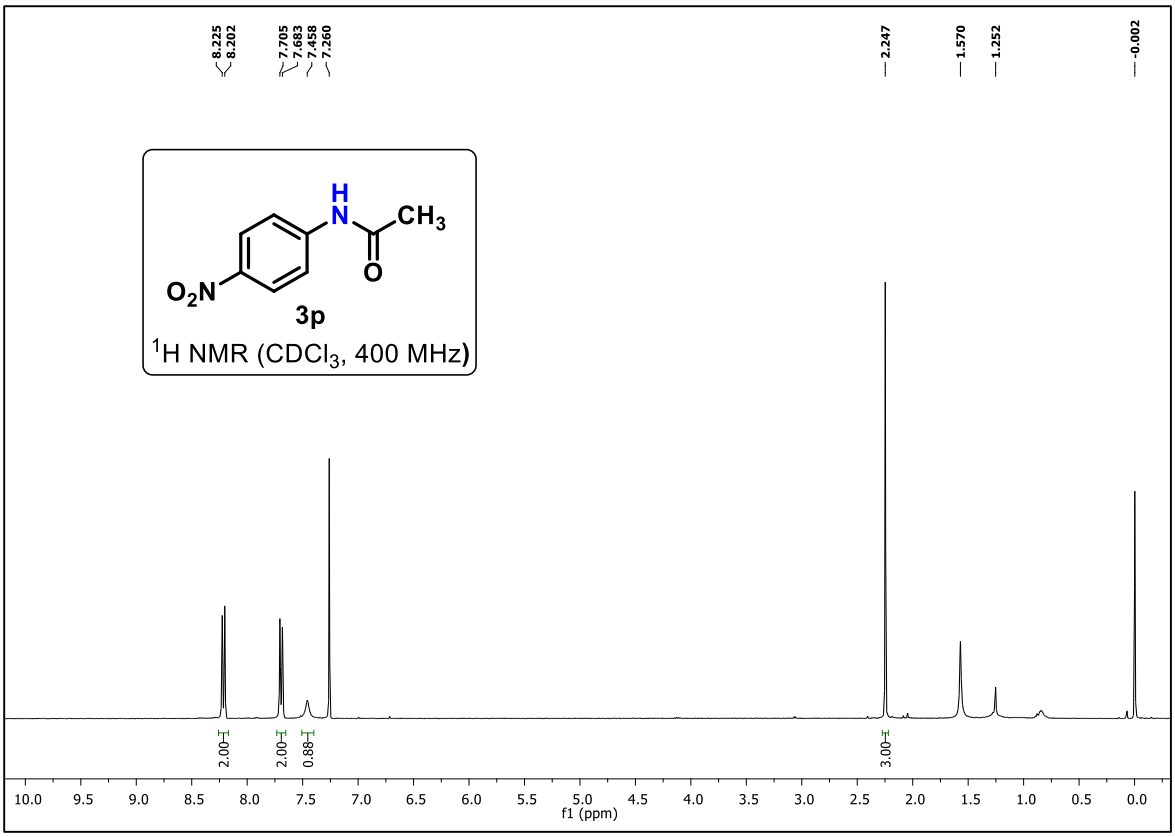

7.439
7.416
7.409
7.385
7.260
7.184
2.173
1.592
-0.002
H
N
CH3
O
Br
3k
1H NMR (CDCl3, 400 MHz)
3.90
0.80
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

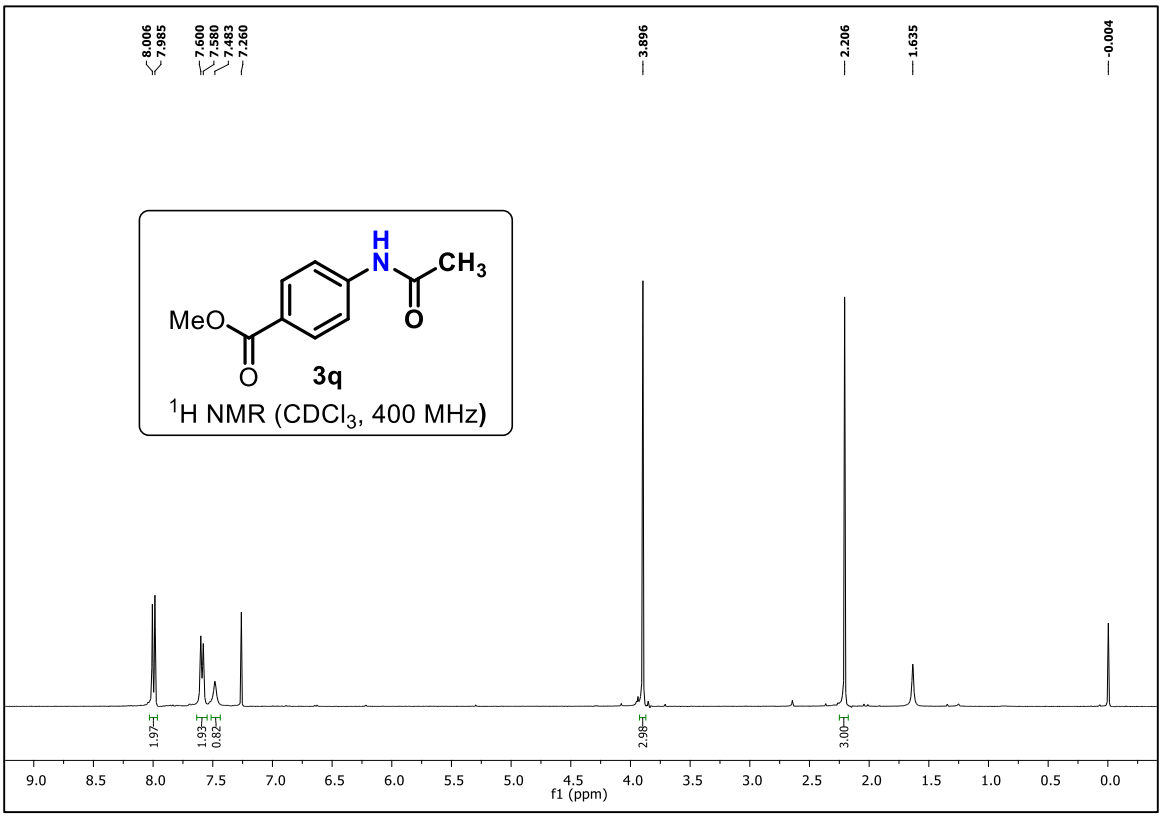

7.459
7.438
7.282
7.260
2.170
1.620
-0.003
H
N
CH3
O
Cl
3l
1H NMR (CDCl3, 400 MHz)
2.00
2.52
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

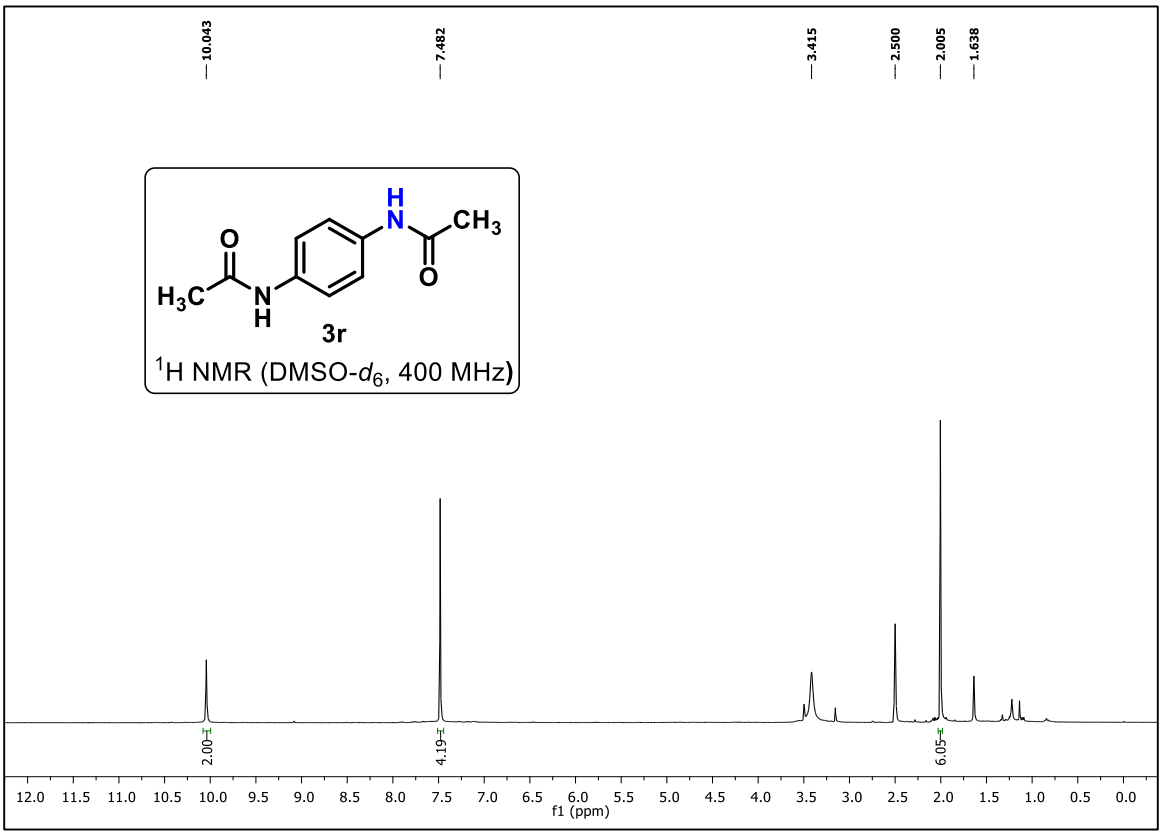

7.462
7.450
7.440
7.429
7.379
7.266
7.099
7.090
6.998
6.977
2.159
1.675
-0.004
H
N
CH3
O
F
3m
1H NMR (CDCl3, 400 MHz)
2.06
0.75
2.01
3.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

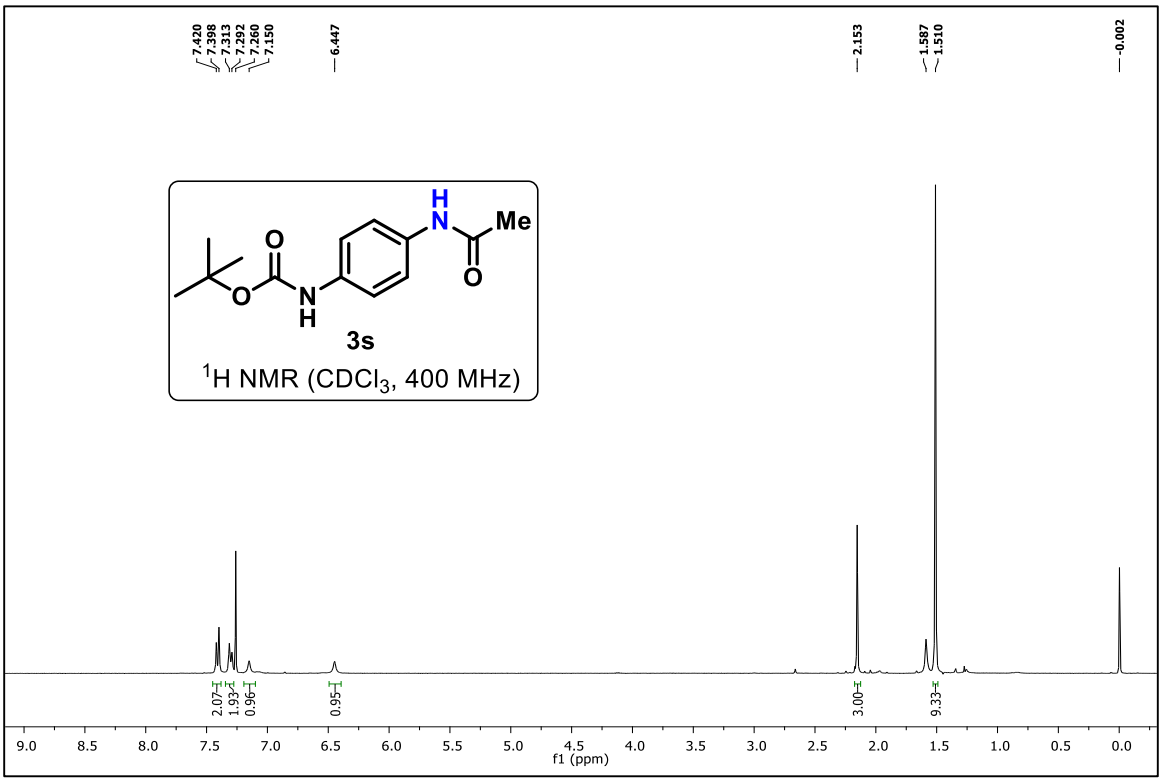

7.756
7.412
7.393
7.260
7.244
7.224
7.192
7.172
7.152
7.138
2.178
1.591
-0.002
H
N
CH3
O
Br
3n
1H NMR (CDCl3, 400 MHz)
0.94
1.00
2.70
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

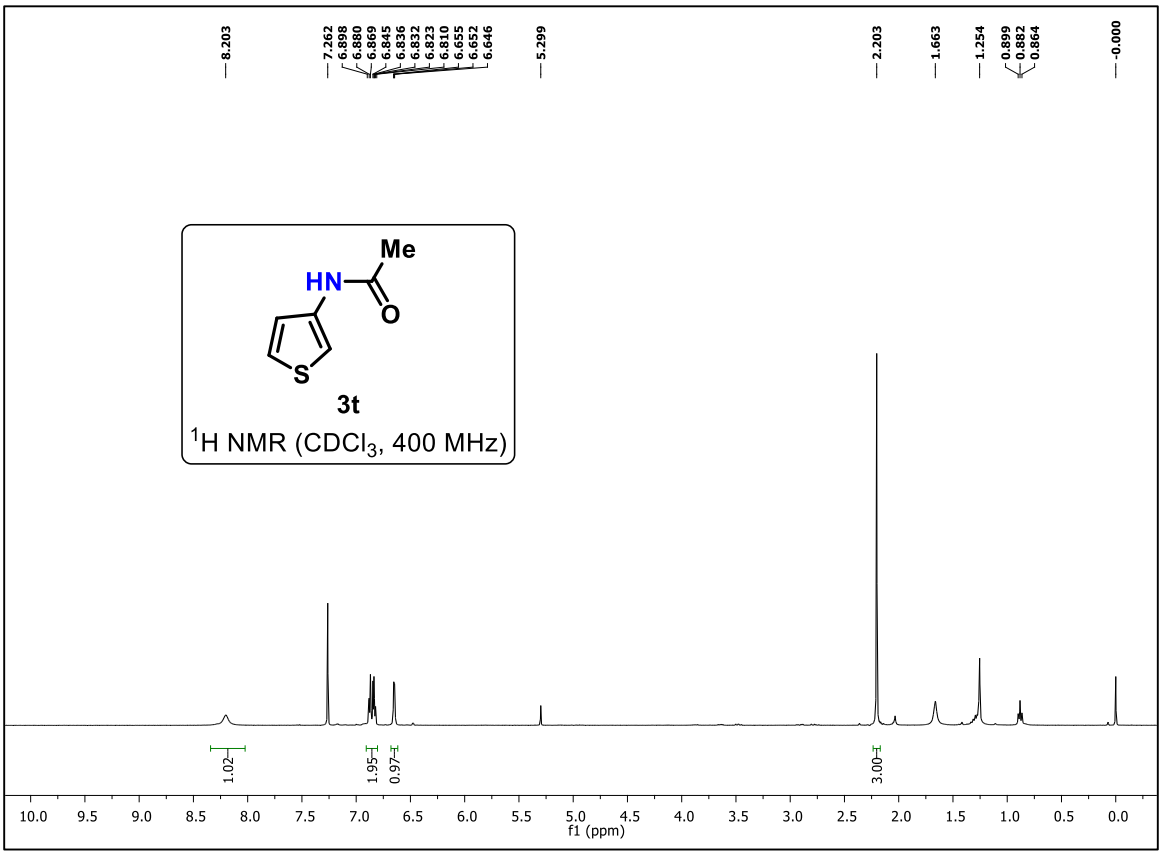

8.346
8.324
7.559
7.376
7.370
7.260
7.254
7.249
7.234
7.233
7.227
2.237
1.252
-0.003
Cl
H
N
CH3
O
Cl
3o
1H NMR (CDCl3, 400 MHz)
0.99
0.92
1.03
1.00
3.02
f1 (ppm)

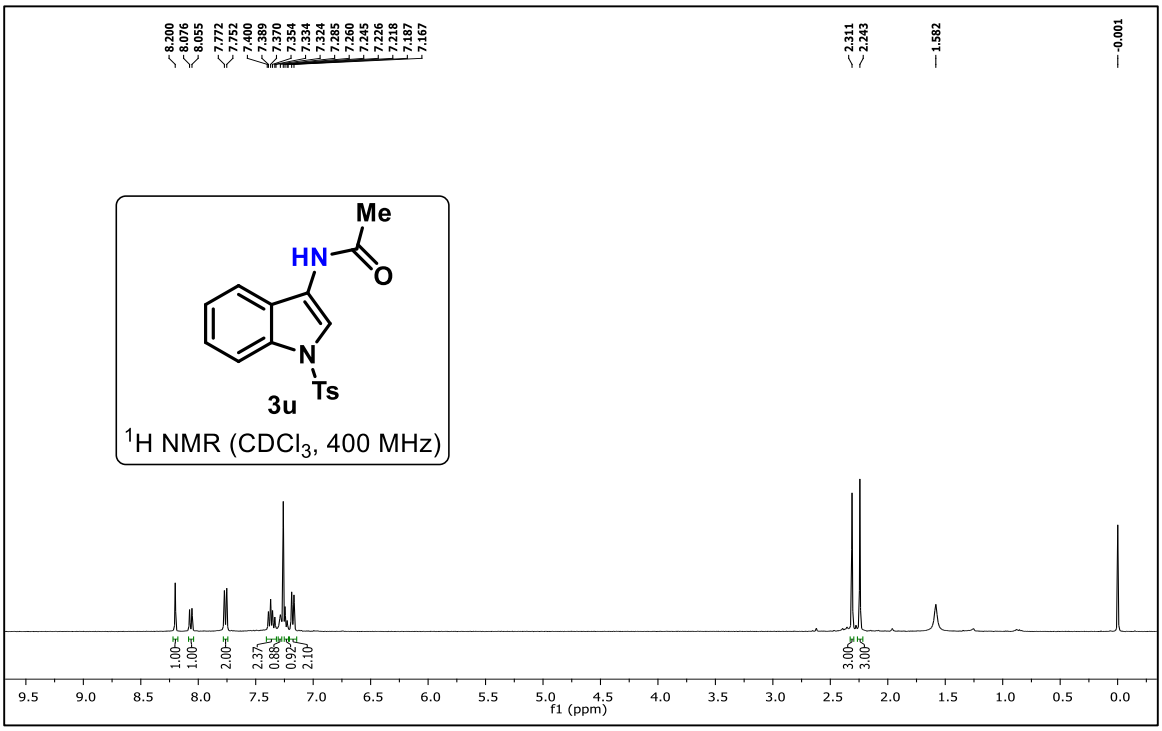

8.225
8.202
7.705
7.683
7.458
7.260
2.247
1.570
1.252
-0.002
H
N
CH3
O
O2N
3p
1H NMR (CDCl3, 400 MHz)
2.00
2.00
0.88
3.00
f1 (ppm)

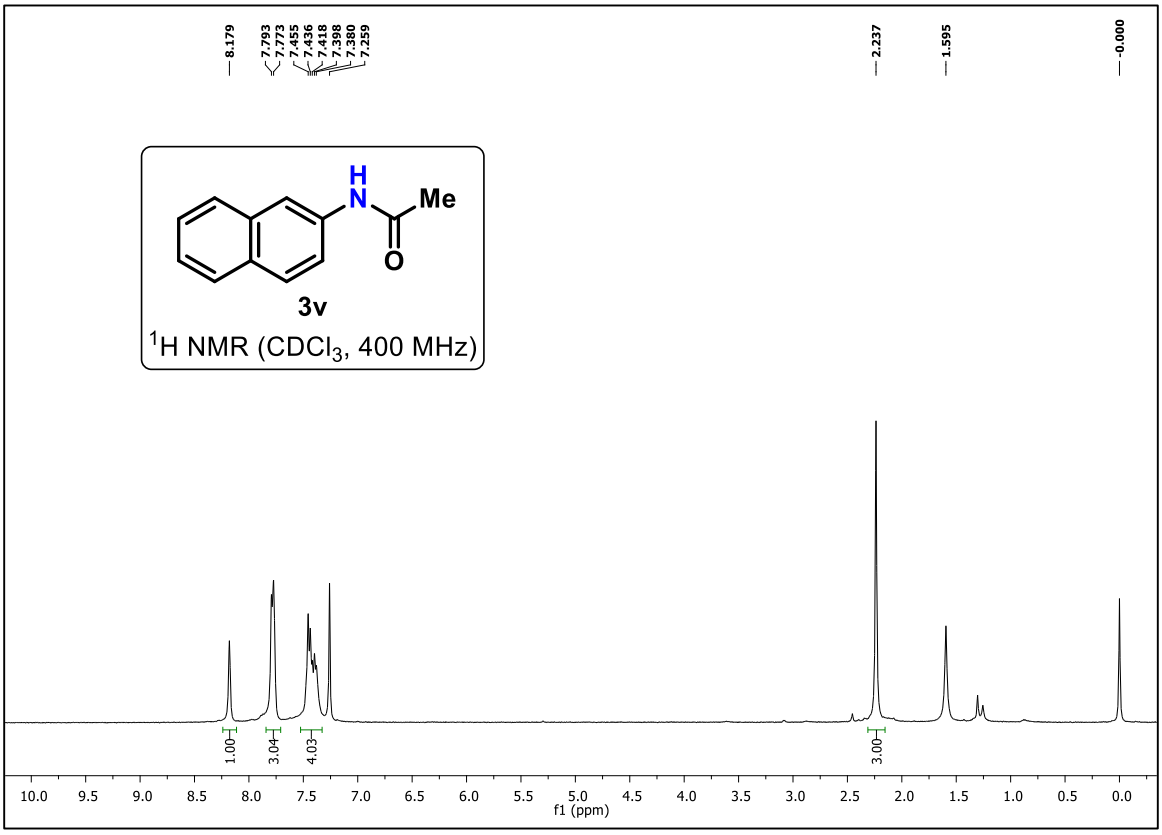

8.006
7.985
7.600
7.580
7.483
7.260
3.896
2.206
1.635
-0.004
MeO
O
H
N
CH3
O
3q
1H NMR (CDCl3, 400 MHz)
1.97
1.93
0.82
2.98
3.00
f1 (ppm)


10.043
7.482
3.415
2.500
2.005
1.638
H3C
O
N
H
H
N
CH3
O
3r
1H NMR (DMSO-d6, 400 MHz)
2.00
4.19
6.05
f1 (ppm)


7.420
7.398
7.313
7.292
7.260
7.150
6.447
2.153
1.587
1.510
-0.002
3s
^{1}H NMR ($CDCl_3$, 400 MHz)
2.07
1.93
0.96
0.95
3.00
9.33
f1 (ppm)


8.203
7.262
6.898
6.880
6.869
6.845
6.836
6.832
6.823
6.810
6.655
6.652
6.646
5.299
2.203
1.663
1.254
0.899
0.882
0.864
-0.000
3t
^{1}H NMR ($CDCl_3$, 400 MHz)
1.02
1.95
0.97
3.00
f1 (ppm)


8.200
8.076
8.055
7.772
7.752
7.400
7.389
7.370
7.354
7.334
7.324
7.285
7.260
7.245
7.226
7.218
7.187
7.167
2.311
2.243
1.582
-0.001
Me
HN
O
N
Ts
3u
1H NMR (CDCl3, 400 MHz)
1.00
1.00
2.00
2.37
0.86
0.92
2.10
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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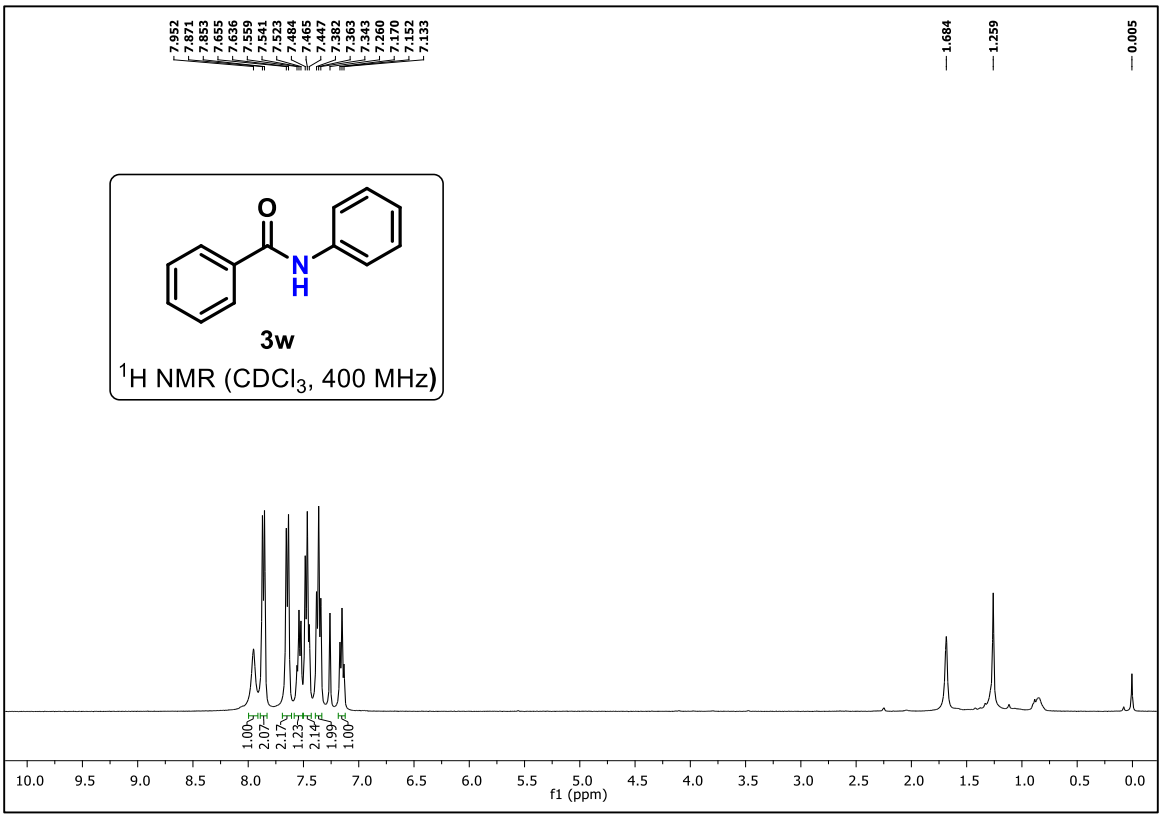
7.793
7.773
7.455
7.436
7.418
7.398
7.380
7.259
2.237
1.595
-0.000
H
N
Me
O
3v
1H NMR (CDCl3, 400 MHz)
1.00
3.04
4.03
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


7.952
7.871
7.853
7.655
7.636
7.559
7.541
7.523
7.484
7.465
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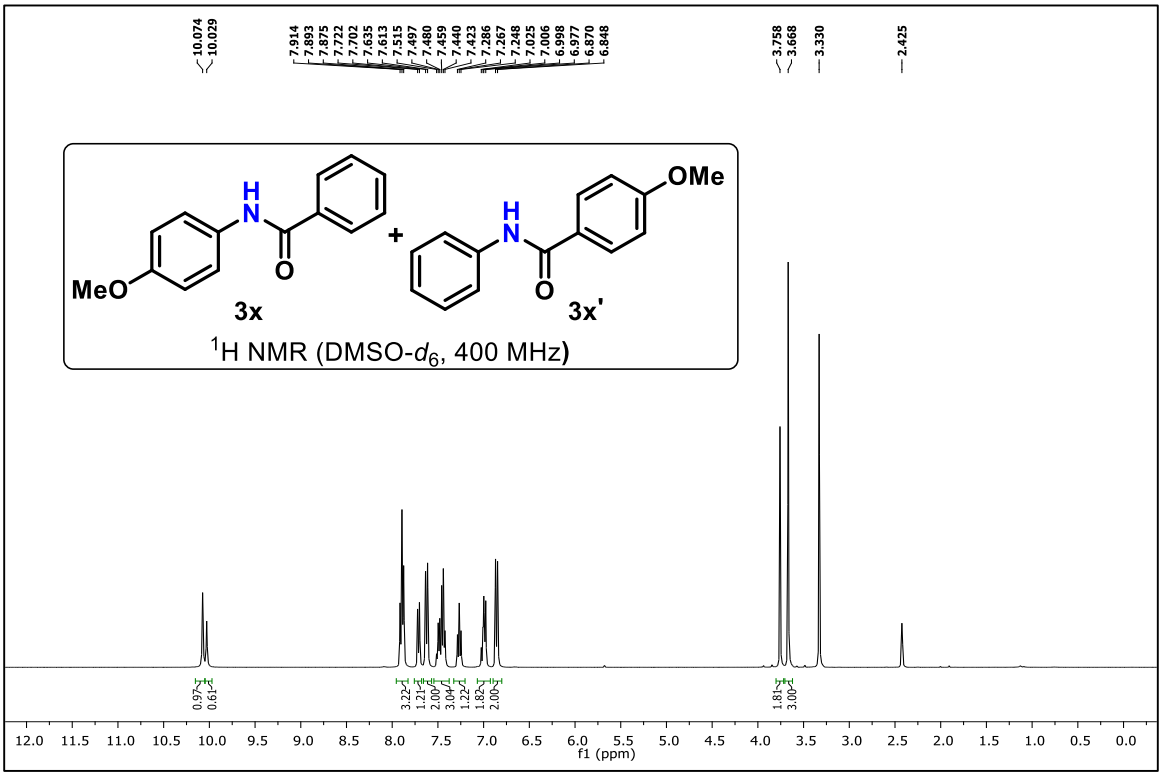
7.382
7.363
7.343
7.260
7.170
7.152
7.133
1.684
1.259
0.005
O
N
H
3w
1H NMR (CDCl3, 400 MHz)
1.00
2.07
2.17
1.23
2.14
1.99
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


10.074
10.029
7.914
7.893
7.875
7.722
7.702
7.635
7.613
7.515
7.497
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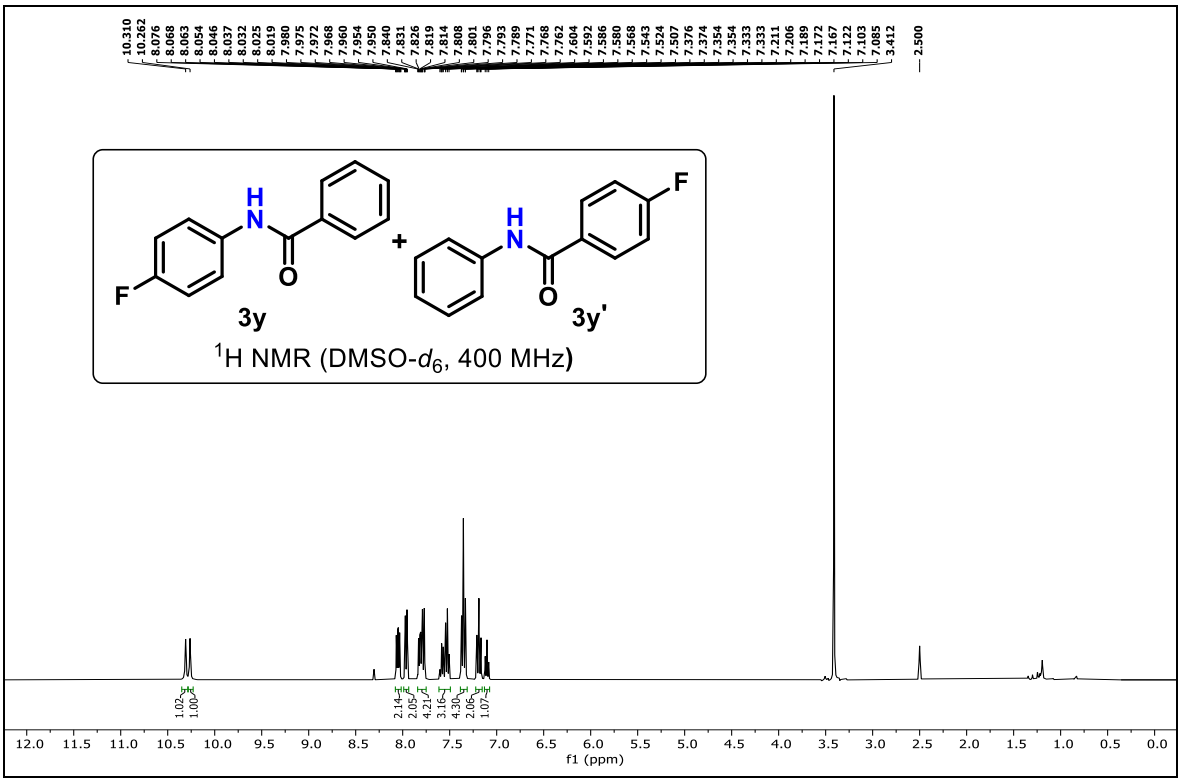
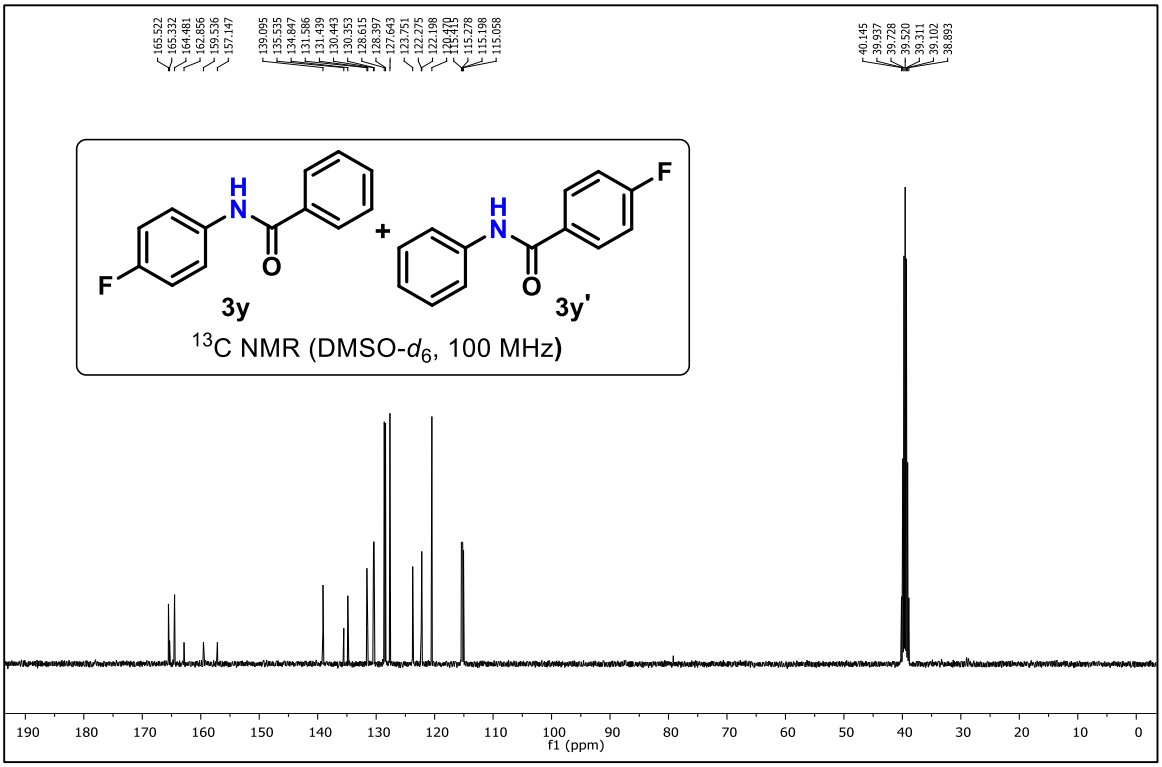
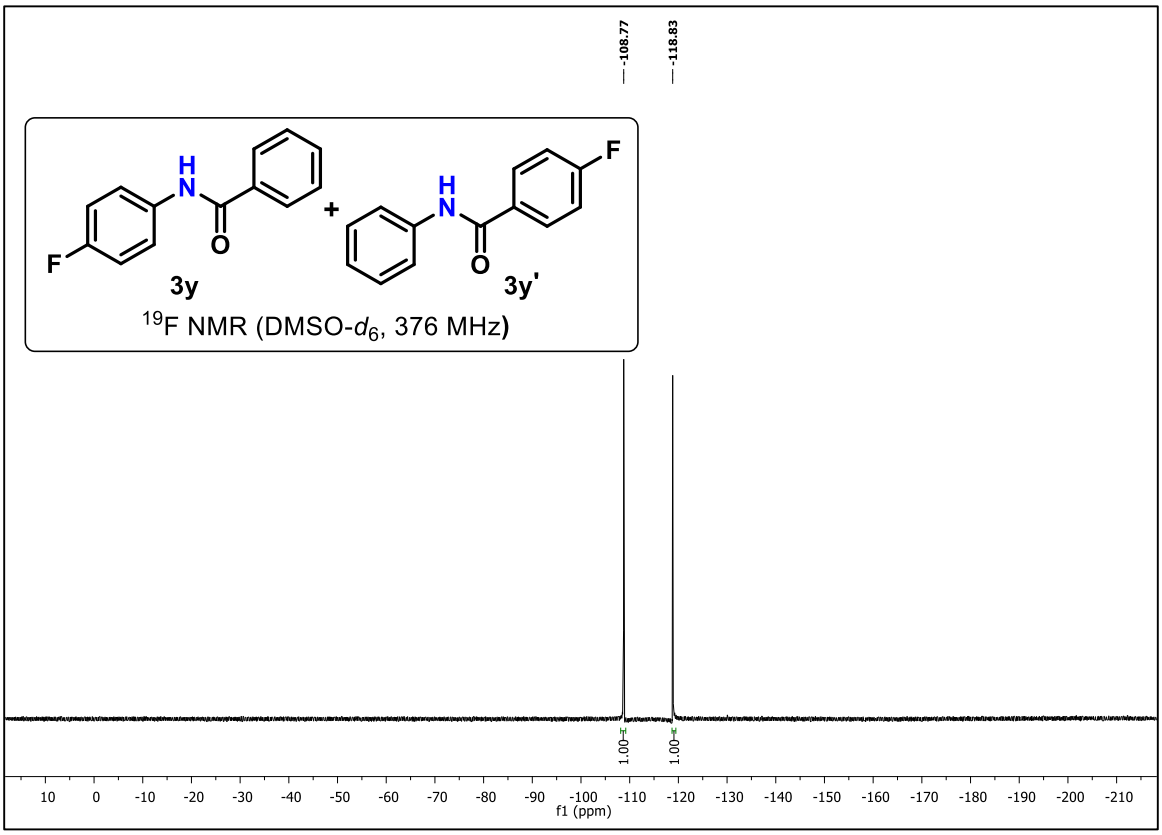
7.440
7.423
7.286
7.267
7.248
7.025
7.006
6.998
6.977
6.870
6.848
3.758
3.668
3.330
2.425
H
N
O
MeO
3x
+
H
N
O
OMe
3x'
1H NMR (DMSO-d6, 400 MHz)
0.97
0.61
3.22
1.21
2.00
3.04
1.22
1.82
2.00
1.81
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


3y
3y'
^{1}H NMR (DMSO-d_6, 400 MHz)
f1 (ppm)


3y
3y'
^{13}C NMR (DMSO-d_6, 100 MHz)
f1 (ppm)


-108.77
-118.83
3y
3y'
^{19}F NMR (DMSO-d_6, 376 MHz)
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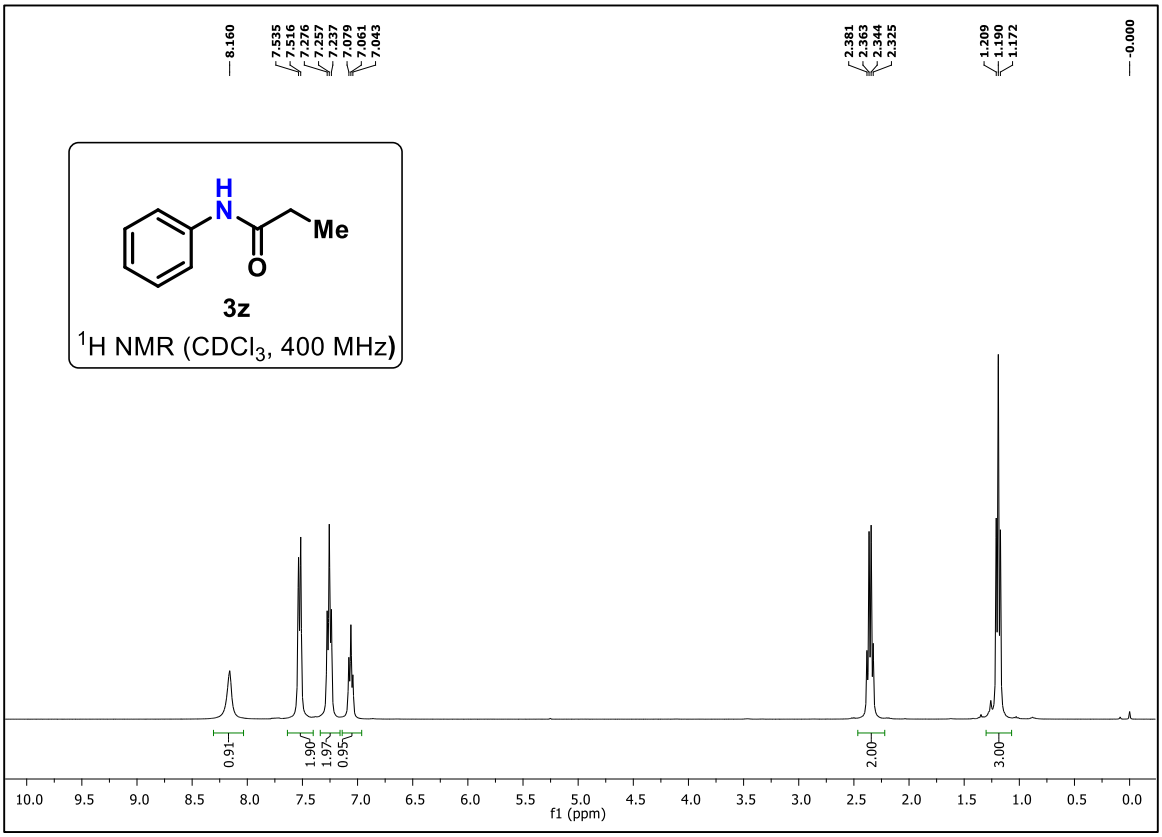
1.00
f1 (ppm)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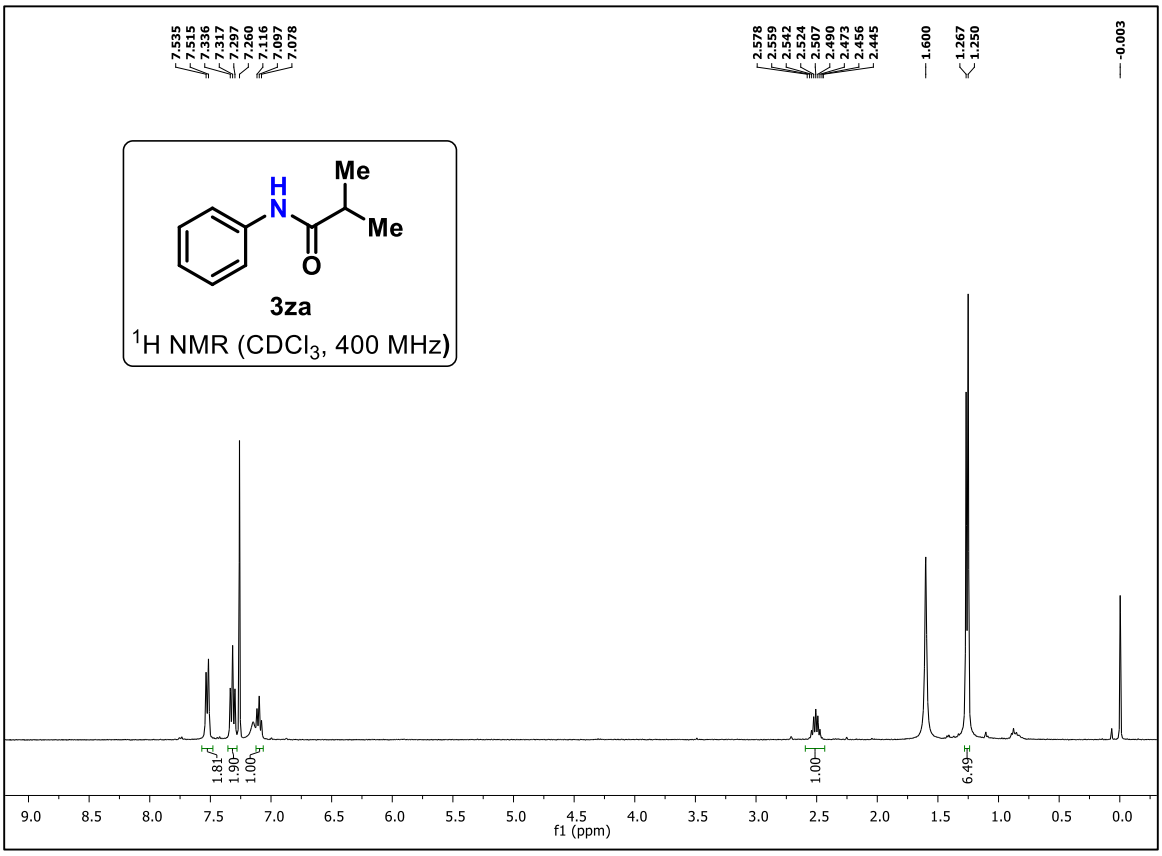
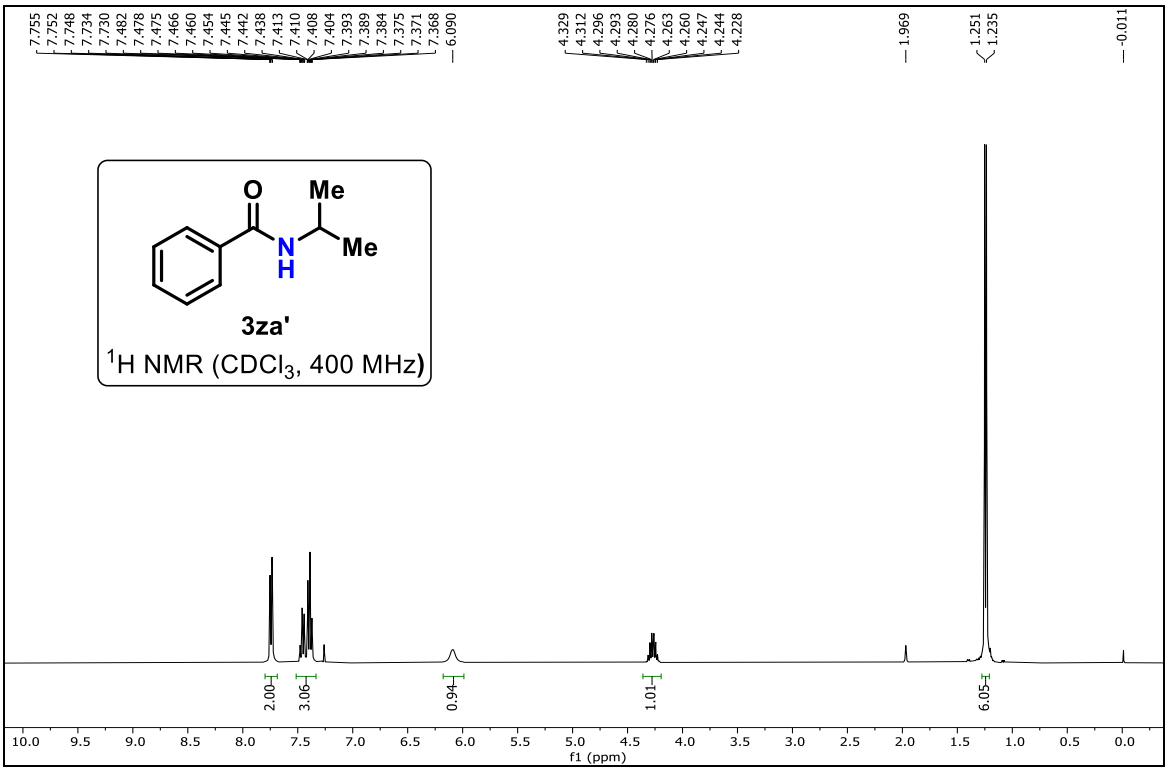
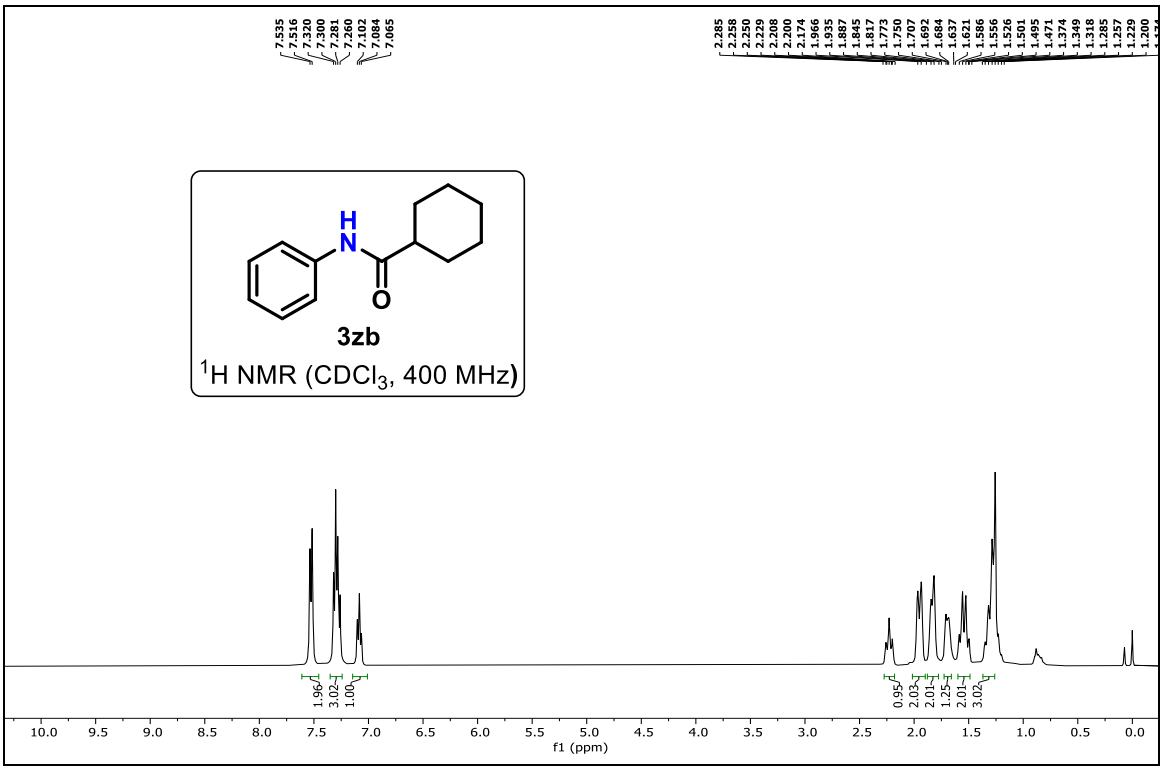
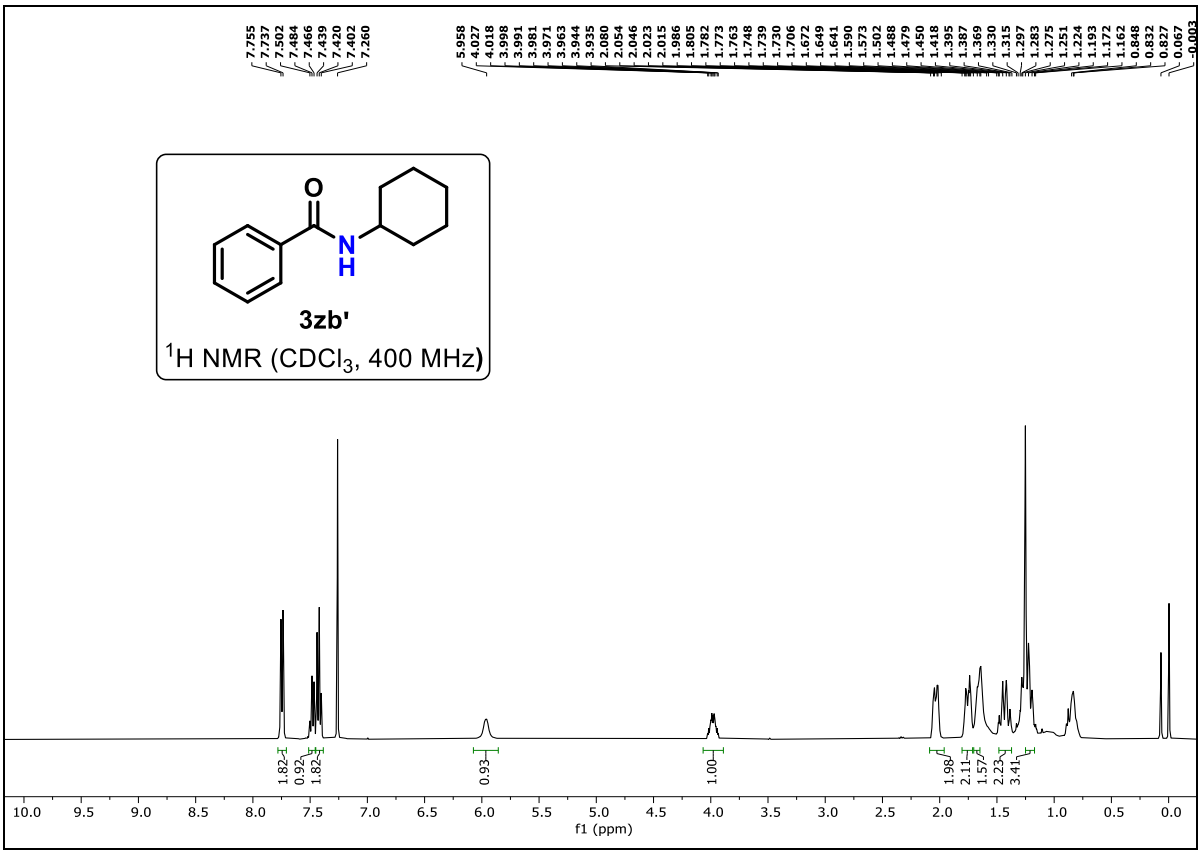
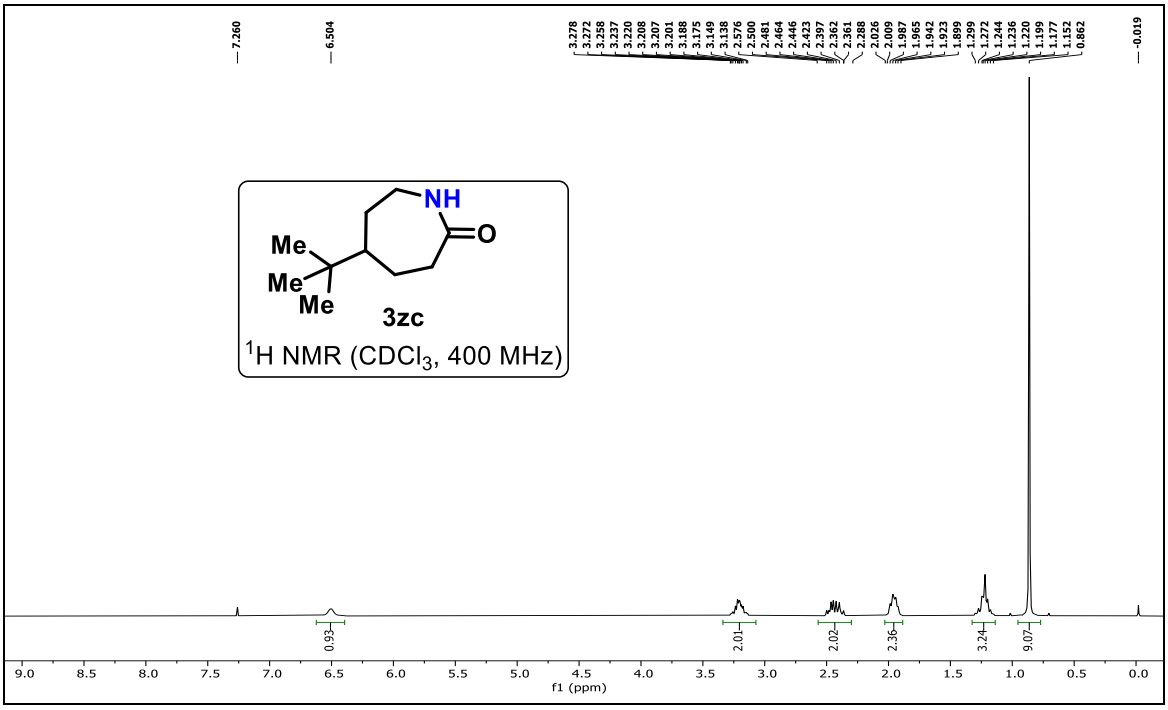
7.535
7.516
7.276
7.257
7.237
7.079
7.061
7.043
2.381
2.363
2.344
2.325
1.209
1.190
1.172
-0.000
Me
3z
^{1}H NMR (CDCl$_3$, 400 MHz)
0.91
1.90
1.97
0.95
2.00
3.00
f1 (ppm)

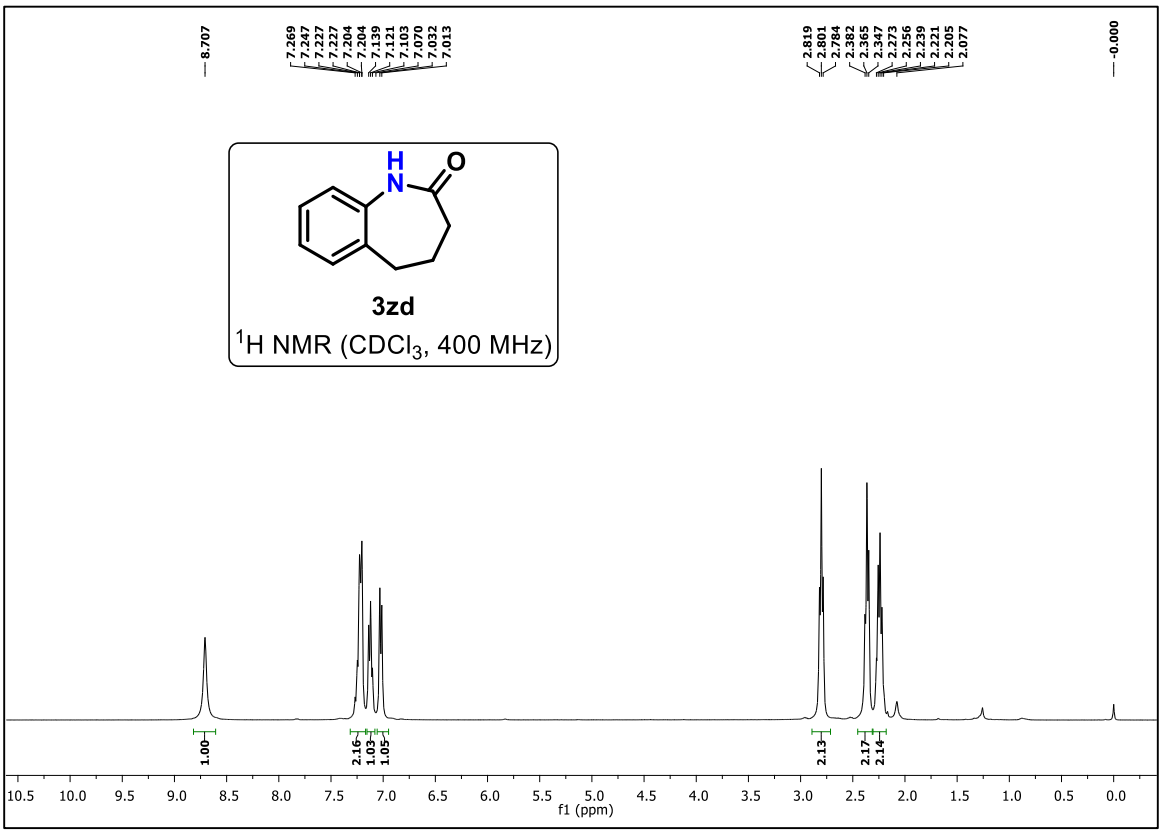

7.535
7.515
7.336
7.317
7.297
7.260
7.116
7.097
7.078
2.578
2.559
2.542
2.524
2.507
2.490
2.473
2.456
2.445
1.600
1.267
1.250
-0.003
Me
H
N
Me
O
3za
1H NMR (CDCl3, 400 MHz)
1.81
1.90
1.00
1.00
6.49
f1 (ppm)

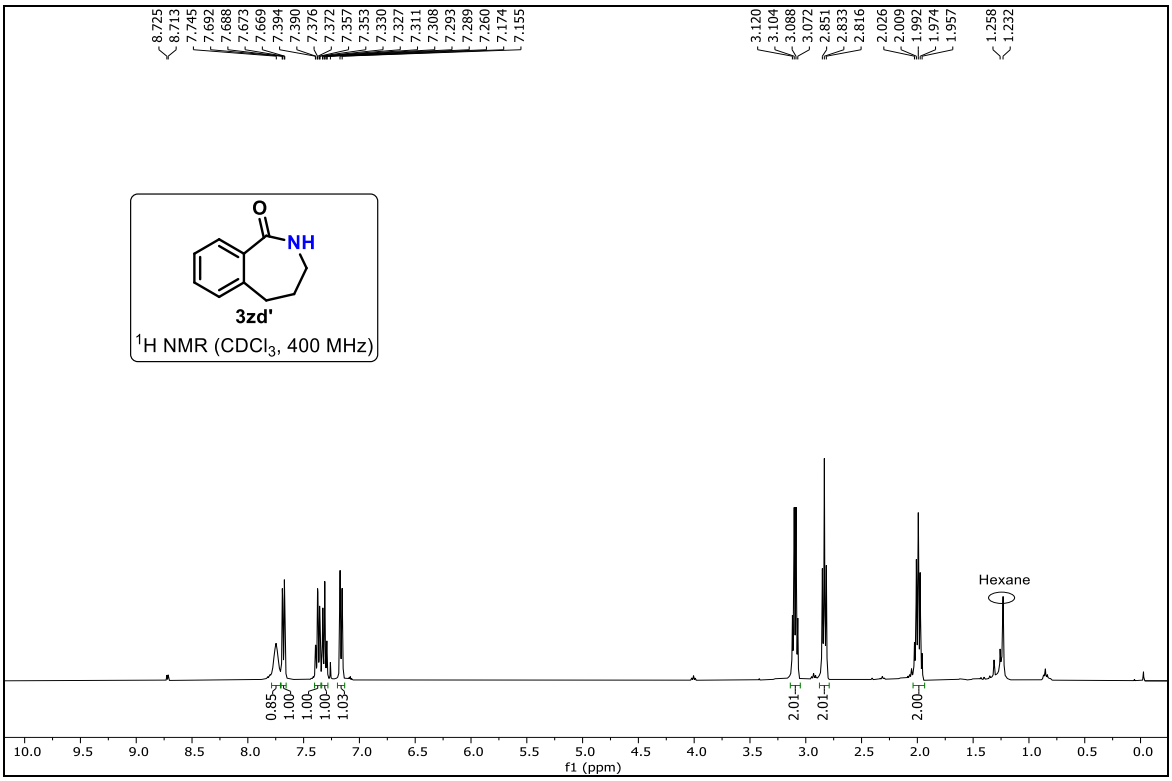

7.755
7.752
7.748
7.734
7.730
7.482
7.478
7.475
7.466
7.460
7.454
7.445
7.442
7.438
7.413
7.410
7.408
7.404
7.393
7.389
7.384
7.375
7.371
7.368
6.090
4.329
4.312
4.296
4.293
4.280
4.276
4.263
4.260
4.247
4.244
4.228
1.969
1.251
1.235
-0.011
O
Me
N
H
Me
3za'
1H NMR (CDCl3, 400 MHz)
2.00
3.06
0.94
1.01
6.05
f1 (ppm)


3zb
^{1}H NMR (CDCl$_3$, 400 MHz)
f1 (ppm)


3zb'
^{1}H NMR (CDCl$_3$, 400 MHz)
f1 (ppm)


NH
O
Me
Me
Me
3zc
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)


H
N
O
3zd
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)


8.725
8.713
7.745
7.692
7.688
7.673
7.669
7.394
7.390
7.376
7.372
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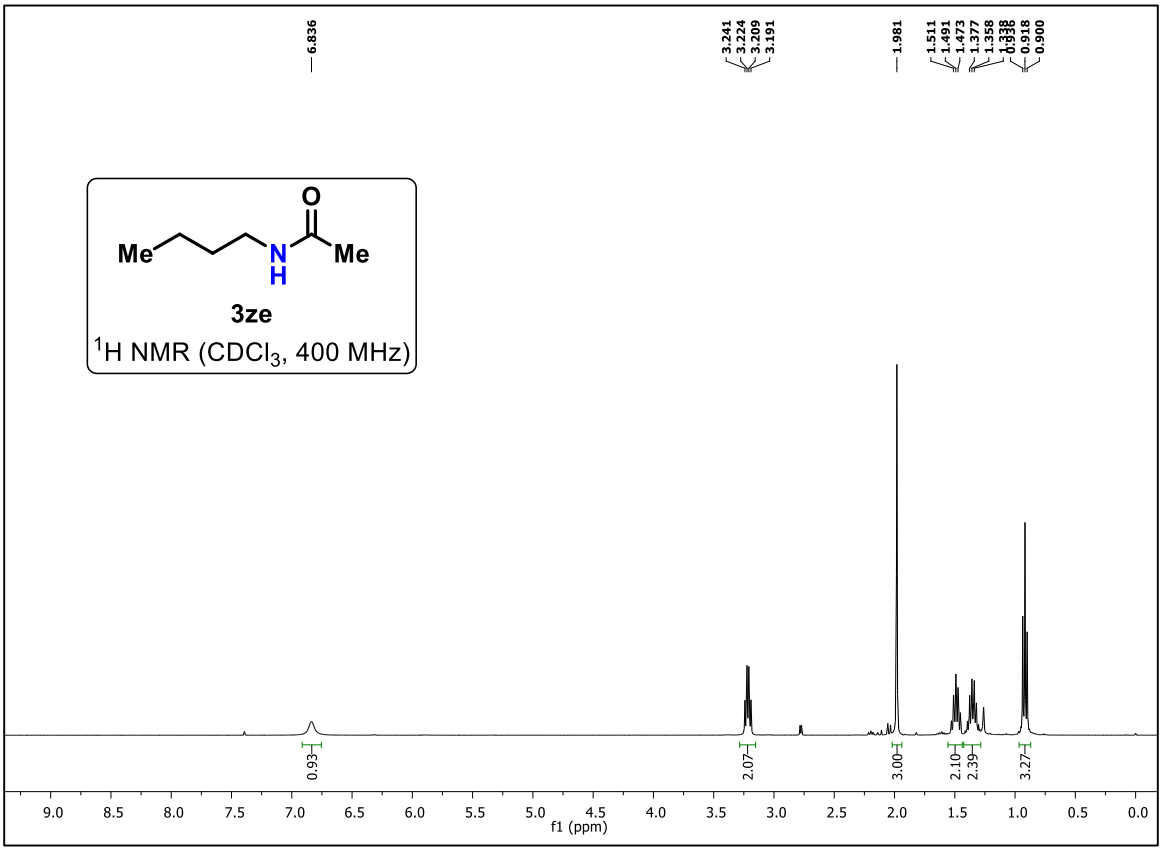
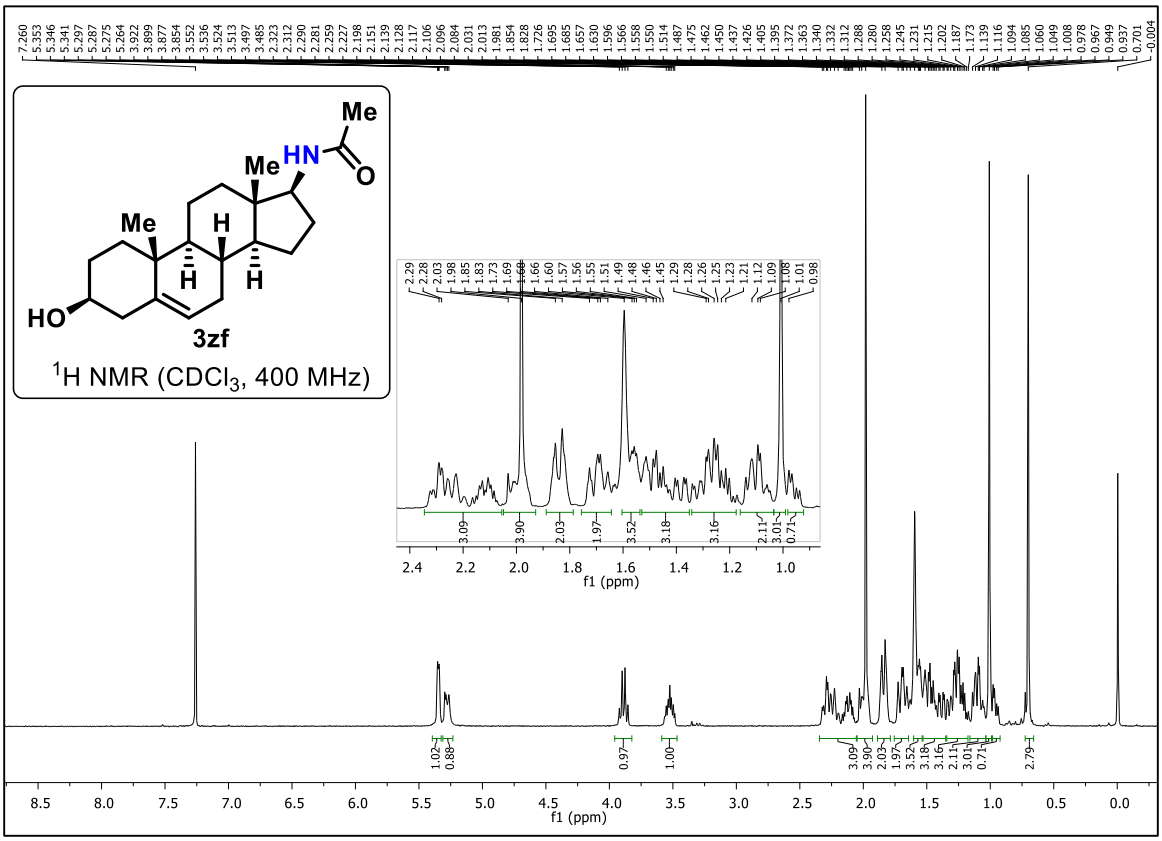
7.353
7.330
7.327
7.311
7.308
7.293
7.289
7.260
7.174
7.155
3.120
3.104
3.088
3.072
2.851
2.833
2.816
2.026
2.009
1.992
1.974
1.957
1.258
1.232
O
NH
3zd'
1H NMR (CDCl3, 400 MHz)
Hexane
0.85
1.00
1.00
1.00
1.03
2.01
2.01
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


6.836
3.241
3.224
3.209
3.191
1.981
1.511
1.491
1.473
1.377
1.358
0.938
0.918
0.900
O
Me
N
H
Me
3ze
1H NMR (CDCl3, 400 MHz)
0.93
2.07
3.00
2.10
2.39
3.27
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
HN
O
Me
Me
H
H
H
HO
3zf
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)

2.9 References

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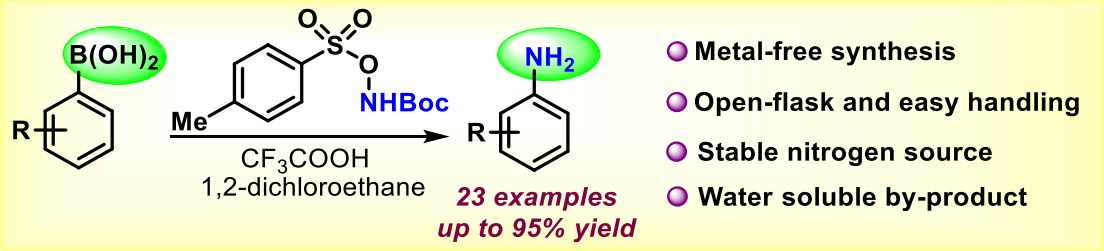
Chapter 3

Direct and metal-free transformation of aryl boronic acid into aromatic amines using *N*-Boc-*O*-tosylhydroxylamine reagent

This chapter describes the direct and metal-free method for the synthesis of aromatic amines from aromatic boronic acids and esters by using the TsONHBoc as an aminating reagent. This reagent is extremely stable, easy to use, and produces a non-interfering by-product (*i.e.* TsOH) that is easily removed by a basic aqueous workup. Under acidic conditions, the method applies to boronic acids having electron-withdrawing as well as electron-donating groups to produce the corresponding anilines in good to excellent yields. The existing method could be utilized to obtain aromatic primary amines at the gram scale.



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3.1 Introduction

Primary aryl amines are present in several drugs, biologically active compounds, agrochemicals, dyes, and polymeric substances.[1] Otto Unverdorben discovered the aniline which was isolated from the destructive distillation of indigo. Additionally, arylamines are utilized as transition metal ligands,[2] as well as in the development of conductive polymer[3] and other electronic materials of interest.[4] Aromatic amines' historical and industrial value inspired to development of newer synthetic methods. Arylamines have so many different uses, hence they are desirable targets for chemical synthesis (Figure 3.1-3.3).[1]

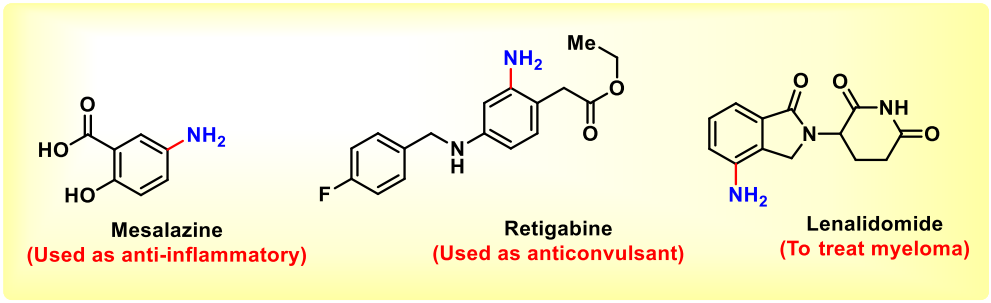


Figure. 3.1. Some drug molecules having primary amines[1]

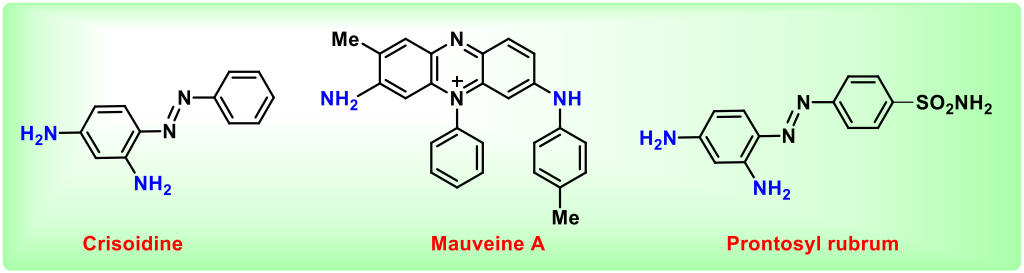


Figure. 3.2. Selected examples of aniline derived dyes[1]

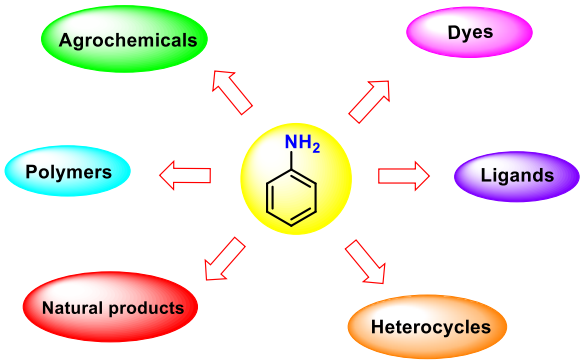
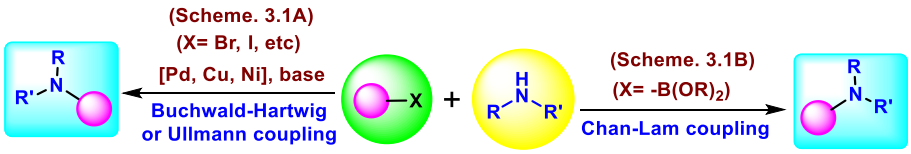
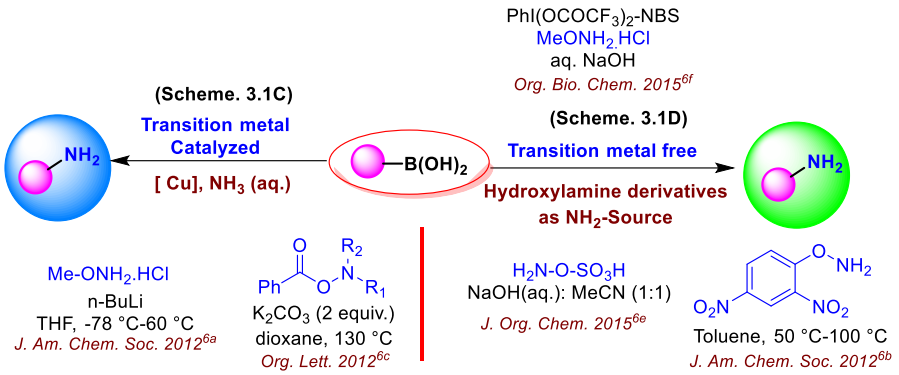


Figure 3.3. Important applications of anilines

3.2 Literature review for the synthesis of aromatic amines

Traditional synthesis of amines involves the introduction of nitro group on aromatic compounds which was further reduced *via* metallic reduction or catalytic hydrogenation.[5] Towards a milder alternative to the traditional method, transition metal catalyzed coupling of aryl halides and amines was developed.[6] Later on amination reactions catalyzed by palladium metal have attracted great attention.[7] To eliminate the need for expensive palladium catalysts and strong bases, copper-based oxidative amination of arylboronic acids has been further investigated. This approach is useful as it gives access to a large number of functionalized and stable boronic acids, however, it only allows access to *N*-substituted aromatic amines (Scheme 3.1A).[8] Fu and coworkers reported the preparation of primary aromatic amines from boronic acid using Cu(I)O and aq. NH_3 as a nitrogen source (Scheme 3.1B).[9] First transition metal-free synthesis of anilines has been reported by the Kürti group using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as a nitrogen source.[10]



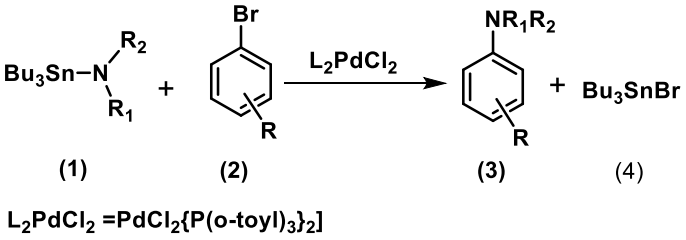


Scheme 3.1. Synthesis of primary anilines from arylboronic acids and aryl halides

The up-to-date literature study for the synthesis of arylamines are summarized below:

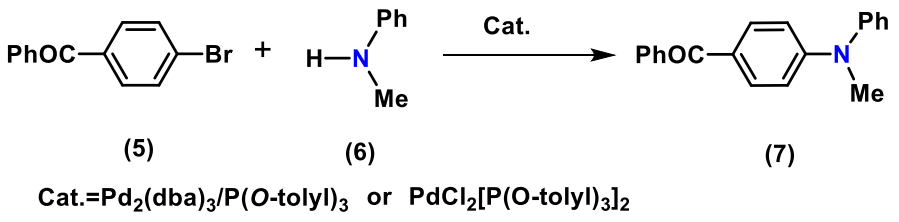
3.2.1 Pd-catalyzed selective amination *via* coupling reactions

i) Kosugi and Migita were the first to describe the C-*N* coupling of aryl halides with tin amides using palladium catalysts and tri-*O*-tolylphosphine as a ligand.[11,12] Palladium complexes could catalyze the aromatic C-N bond formation in a synthetically useful manner. The limited scope and toxicity of tin-amide limit its wider application (Scheme 3.2).



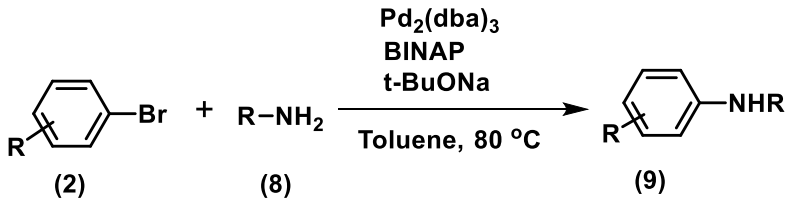
Scheme 3.2. Pd-catalyzed amination of arylbromides

ii) Hartwig[13] and Buchwald group,[14] reported the first catalytic amination of aryl bromides using unprotected amine (Scheme 3.3).

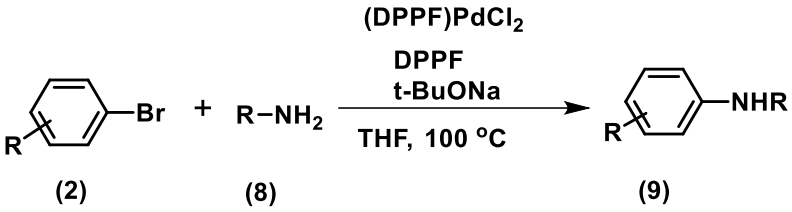


Scheme 3.3. Pd-catalyzed amination of arylbromides with free amine

The same group later on employed BINAP[15] and DPPF Pd-complexes for the synthesis of *N*-substituted anilines from aryl halides. They discovered that using $Pd_2(dba)_3$ and BINAP catalyst in the presence of *t*-BuONa improved the cross-coupling of amines with aryl bromides (Scheme 3.4-3.5).[16]

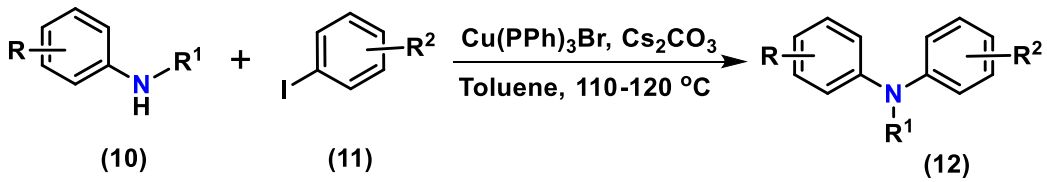


Scheme 3.4. BINAP-catalyzed amination of arylbromides



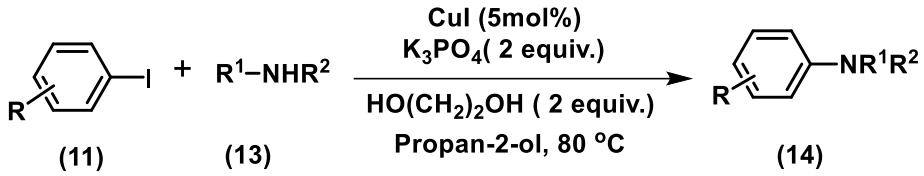
Scheme 3.5. DPPF-catalyzed amination of arylbromides

iii) Ullmann condensation is another widely used method for amination of aryl halides, in which an amine and an aryl halide were reacted in presence of a base and a copper catalyst. It is one of the most frequently adopted processes for the preparation of arylamines.[17] These reactions required elevated temperatures (200 °C) and stoichiometric amounts of copper catalyst, which might lead to waste disposal issues when used on large scale.[18] Gujadhur and coworkers describe an amination of mono- and diarylamines using $Cu(PPh_3)_3Br$ in the presence of Cs_2CO_3 base at 120 °C (Scheme 3.6).[19-20]



Scheme 3.6. $Cu(PPh_3)Br$-catalyzed amination of aryliodides

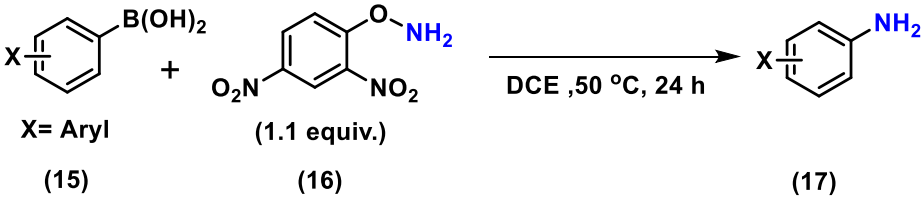
iv) Buchwald *et al.* described a moderate, useful Cu-catalyzed amination of functionalized aryl iodides using air-stable CuI catalyst and ethylene glycol as the ligand (Scheme 3.7).[21]



Scheme 3.7. CuI-catalyzed amination of aryliodides

3.2.2 Synthesis of amines from aromatic boronic acids using DPH reagent

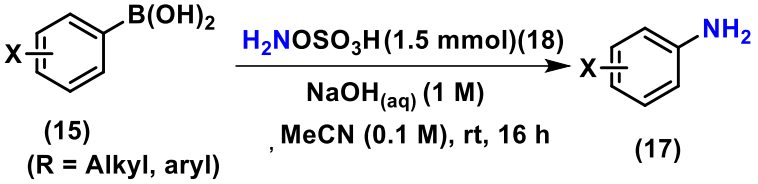
Chen Zhu and co-workers reported the first metal-free synthesis of primary aromatic amines (**17**) in good yields directly from arylboronic acids (**15**) using DPH as a nitrogen source (Scheme 3.8). This methodology failed with aliphatic substrates and also provided poor yields with electron deficient substrates. This method produced the anilines in good yields. However, the generated toxic by-product (2,4-dinitrophenol) limits its application in industries.[22]



Scheme 3.8. Synthesis of aryl anilines from boronic acids using DPH

3.2.3 Metal-free Synthesis of aromatic amines from aryl boronic acids using HOSA

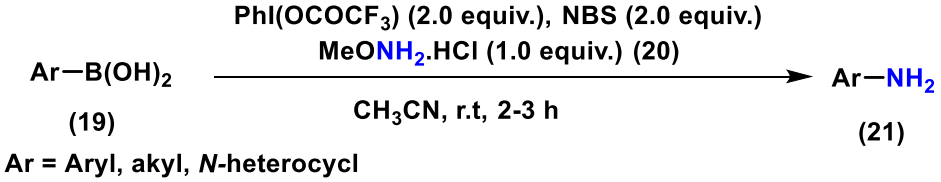
Voth *et al.* have developed an effective transition metal-free method for converting phenylboronic acid directly into primary anilines using HOSA as aminating agents. The corresponding aniline (**17**) was produced in excellent yield when boronic acid (**15**) was reacted with HOSA (**18**) in the presence of aqueous NaOH in MeCN at room temperature. This method has several limitations such as the requirement of a strong base (NaOH). Substrates containing strongly electron-withdrawing groups provided very poor yield along with a longer reaction time (Scheme 3.9).[23]



Scheme 3.9. Synthesis of anilines from boronic acids

3.2.4 *Ipso*-amination of organo-boronic acids using PIFA

In 2015, Nachiketa Chatterjee *et al*. reported the *ipso*-amination of substituted boronic acids **(19)** using PIFA with *N*-bromosuccinimide (NBS). They used methoxyamine hydrochloride as a nitrogen source **(20)** under metal and base-free conditions to access desired anilines **(21)** with good to excellent yields. Indeed this methodology works well but it has some limitations such as aminating agent is highly hygroscopic and needed an excessive amount of additives (Scheme 3.10).[24]

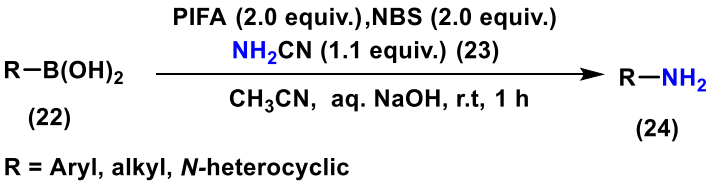


Scheme 3.10. Synthesis of primary anilines using PIFA

3.2.5 Chemoselective approach for the preparation of primary anilines to boronic acids using cyanamidyl/arylcyanamidyl radical as a nitrogen source

In 2016, Nachiketa Chatterjee and coworkers reported a practical, efficient method for the synthesis of primary anilines from boronic acids in the presence of PIFA, NBS, and cyanamidyl/arylcyanamidyl radicals as a nitrogen source (Scheme 3.11). Primay amines were obtained in the form of ammonium trifluroacetate salts which were then treated with aqueous NaOH to yield the free amines. Quantum chemical calculations in combination with experimental data show that the boron atoms of the boronic acids interact regiospecifically with the nitrile-*N* centre of the cyanamidyl/arylcyanamidyl radical. This methodology works very well with all types of boronic acids such as electron-rich,

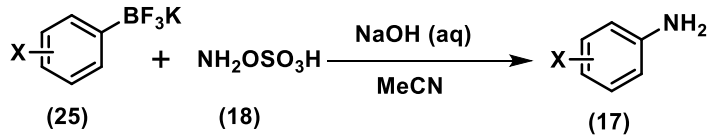
electron-deficient, heterocyclic and aliphatic boronic acids generated corresponding primary amines with good to excellent yields.[25]



Scheme 3.11. Synthesis of primary amines from boronic acids using PIFA-NBS.

3.2.6 Synthesis of primary aryl amines using microwave and sonication method from potassium arylfluoroborates and arylboronic acids

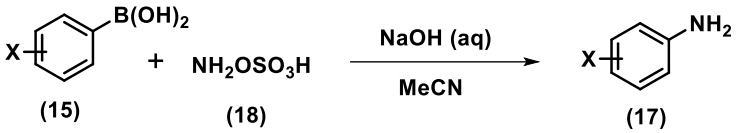
i) Dale kuik and co-workers have developed metal-free benign microwave assisted methodology to synthesize primary arylamines from potassium arylfluoroborates using hydroxylamine-*O*-sulfonic (HOSA) as aminanting agent. Aryltrifluoroborates (**25**) were treated with HOSA (**18**) using aqueous NaOH in acetonitrile under two different conditions: sonication as well as microwave irradiation to obtain corresponding arylamines (**17**) in good yields (Scheme 3.12A). Electron rich substrates reacted in a faster rate than electron-deficient substrates to produce primary aryl amines in better to good yields under sonication. Similar transformations under a microwave reactor proceeded well to afford better yields of aryl amines in contrast with the sonication process (Scheme 3.12B). 2-naphthyl and thiophene derivatives afforded better yields under microwave irradiation. However, 4-iodophenylfluoroborate and 2,6-dimethoxyphenylfluoroborate afforded proximal yields under both conditions.[26]



Scheme 3.12A; Sonication: HOSA (1.5 equiv.), MeCN (2.5 mL)
NaOH (5 equiv.) 1-3 h
Scheme 3.12B; Microwave : HOSA (1.5 equiv.), MeCN (2.0 mL)
NaOH (5 equiv.) 30 min. 100 ^{0}C,15min

Scheme 3.12. Synthesis of primary aryl amines

ii) After the successful synthesis of arylamines from aryltrifluorborate under sonication and microwave irradiation, the author further developed the transformation of arylboronic acids into arylamines using HOSA. Arylboronic acids (**15**) were treated with HOSA (**18**) using aqueous NaOH in acetonitrile at r.t. to obtain the desired primary arylamine (**17**) in better to satisfactory yields with a much longer reaction time (Scheme 3.13A).[27] However, the same reaction under sonication was completed within 30 min with better yields of aryl amines (Scheme 3.13B). It was observed that electron-rich substrates afforded better yields than electron-deficient substrates under sonication. To improve the yields, further the same reaction was exposed under microwave irradiation which was completed within 15 min at 100 ^{o}C to provide the best yields of desired products (Scheme 3.13C).



Scheme 3.13A Method C; r. t.: HOSA (1.5 equiv.), NaOH (5 equiv.) MeCN (5.0 mL) , 16 h, r.t

Scheme 3.13B Method D; Sonication: HOSA (1.5 equiv.), NaOH (5 equiv.) MeCN (5.0 mL) , 30 min.

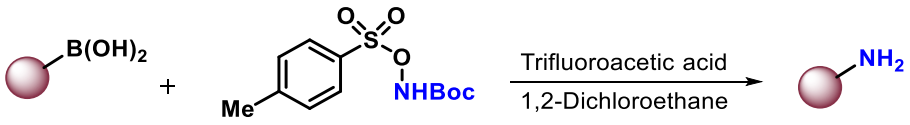
Scheme 3.13C Method E; Microwave: HOSA (1.5 equiv.), NaOH (5 equiv.) MeCN (2-10 mL) , 100 ^{0}C, 15 min

Scheme 3.13. Synthesis of amines from aryl boronic acids

In conclusion, only a few reports have been established to synthesize primary anilines from boronic acids by using various aminating agents, such as HOSA (HSO_3ONH_2), $MeONH_2$.HCl, aminoazanium of DABCO (H_2N-DABCO)[28] and others.[29] Although these protocols effectively access desired primary amines, used $+NH_2$ reagents (such as DPH) must be stored at 0 ^{o}C and release hazardous, explosive, and interfering byproducts (2,4-dinitrophenol). *O*-benzoylhydroxylamine derivatives only generated substituted anilines. Methoxyamine hydrochloride and hydroxylamine-*O*-sulphonic acid, need an excessive amount of strong bases like NaOH and *n*-BuLi. In light of the limitations and potential problems of previously described protocols, the development of an easy-to-use method for the synthesis of primary anilines from boronic acid/ester is highly desirable.

3.3 Objective of the work

The objective of this part of the thesis is to develop a novel transition metal-free direct method for the synthesis of primary amines from aryl boronic acid/ester using TsONHBoc as the nitrogen source (Scheme 3.14).

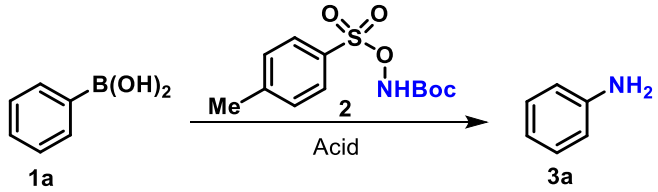


Scheme 3.14. Synthesis of anilines from aryl boronic acids

3.4 Results and discussion

3.4.1 Optimization of the reaction condition

Table 3.1 Optimization of the reaction conditions[a]



S.No.	Solvent	Additives	Amount (equiv.)	Yield (%)[b]
1	TFE	-	-	45%
2	TFE	AcOH	1.5	56%
3	TFE	$(COOH)_2$	1.5	50 %
4	TFE	TFA	1.5	69%
5[c]	TFE	TFA	3.0	82%
6	CH_2Cl_2	TFA	3.0	89%
7[d]	DCE	TFA	3.0	95%
8	Toluene	TFA	3.0	90%

9	CH_3CN	TFA	3.0	30%
10	MeOH	TFA	3.0	20%
11	DCE	-	-	0%

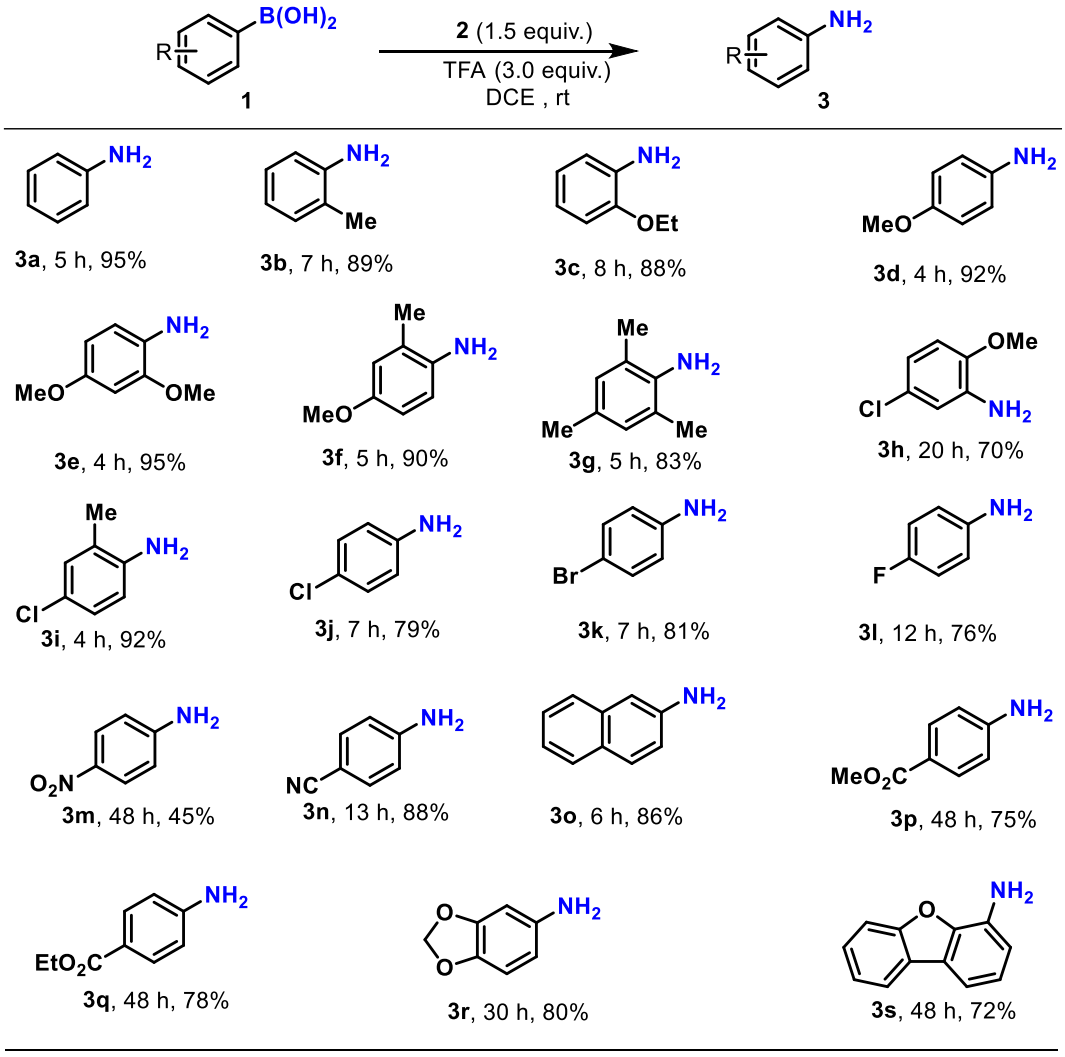
[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), **2** (0.75 mmol, 1.5 equiv.), acid (1.5-3.0 equiv.), Solvents, (CH_2Cl_2, DCE (1,2-dichloroethane), Toluene, CH_3CN, MeOH (1.0 mL), rt, 16 h. [b]Isolated yield.[c-d] Reaction was completed in 6 h and 5 h respectively.

In our earlier investigation, we observed that TsONHBoc generates an active amine reagent ($TsONH_2$) in TFE solvent.[30] On the next move, we wish to use this methodology for the transformation of boronic acid to amines. We started the investigation using phenylboronic acid as a model substrate which was aminated in TFE to produce aniline **3a** with a moderate yield of (45%, Table 3.1, Entry 1). With this encouraging outcome, we proposed the hypothesis that exogenous acid could accelerate the reaction by easily deprotecting the Boc-group. We observe that, out of all the used acids (Entries 2-4), TFA turns out to be the best choice (Table 3.1, Entry 4-5). Additionally, a study of different solvents revealed that dichloroethane is the most efficient solvent (Table 3.1, entries 7-11).

3.4.2 Substrate scope

After the optimized reaction condition in hand, we next studied the effect of favorable electron-releasing groups (Scheme 3.15). It is noteworthy that substrates with electron-donating groups (Me, OEt) at the *o*-position were readily transformed to the desired amines (**3b**-**3c**). In addition, the *p*-methoxy (**1d**) substituent efficiently formed the corresponding amine (**3d**). Di-methoxy (**1e**) and mesitylboronic acid (**1g**) were found to be consistent at these reaction conditions, and the desired anilines (**3e** and **3g**) were obtained in high yields. Similar to this, 2-methyl-4-methoxyphenylboronic acid (**1f**) transformed into the desired amine (**3f**) with excellent yields. The transition metal-catalyzed amination procedure is frequently challenging to prepare halogen substituted aromatic anilines. Halogenated phenylboronic acids in particular (**1h-l**) were readily transformed with good to high yields (**3h-l**). In addition, the phenylboronic acid having electron-withdrawing cyano group at *para* position efficiently transformed into the corresponding anilines **3n** with 88% yields. *Para* nitro phenylboronic acids converted into the corresponding amine (**3m**) in moderate

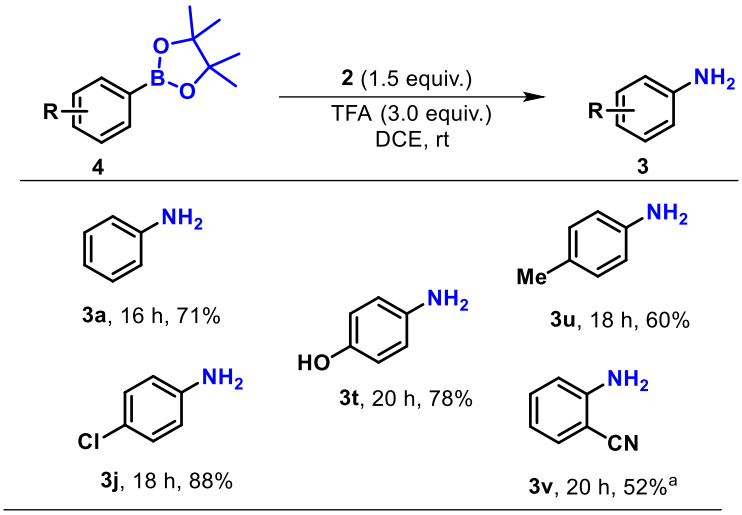
yield (45 %). Amine **3o** was produced in good yield from naphthyl-2-boronic acid. Substrates 4-methoxy and 4-ethoxycarbonylphenylboronic acid (**1p-q**) having labile groups performed very well and produced corresponding anilines in excellent yields. Under our optimized reaction condition, phenethylboronic acid and cyclohexylboronic acid did not produce the product. Heterocyclic substrates such as 3,4-(methylenedioxy)phenylboronic acid (**1r)** as well as dibenzofuran boronic acid (**1s**) were generated the corresponding amines **3r-s** in a high yield.



[a]Reaction conditions: 1 (0.5 mmol, 1.0 equiv.), 2 (0.75 mmol, 1.5 equiv.), TFA (1.5 mmol, 3.0 equiv.), DCE (1.0 mL), rt, [b]isolated yield.

Scheme 3.15. Synthesis of primary amines from boronic acids

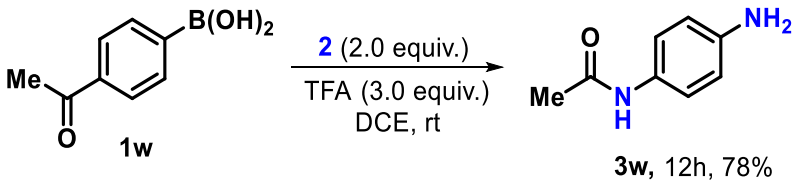
On the next move, boronate ester **4a**, produced aniline **3a** in an excellent yield. Further study of various boronate esters substituted at different positions produced the respective anilines in good yields **4j** & **4v** (Scheme 3.16).



Yields are reported after isolation. [a]Reaction was performed in Toluene.

Scheme 3.16. Synthesis of primary amines synthesized from boronic esters

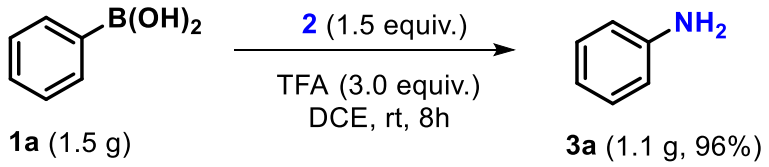
To test the chemoselectivity of this method we reacted (4-acetylphenyl) boronic acid **1w** with aminating agent **2** (1.0 equiv.). The boron center was left unreacted while the ketonic group was changed into the equivalent amide. When we added another **1** equivalent of aminating agent then the boronic acid group converted into the amino group **3w** (Scheme 3.17).



Scheme 3.17. Conversion of both boronic acid and ketonic groups simultaneously

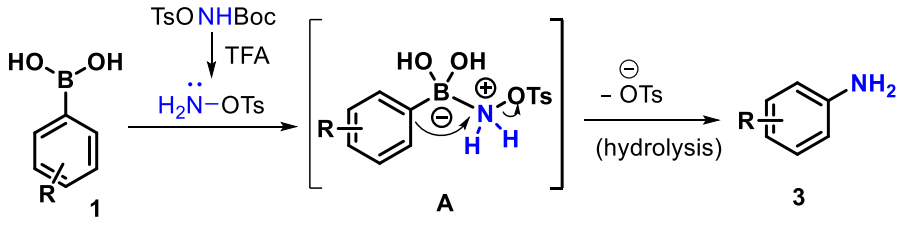
The favorable results found in the mmol scale motivated us to further examine the scalability of this method. This amination reaction has been examined for its practical use

by employing gram-scale transformation of phenylboronic acid **1a** to aniline **3a** in quantitative yield (Scheme 3.18).



Scheme 3.18. Synthesis of aniline at gram scale.

This method follows the same mechanistic pathways as proposed by the Kürti group (Scheme 3.19).[10]



Scheme 3.19. Proposed mechanism of reaction

3.5 Conclusion

In conclusion, we have developed an operationally simple method for the synthesis of different primary anilines from different aromatic boronic acids and esters having various functional groups at different positions. Substrates containing electron donating and electron withdrawing groups both, as well as heterocyclic boronic acids, were tolerated well. *In situ* generated active amino ($TsONH_2$) by *N*-Boc protected aminating agent overcome the several drawbacks of using isolated -NH_2 reagents. We hope this method may find suitable synthetic applications.

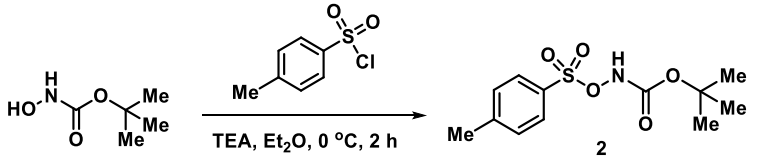
3.6 Experimental section

3.6.1 General Information:

Reactions, unless otherwise stated, were carried out using oven-dried glassware under open atmosphere. Commercially available boronic acids were used as received without further

purification. TLC was carried out on precoated plates (Merck silica gel 60, F_{254}), and the spots were visualized with UV light or by charring the plates dipped in ninhydrin solution. The compounds were purified by flash column chromatography using silica gel (100-200 mesh) and ethyl acetate/hexane as the mobile phase. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz in $CDCl_3$ or DMSO-d_6 respectively as the solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm; DMSO-d_6: δ H = 2.5 ppm, δ C = 39.52 ppm). High-resolution mass spectrometry (HRMS) was performed on agilent 6530 Q-TOF using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and brs = broad signal.

Preparation of N-Boc-O-tosylhydroxylamine (2):[29] 4-Toluenesulfonyl chloride (2.0 g, 10.49 mmol, 1.0 equiv.) and *tert*-butyl *N*-hydroxycarbamate (1.39 g, 10.49 mmol, 1.0 equiv.) were dissolved in diethyl ether (30 mL). The mixture cooled to 0 °C, and then triethylamine (1.6 mL, 11.54 mmol, 1.1 equiv.) was added dropwise, formation of white precipitate was observed and the mixture was stirred at 0 °C for 2 h. The reaction was monitored by TLC. After 2 h, the reaction mixture was filtered and the cake was washed with ethyl acetate (20 mL). The collected solvent was washed with water (2×30 mL) and brine solution (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The syrupy crude obtained, was dissolved in *n*-hexane (25 mL) and stirred for 10 minutes; a white solid appeared which was filtered, and dried under reduced pressure to get TsONHBoc as a white solid (2.6 g, 90% yield) (Scheme 3.20).



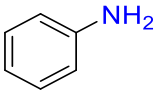
Scheme 3.20. Synthesis of aminating reagent

General procedure for preparation of anilines from boronic acid: To a round-bottom flask equipped with a magnetic stirring bar were added boronic acid **1** (0.5 mmol, 1.0

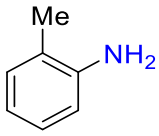
equiv.) and *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) **2** (1.5 equiv.) in DCE solvent (1 mL) at room temperature. To this stirred solution TFA (3 equiv.) was added. The reaction mixture was further stirred at this temperature for the specified duration and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 x 5 mL). The organic layer was washed with brine solution (5 mL) and dried over anhydrous Na_2SO_4. The crude product obtained after removal of all of the volatiles was purified by a silica gel column chromatography to afford the pure desired product **3** using EtOAc/hexane as an eluent.

3.7 Characterization of the products

***Aniline* (3a)**:[10] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); brown liquid; 44 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dt, *J* = 8.5, 4.2 Hz, 2H), 6.81-6.69 (m, 1H), 6.63 (d, *J* = 8.3 Hz, 2H), 3.54 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.42, 129.28, 118.46, 115.08.

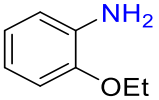


***o-Toluidine* (3b)**:[23] Purified by column choromatography on silica gel (hexane/ethyl acetate = 9:1, v/v); brown liquid; 48 mg, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, *J* = 7.8 Hz, 2H), 6.71 (dd, *J* = 17.6, 7.6 Hz, 2H), 3.49 (brs, 2H), 2.18 (s, 3H).

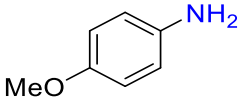


^{13}C NMR (100 MHz, $CDCl_3$) δ 144.57, 130.56, 127.07, 122.49, 118.80, 115.10, 17.45.

***2-Ethoxyaniline* (3c)**:[31] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); syrupy liquid; 60 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85-6.79 (m, 2H), 6.77-6.72 (m, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.83 (brs, 2H), 1.47 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.66, 136.35, 121.02, 118.45, 115.09, 111.52, 63.76, 15.04.

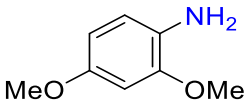


***4-Methoxyaniline* (3d)**:[32] Purified by column choromatography on silica gel (hexane/ethyl acetate = 4:1, v/v); dark brown solid; m.p. = 54-55 °C; 57 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79-6.71 (m, 2H), 6.70-6.61



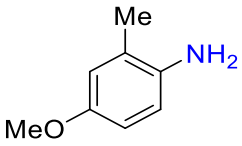
(m, 2H), 3.75 (s, 3H), 3.40 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.89, 140.00, 116.54, 114.88, 55.83.

2,4-Dimethoxyaniline **(3e)**:[23] Purified by column choromatography on silica gel



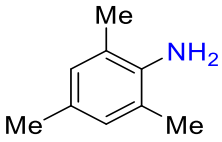
(hexane/ethyl acetate = 4:1, v/v); dark brown liquid; 73 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.35 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.41 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.25, 148.46, 129.78, 115.36, 104.28, 99.45, 55.84, 55.56

4-Methoxy-2-methylaniline **(3f)**:[23] Purified by column choromatography on silica gel



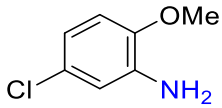
(hexane/ethyl acetate = 9:1, v/v); dark brown liquid; 62 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.67-6.60 (m, 2H), 3.75 (s, 3H), 3.31 (brs, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.72, 138.26, 124.05, 116.41, 116.06, 112.13, 55.73, 17.73.

2,4,6-Trimethylaniline **(3g)**:[9] Purified by column choromatography on silica gel



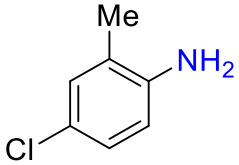
(hexane/ethyl acetate = 19:1, v/v); yellow oil; 56 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88-6.69 (s, 2H), 2.22 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.64, 129.00, 127.76, 122.42, 20.51, 17.79.

5-Chloro-2-methoxyaniline **(3h)**:[33] Purified by column choromatography on plug of silica



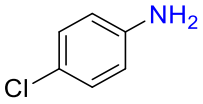
gel (hexane/ethyl acetate = 19:1, v/v); yellowish liquid; 55 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.67 (m, 1H), 6.67 (d, *J* = 1.1 Hz, 2H), 3.82 (s, 3H), 3.62 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.98, 137.35, 125.92, 117.78, 114.67, 111.17, 55.79.

4-chloro-2-methylaniline **(3i)**:[10] Purified by column choromatography on silica gel

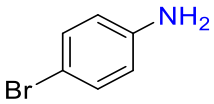


(hexane/ethyl acetate = 19:1, v/v); dark brown liquid; 65 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-6.92 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 3.58 (brs, 2H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.25, 130.12, 126.74, 124.08, 123.01, 116.01, 17.37.

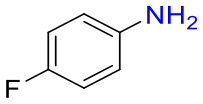
4-Chloroaniline **(3j)**:[34] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); yellowish solid; 50 mg, 79% yield, mp = 70-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.03 (m, 2H), 6.66-6.53 (m, 2H), 3.58 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.04, 129.22, 123.24, 116.34.



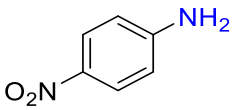
4-Bromoaniline **(3k)**:[32] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); yellow solid; 70 mg, 81% yield; mp= 60–61 ° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (m, 2H), 6.62-6.51 (m, 2H), 3.42 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.53, 132.14, 116.85, 110.34.



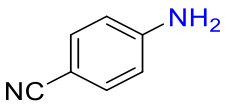
4-Fluoroaniline **(3l)**:[23] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); yellowish liquid; 42 mg, 76% yield; mp = 166; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94-6.81 (m, 2H), 6.66-6.56 (m, 2H), 3.56 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.51, 155.17, 142.56, 142.54, 116.08, 116.01, 115.73, 115.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.89.



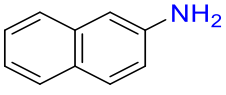
4-Nitroaniline **(3m):**[32] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); light yellow solid; 31 mg, 45% yield; mp = 142-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2H), 6.68-6.58 (m, 2H), 4.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.66, 139.26, 126.49, 113.51



4-Aminobenzonitrile **(3n)**:[32] Purified by column choromatography on silica gel (hexane/ethyl acetate = 19:1, v/v); light yellow solid; 52 mg, 88% yield, mp = 84-85 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.64, 133.85, 120.31, 114.50, 99.98.

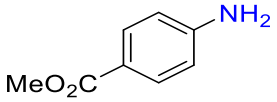


Naphthalen-2-amine **(3o)**:[9] Purified by column choromatography on plug of silica gel (hexane/ethyl acetate = 19:1, v/v); off yellowish solid; 61mg, 86% yield; m.p = 105-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.62 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.38-7.33 (m, 1H), 7.27-7.17 (m, 1H), 7.01-6.89 (m, 2H),



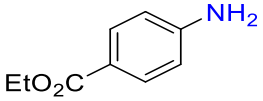
3.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.21, 135.03, 129.33, 128.10, 127.84, 126.47, 125.92, 122.60, 118.36, 108.73.

Methyl-4-aminobenzoate **(3p)**:[9] Purified by column choromatography on silica gel



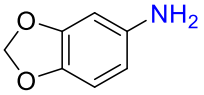
(hexane/ethyl acetate = 19:1, v/v); white solid; 57 mg, 75% yield; m.p. = 105-107 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.72 (m, 2H), 6.78-6.45 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.35, 150.98, 131.71, 119.73, 113.90, 51.75.

Ethyl-4-aminobenzoate **(3q)**:[32] Purified by column choromatography on silica gel



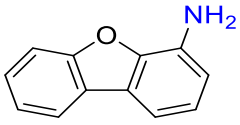
(hexane/ethyl acetate = 19:1, v/v); white solid; 64 mg, 78% yield; m.p. = 87-88 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.12 (brs, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.85, 150.99, 131.59, 119.95, 113.81, 60.36, 14.47.

Benzo[d][1,3]dioxol-5-amine **(3r)**:[23] Purified by column choromatography on plug of



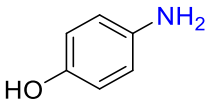
silica gel (hexane/ethyl acetate = 4:1, v/v); white solid; 55 mg, 80% yield; mp = 38-41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.13 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.85 (s, 2H), 3.34 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.32, 141.47, 140.50, 108.68, 107.02, 100.76, 98.21.

Dibenzo[b,d]furan-3-amine **(3s)**:[9] Purified by column choromatography on silica gel



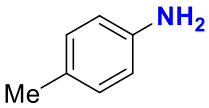
(hexane/ethyl acetate = 19:1, v/v); brown solid; 66 mg, 72% yield; mp = 75-77 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.30-7.18 (m, 2H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 3.94 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.06, 145.01, 132.03, 126.96, 125.03, 124.69, 123.61, 122.73, 121.03, 113.11, 111.75, 110.60.

4-Aminophenol **(3t)**:[35] Purified by column choromatography on silica gel (hexane/ethyl

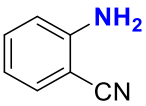


acetate = 4:1, v/v); brown liquid; 42 mg, 78% yield ^{1}H NMR (400 MHz, DMSO) δ 6.53-6.42 (m, 4H). ^{13}C NMR (100 MHz, DMSO) δ 148.94, 140.87, 116.40, 116.23.

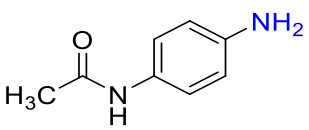
p-Toluidine **(3u)**:[10] Purified by column choromatography on silica gel (hexane/ethyl acetate = 4:1, v/v); brown solid; mp = 44-46 °C; 32 mg, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 2H), 3.56 (br s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.90, 129.80, 127.77, 115.31, 20.51.



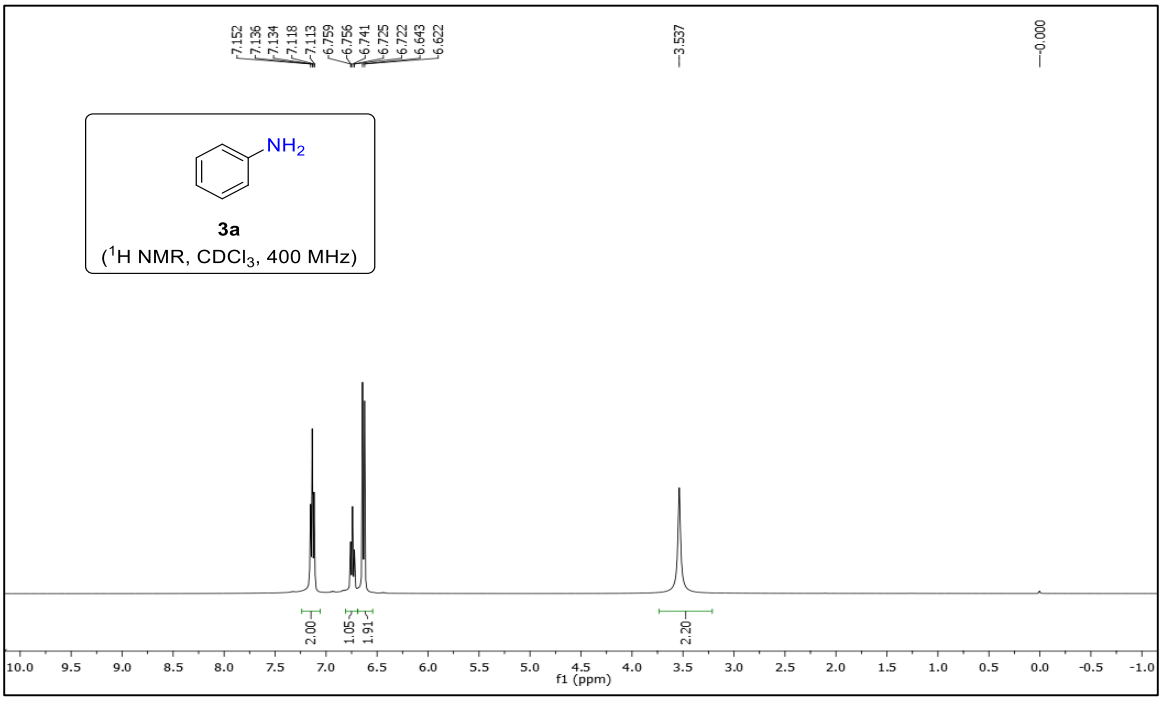
2-aminobenzonitrile **(3v)**:[36] Purified by column choromatography on silica gel (hexane/ethyl acetate = 4:1, v/v); yellow solid; mp = 49-51 °C; 31 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 2H), 6.80-6.60 (m, 2H), 4.49 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.77, 134.03, 132.28, 117.85, 117.77, 115.20, 95.73.

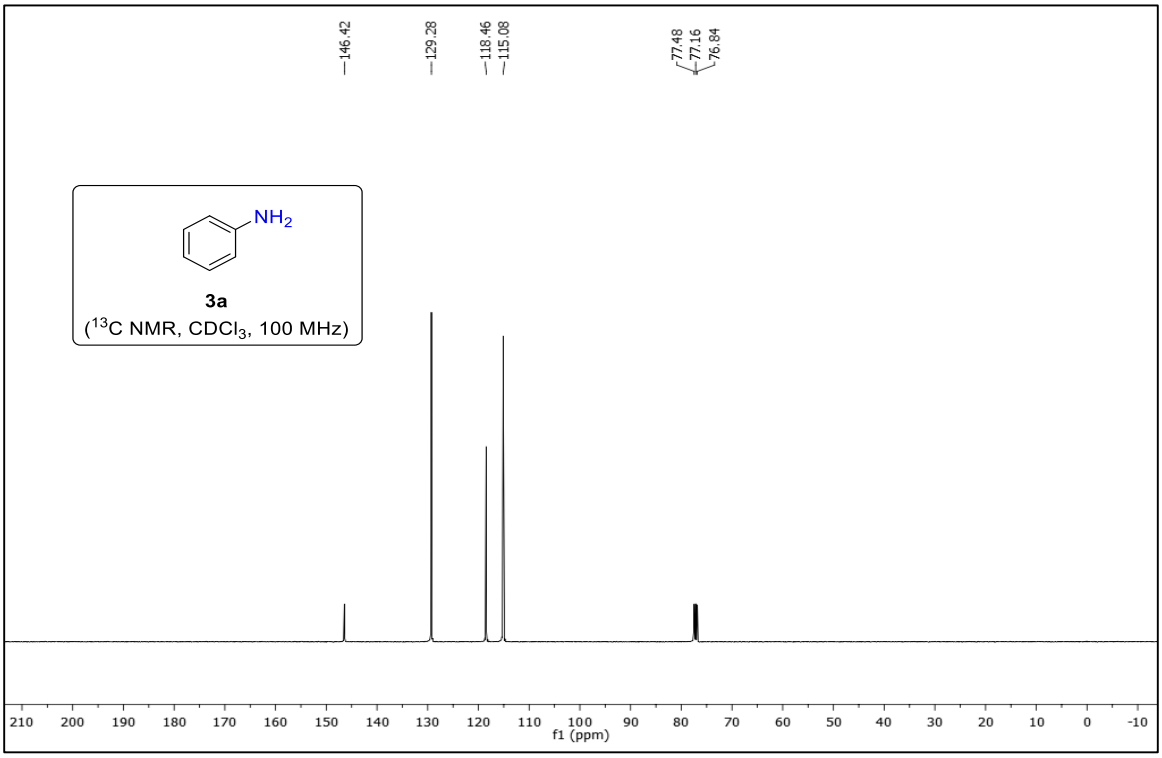


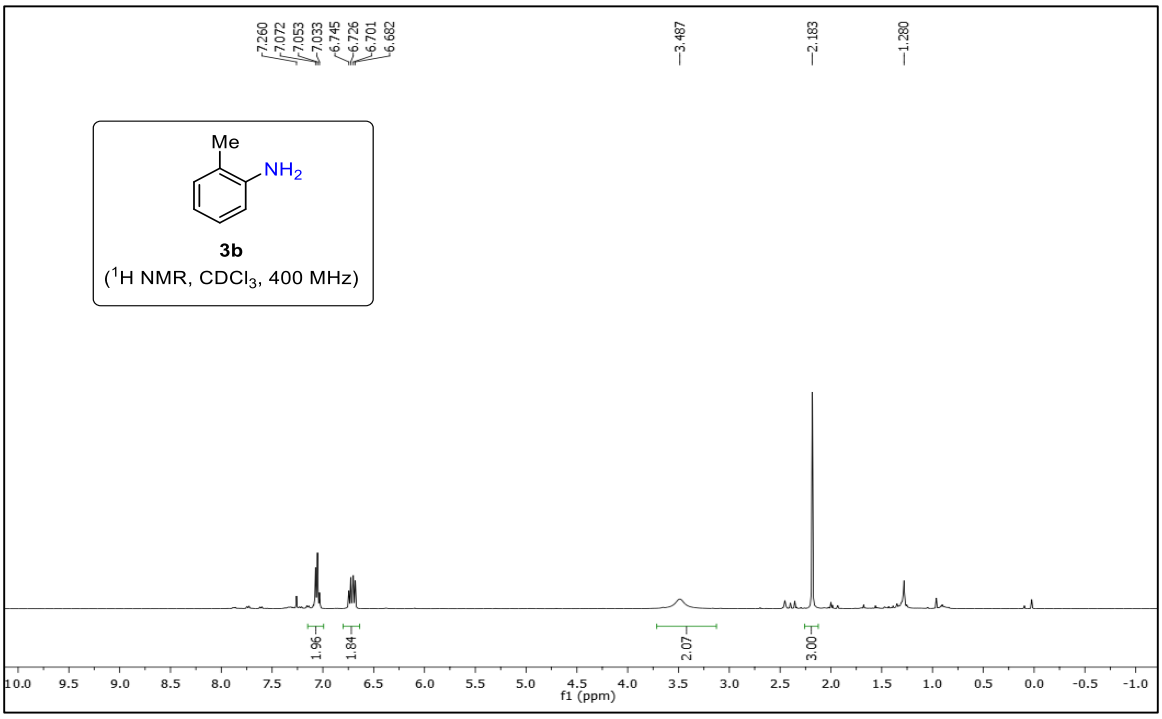
N-(4-aminophenyl)acetamide **(3w):**[37] Purified by column choromatography on silica gel (hexane/ethyl acetate = 1:1, v/v); white solid; 58 mg, 78% yield; mp = 162–165 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.47 (br s, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.48 (d, *J* = 8.5 Hz, 2H), 4.81 (br s, 2H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 167.23, 144.60, 128.60, 120.86, 113.81, 23.69.

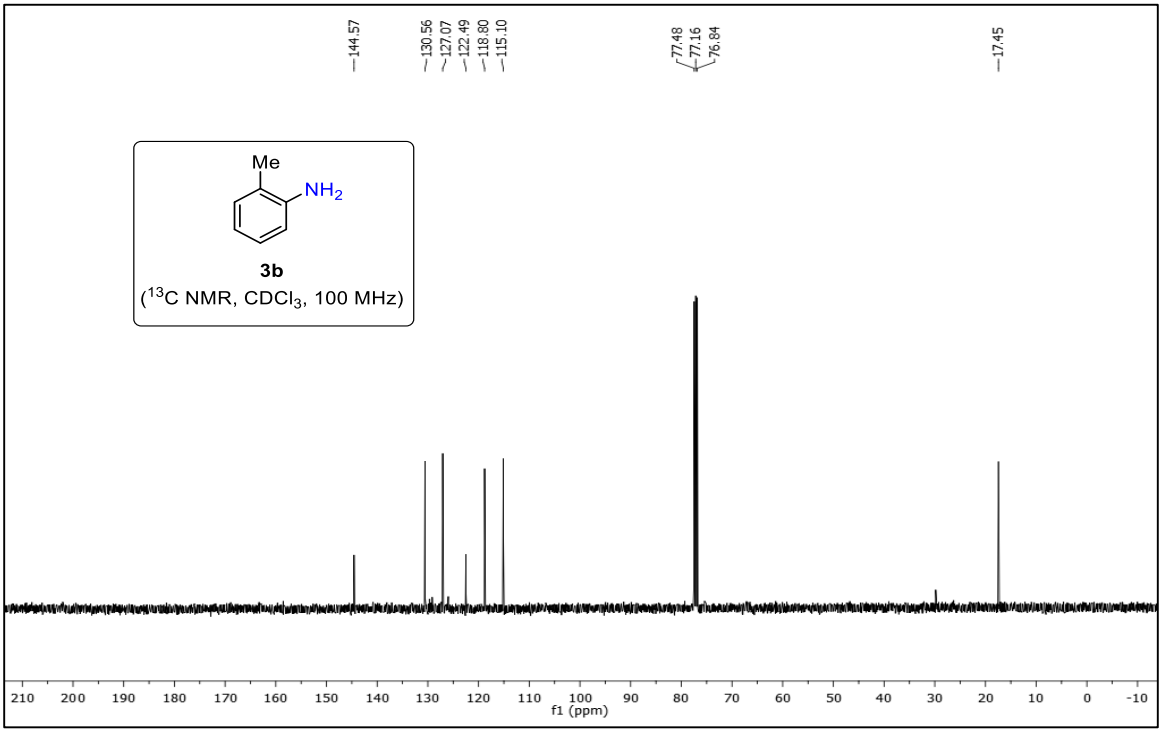


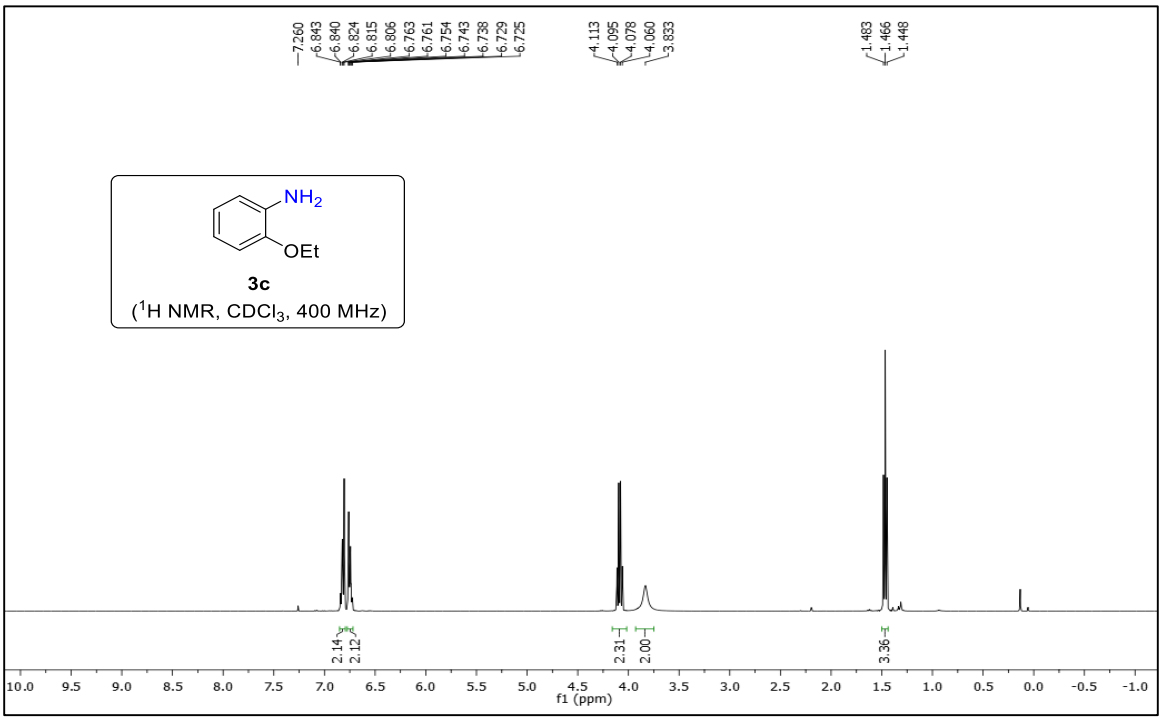
3.8 ^{1}H, ^{13}C and ^{19}F NMR Spectra of the products

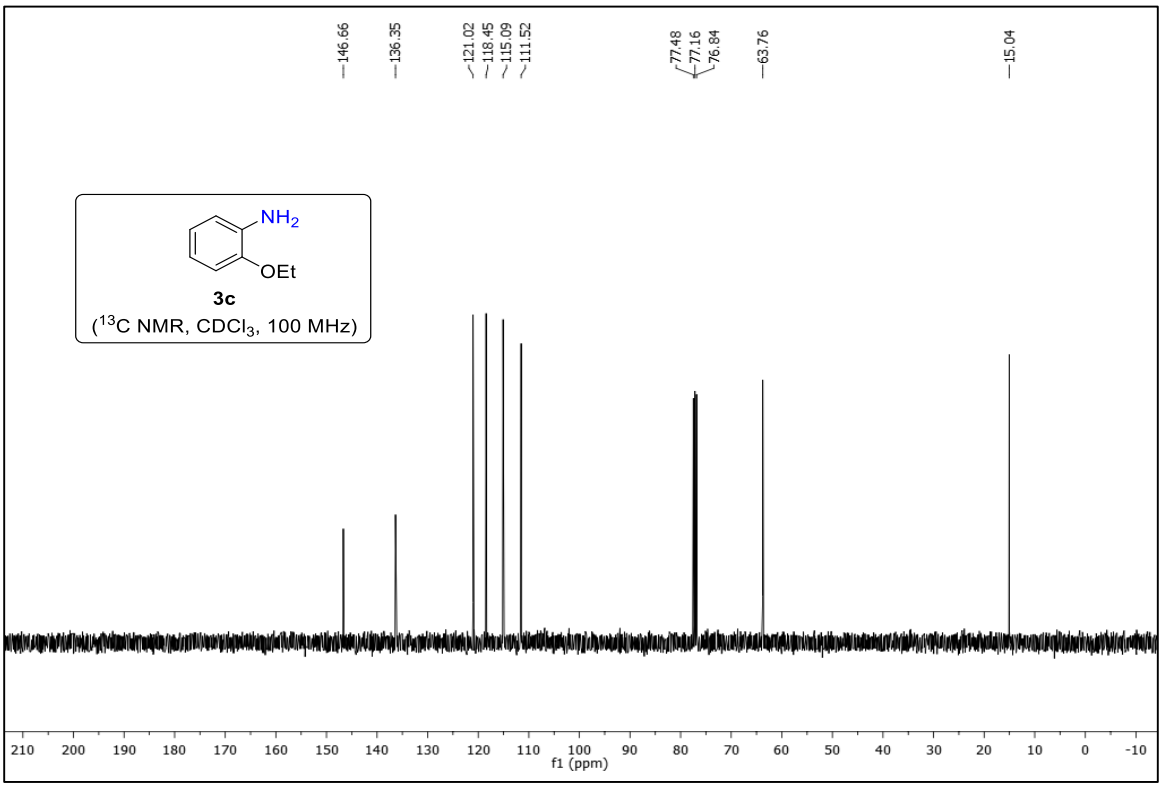


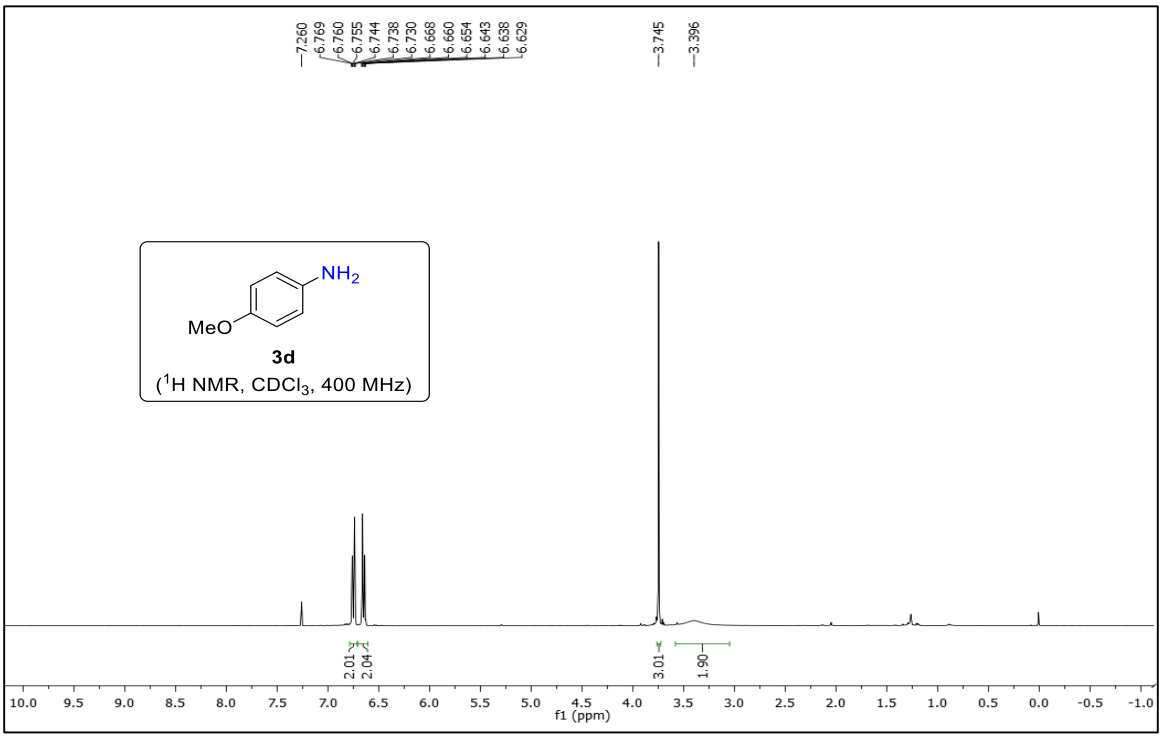


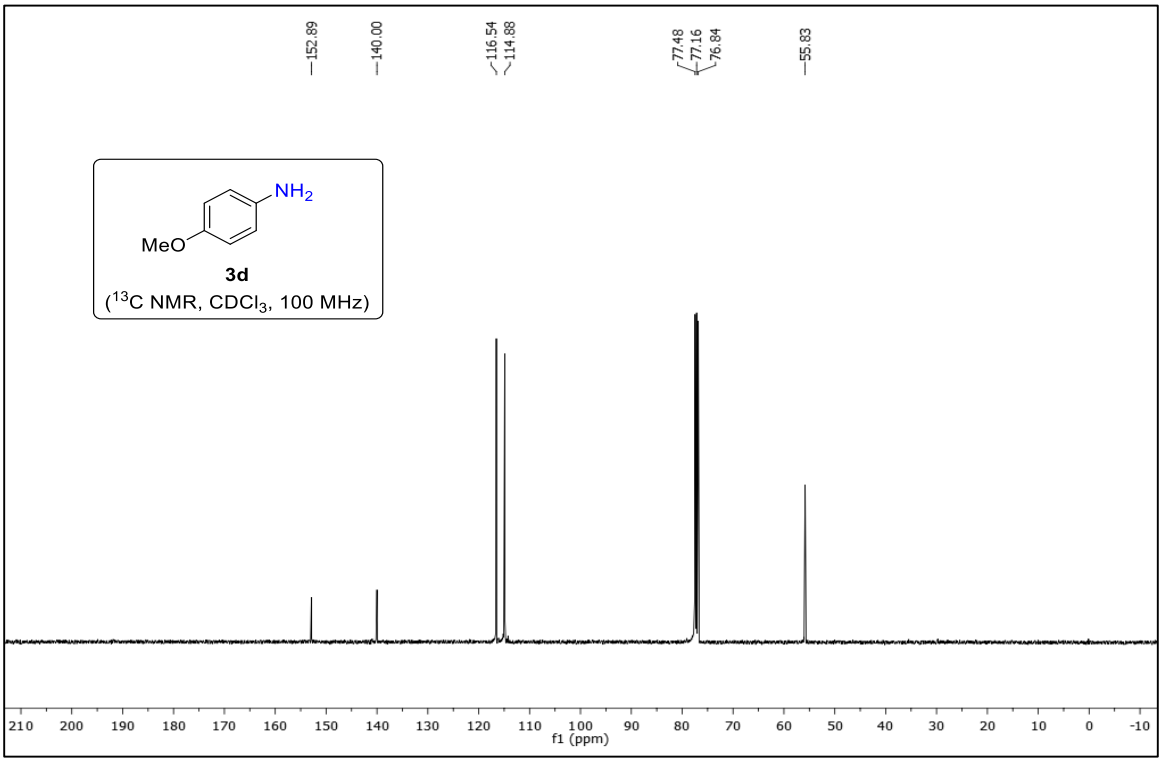

7.260
7.072
7.053
7.033
6.745
6.726
6.701
6.682
3.487
2.183
1.280
Me
NH2
3b
(1H NMR, CDCl3, 400 MHz)
1.96
1.84
2.07
3.00
f1 (ppm)

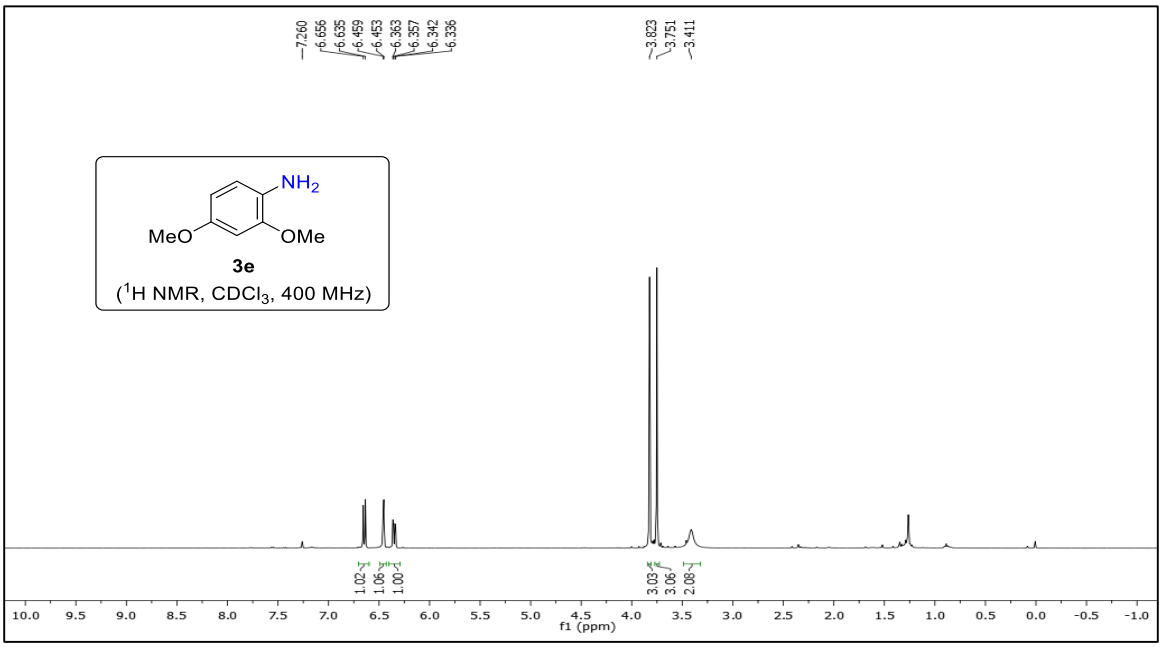

144.57
130.56
127.07
122.49
118.80
115.10
77.48
77.16
76.84
17.45
Me
NH2
3b
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

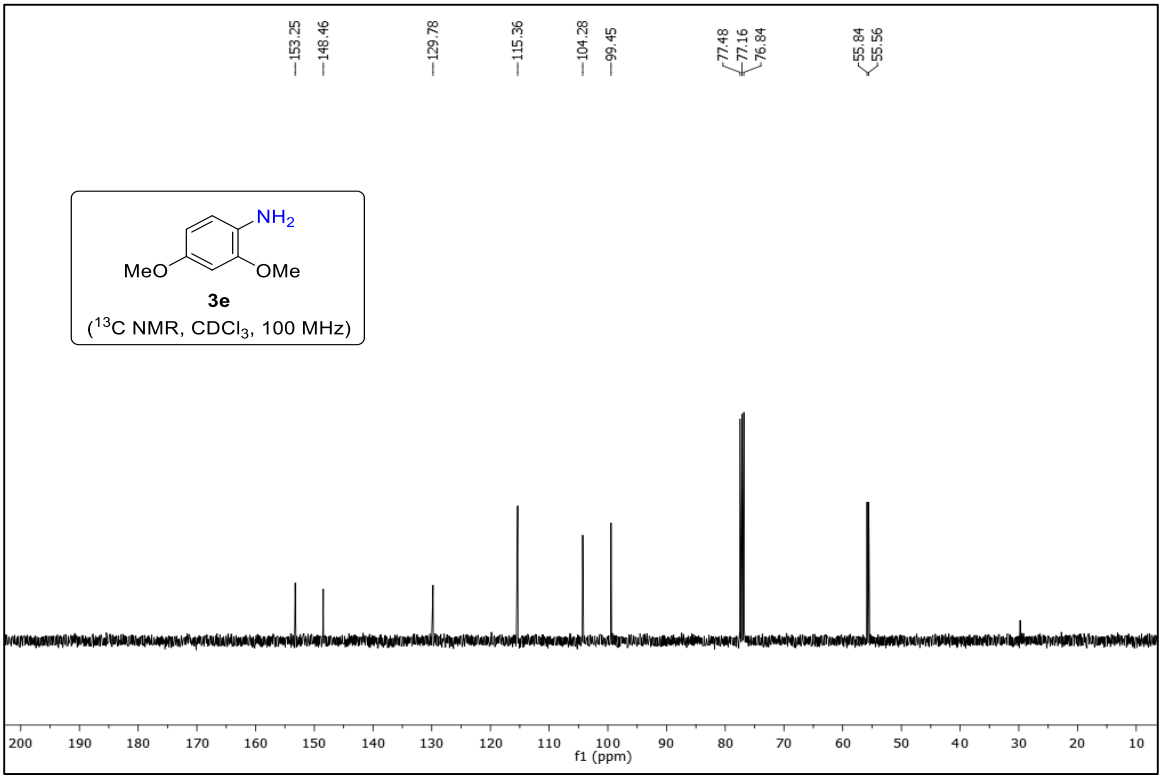

7.260
6.843
6.840
6.824
6.815
6.806
6.763
6.761
6.754
6.743
6.738
6.729
6.725
4.113
4.095
4.078
4.060
3.833
1.483
1.466
1.448
NH2
OEt
3c
(1H NMR, CDCl3, 400 MHz)
2.14
2.12
2.31
2.00
3.36
f1 (ppm)

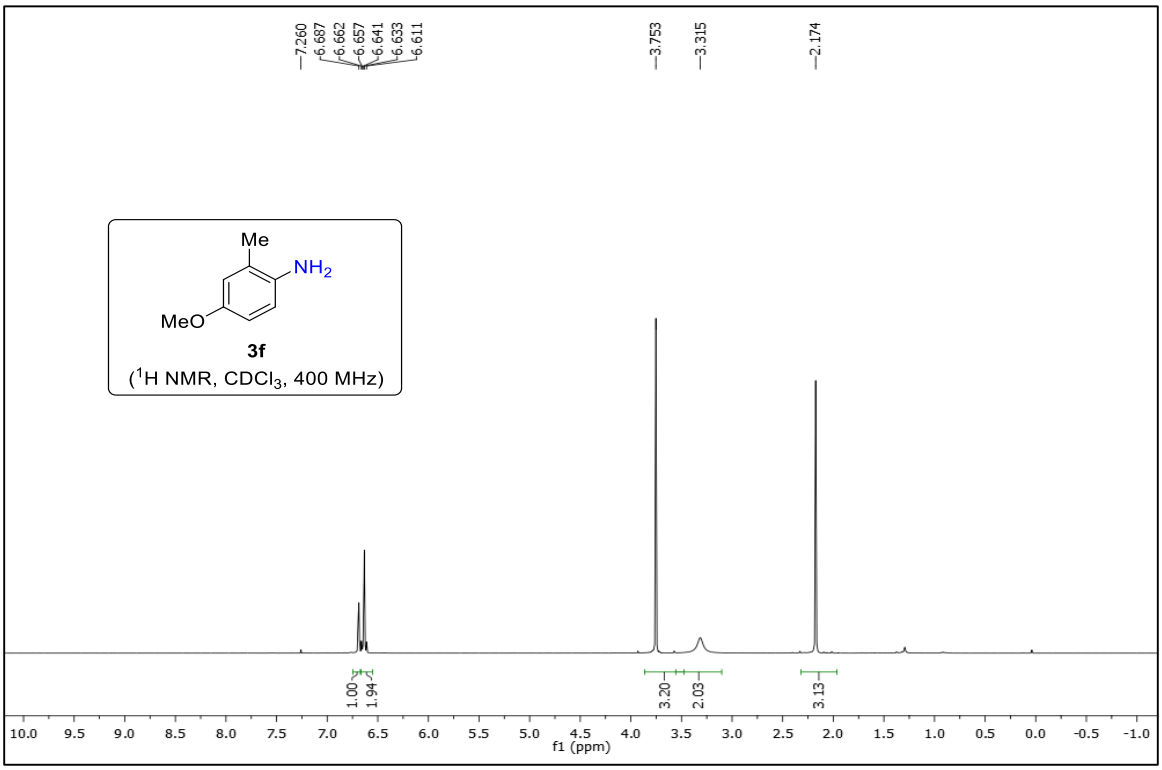

146.66
136.35
121.02
118.45
115.09
111.52
77.48
77.16
76.84
63.76
15.04
NH2
OEt
3c
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

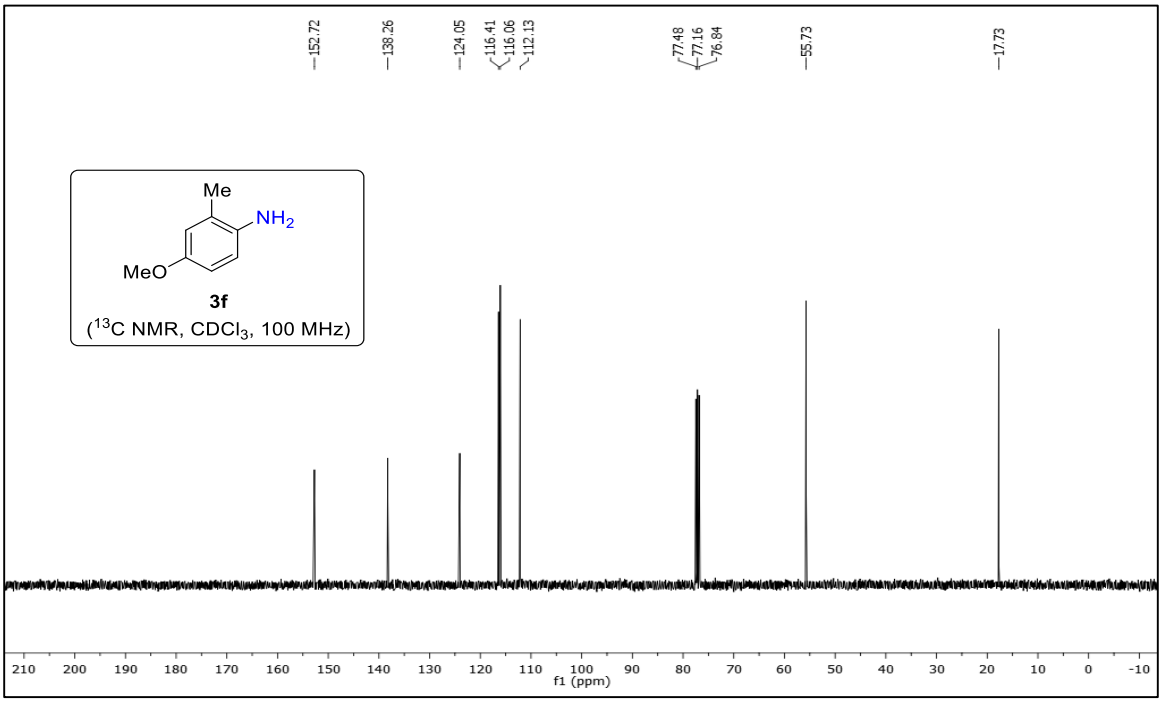

7.260
6.769
6.760
6.755
6.744
6.738
6.730
6.668
6.660
6.654
6.643
6.638
6.629
3.745
3.396
NH2
MeO
3d
(1H NMR, CDCl3, 400 MHz)
2.01
2.04
3.01
1.90
f1 (ppm)

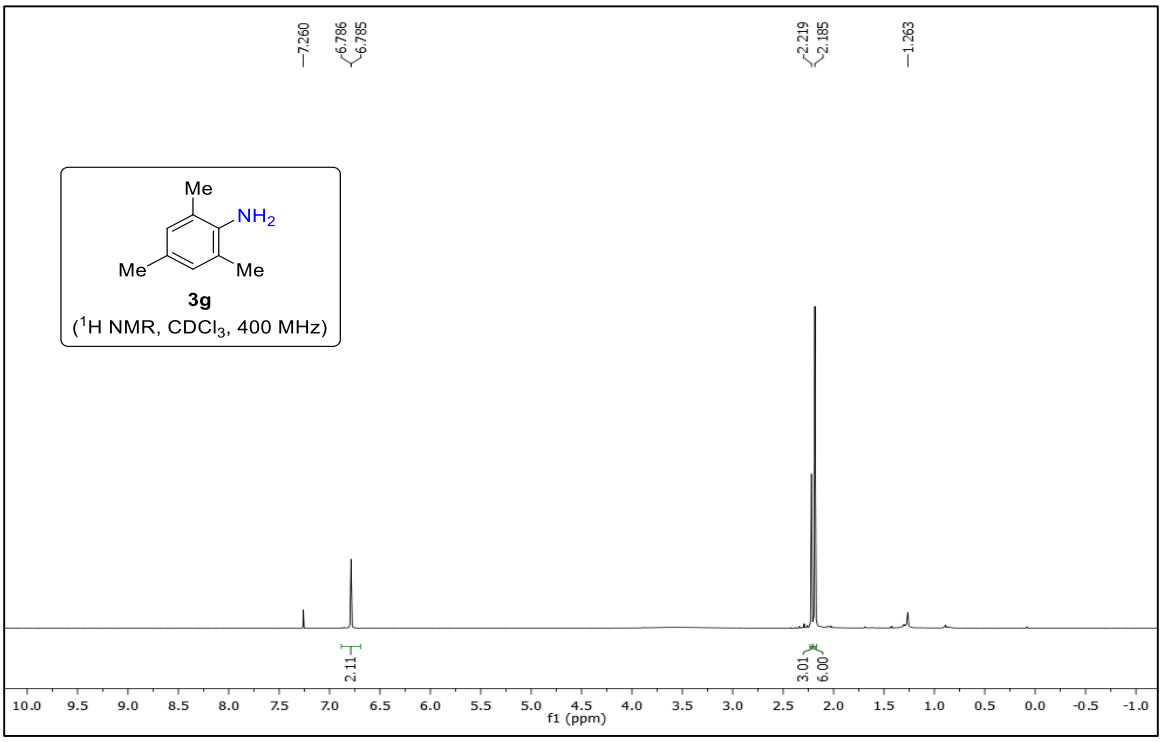

152.89
140.00
116.54
114.88
77.48
77.16
76.84
55.83
NH2
MeO
3d
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

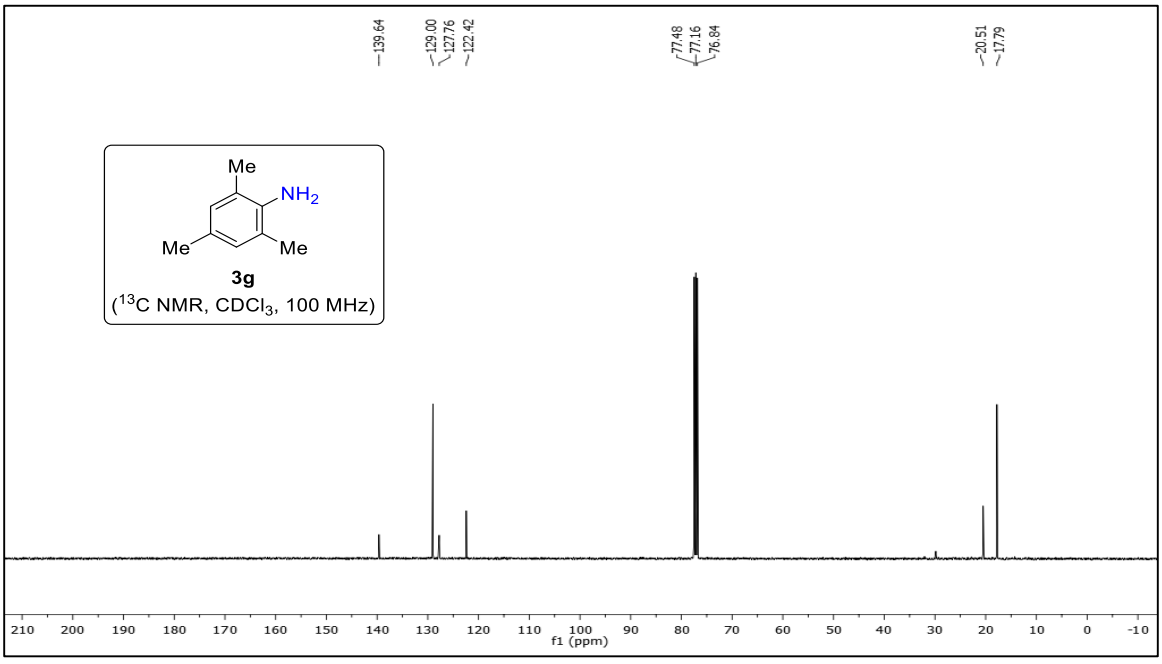

7.260
6.656
6.635
6.459
6.453
6.363
6.357
6.342
6.336
3.823
3.751
3.411
NH2
MeO
OMe
3e
(1H NMR, CDCl3, 400 MHz)
1.02
1.06
1.00
3.03
3.06
2.08
f1 (ppm)

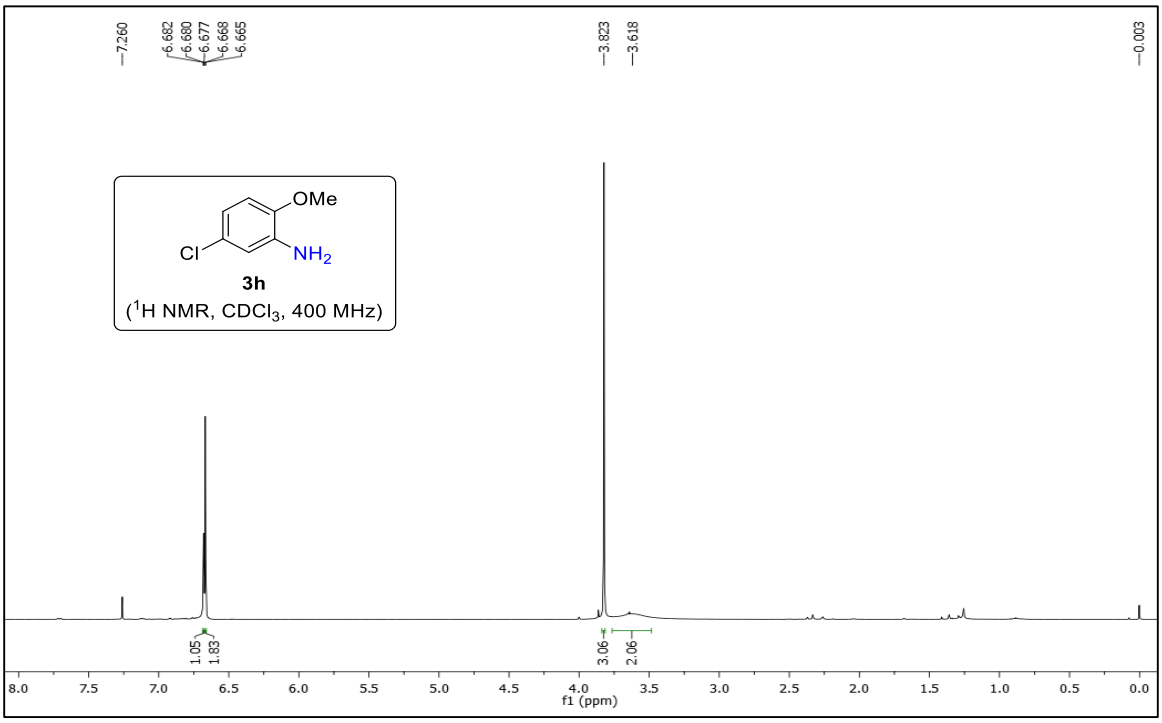

153.25
148.46
129.78
115.36
104.28
99.45
77.48
77.16
76.84
55.84
55.56
NH2
MeO
OMe
3e
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

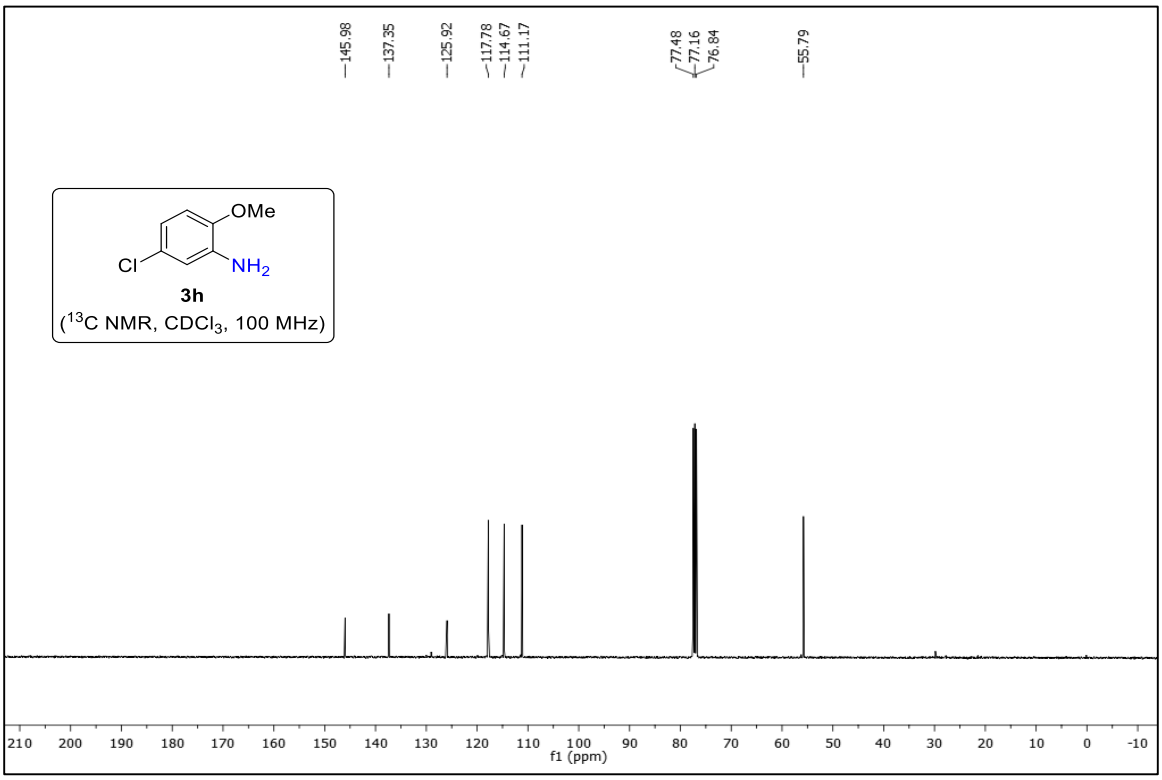

7.260
6.687
6.662
6.657
6.641
6.633
6.611
3.753
3.315
2.174
Me
NH2
MeO
3f
(1H NMR, CDCl3, 400 MHz)
1.00
1.94
3.20
2.03
3.13
f1 (ppm)

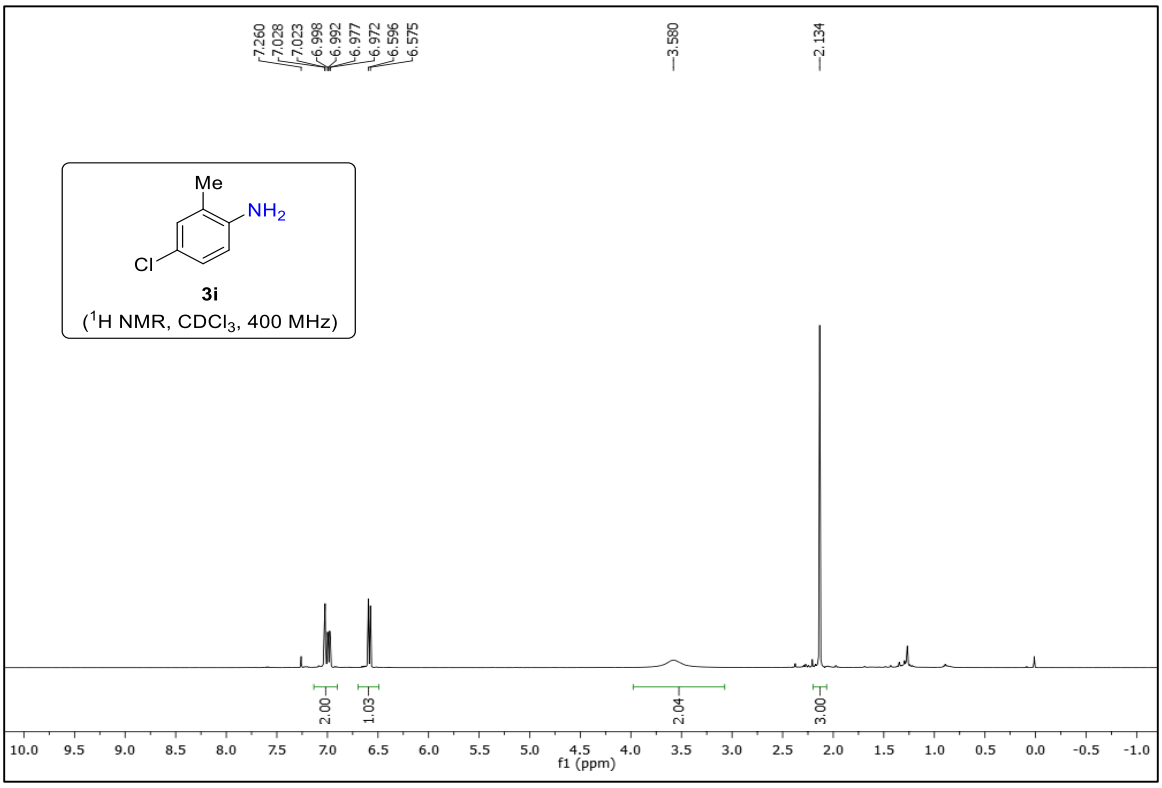

152.72
138.26
124.05
116.41
116.06
112.13
77.48
77.16
76.84
55.73
17.73
Me
NH2
MeO
3f
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

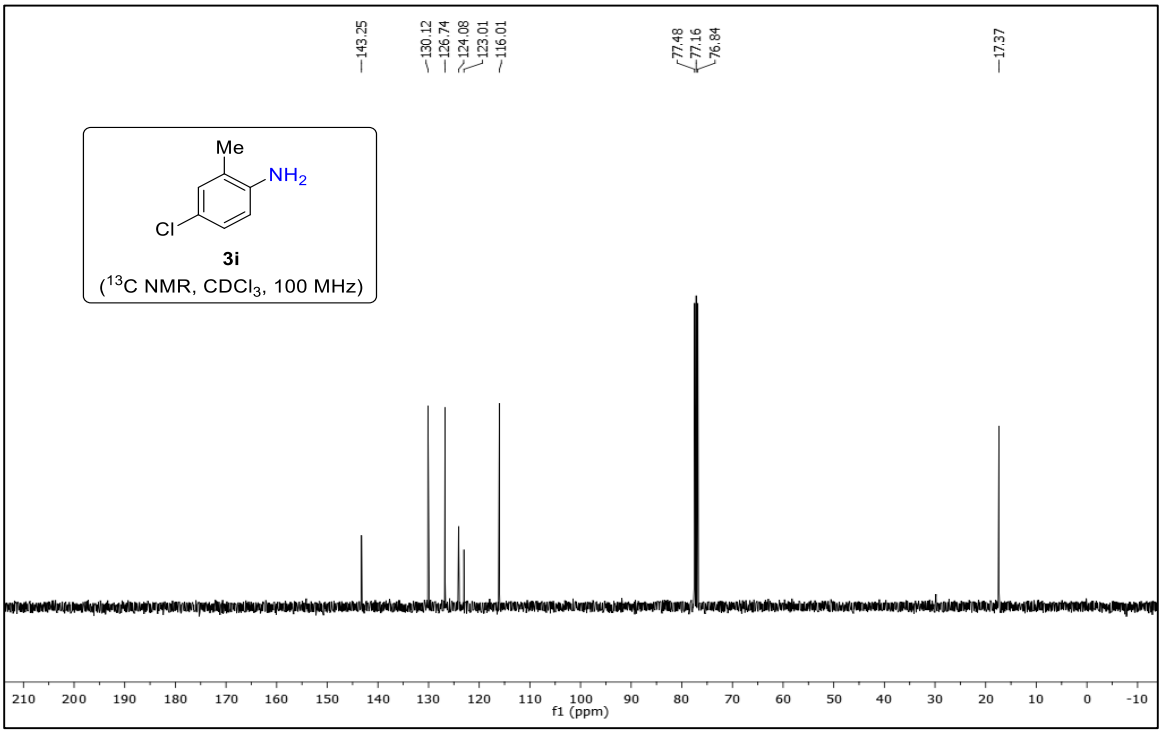

7.260
6.786
6.785
2.219
2.185
1.263
Me
NH2
Me
Me
3g
(1H NMR, CDCl3, 400 MHz)
2.11
3.01
6.00
f1 (ppm)

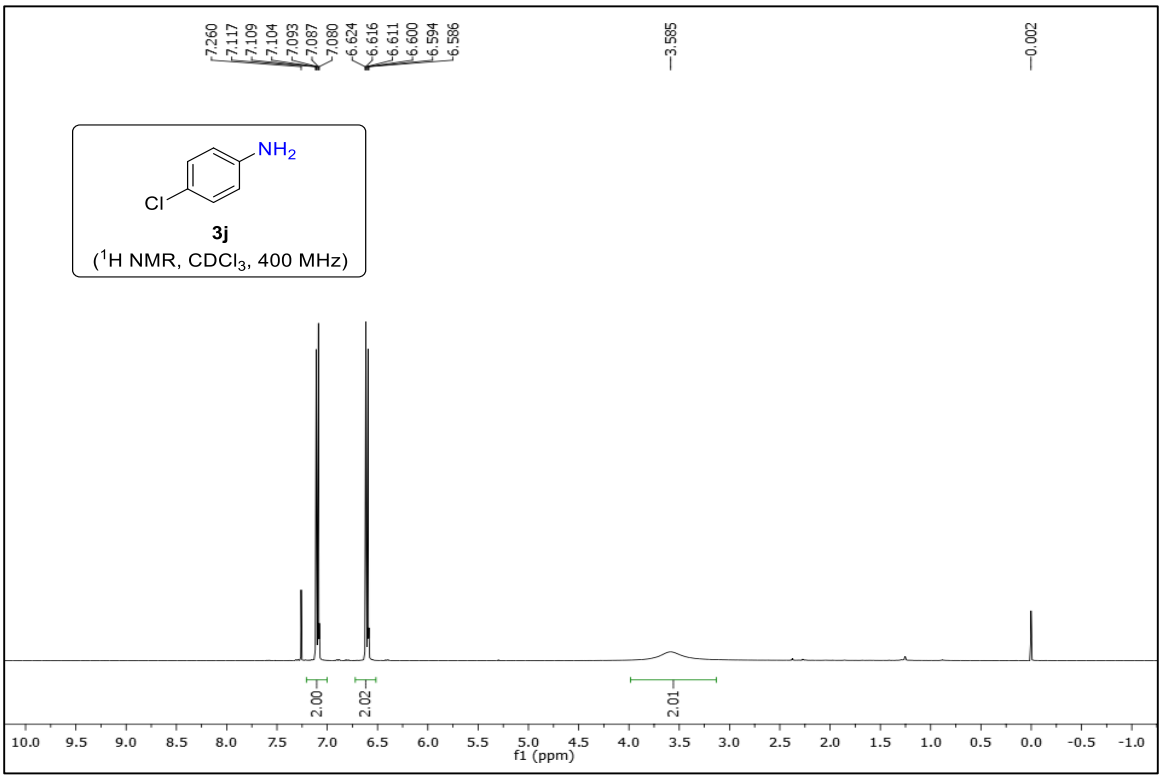

139.64
129.00
127.76
122.42
77.48
77.16
76.84
20.51
17.79
Me
NH2
Me
Me
3g
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

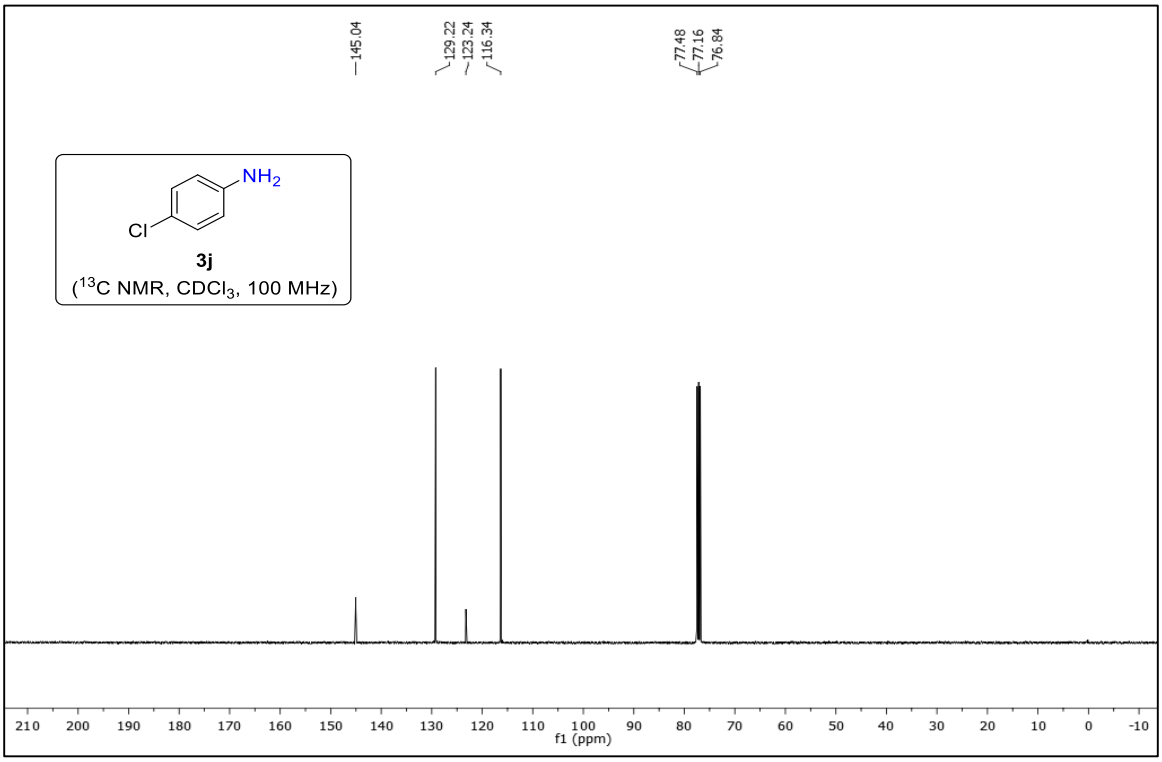

7.260
6.682
6.680
6.677
6.668
6.665
3.823
3.618
0.003
OMe
Cl
NH2
3h
(1H NMR, CDCl3, 400 MHz)
1.05
1.83
3.06
2.06
f1 (ppm)

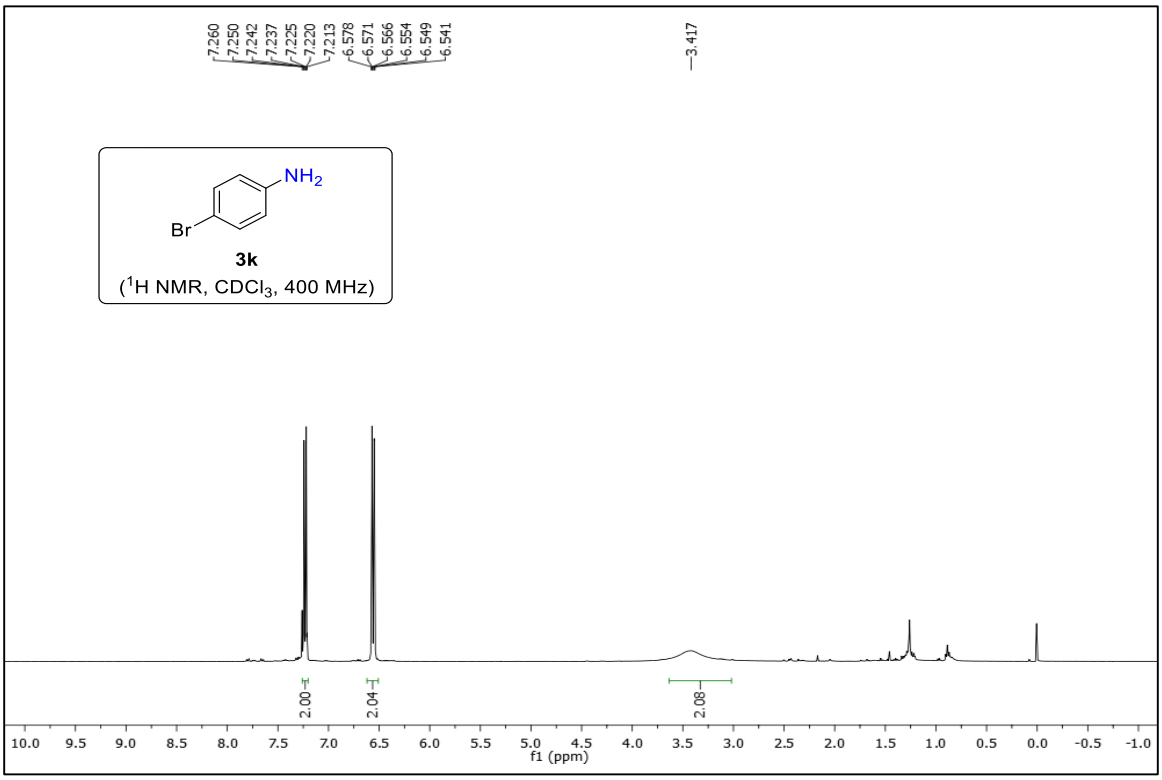

145.98
137.35
125.92
117.78
114.67
111.17
77.48
77.16
76.84
55.79
OMe
Cl
NH2
3h
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

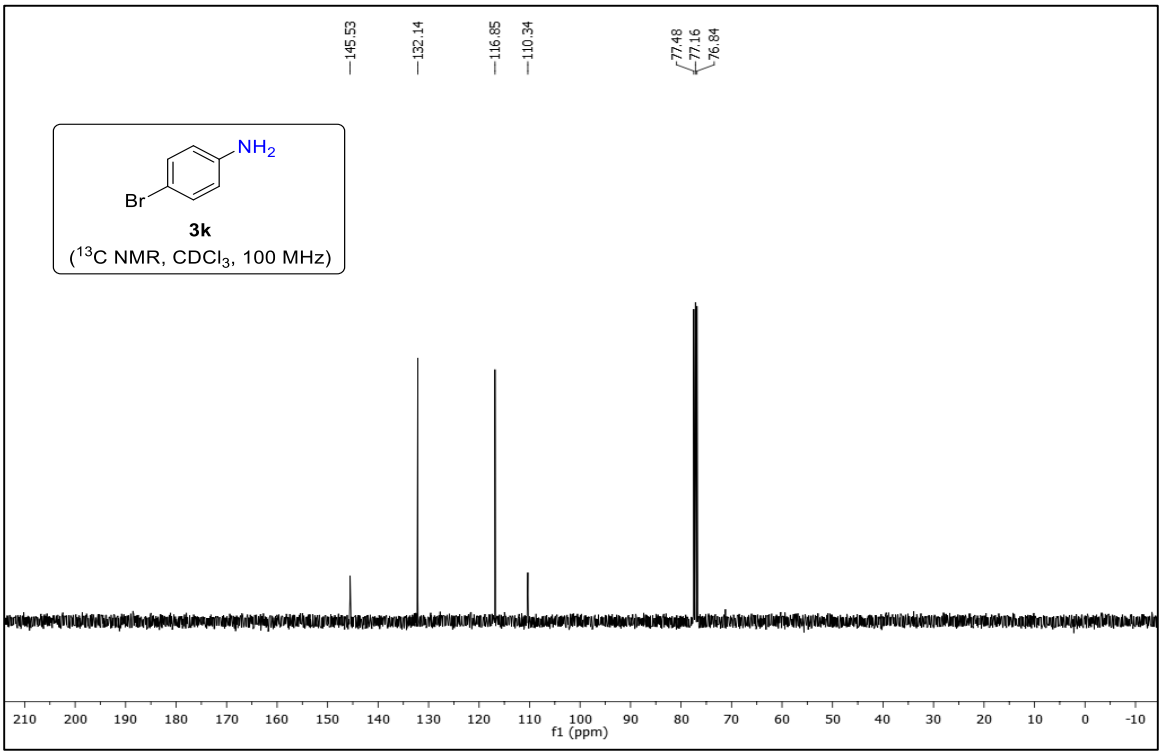

7.260
7.028
7.023
6.998
6.992
6.977
6.972
6.596
6.575
3.580
2.134
Me
NH2
Cl
3i
(1H NMR, CDCl3, 400 MHz)
2.00
1.03
2.04
3.00
f1 (ppm)

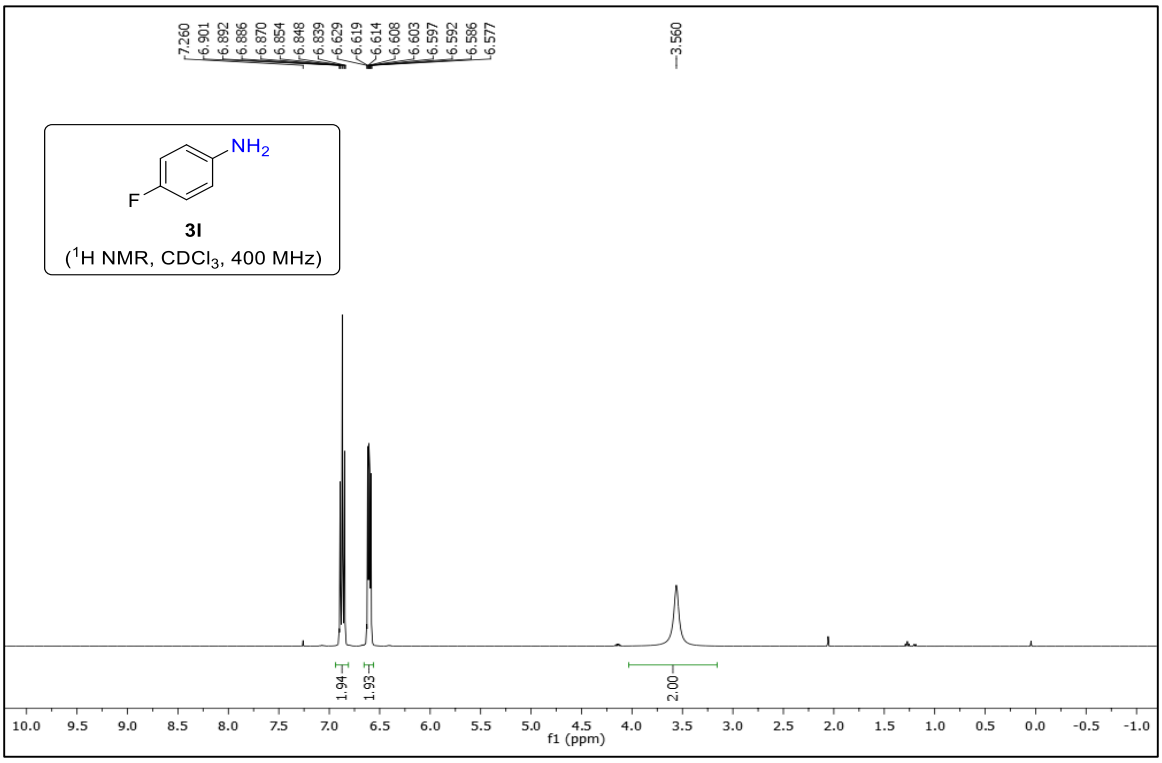

143.25
130.12
126.74
124.08
123.01
116.01
77.48
77.16
76.84
17.37
Me
NH2
Cl
3i
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

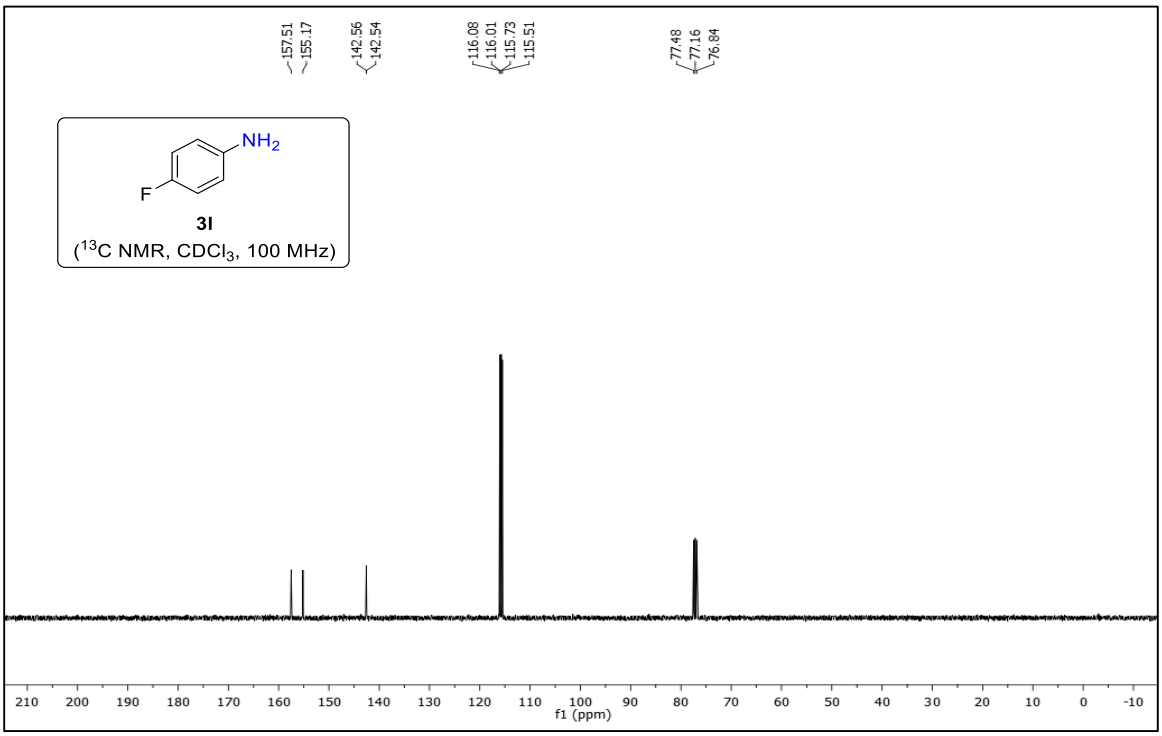

7.260
7.117
7.109
7.104
7.093
7.087
7.080
6.624
6.616
6.611
6.600
6.594
6.586
3.585
0.002
NH2
Cl
3j
(1H NMR, CDCl3, 400 MHz)
2.00
2.02
2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

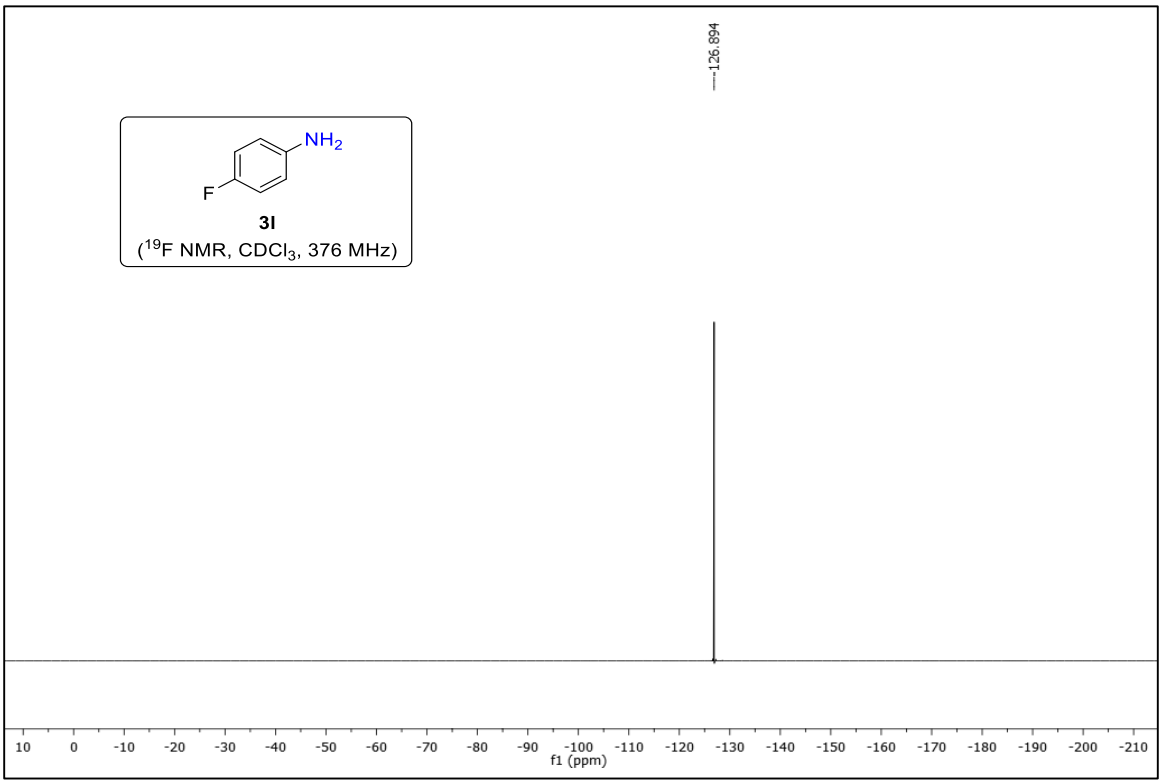

145.04
129.22
123.24
116.34
77.48
77.16
76.84
NH2
Cl
3j
(13C NMR, CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

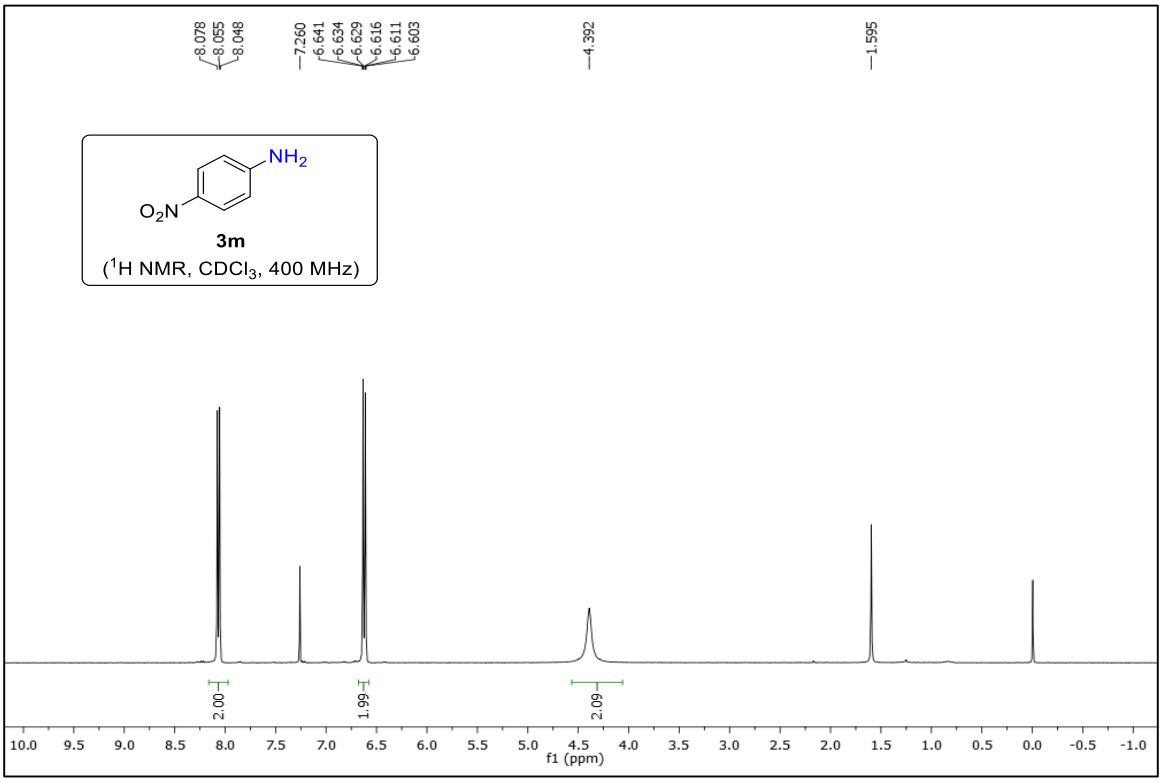

7.260
7.250
7.242
7.237
7.225
7.220
7.213
6.578
6.571
6.566
6.554
6.549
6.541
3.417
NH2
Br
3k
(1H NMR, CDCl3, 400 MHz)
2.00
2.04
2.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

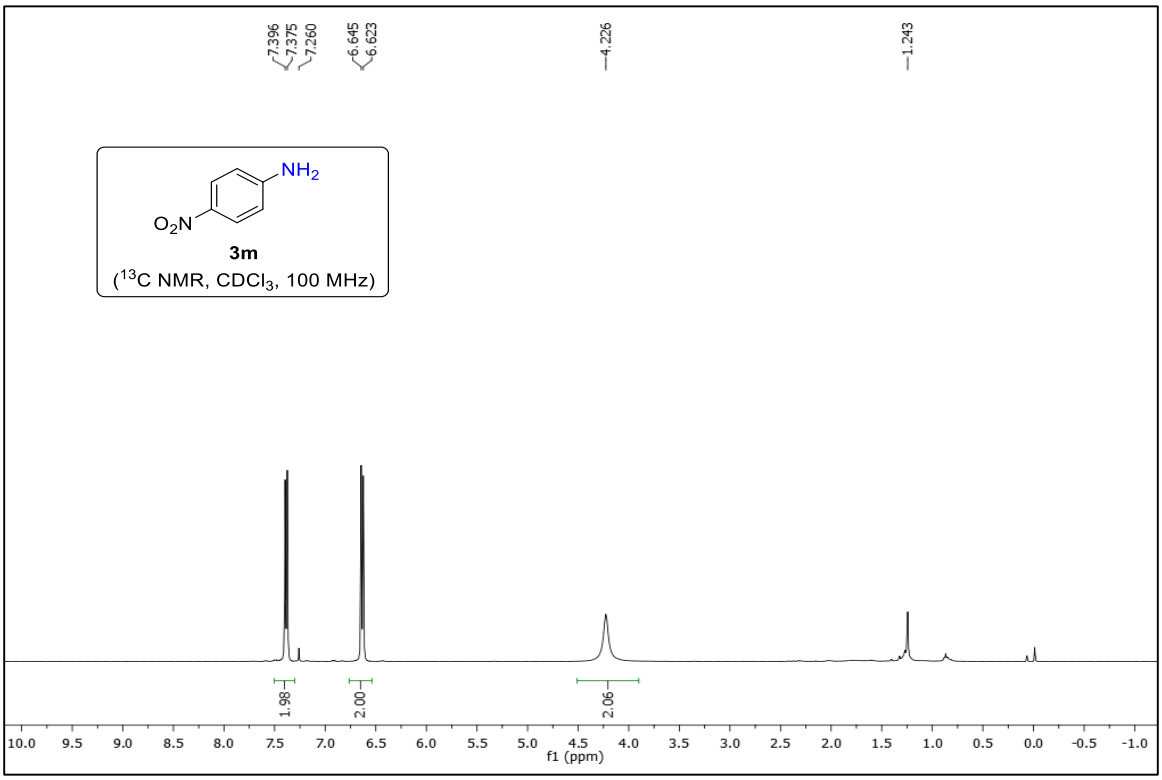

145.53
132.14
116.85
110.34
77.48
77.16
76.84
NH2
Br
3k
(13C NMR, CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

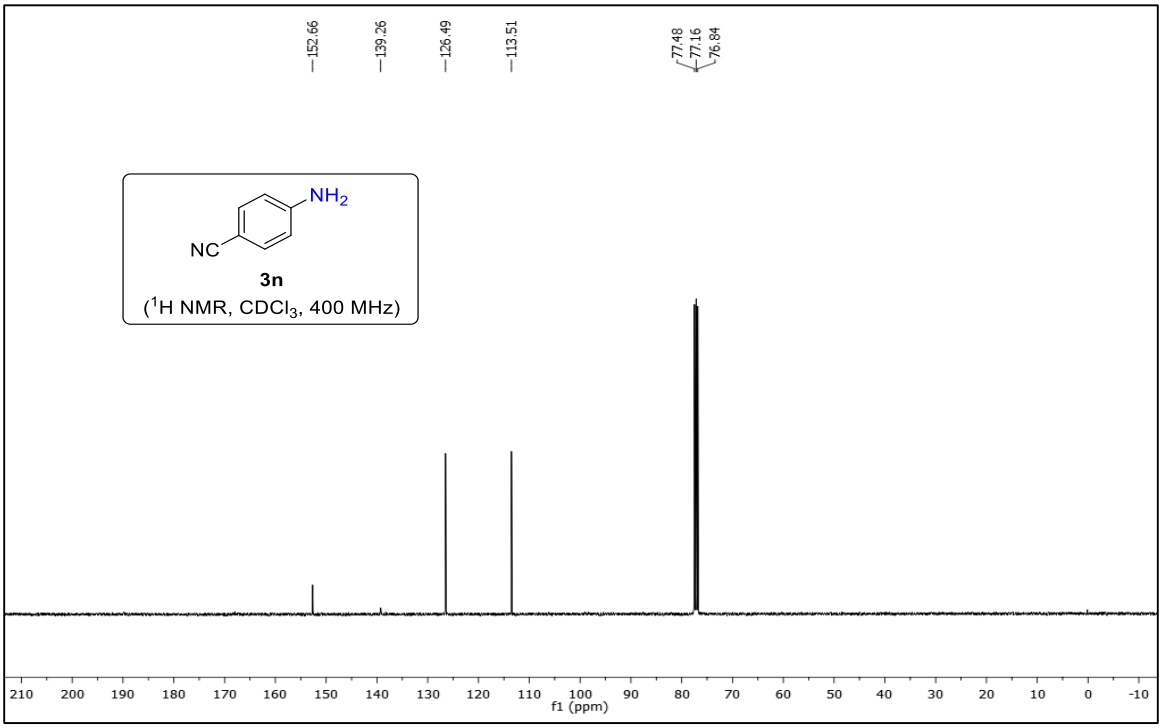

7.260
6.901
6.892
6.886
6.870
6.854
6.848
6.839
6.629
6.619
6.614
6.608
6.603
6.597
6.592
6.586
6.577
3.560
NH2
F
3l
(1H NMR, CDCl3, 400 MHz)
1.94
1.93
2.00
f1 (ppm)

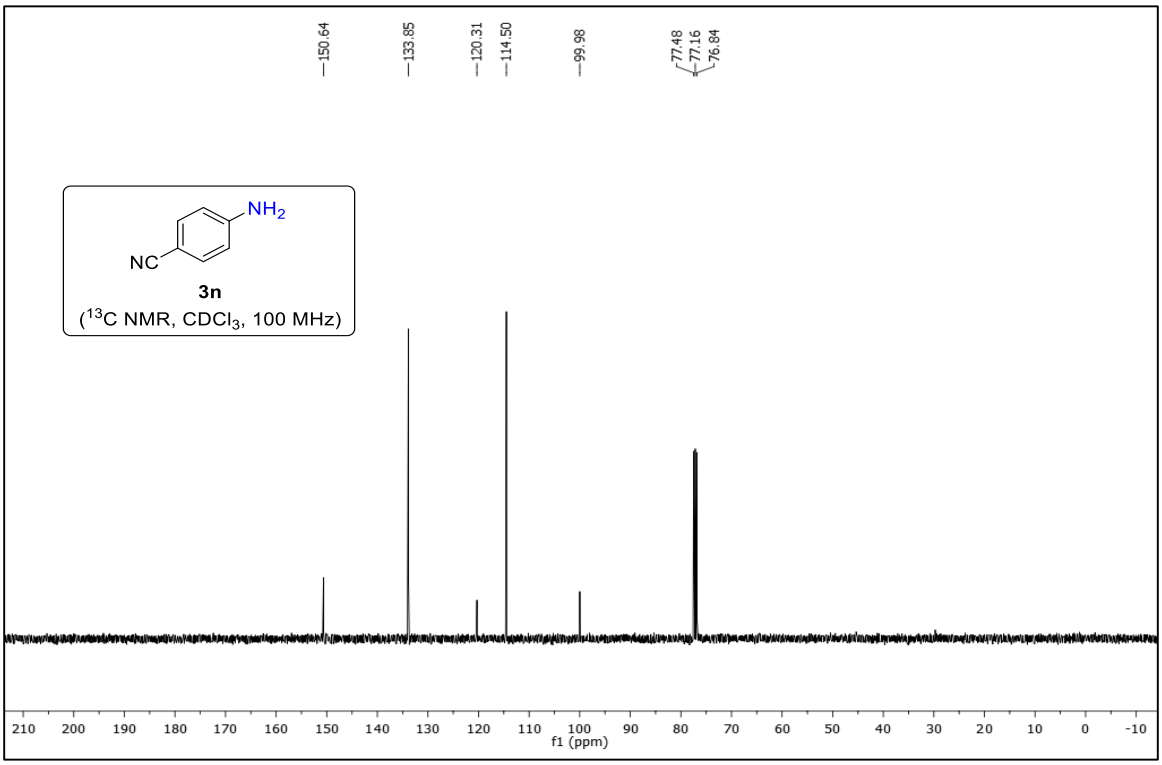

157.51
155.17
142.56
142.54
116.08
116.01
115.73
115.51
77.48
77.16
76.84
NH2
F
3l
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)

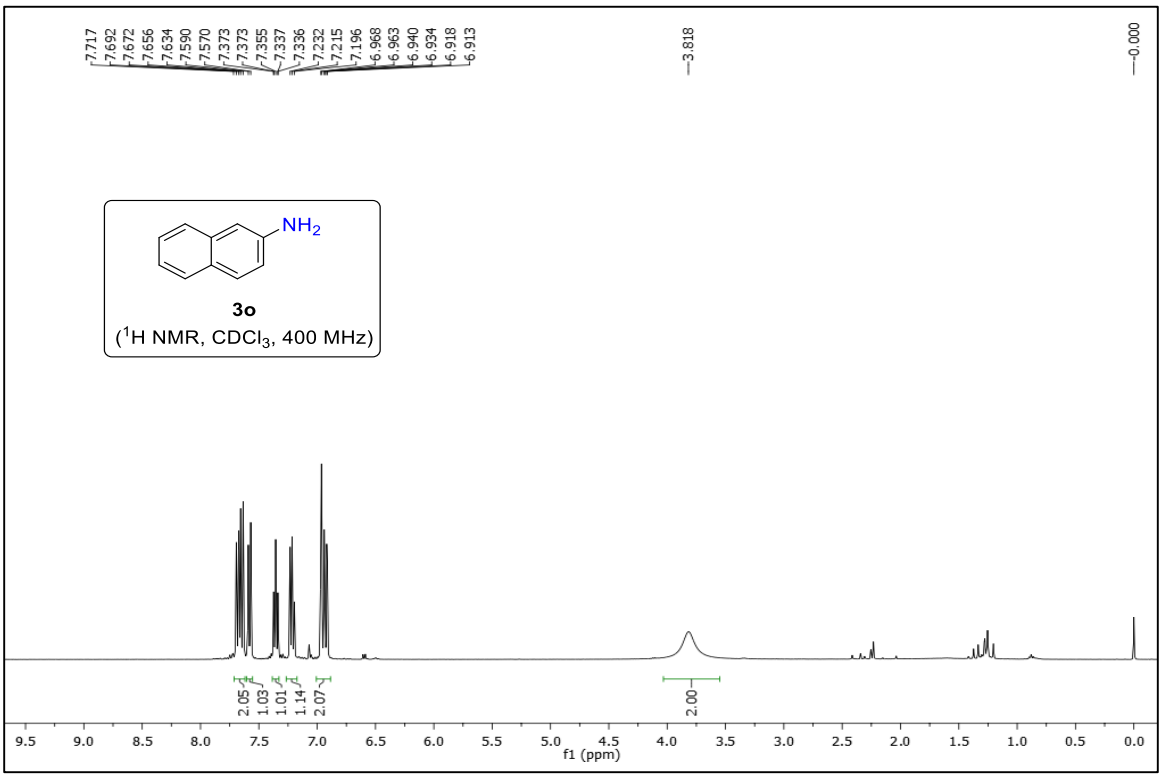

-126.894
NH2
F
3l
(19F NMR, CDCl3, 376 MHz)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

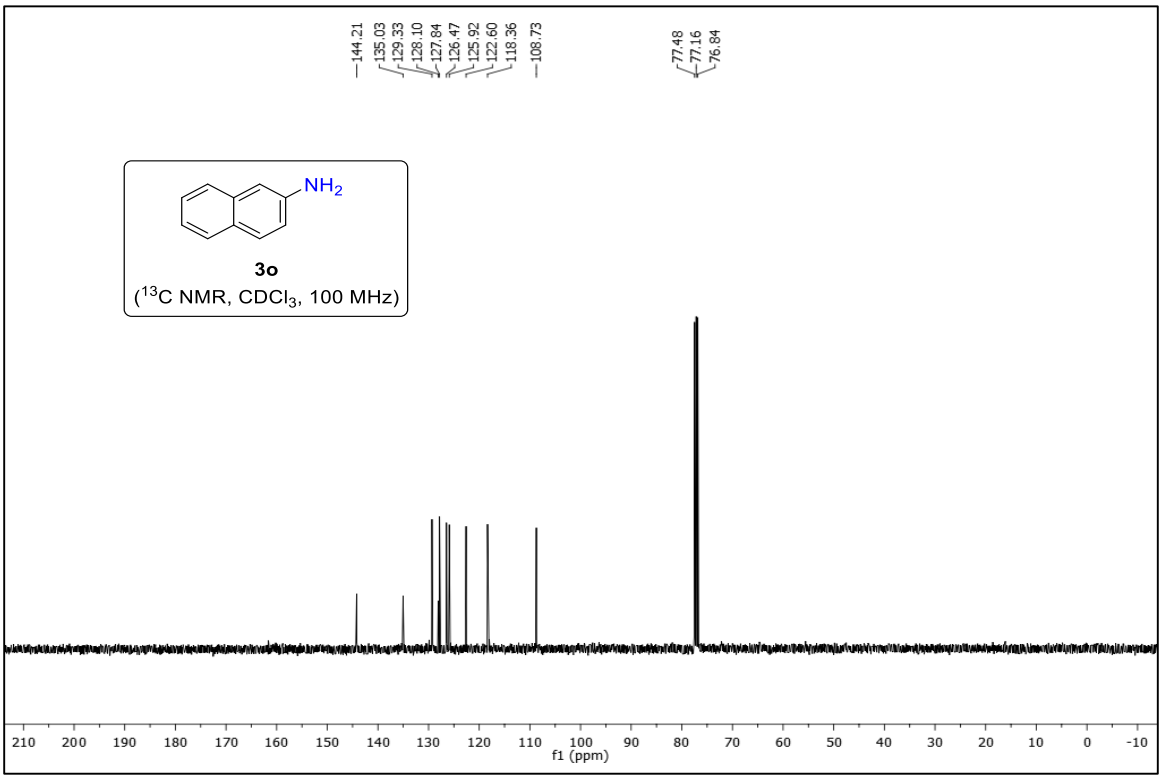

8.078
8.055
8.048
7.260
6.641
6.634
6.629
6.616
6.611
6.603
4.392
1.595
NH2
O2N
3m
(1H NMR, CDCl3, 400 MHz)
2.00
1.99
2.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

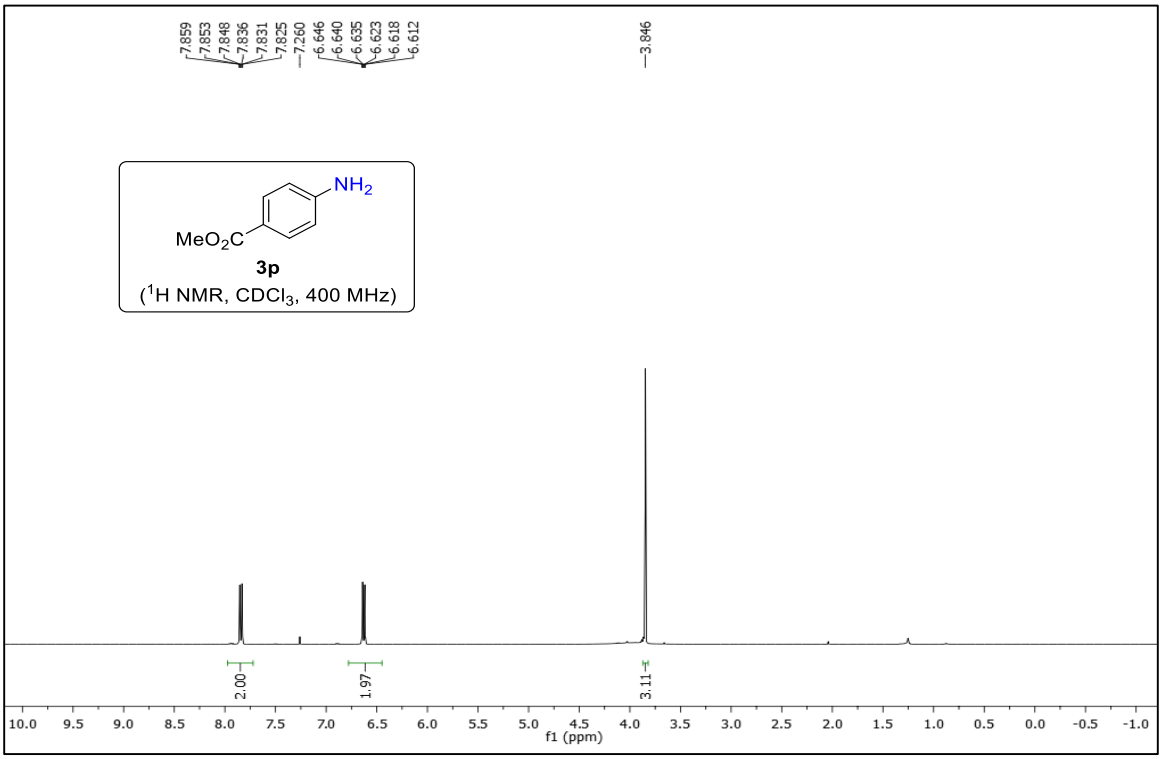

7.396
7.375
7.260
6.645
6.623
4.226
1.243
NH2
O2N
3m
(13C NMR, CDCl3, 100 MHz)
1.98
2.00
2.06
f1 (ppm)

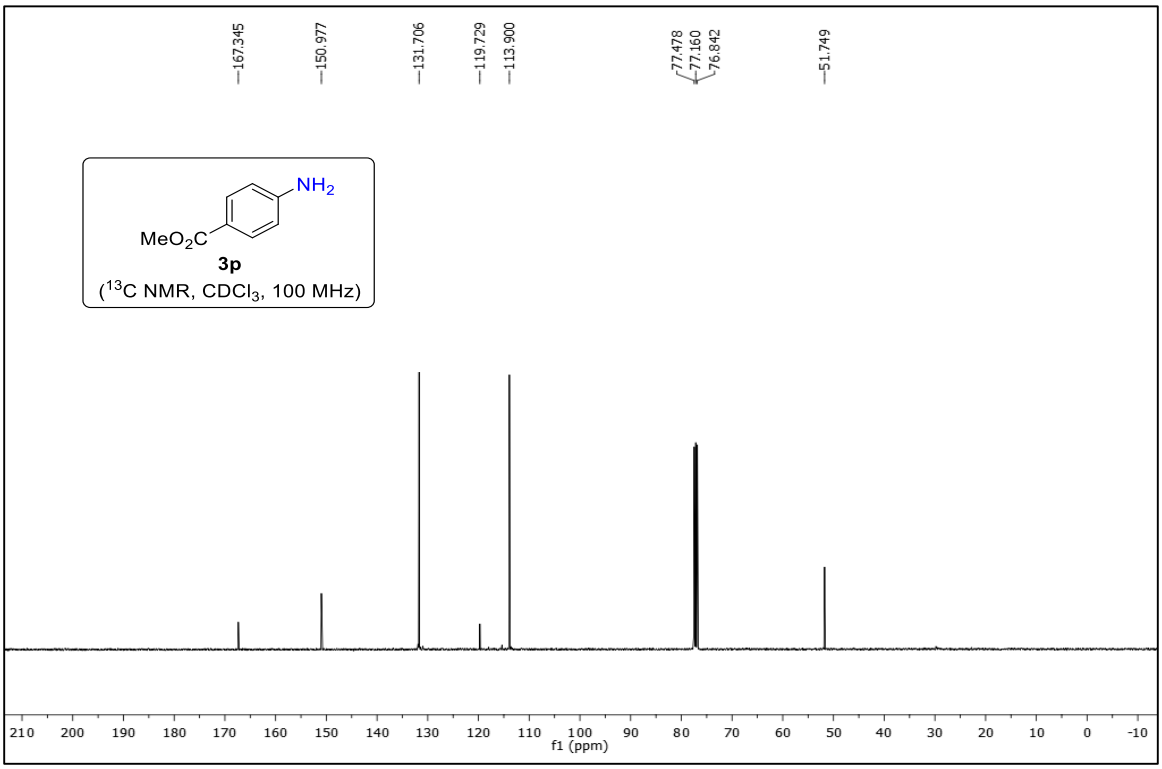

152.66
139.26
126.49
113.51
77.48
77.16
76.84
NH2
NC
3n
(1H NMR, CDCl3, 400 MHz)
f1 (ppm)


150.64
133.85
120.31
114.50
99.98
77.48
77.16
76.84
NH2
NC
3n
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)


7.717
7.692
7.672
7.656
7.634
7.590
7.570
7.373
7.373
7.355
7.337
7.336
7.232
7.215
7.196
6.968
6.963
6.940
6.934
6.918
6.913
3.818
0.000
NH2
3o
(1H NMR, CDCl3, 400 MHz)
2.05
1.03
1.01
1.14
2.07
2.00
f1 (ppm)


144.21
135.03
129.33
128.10
127.84
126.47
125.92
122.60
118.36
108.73
77.48
77.16
76.84
NH2
3o
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)


7.859
7.853
7.848
7.836
7.831
7.825
7.260
6.646
6.640
6.635
6.623
6.618
6.612
3.846
NH2
MeO2C
3p
(1H NMR, CDCl3, 400 MHz)
2.00
1.97
3.11
f1 (ppm)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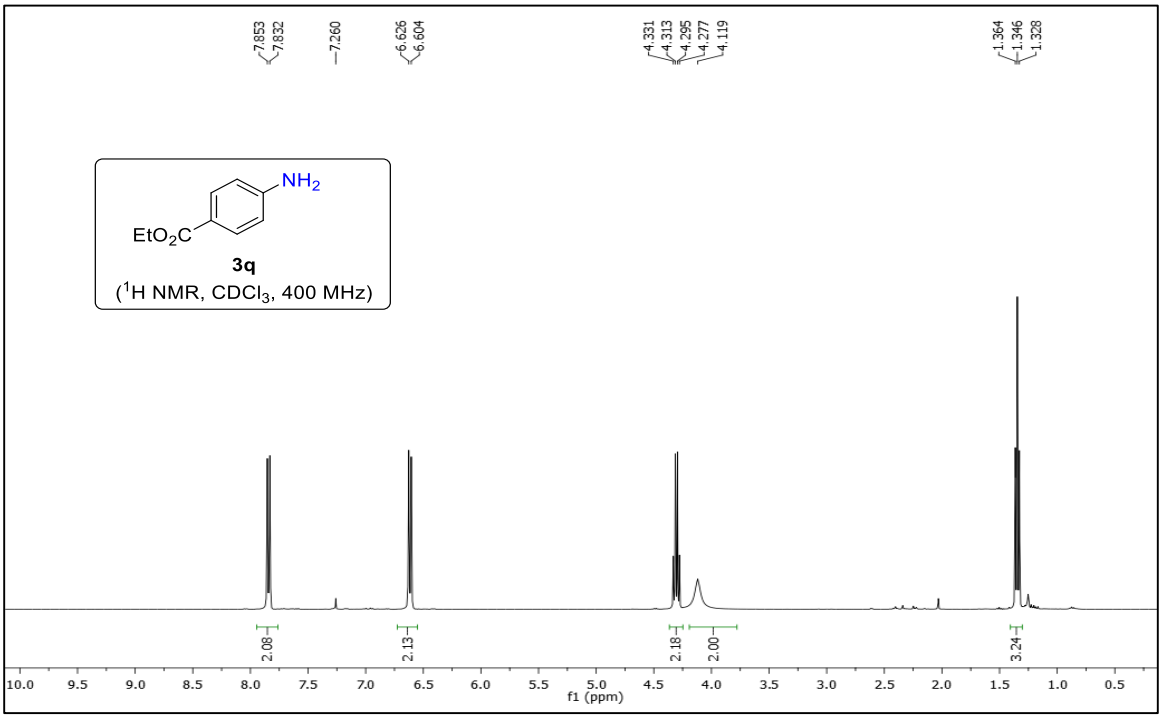
f1 (ppm)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6.604
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4.295
4.277
4.119
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1.328
NH2
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3q
(1H NMR, CDCl3, 400 MHz)
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2.18
2.00
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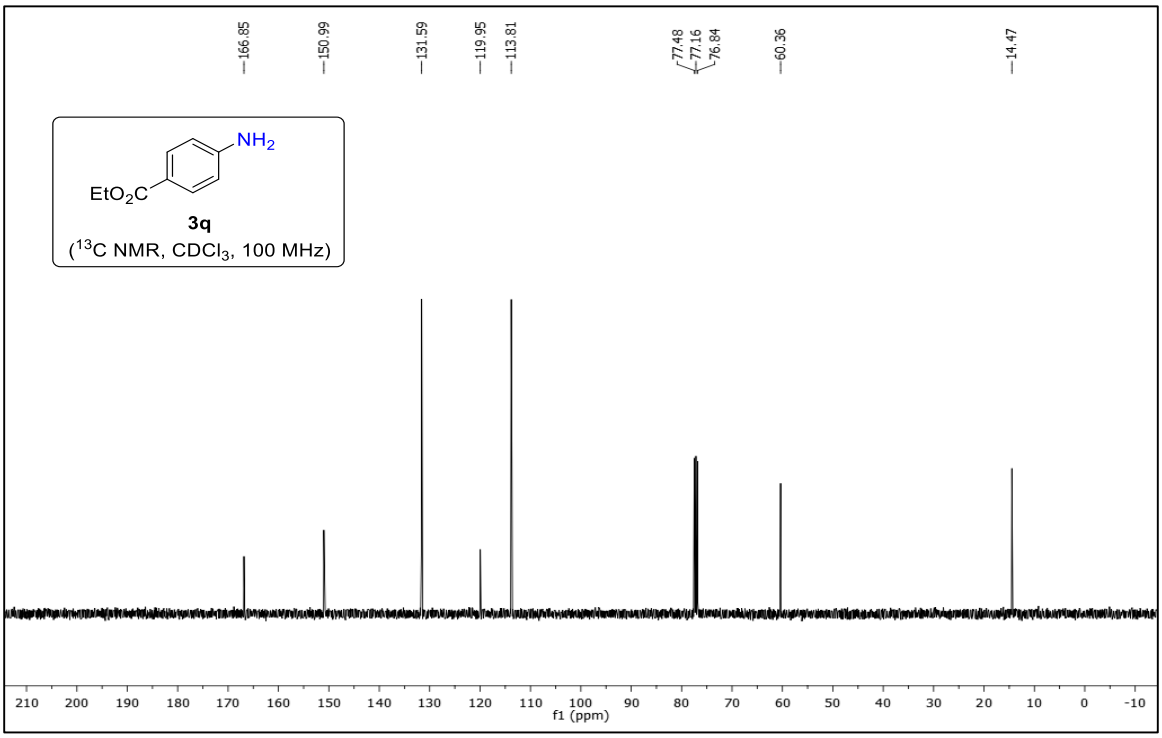
f1 (ppm)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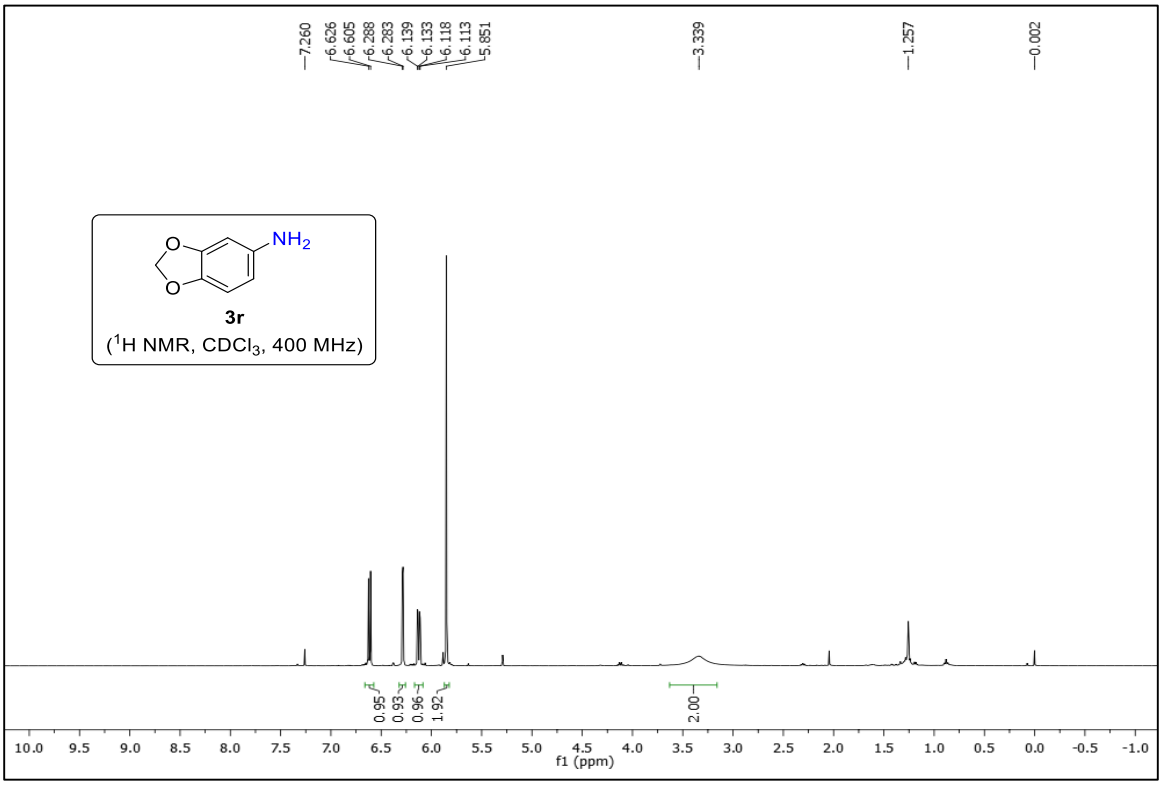
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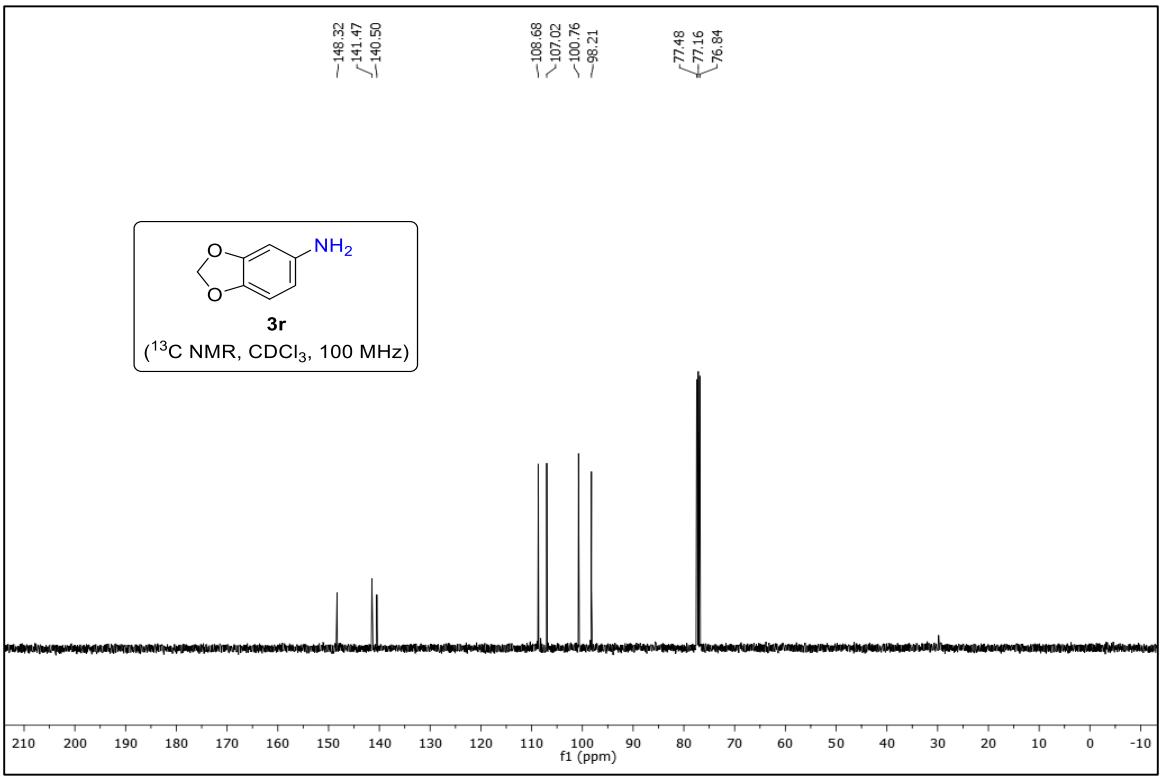
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76.84
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O
O
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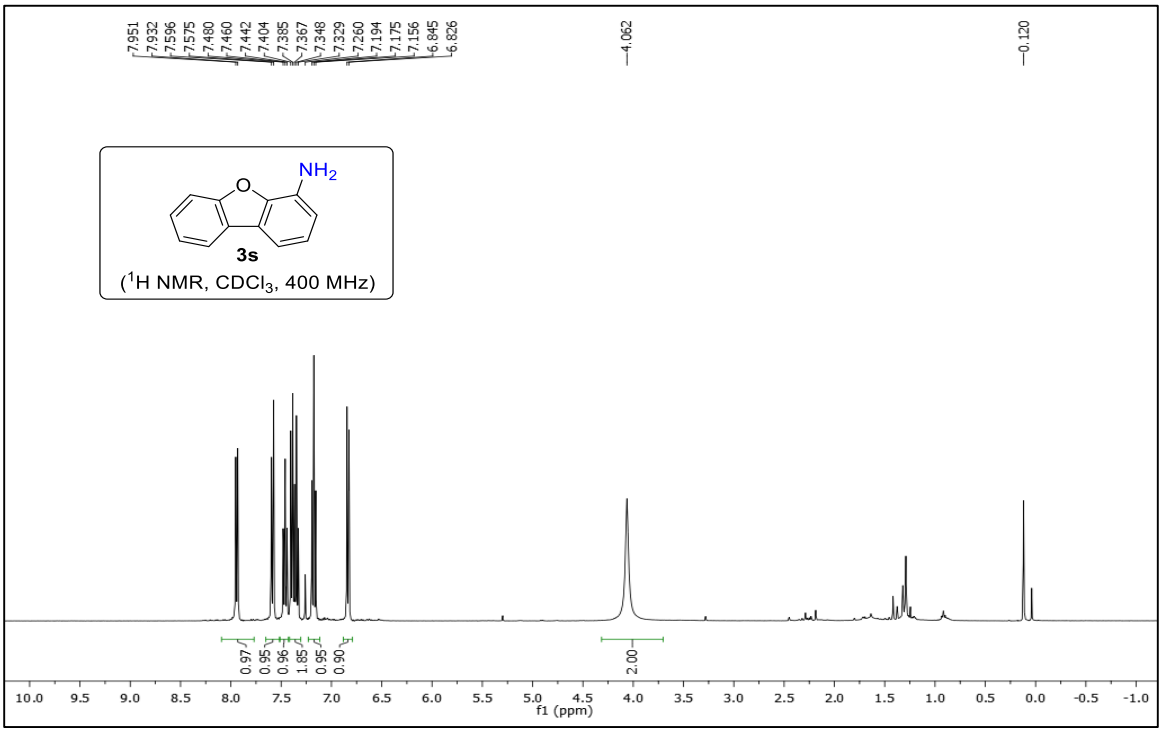
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)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7.404
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7.260
7.194
7.175
7.156
6.845
6.826
4.062
0.120
NH2
O
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(1H NMR, CDCl3, 400 MHz)
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0.90
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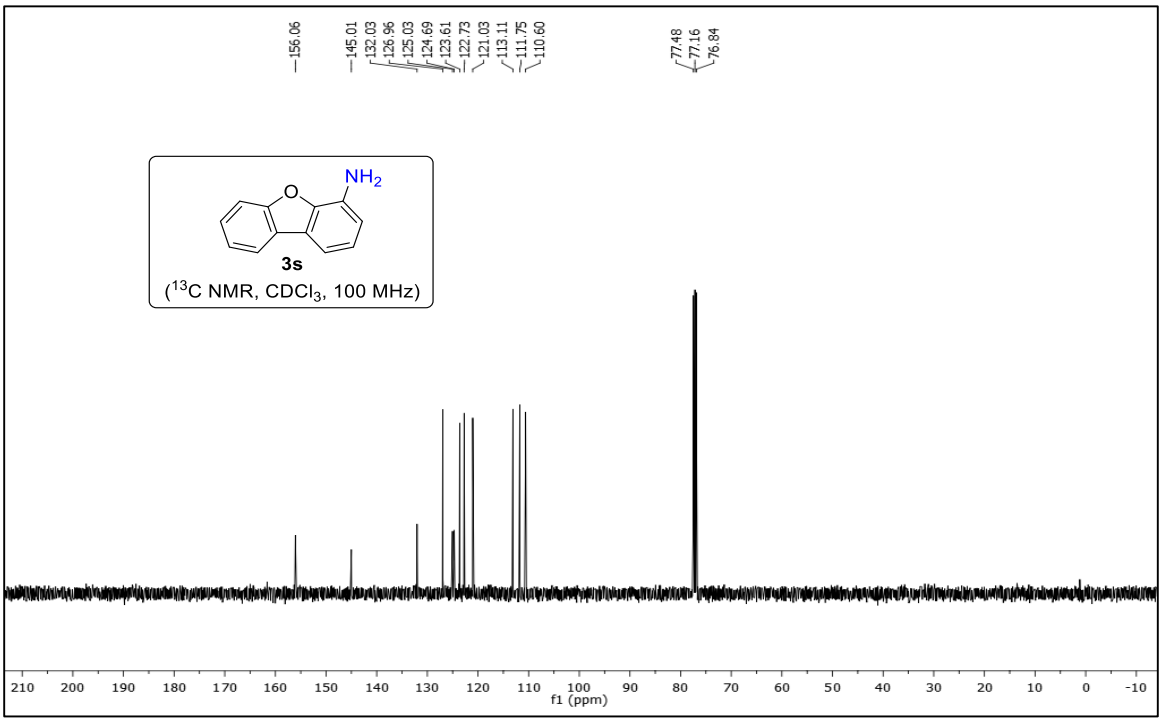
f1 (ppm)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126.96
125.03
124.69
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122.73
121.03
113.11
111.75
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77.48
77.16
76.84
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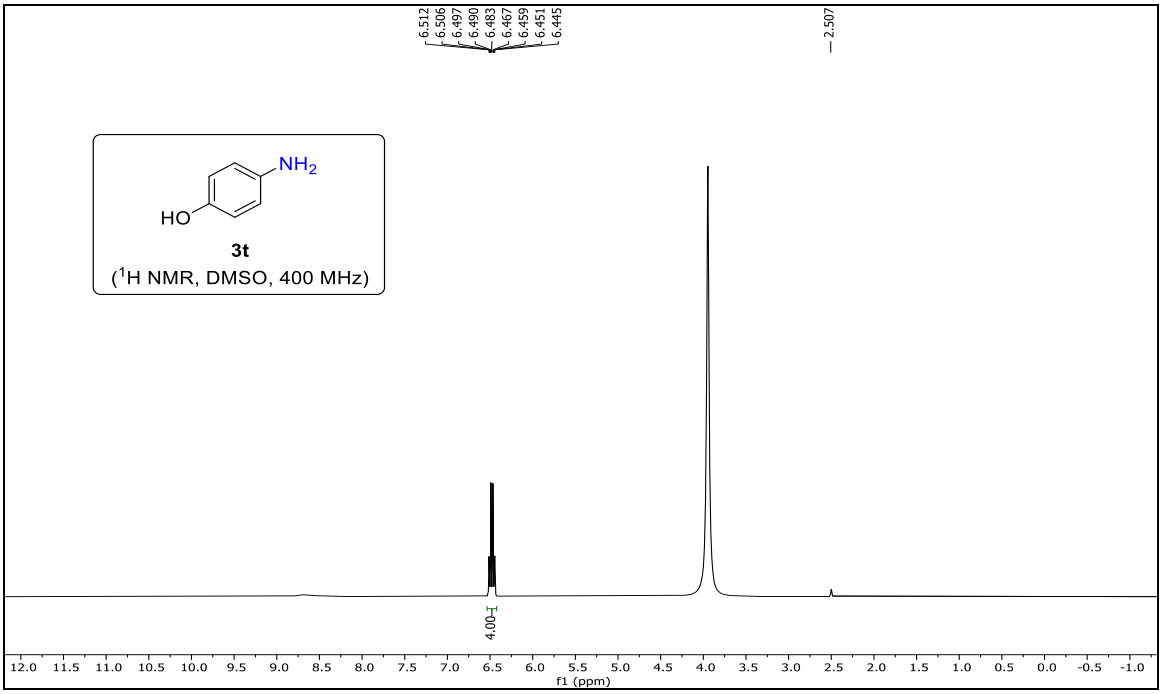
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)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6.483
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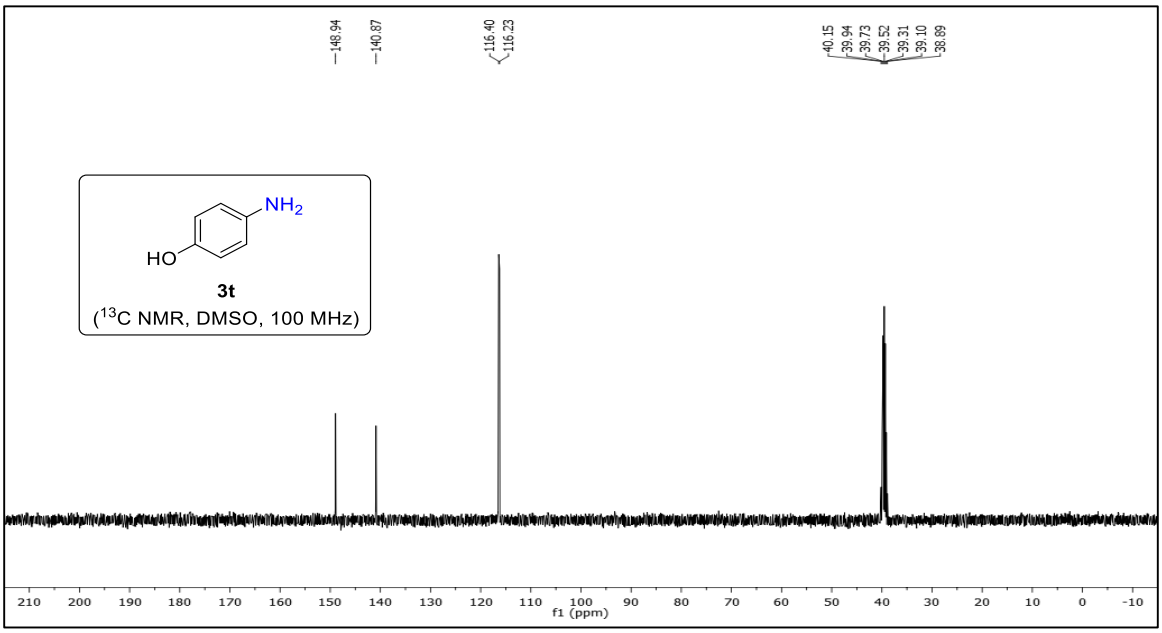
4.00
f1 (ppm)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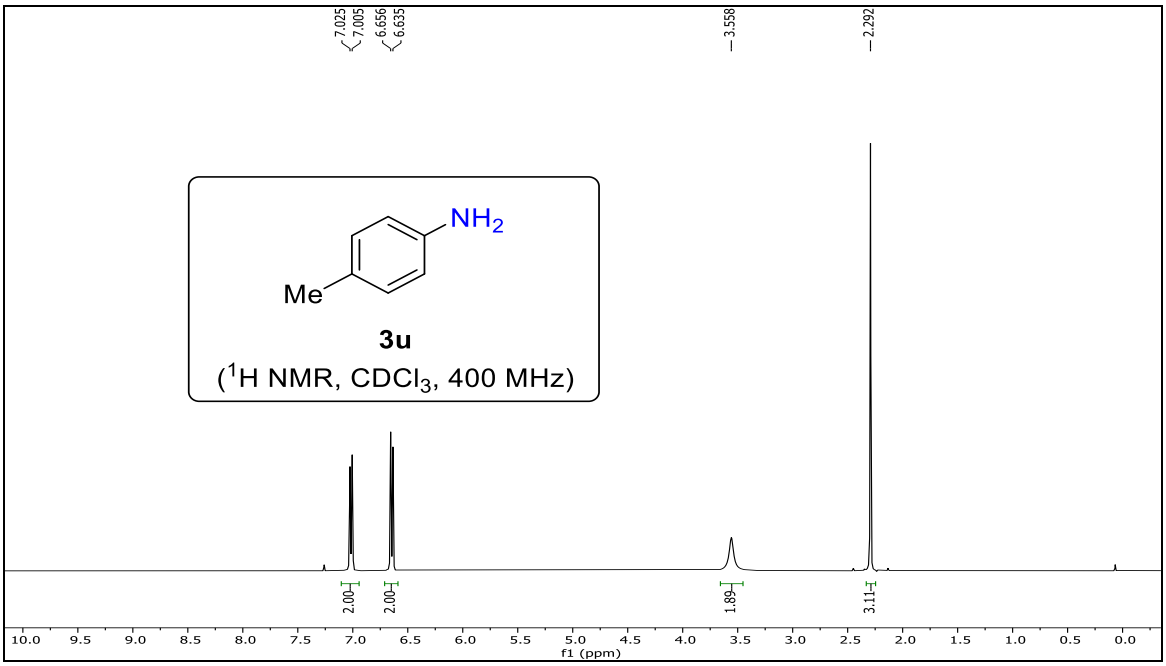
HO
3t
(13C NMR, DMSO, 100 MHz)
f1 (ppm)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3u
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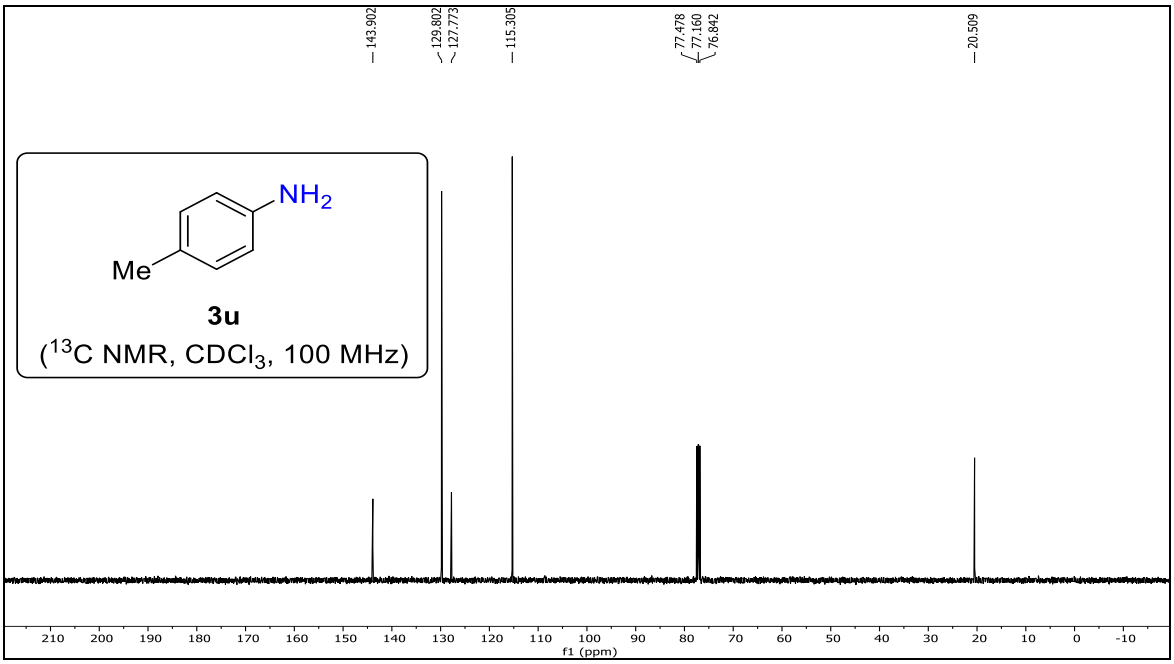
2.00
1.89
3.11
f1 (ppm)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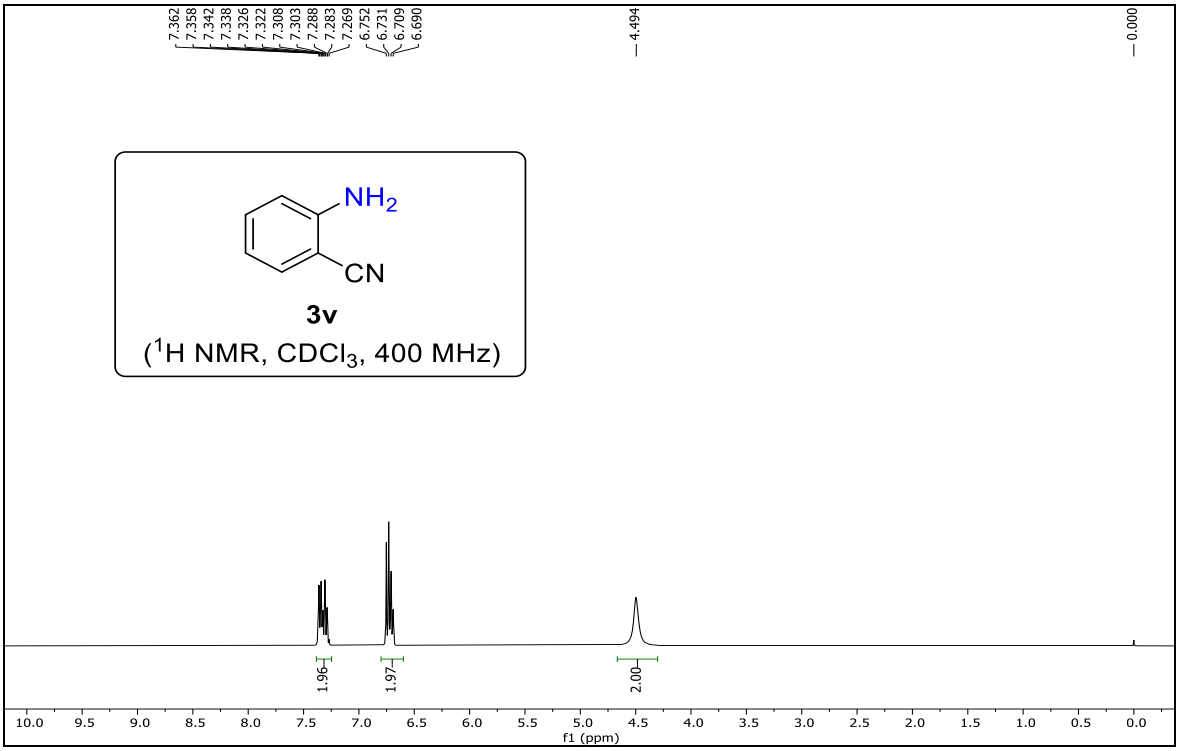
77.478
77.160
76.842
20.509
NH2
Me
3u
(13C NMR, CDCl3, 100 MHz)
f1 (ppm)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7.326
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7.308
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7.283
7.269
6.752
6.731
6.709
6.690
4.494
0.000
NH2
CN
3v
(1H NMR, CDCl3, 400 MHz)
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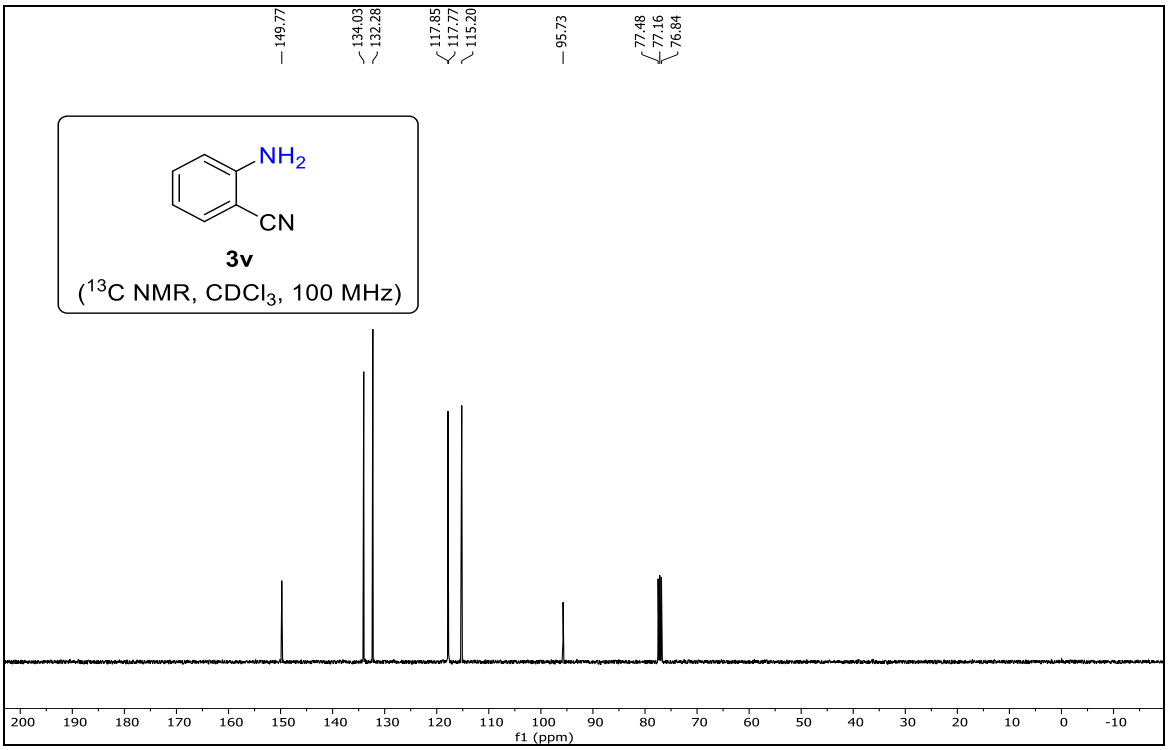
1.97
2.00
f1 (ppm)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134.03
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117.77
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76.84
NH2
CN
3v
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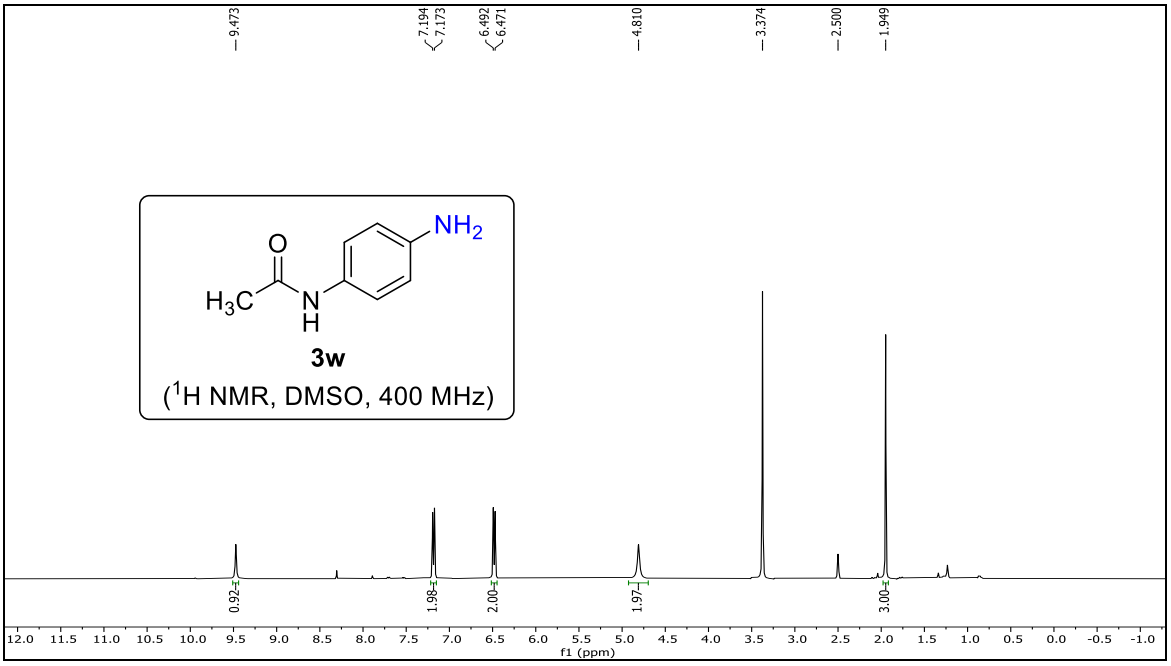
f1 (ppm)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2.500
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O
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N
H
3w
(1H NMR, DMSO, 400 MHz)
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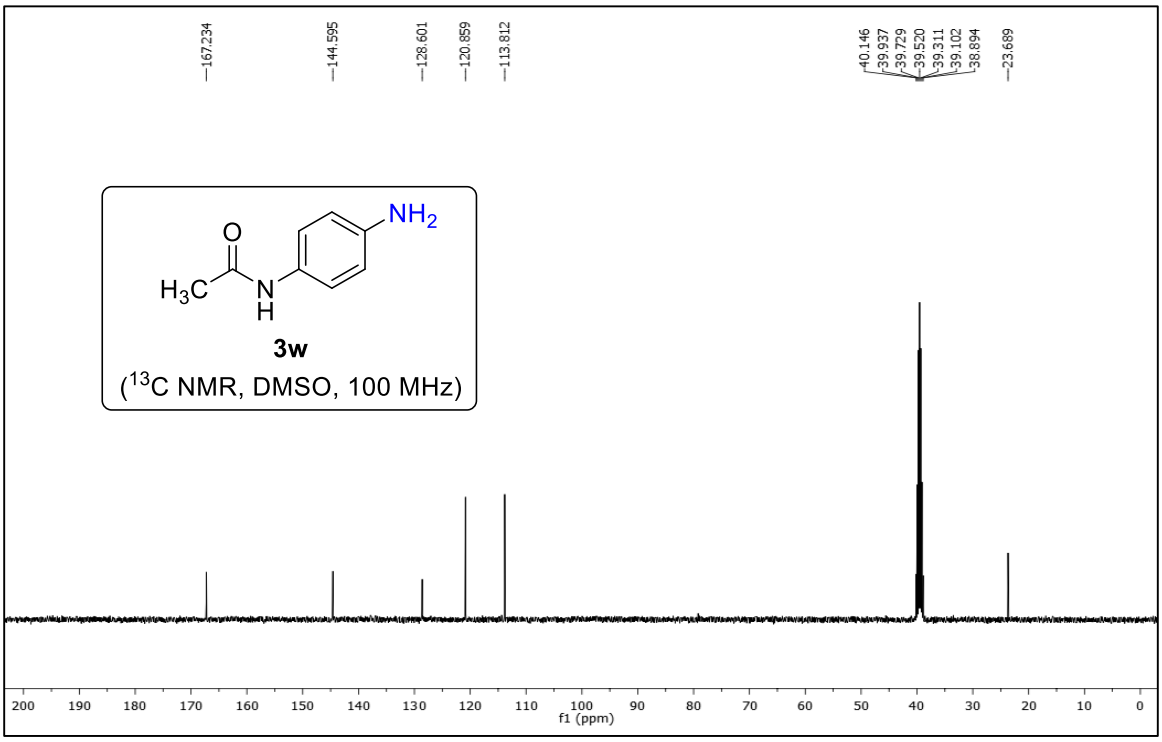
2.00
1.97
3.00
f1 (ppm)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39.102
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23.689
NH2
O
H3C
N
H
3w
(13C NMR, DMSO, 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

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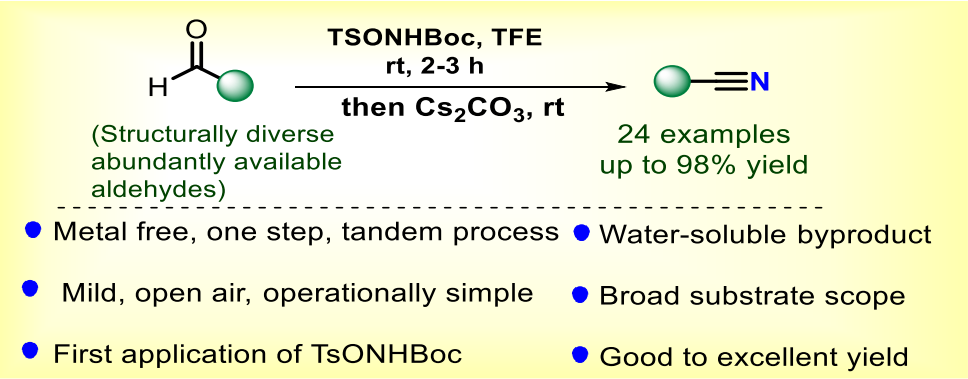
Chapter 4

Metal-free transformation of aldehydes into nitriles using TsONHBoc reagent

Herein, we describe the economical and practical synthesis of nitriles from readily available aldehydes using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as an aminating agent. This direct and metal-free synthesis of nitriles provided good to excellent yields of products and tolerates a wide range of substituted aromatic, aliphatic, allylic, heteroaryl, and *α,β*-unsaturated aldehydes. Shelf-stability, low cost, and ease-handling of TsONHBoc introduce an additional advantages.



4.1 Introduction

The nitrogen atom is present in approximately 84% of small pharmaceutical molecules. Numerous potent bioactive products, synthetic, semisynthetic compounds and polymers contain nitriles in their structural motif (fig 4.1-4.3).[1] Noteworthy, some of the FDA approved drugs also contain nitrile functionality.[1k]

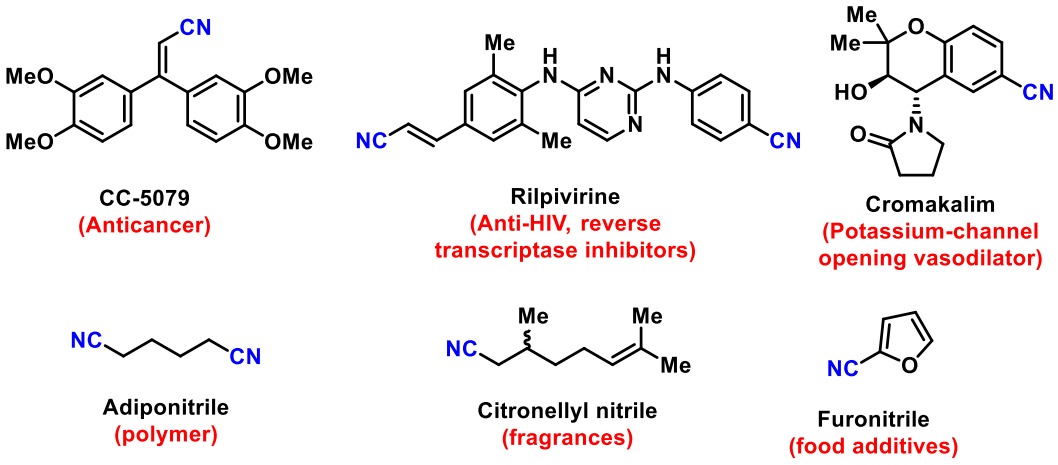


Fig. 4.1. Presence of nitrile moiety in various useful compounds

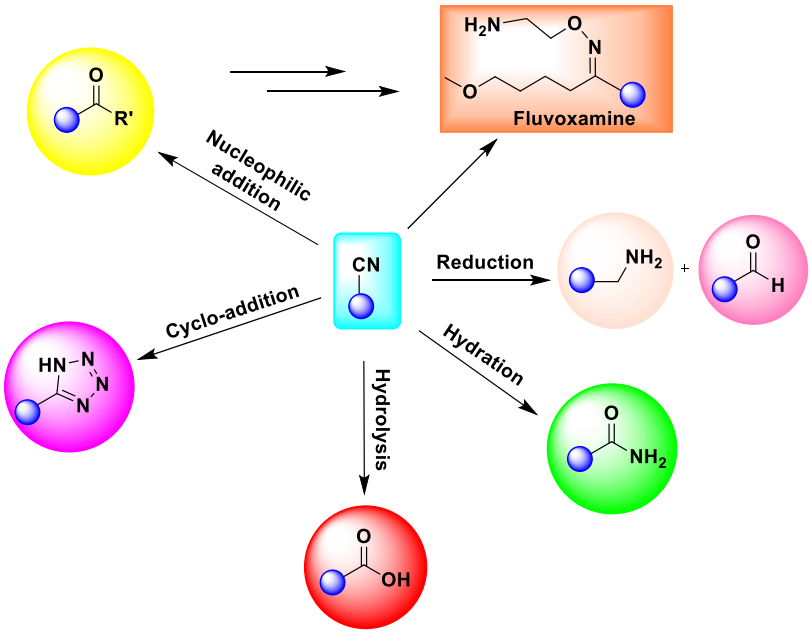


Fig. 4.2. Some important synthetic transformation of nitrile

In addition, they play a prominent role as a versatile synthetic intermediate for the formation of the corresponding amines, amides, esters, acids, and aldehydes along with the synthesis of nitrogen-containing heterocyclic compounds.[2] The Sandmeyer and Rosenmund-von Braun reactions[3] and cyanide-halide exchange reactions are the most used classical methods for nitrile synthesis.[4] In these methods, alkali metal cyanide, $Zn(CN)_2$, and metalloid cyanides, such as CuCN, are still used in stoichiometric amounts.[4] Further, the dehydration of amides[5] or aldoximes[6] were developed as cyanide-free alternative ways for nitrile synthesis under high reaction temperature and using tedious procedure. The wide availability of aldehydes attracted the attention for its usage as low-cost starting material for the synthesis of nitriles. In this context, Schmidt reaction provides direct access of nitrile from aldehydes but uses highly toxic and explosive sodium azide as a nitrogen source.[7] The other nitrogen source used for nitrile synthesis are hydroxylamine[8] and derivatives[9] and trapped ammonia[10]. However, the described nitrogen sources required an oxime activator or have explosive nature.

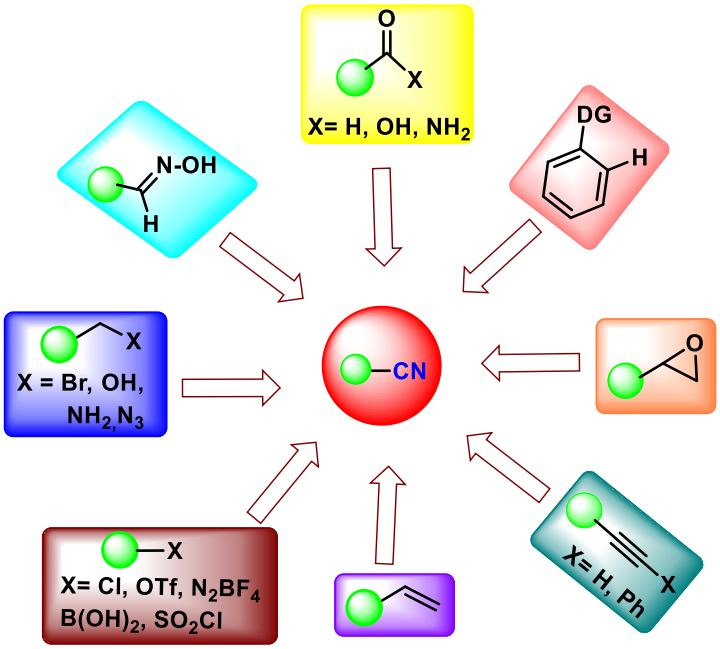


Fig. 4.3. Different synthetic approaches for the nitrile synthesis

The up-to-date literature study for the synthesis of nitriles are summarized in section 4.2.

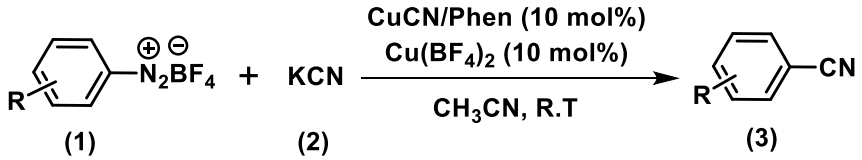
4.2 Literature review of nitrile synthesis

There have been great achivements in synthesis of nitriles in existing literature. Selected literature review are sumrized below.

4.2.1 $Cu(BF_4)_2$ -Catalyzed synthesis of nitriles from aryl diazonium salts

The Sandmeyer reaction, one of the most traditional transformations in organic synthesis. This process has several limitations, including the usage of a stoichiometric amount of poisonous CuCN and harsh reaction conditions. Efforts are being made over the past few years to overcome these challenges.[11a-d]

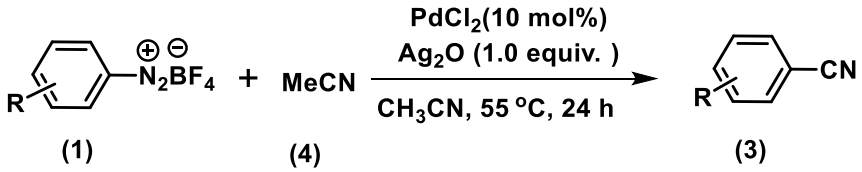
Beletskaya and colleagues published a catalytic Sandmeyer reaction in 2004.[11d] The reactions with aryl diazonium salts containing electron-withdrawing groups produced the desired nitriles with excellent yields in the presence of $Cu(BF_4)_2$ co-catalyst.This method required toxic KCN in stoichiometric amounts (Scheme 4.1).



Scheme 4.1. $Cu(BF_4)_2$-catalyzed synthesis of nitrile from aryldiazonium salt

4.2.2 Pd -Catalyzed synthesis of nitriles from aryldiazonium salts

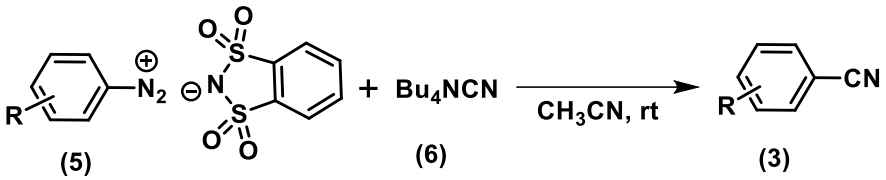
Li *et al.* demonstrated the Pd-catalyzed synthesis of aryl nitriles from aryldiazonium tetrafluoroborates in cost-effective acetonitrile solvent (Scheme 4.2).[11c-d] However, the poor substrate scope and low to moderate yields limit its applications.



Scheme 4.2. Pd-catalyzed synthesis of nitrile from aryldiazonium salt

4.2.3 Metal-free synthesis of nitriles from aryldiazonium salts

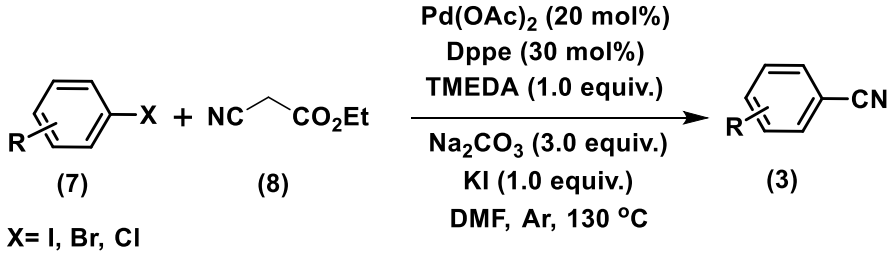
Dughera and colleagues discovered the transition metal free transformation of aryldiazonium salts into the nitrile (Scheme 4.3)[11d]



Scheme 4.3. Metal free synthesis of nitrile from aryldiazonium salt

4.2.4 Palladium-Catalyzed synthesis of nitriles from aryl halides using ethyl cyanoacetate

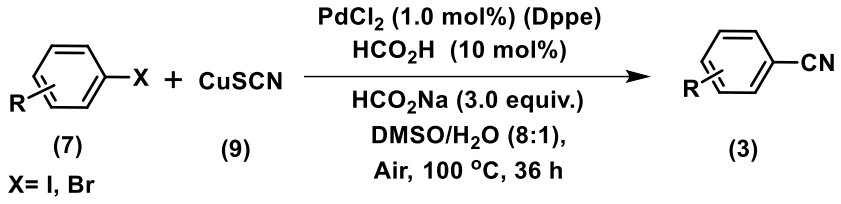
Shen *et al.* developed a Palladium-catalyzed synthesis of aryl nitriles from aryl halides using ethyl cyanoacetate as a source of CN (Scheme 4.4).[12]



Scheme 4.4. Synthesis of nitrile using ethyl cyanoacetate as a source of CN

4.2.5 Pd -Catalyzed synthesis of nitriles from aryl halides using cuprous thiocyanate

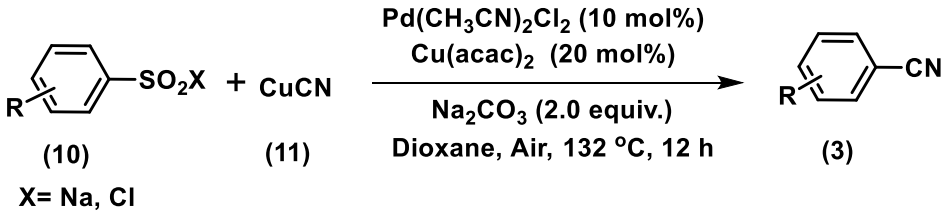
In 2013, Cheng *et al.* found cuprous thiocyanate as a reliable cyanide source for the cyanation of aryl halides (Scheme 4.5).[13] This approach provided a good yield of the desired nitrile and tolerance of several sensitive functional groups.



Scheme 4.5. Pd -Catalyzed synthesis of nitriles from aryl halides using CuSCN

4.2.6 Synthesis of aryl nitriles from arylsulfonyl chlorides

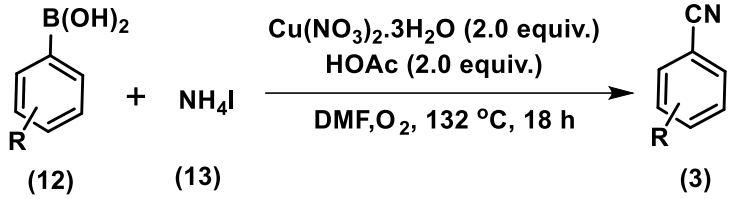
Arylsulfonyl chlorides are important intermediates in synthetic organic chemistry. Cheng *et al.*, reported palladium-catalyzed cyanation of arylsulfonyl chlorides using sodium sulfinates and CuCN as a source of CN (Scheme 4.6).[14]



Scheme 4.6. Synthesis of aryl nitriles from arylsulfonyl chlorides

4.2.7 Cu-Catalyzed synthesis of aryl nitriles from aryboronic acids

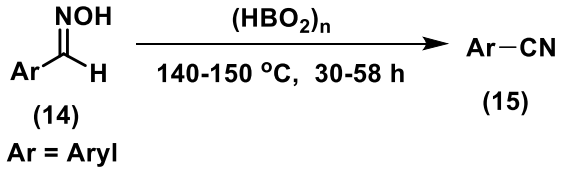
A Cu-catalyzed synthesis of aryl nitrile from aryl boronic acids using NH_4I and DMF as a cumulative source of CN was reported by Chang *et. al.* This protocol can also be used for the transformation of Boronate esters, borate salts (Scheme 4.7.)[15] This method required high temperature and it works with aromatic substrates only.



Scheme 4.7. Cu-catalyzed synthesis of aryl nitriles from aryboronic acids

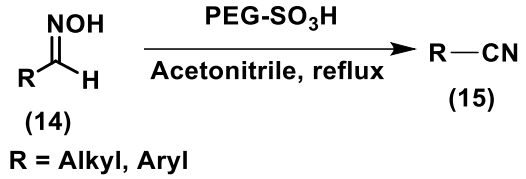
4.2.8 Synthesis of nitriles from aldoximes

i) Chandrasekhar *et al.* developed a metaboric acid catalyzed methodology for the preparation of nitriles from corresponding aldoximes (Scheme 4.8). This method provided the mixture of products containing starting material, amide, and nitrile.[16]



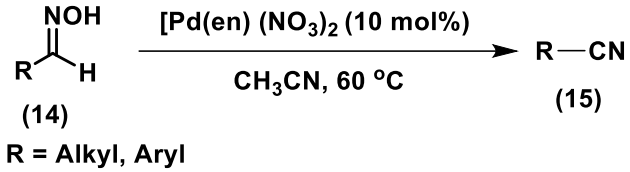
Scheme 4.8. **Acid-catalyzed synthesis of aryl nitriles from aldoximes**

ii) In 2009, X.C. Wang reported the transformation of aldoximes into the desired nitrile using poly (ethylene glycol)s (PEG)-bounded sulfonic acid (PEG-SO_3H) in acetonitrile solvent. (Scheme 4.9)[17]



Scheme 4.9. PEG-SO_3H mediated synthesis of nitriles from aldoximes

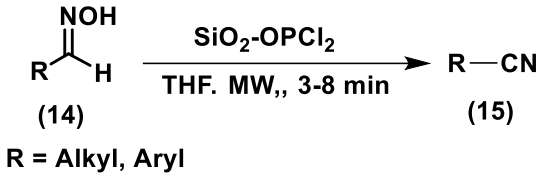
iii) K. Tambara *et el.* described the Pd-catalyzed preparation of nitriles from corresponding aldoximes using [Pd(en) $(NO_3)_2$] catalyst in acetonitrile at 60 ^oC (Scheme 4.10).[18]



Scheme 4.10. Pd-catalyzed synthesis of nitriles from aldoximes

iv) Microwave-assisted synthesis of nitriles from aldoximes

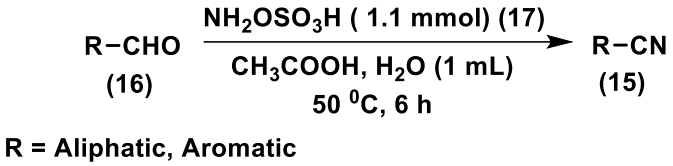
Li and coworkers observed that under microwave conditions, silica-supported phosphorus chloride works as a reliable and effective catalyst for the conversion of various aldoximes into their corresponding nitriles (Scheme 4.11).[19]



Scheme 4.11. Microwave-assisted synthesis of nitriles from aldoximes

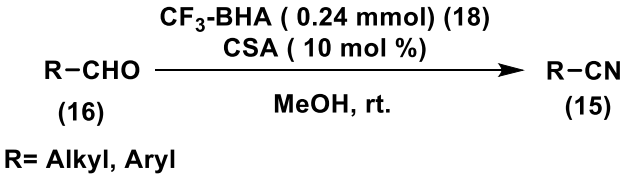
4.2.9 Dircet synthesis of nitriles from aldehydes

i) Quinn *et al.* developed an efficient approach to convert aldehydes into nitriles using HOSA. The aldehydes were heated with HOSA (1.1 eq.) at 50 °C in acidic water to produce the desired nitriles in excellent yields. Other acids such as TFA, tetramethylguanidinium propane sulfonic acid trifluoromethylacetate (TMGHPS.TFA), and tetramethylguanidinium lactate (TMG.LA) *etc.* were also screened, but the better results were obtained with acetic acid. Many aliphatic and aromatic aldehydes were transformed into the corresponding nitriles. However, aldehydes having electron-withdrawing groups required a longer reaction time to generate the corresponding nitriles (Scheme 4.12).[20]



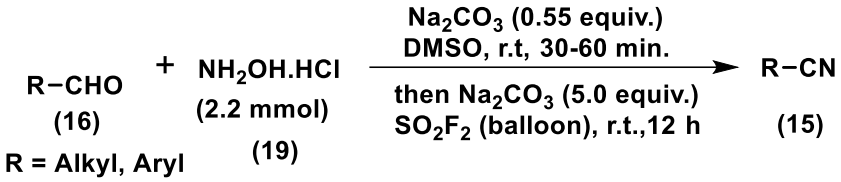
Scheme 4.12. Direct synthesis of nitriles from aldehydes

ii) Xiao-De and Shouyun reported an operationally simple, mild, and effective protocol that uses CF_3-benzoyl)-hydroxylamine (CF_3-BHA) as a nitrogen source in the presence of CSA. This methodology works very well for aliphatic, aromatic and heterocyclic aldehydes resulted in corresponding nitriles with good to excellent yields (Scheme 4.13).[21]



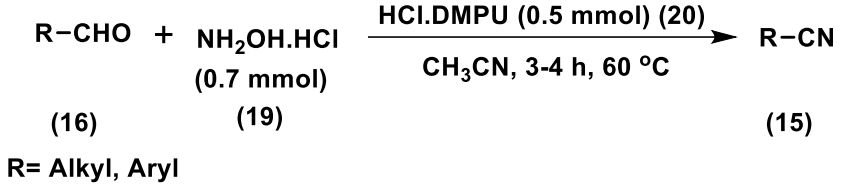
Scheme 4.13. Preparation of nitriles from aldehydes using CF_3-BHA

iii) Wan-Yin Fand *et al.* developed a simple, effective, and straightforward method for nitriles synthesis from aldehydes using $NH_2OH/Na_2CO_3/SO_2F_2$ in DMSO solvent. This protocol provided excellent yields of nitriles with both electron rich as well as electron deficient substrates. Heterocyclic aldehydes also survived very well and generated the desired nitrile with good to excellent yield.[22] Aldehydes containing double and triple bonds tolerated well and provided the desired nitrile with excellent yields (Scheme 4.14).



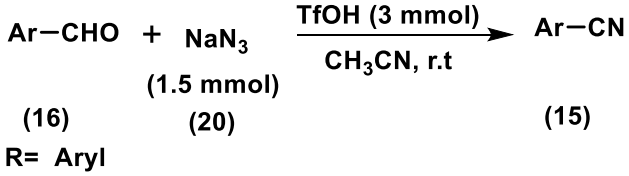
Scheme 4.14. Direct synthesis of nitriles from aldehydes

iv) Sagar R. Mudshinge and coworkers reported the conversion of aldehydes into nitriles using HCl•DMPU. Functionalized allylic, aliphatic, and aromatic aldehydes were successfully transformed into nitriles in good to excellent yields. Additives and poor atom economy are the major drawbacks of this method (Scheme 4.15).[23]



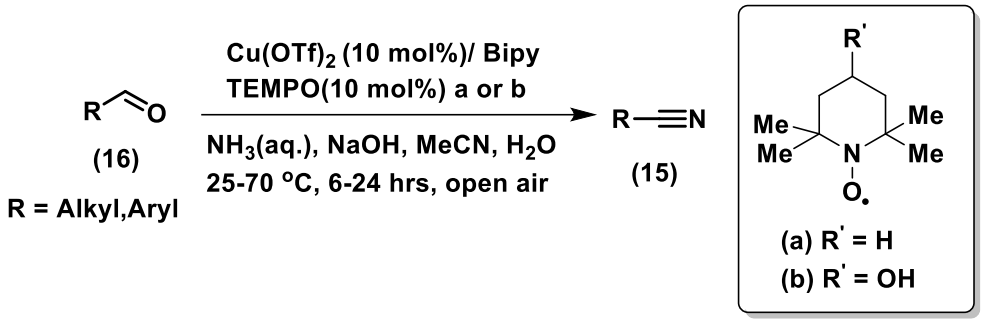
Scheme 4.15. HCl•DMPU assisted direct synthesis of nitriles from aldehydes

v) B. V. Roade *et al.* reported a TfOH-mediated chemoselective Schmidt reaction for the synthesis of nitriles. They treated aldehydes with NaN_3 using TfOH acid in acetonitrile solvent. This approach exhibits good to excellent yields of the corresponding nitriles together with a broad array of functional group tolerance (Scheme 4.16).[24]



Scheme 4.16. TfOH catalyzed chemoselective synthesis of nitriles from aldehydes

vi) Laura M. Dorman and coworkers developed an efficient copper/TEMPO catalyzed method for the synthesis of nitriles from aldehydes using aq. ammonia. This method works very well with aromatic aldehydes and provided the nitriles with good to excellent yields. However, this protocol was very less explored with aliphatic aldehydes (Scheme 4.17).[25]

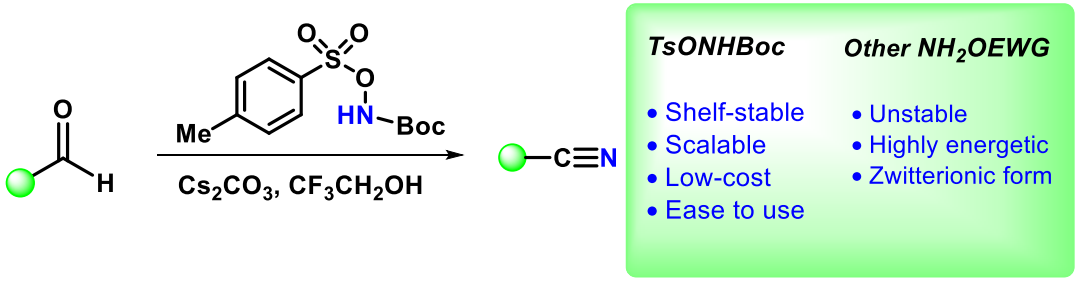


Scheme 4.17. Copper/TEMPO catalyzed synthesis of nitriles from aldehydes

Despite the significant advancements made in the field of nitrile synthesis, there are still several restrictions, such as the use of hazardous chemicals, unfavorable reaction conditions, poor functional group tolerance, and limited substrates scope. *O*-substituted hydroxylamines have been recognized as powerful *N*-transfer reagents, used in the nitrogen-insertion reaction in various organic molecules. Besides serving as important aminating agents, *O*-substituted hydroxylamine derivatives having a free primary-amino group (for example; MSH, DPH, HOSA) are highly energetic, require storage of 0 °C or below, generating interfering by-product (2,4-dinitrophenol) *etc*. Hence, mild reaction condition and selection of safe nitrogen source in this direction is highly desirable.

4.3 Objective of the work

The objective of this part of the thesis was the development of a new methodology for the synthesis of nitriles from aldehydes under mild conditions using TsONHBoc as a bench stable aminating agent (Scheme 4.18).



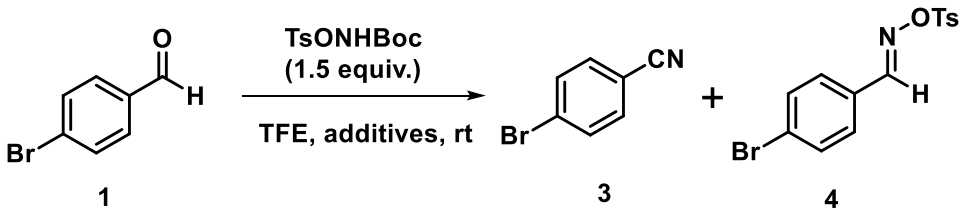
Scheme 4.18. Synthesis of nitriles from aldehydes

4.4 Results and discussion

4.4.1 Optimization of the reaction condition

Based on other in-progress results in our laboratory,[12] we observed that highly reactive $TsONH_2$ could be *in situ* generated from the boc deprotection of TsONHBoc in a weakly acidic solvent (TFE or HFIP). Based on this observation, herein, we used *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as aminating agent for direct conversion of aldehydes to corresponding nitriles in TFE solvent. We started the reaction condition optimization using benzaldehyde as the model substrate without any additive, unfortunately, the reaction did not proceed further from the oxime intermediate (4) (Table 4.1, entry 2-5).

Table 4.1: Optimization of reaction condition[a]



1 3 4

Entry	Additives	Time	% Yield of 3[b]	% Yield of 4[b]
1	-	24 h	0	100
2	PTSA	24 h	20	80
3	CH_3COOH	24 h	10	90
4	TFA	24 h	10	90
5	Oxalic acid	24 h	5	95
6	NEt_3	10 h	75	25
7	LiOH	10 h	50	50
8	$NaHCO_3$	10 h	40	60
9	**CS_2CO_3**	**6 h**	**95**	**5**
10[c]	CS_2CO_3	6 h	80	20

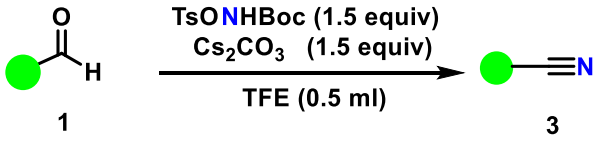
[a]Reaction condition: **1** (0.5 mmol, 1.0 equiv.), TsONHBoc **2** (0.75 mmol, 1.5 equiv.), additives (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt; [b]Isolated yield. [c]TsONHBoc and CS_2CO_3 (1.0 equiv.), PTSA= *p*-toluenesulfonic acid, TFA= Trifluoroacetic acid

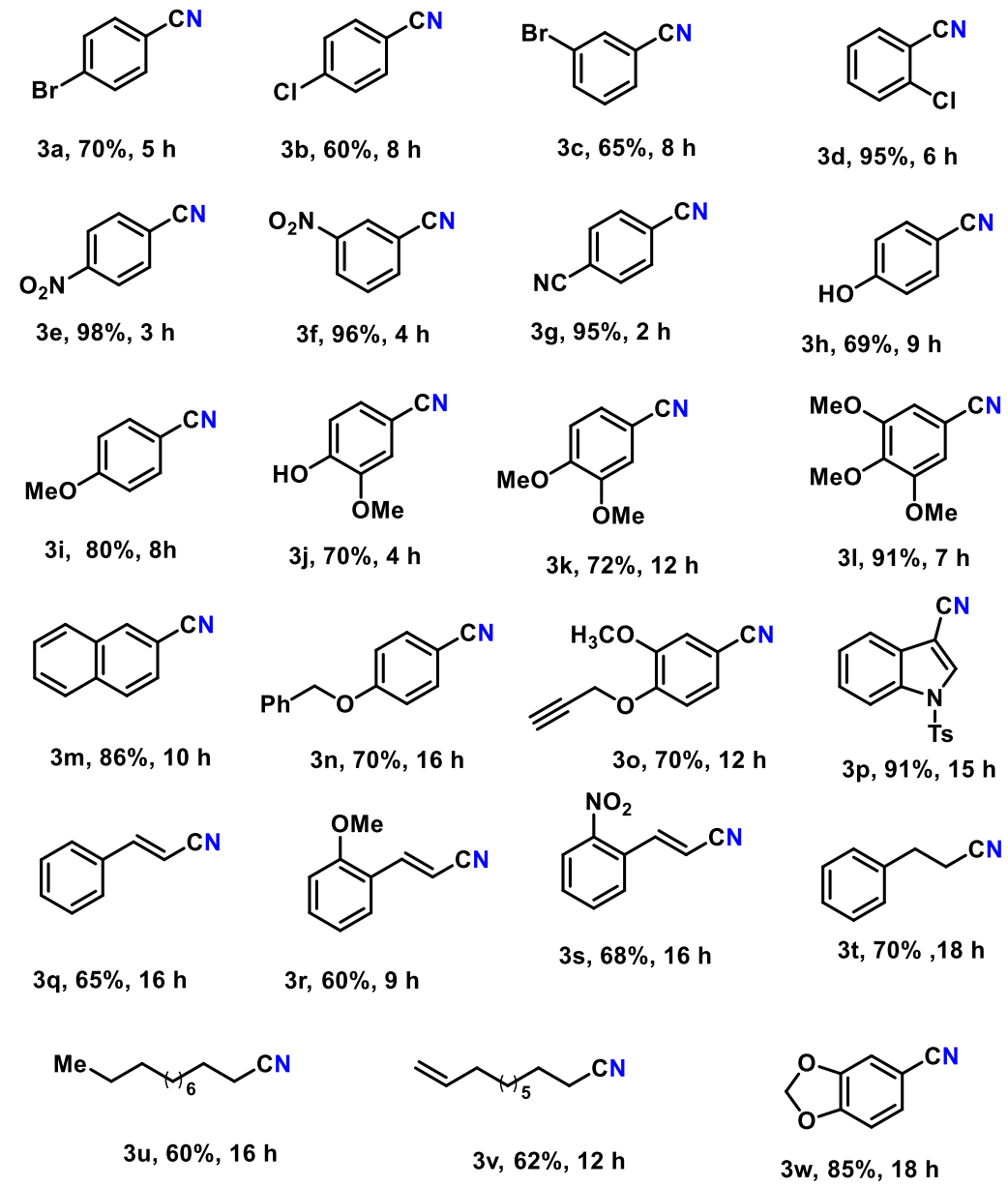
Next, we commenced the screening of various acids (Table 4.1, entry 2-5), such as PTSA, AcOH, TFA and oxalic acid. However, they failed to convert the *in situ* formed oxime intermediate into the desired nitriles. Furthermore, among the screened bases (Table 4.1, entry 6-9), NEt_3 furnished the desired nitrile in 75% yield (Table 4.1, entry 6), while the

other inorganic bases, such as LiOH and $NaHCO_3$, were not effective. We obtained the best result with CS_2CO_3 which provided a 95% yield of the nitrile product (Table 4.1, entry 9). Decreasing the amount of TsONHBoc and CS_2CO_3 resulted the low conversion (Table 4.1, entry 10).

4.4.2 Substrate scope

Next, we explored the substrate scope for the direct transformation of aldehydes into nitriles under basic conditions (Scheme 4.19). Substituted benzaldehydes provided the products in excellent yields. We investigated the halogen substituents at the *ortho*, *meta*, and *para* positions and observed a cleaner reaction providing a good to the excellent yield of the nitriles **(3b-d**). Strong electron-withdrawing groups such as $–NO_2$ and –CN proceeded in a very smooth manner and yielded the desired product **(3e-g)** in very good yield. On the next move, the substrates having methoxy group at *para*-position, as well as di-and tri-methoxy substituted aldehydes were transformed to their nitriles with good to excellent yield (**3i-l**).

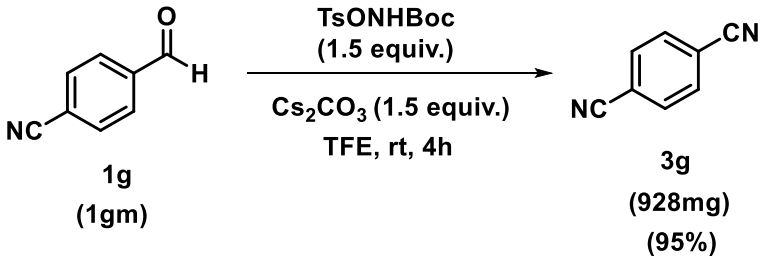




[a]Reaction condition: **1** (0.5 mmol, 1.0 equiv.), TsONHBoc **2d** (0.75 mmol, 1.5 equiv.), Cs_2CO_3 (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt; [b]Isolated yield.

Scheme 4.19. Synthesis of nitriles from aldehydes

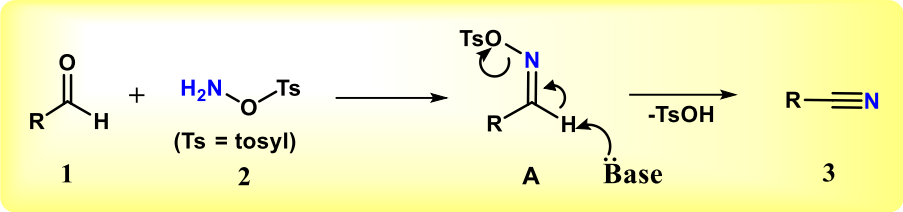
Similarly, 4-hydroxy-3-methoxybenzonitrile was isolated with 70% of yield. Tolerance of reactive functional groups, such as free hydroxyl group (**1h** and **1j**), an ether (**1n**), and a triple bond (**1o**) with a quantitative yield of nitriles described the mildness of this reaction condition. Next, we examined *N*-protected indole (**1p**) which behaved very well. We next explored the scope of *α,β*-unsaturated aldehydes, a simple as well as substituted cinnamaldehydes with electronically rich (-OMe, **1r**) and electronically deficient (-NO_2, **1s**) were converted to nitriles (**3r-s**) in excellent yields. It is noteworthy that in these cases no Michael adduct was observed. To our pleasure, aliphatic aldehydes embedded with an aryl (**1t**), simple chain (**1u**), and containing double bond (**1v**) also smoothly afforded the corresponding nitriles (**3t-3v**) in good yield depicting the versatility of this method. Heteroatomic substrate (**1w**) was also well tolerated under these reaction conditions. The favorable results found in mmol scale motivated us to further examine the scalabiliy of this method. This cynation reaction has been examined for its practical use by employing gram-scale transformation of aldehyde **1g** to nitrile **3g** in quantitative yield (Scheme 4.20).



Scheme 4.20. Production of nitrile at gram scales

4.5 Plausible reaction mechanism

A plausible reaction mechanism for nitrile synthesis is described in Scheme 4.21. At first, *in situ* generated *O*-tosylhydroxylamine reacted with aldehydes, generating *O*-protected aldoxime intermediate **A** which experiences proton abstraction in presence of base followed by removal of tosyl group to provide the desired nitrile.



Scheme 4.21. Proposed reaction mechanism for nitrile formation

4.6 Conclusion

We have demonstrated the direct synthesis of nitriles using commercially available TsONHBoc reagent from readily available aldehydes. This tandem chemistry of *in situ* nitrogen insertion appears to have a considerably higher scope than the use of isolated active aminating agents. This metal-free method provided rapid access to the desired products with high yield and scalable quantity.

4.7 Experimental section

4.7.1 General Information

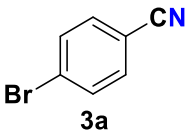
Unless otherwise stated, all the reactions were carried out using oven dried glassware under an open atmosphere in a round bottom flask with magnetic stirring bar at room temperature. Ketones were used as received without further purification. The aminating reagents were also prepared by following reported literature. TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}) and the spots were visualized with UV light or by charring the plates dipped in PMA or Ninhydrin or DNP solution. The compounds were purified by flash column chromatography using silica gel (100-200 mesh) with distilled solvents (EtOAc:Hexane) as mobile phase otherwise mentioned. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz instruments respectively in $CDCl_3$ or DMSO-d_6 solvents. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, DMSO-d_6: δ H = 2.5 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

4.7.2 General Procedure for the synthesis of nitriles from aldehydes

In an open round bottom flask aldehydes (0.5 mmol, 1.0 equiv.) and aminating agent (0.75 mmol, 1.5 equiv.) were dissolved in TFE solvent (0.5 mL) at room temperature for 2-3 h. After the formation of aldoxime (monitored by TLC), Cs_2CO_3 (1.5 equiv) was added, and the reaction mixture was stirred again at room temperature for the duration of time shown in Scheme 3. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate (15 mL), the organic layer was washed with brine solution (5 mL), and the organic layer was dried over anhydrous Na_2SO_4. After removal of all the volatiles, the crude product was purified using column chromatography with EtOAc/hexane as the eluent.

4.8 Characterization of the products

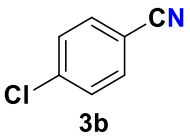
4-Bromobenzonitrile **(3a):** Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (64 mg, 70% yield; m. p. = 107-110 °C) whose spectral data were consistent with the literature values.[26]



3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H).

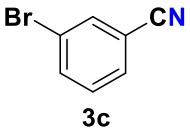
4-Chlorobenzonitrile **(3b):** Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (47 mg, 68% yield; m. p. = 86-90 °C) whose spectral data were consistent with the literature values.[26]



3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.65, 133.48, 129.80, 118.05, 110.90.

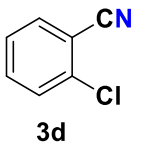
3-Bromobenzonitrile **(3c):** Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (59 mg, 65% yield; m. p. = 35-38 °C) whose spectral data were consistent with the literature values.[26]



3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H).

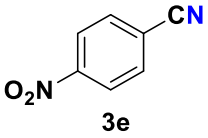
2-Chlorobenzonitrile **(3d):** Prepared according to general procedure and crude was purified by silica gel column choromatography (hexane/ethyl acetate = 20:1, v/v) afforded the titled compound as white solid (65 mg, 95% yield; m. p. = 36-40 °C) whose spectral data were consistent with the literature values.[27]



3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.59-7.47 (m, 2H), 7.42-7.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.95, 134.11, 133.99, 130.15, 127.26, 116.05, 113.48.

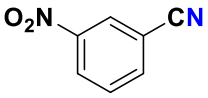
***4-Nitrobenzonitrile* (3e):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled compound as yellow solid (73 mg, 98% yield; m. p. = 144-147 °C) whose spectral data were consistent with the literature values.[28]



3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.13, 133.60, 124.40, 118.43, 116.92.

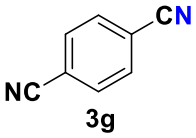
***3-Nitrobenzonitrile* (3f):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled compound as yellow solid (71 mg, 96% yield; m. p. = 112-114 °C) whose spectral data were consistent with the literature values.[29]



3f

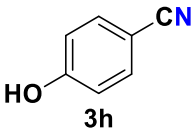
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.47 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.30, 137.71, 130.78, 127.61, 127.28, 116.62, 114.17.

***Terephthalonitrile* (3g):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (61 mg, 95% yield; m. p. = 210-212 °C) whose spectral data were consistent with the literature values.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.91, 117.13, 116.83.



3g

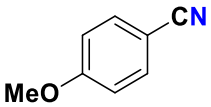
***4-Hydroxybenzonitrile* (3h):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1, v/v) afforded the titled compound as brown solid (41 mg, 69% yield; m. p. = 95-96 °C) whose spectral data were consistent with the literature values.[28]



3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.28, 134.46, 119.38, 116.59, 103.23.

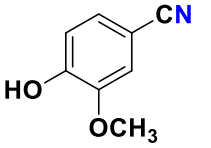
4-Methoxybenzonitrile **(3i):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (53 mg, 80% yield; m. p. = 55-58 °C) whose spectral data were consistent with the literature values.[26]



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 2H), 6.93-6.90 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.86, 133.94, 119.23, 114.77, 103.86, 55.55.

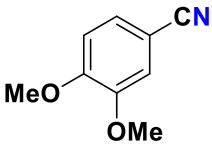
4-Hydroxy-3-methoxybenzonitrile **(3j):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (52 mg, 70% yield; m. p. = 84-86 °C) whose spectral data were consistent with the literature values.[30]



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.19 (br s, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.04, 146.77, 127.10, 119.37, 115.34, 113.88, 103.35, 56.34.

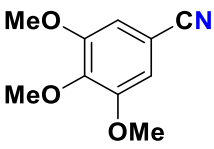
3,4-Dimethoxybenzonitrile **(3k):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (59 mg, 72% yield; m. p. = 65-67 °C) whose spectral data were consistent with the literature values.[27]



3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 1H), 7.06 (d, *J* = 1.9 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.96, 149.28, 126.55, 119.31, 114.02, 111.33, 103.98, 56.22, 56.18.

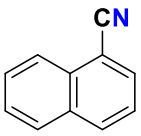
3,4,5-Trimethoxybenzonitrile **(3l):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (88 mg, 91% yield; m. p. = 92-94 °C) whose spectral data were consistent with the literature values.[31]



3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2H), 3.86 (s, 3H), 3.84 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.58, 142.34, 118.99, 109.47, 106.72, 61.05, 56.41.

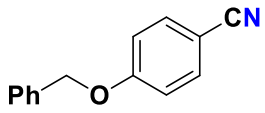
1-Naphthonitrile (**3m**): Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as a brown oil (66 mg, 86% yield) whose spectral data were consistent with the literature values.[26]



3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.92 (t, *J* = 6.5 Hz, 2H), 7.72-7.67 (m, 1H), 7.65-7.59 (m, 1H), 7.58-7.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.39, 133.03, 132.74, 132.46, 128.77, 128.71, 127.66, 125.25, 125.03, 117.93, 110.29.

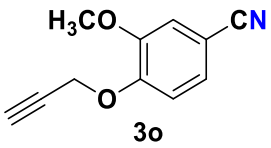
4-(Benzyloxy)benzonitrile **(3n):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as white solid (73 mg, 70% yield; m. p. = 85-87 °C) whose spectral data were consistent with the literature values.[29]



3n

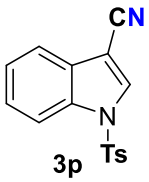
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.50-7.30 (m, 5H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.07, 135.80, 134.12, 128.88, 128.53, 127.58, 119.28, 115.70, 104.32, 70.39.

3-Methoxy-4-(prop-2-yn-1-yloxy)benzonitrile **(3o):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled compound as white solid (65.5 mg, 70% yield; m. p. = 64-67 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1H), 7.21-7.01 (m, 2H), 4.83 (s, 2H), 3.90 (s, 3H), 2.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.65, 149.76, 126.15, 119.10, 114.55, 113.67, 105.17, 77.35, 76.94, 56.70, 56.26. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{11}H_{10}NO_2]^+$ 188.0706, found 188.0712



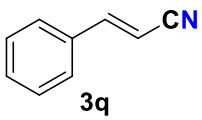
3o

1-Tosyl-1H-indole-3-carbonitrile **(3p):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1, v/v) afforded the titled compound as white solid (135 mg, 91% yield; m. p. = 155-157 °C) whose spectral data were consistent with the literature values.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.50, 134.25, 133.79, 133.27, 130.52, 128.47, 127.36, 126.65, 124.91, 120.42, 113.92, 113.61, 93.80, 21.81.



3p

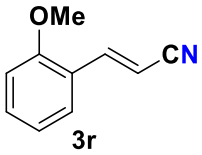
Cinnamonitrile **(3q):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as colourless oil (42 mg, 65% yield) whose spectral data were consistent with the literature values.[29]



3q

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.37 (m, 6H), 5.87 (d, *J* = 16.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.64, 133.58, 131.29, 129.19, 127.43, 118.24, 96.40.

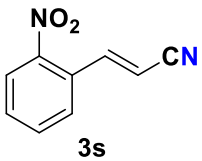
(E)-3-(2-methoxyphenyl)acrylonitrile **(3r):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled compound as yellowish solid (48 mg, 60% yield; m. p. = 88-90 °C) whose spectral data were consistent with the literature values.[32]



3r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.8 Hz, 1H), 7.42-7.34 (m, 2H), 6.99-6.92 (m, 2H), 6.05 (d, *J* = 16.8 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.28, 146.51, 132.41, 128.99, 122.54, 120.88, 119.09, 111.36, 96.96, 55.60.

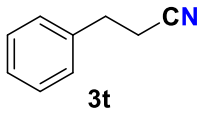
(E)-3-(2-nitrophenyl)acrylonitrile **(3s):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1, v/v) afforded the titled compound as yellowish solid (59 mg, 68% yield; m. p. = 88-90 °C) whose spectral data were consistent with the literature values.[29]



3s

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 16.3 Hz, 1H), 7.71-7.57 (m, 3H), 5.86 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.52, 146.69, 134.16, 131.43, 129.67, 128.81, 125.36, 117.04, 101.57.

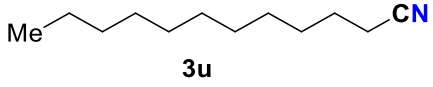
3-Phenylpropanenitrile **(3t):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as colorless oil 46 mg, 70% yield) whose spectral data were consistent with the literature values.[28]



3t

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.15, 128.96, 128.35, 127.32, 119.23, 31.65, 19.42.

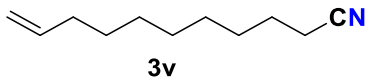
Dodecanenitrile **(3u):** Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as colorless oil (54 mg, 60% yield) whose spectral data were consistent with the literature values.[26]



3u

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (t, *J* = 7.1 Hz, 2H), 1.64 (p, *J* = 7.2 Hz, 2H), 1.49-1.37 (m, 2H), 1.35-1.17 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.93, 31.97, 29.63, 29.58, 29.38, 28.85, 28.74, 25.46, 22.75, 17.19, 14.17.

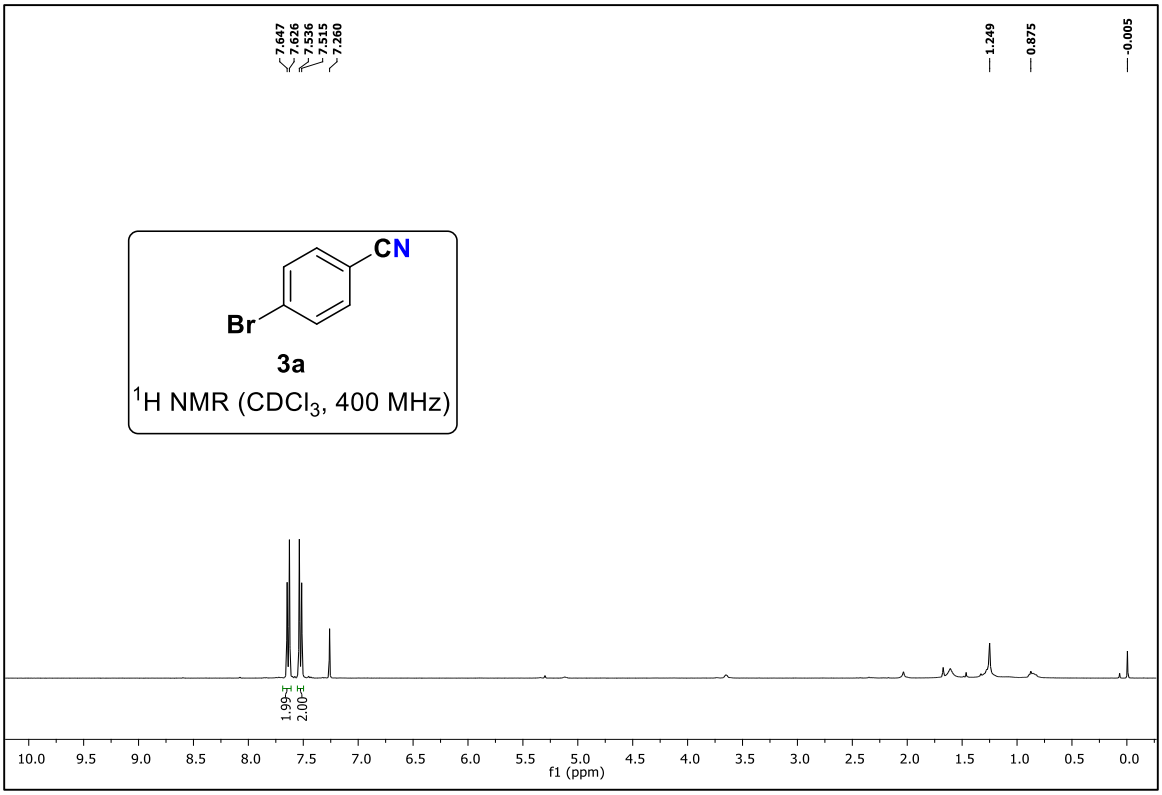
Undec-10-enenitrile (3v): Prepared according to general procedure and crude was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1, v/v) afforded the titled compound as colorless oil (52 mg, 62% yield) whose spectral data were consistent with the literature values.[33]

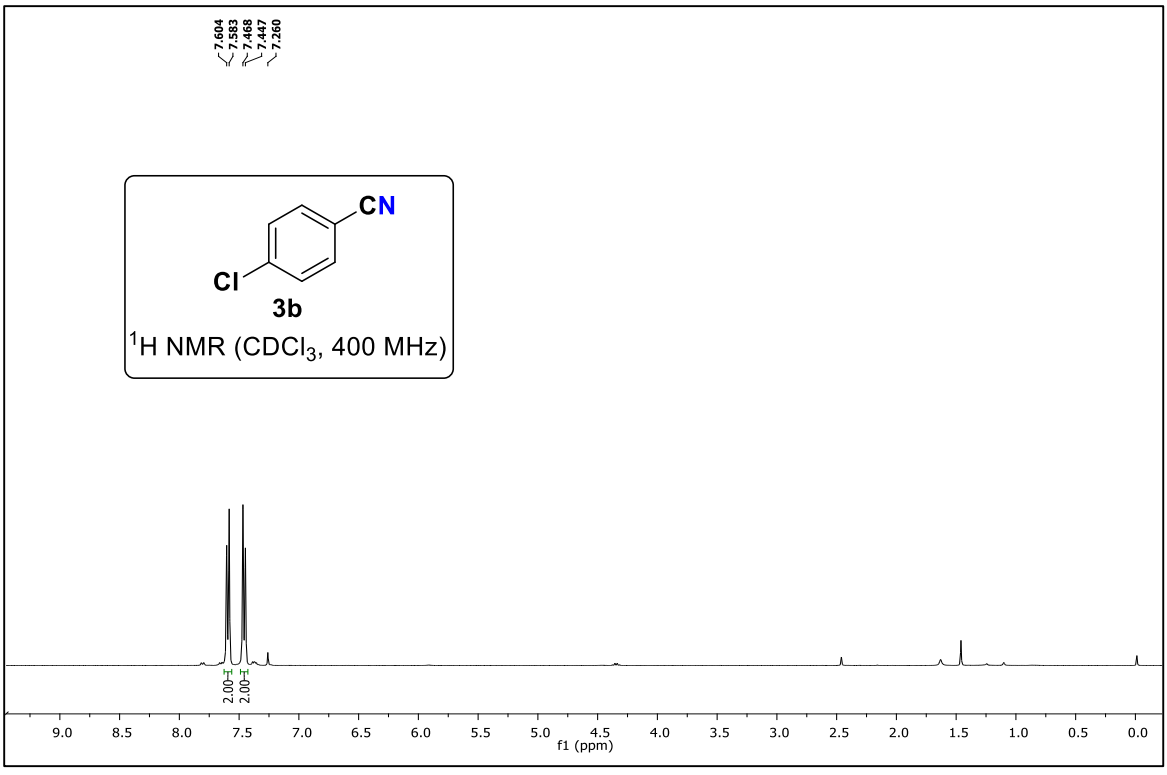


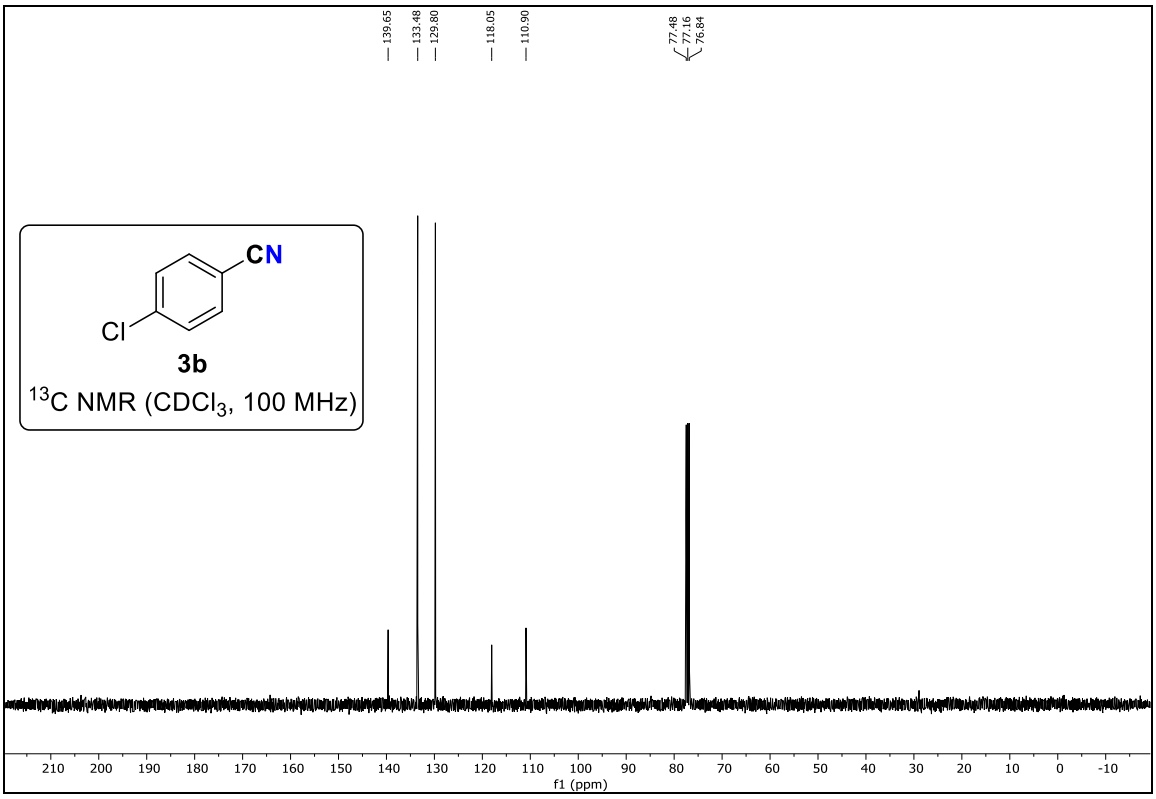
3v

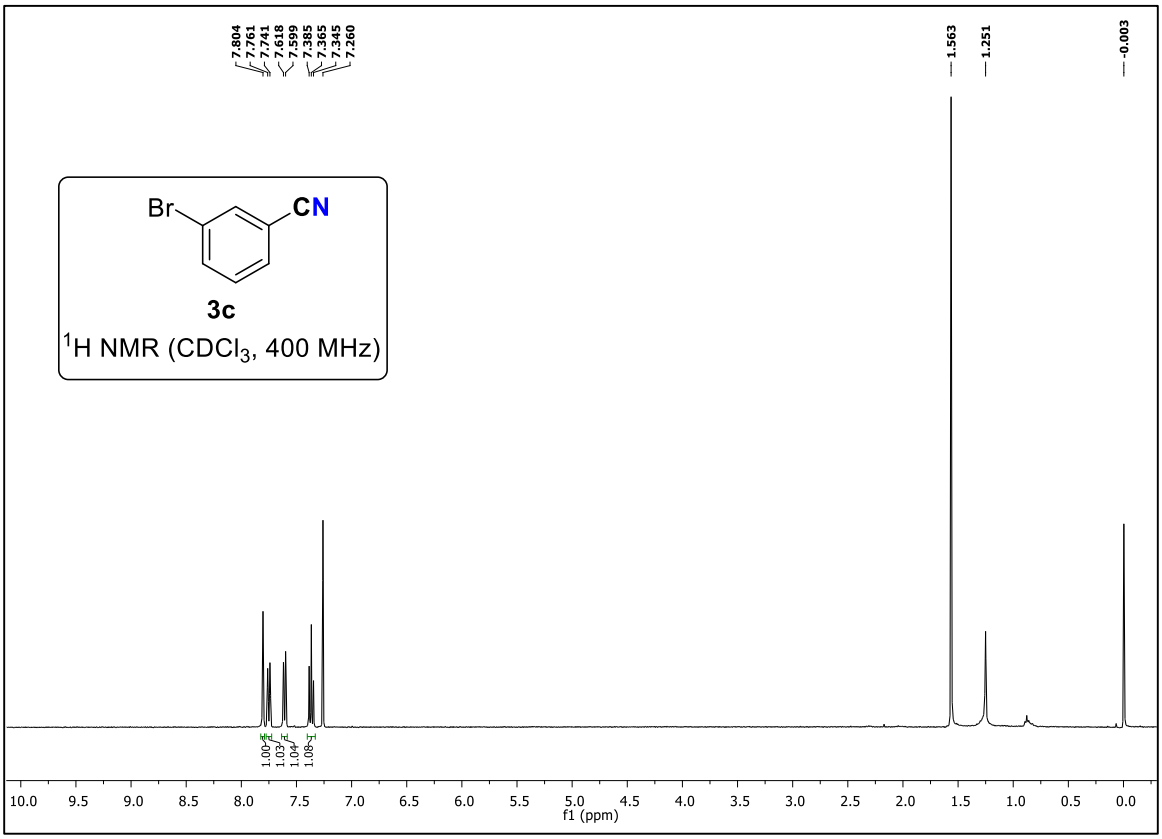
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01-4.91 (m, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 2.07-1.98 (m, 2H), 1.69 – 1.60 (m, 2H), 1.47-1.29 (m, 10H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.72 (m, 1H), 5.05-4.87 (m, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 2.10-1.97 (m, 2H), 1.71-1.60 (m, 2H), 1.47-1.28 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.17, 119.97, 114.36, 33.85, 29.25, 29.06, 28.94, 28.83, 28.76, 25.47, 17.24.

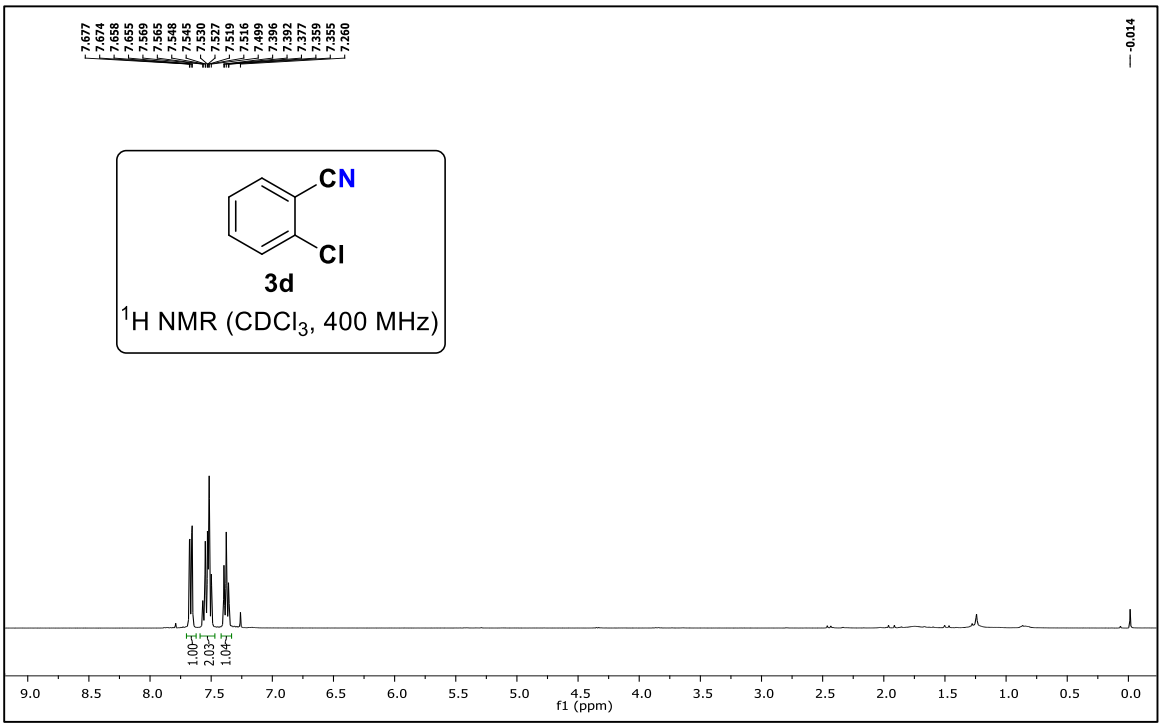
4.9 ^{1}H, ^{13}C NMR of the products

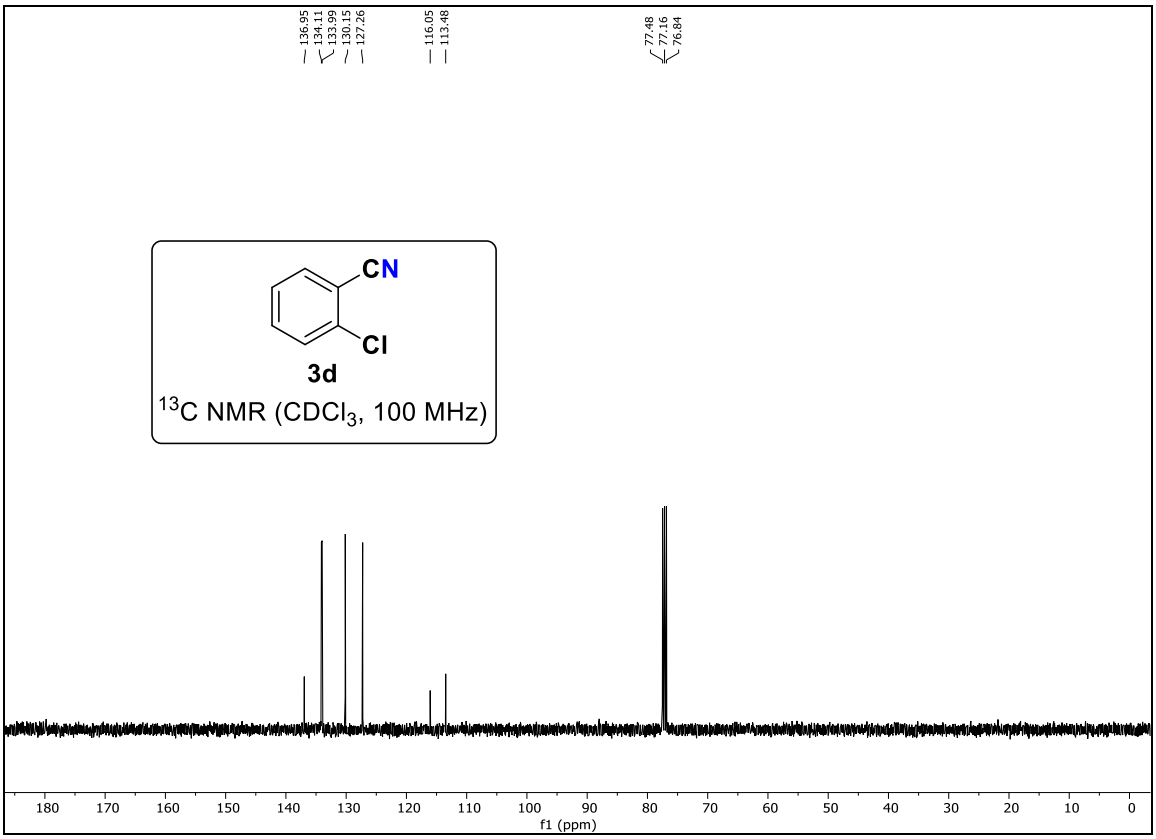


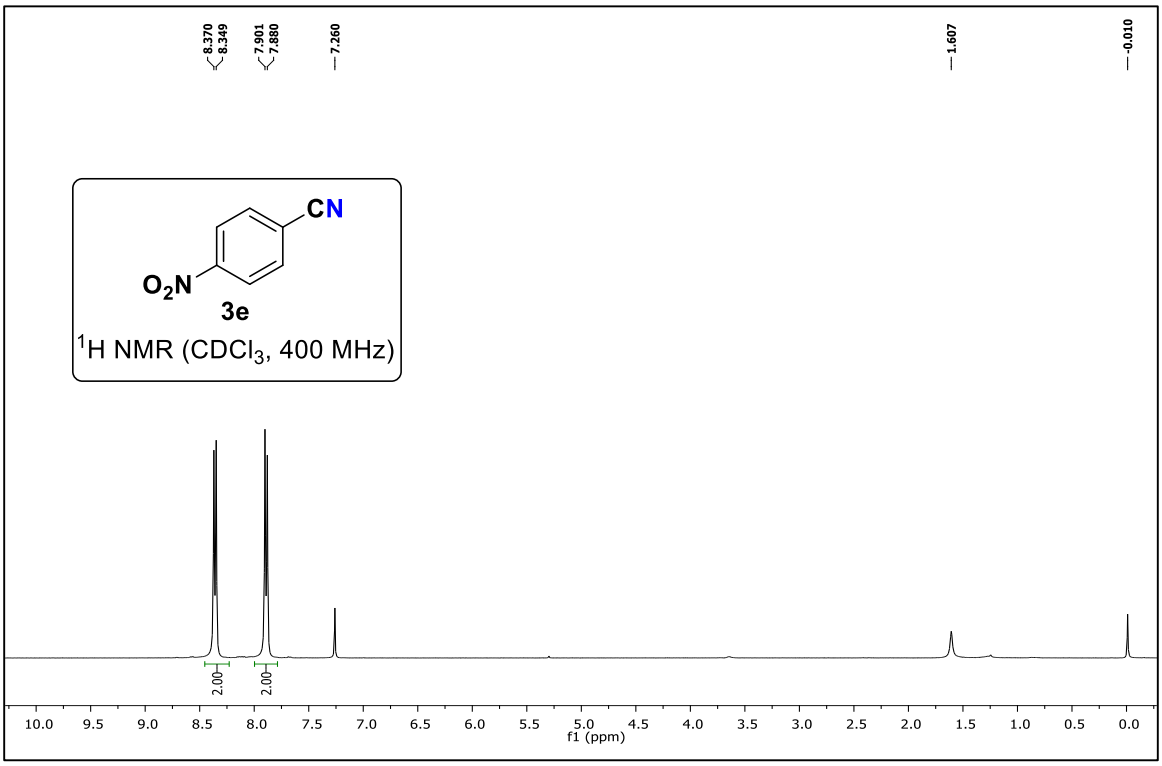



139.65
133.48
129.80
118.05
110.90
77.48
77.16
76.84
CN
Cl
3b
^{13}C NMR ($CDCl_3$, 100 MHz)
f1 (ppm)


7.804
7.761
7.741
7.618
7.599
7.385
7.365
7.345
7.260
1.563
1.251
-0.003
Br
CN
3c
^{1}H NMR ($CDCl_3$, 400 MHz)
1.00
1.03
1.04
1.08
f1 (ppm)


7.677
7.674
7.658
7.655
7.569
7.565
7.548
7.545
7.530
7.527
7.519
7.516
7.499
7.396
7.392
7.377
7.359
7.355
7.260
-0.014
CN
Cl
3d
^{1}H NMR ($CDCl_3$, 400 MHz)
1.00
2.03
1.04
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


136.95
134.11
133.99
130.15
127.26
116.05
113.48
77.48
77.16
76.84
CN
Cl
3d
^{13}C NMR ($CDCl_3$, 100 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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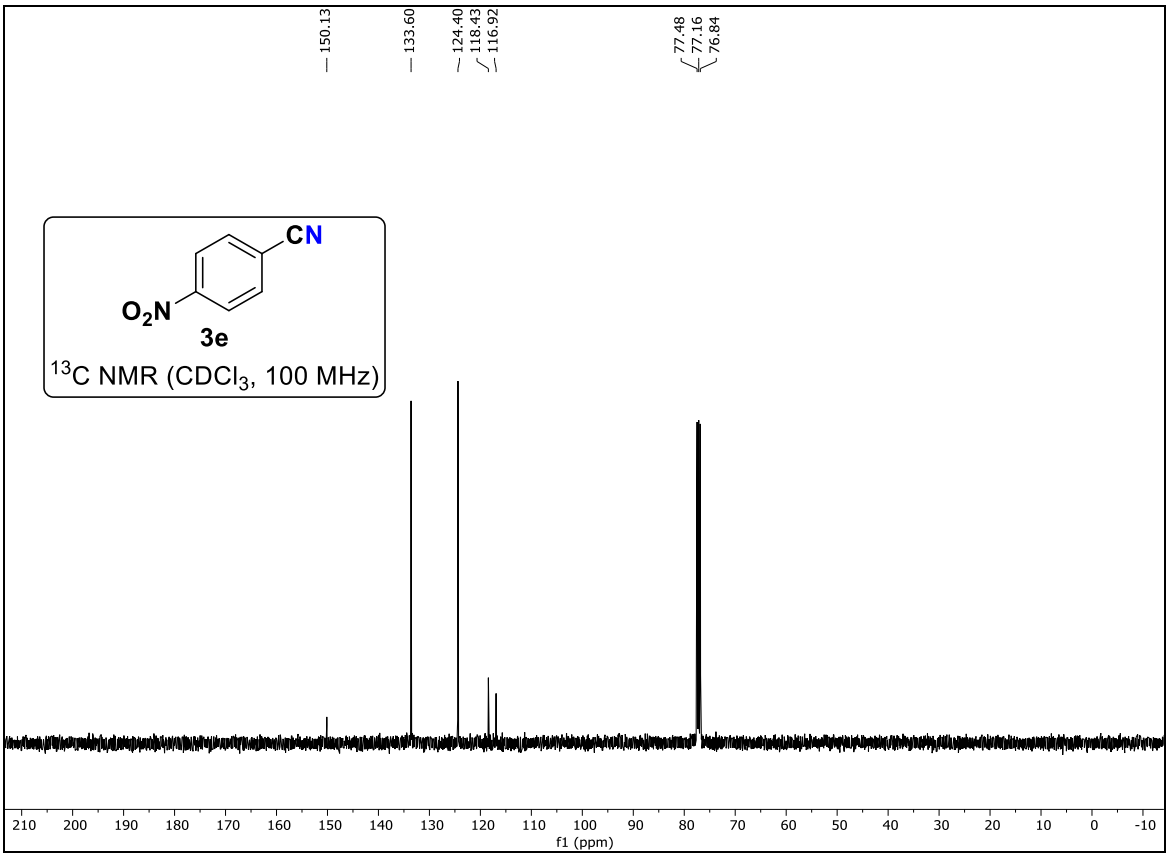
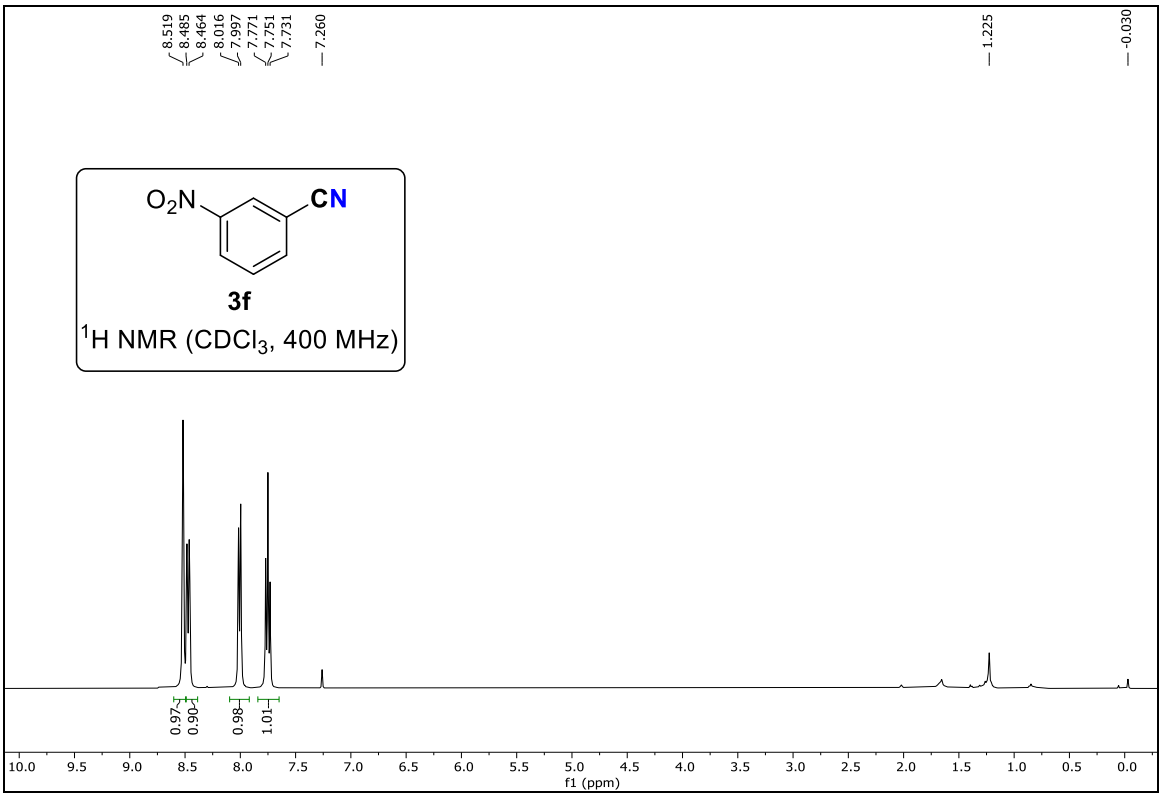
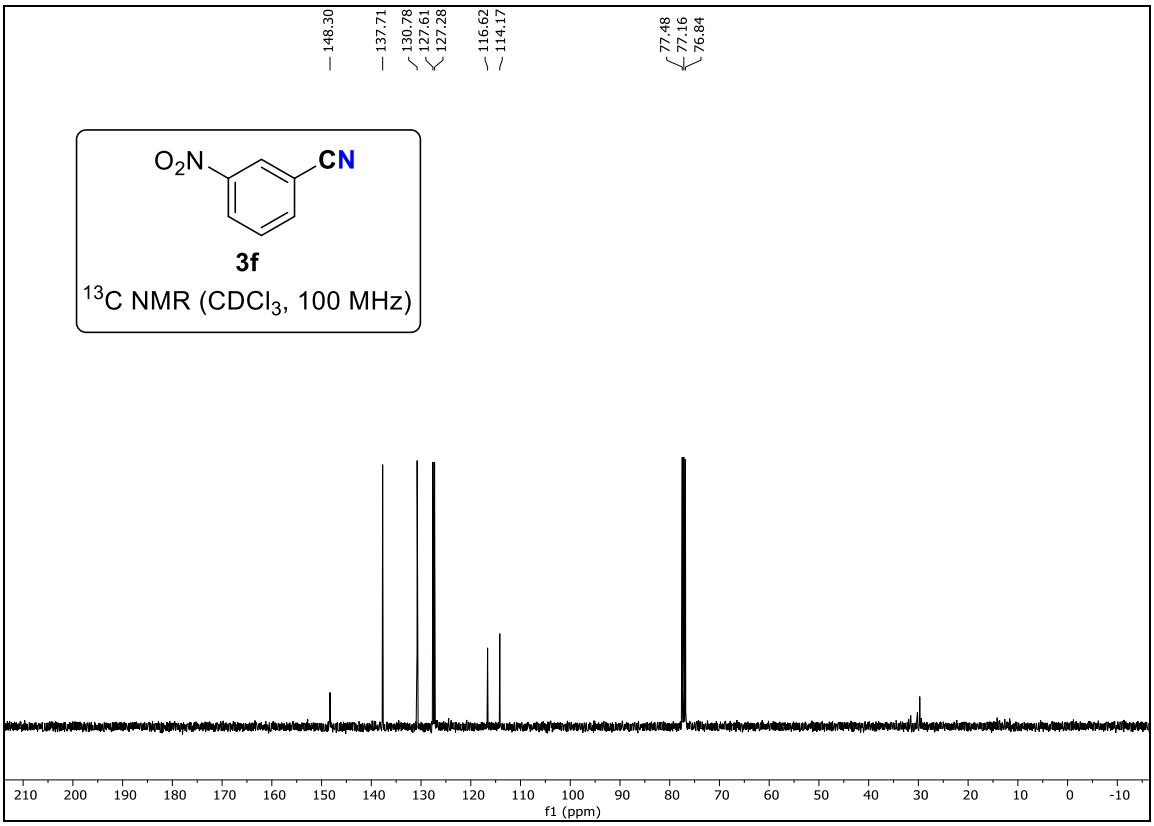
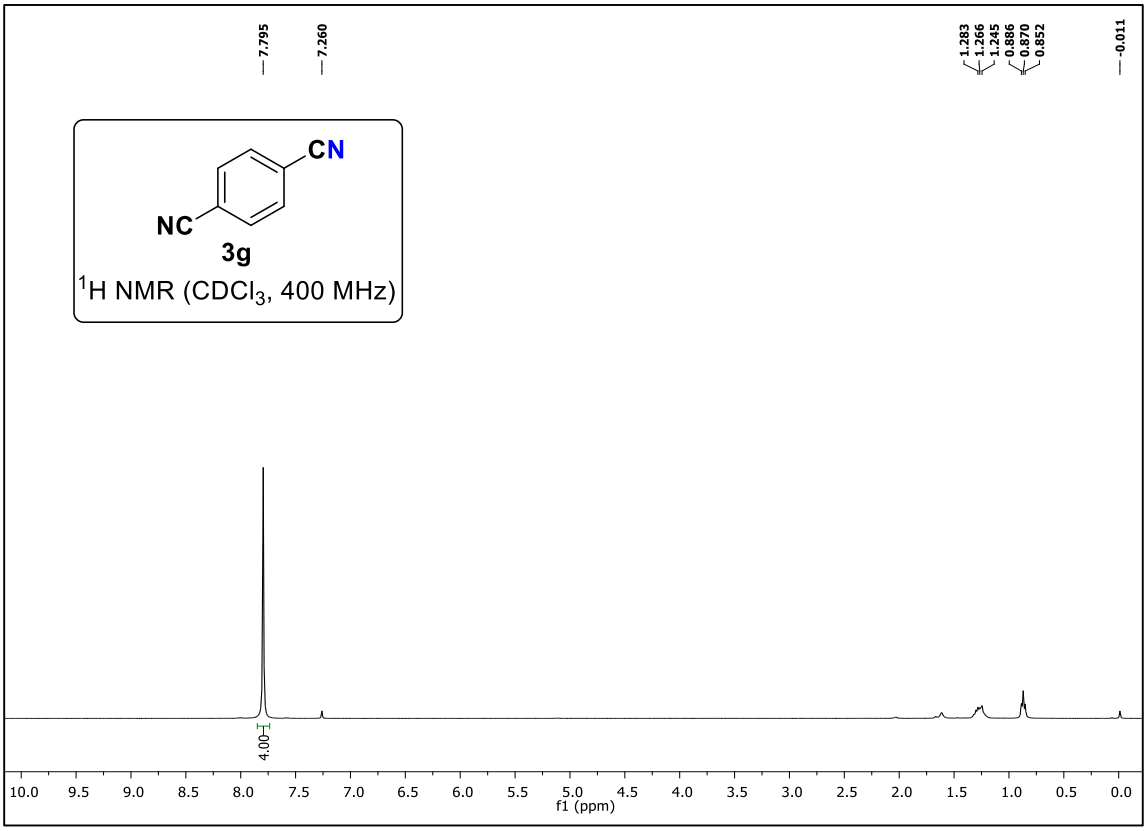
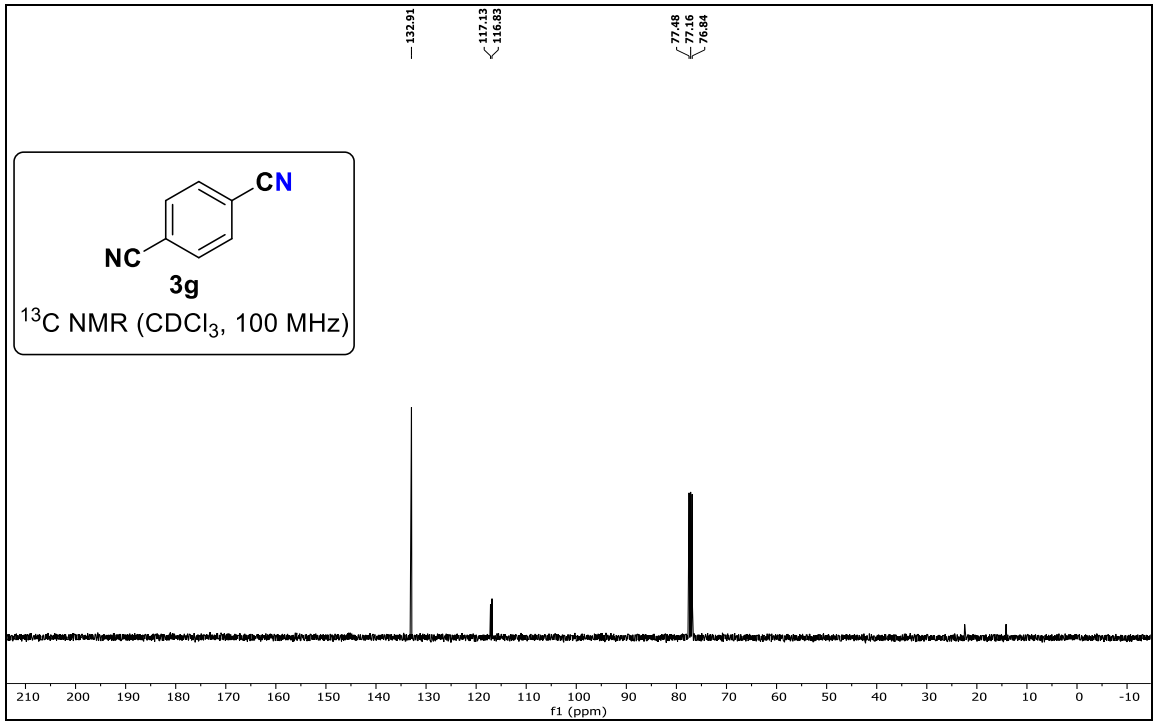
8.349
7.901
7.880
7.260
1.607
-0.010
CN
O2N
3e
1H NMR (CDCl3, 400 MHz)
2.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

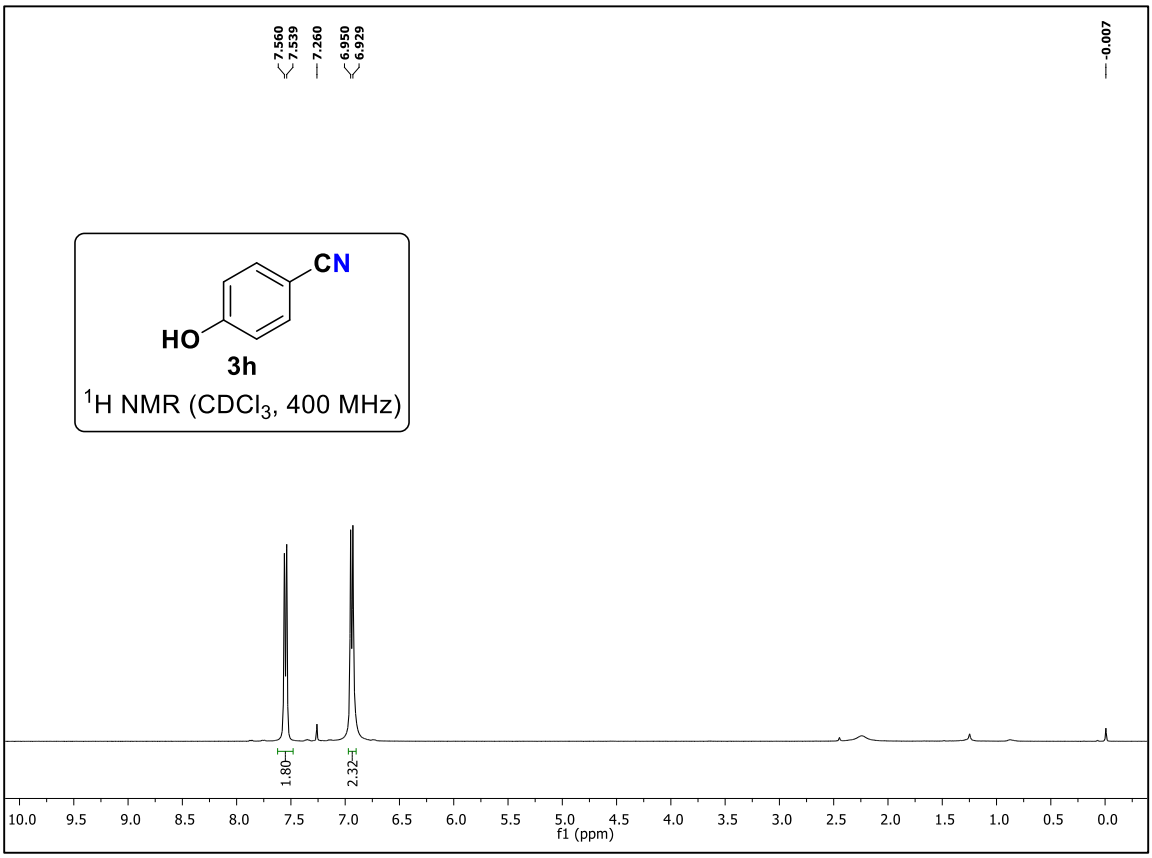

150.13
133.60
124.40
118.43
116.92
77.48
77.16
76.84
CN
O2N
3e
13C NMR (CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

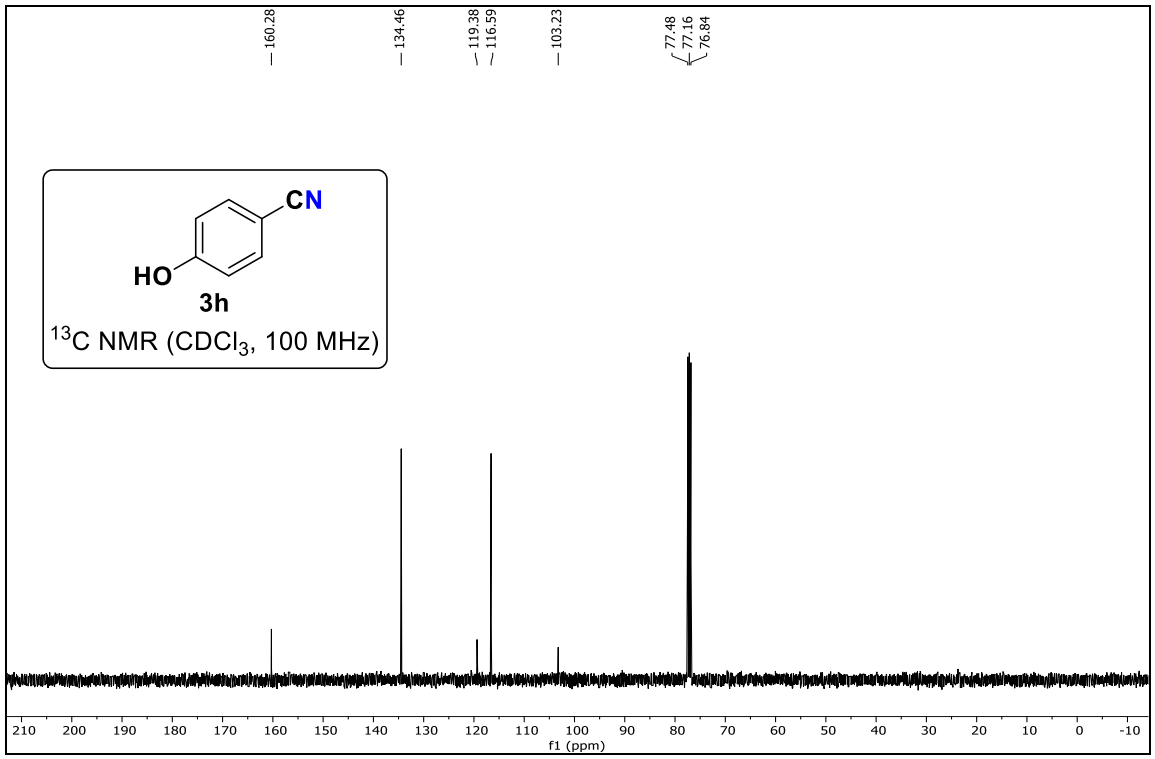

8.519
8.485
8.464
8.016
7.997
7.771
7.751
7.731
7.260
1.225
-0.030
O2N
CN
3f
1H NMR (CDCl3, 400 MHz)
0.97
0.90
0.98
1.01
f1 (ppm)

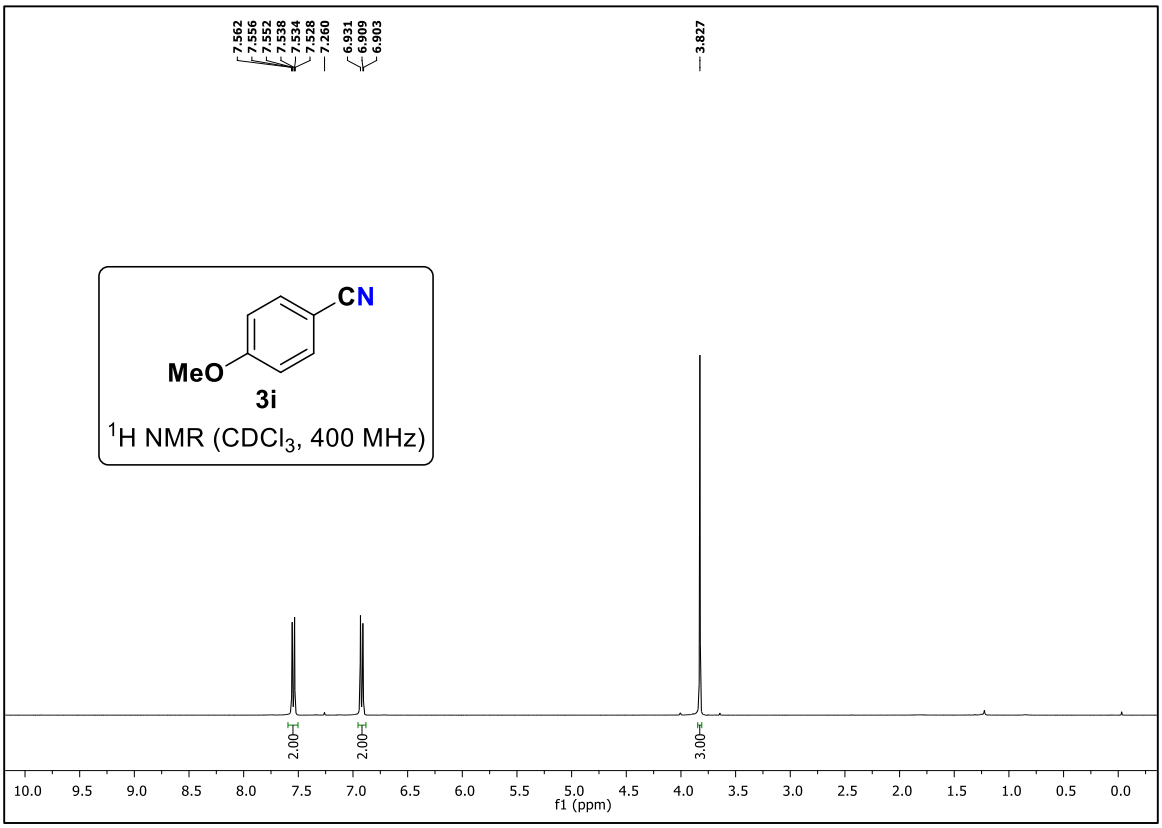

148.30
137.71
130.78
127.61
127.28
116.62
114.17
77.48
77.16
76.84
O2N
CN
3f
13C NMR (CDCl3, 100 MHz)
f1 (ppm)

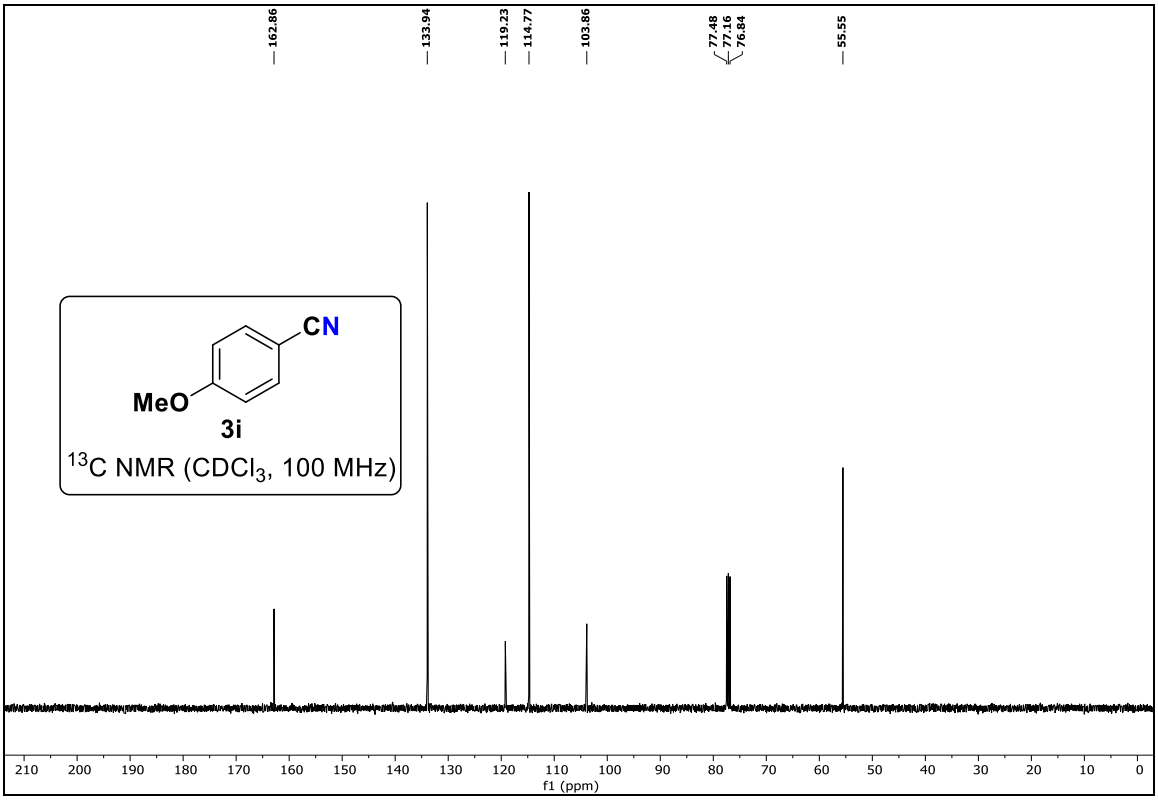

7.795
7.260
1.283
1.266
1.245
0.886
0.870
0.852
-0.011
CN
NC
3g
^{1}H NMR ($CDCl_3$, 400 MHz)
4.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

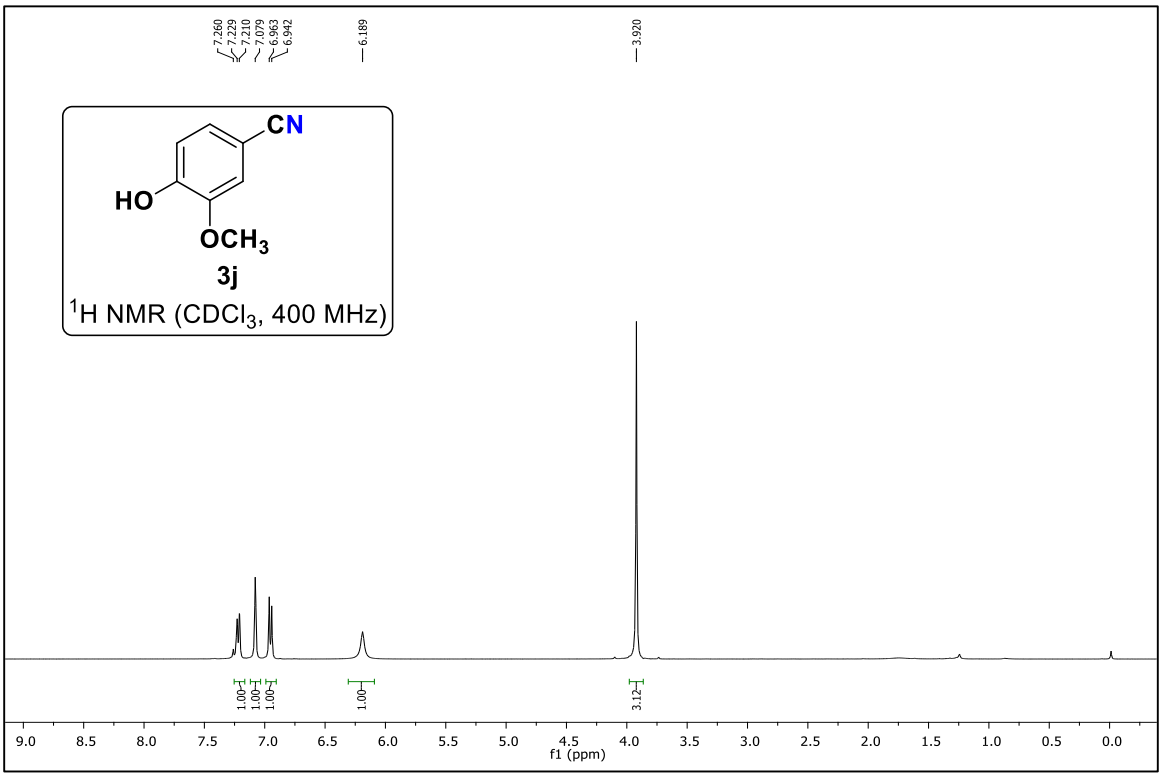

132.91
117.13
116.83
77.48
77.16
76.84
CN
NC
3g
^{13}C NMR ($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

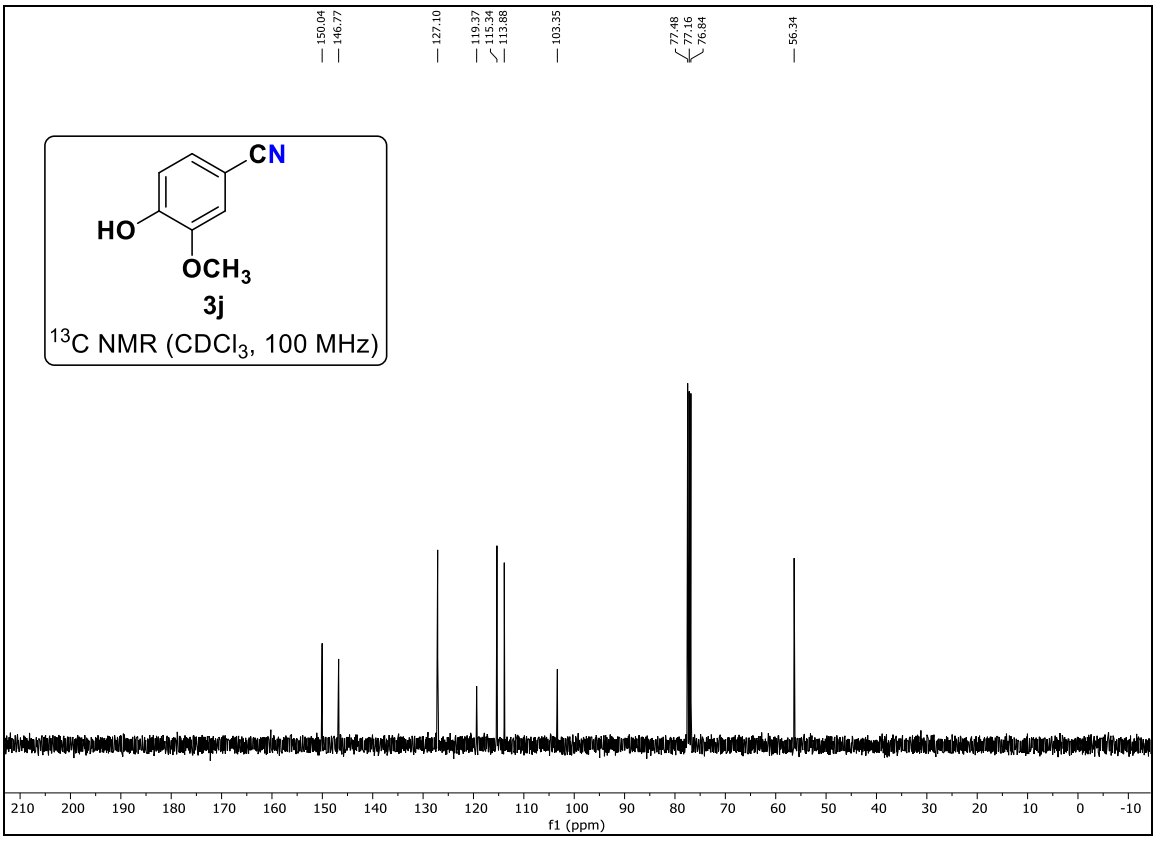

7.560
7.539
7.260
6.950
6.929
-0.007
CN
HO
3h
^{1}H NMR ($CDCl_3$, 400 MHz)
1.80
2.32
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

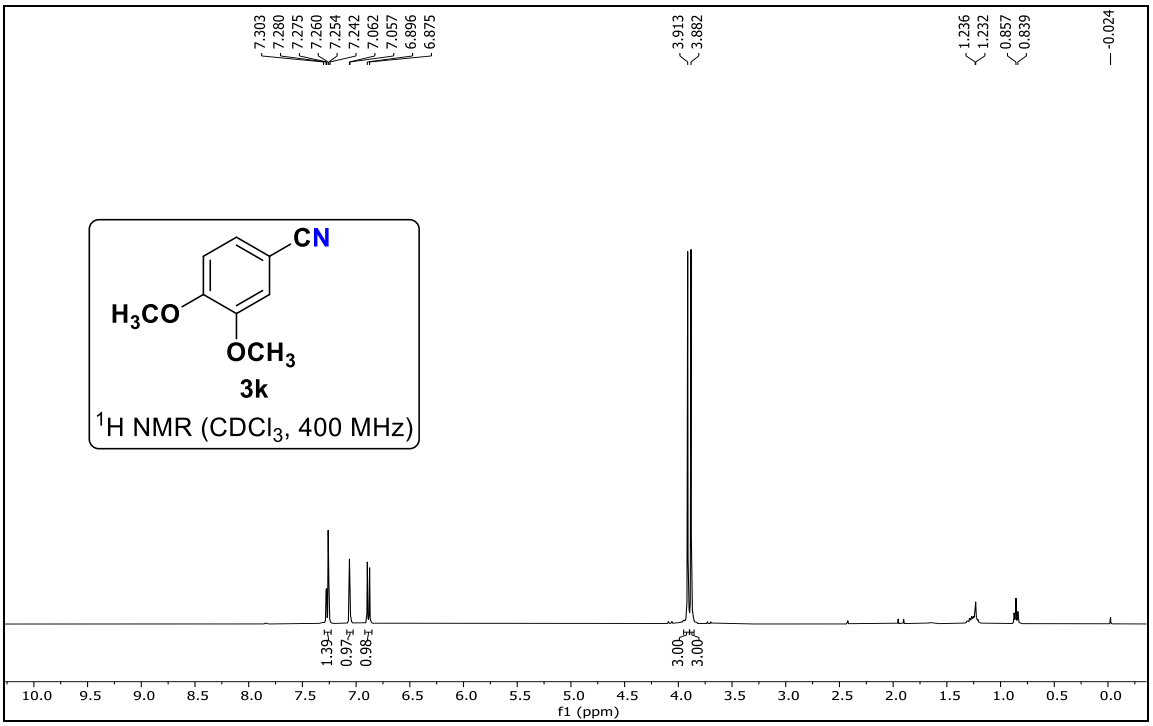

160.28
134.46
119.38
116.59
103.23
77.48
77.16
76.84
CN
HO
3h
^{13}C NMR ($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

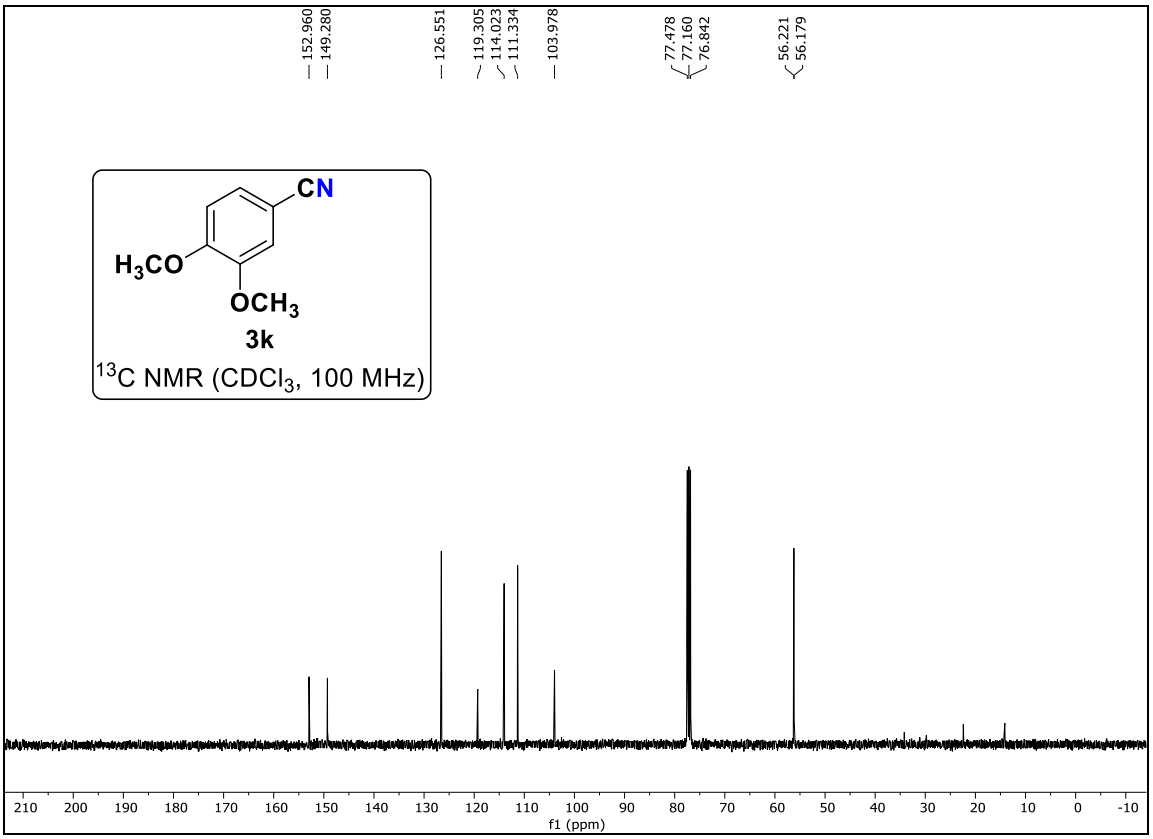

7.562
7.556
7.552
7.538
7.534
7.528
7.260
6.931
6.909
6.903
3.827
CN
MeO
3i
^{1}H NMR (CDCl$_3$, 400 MHz)
2.00
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

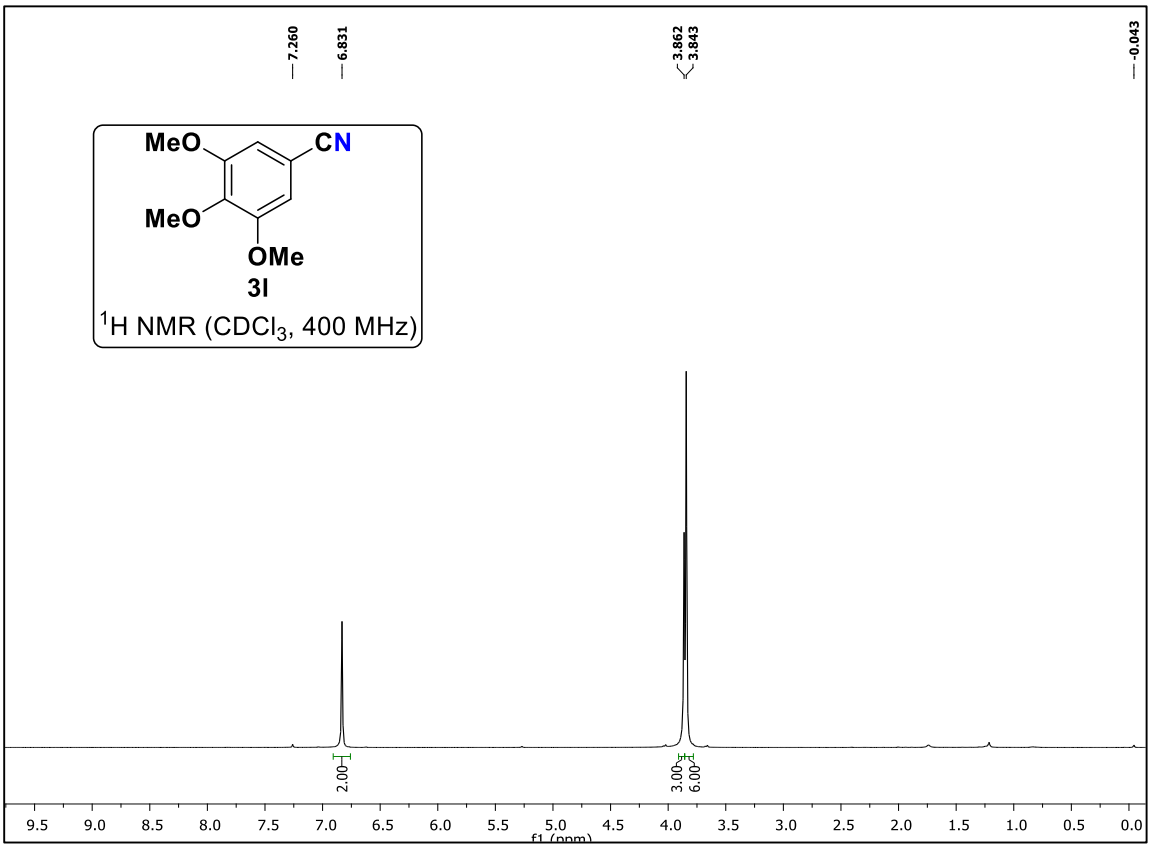

162.86
133.94
119.23
114.77
103.86
77.48
77.16
76.84
55.55
CN
MeO
3i
^{13}C NMR (CDCl$_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

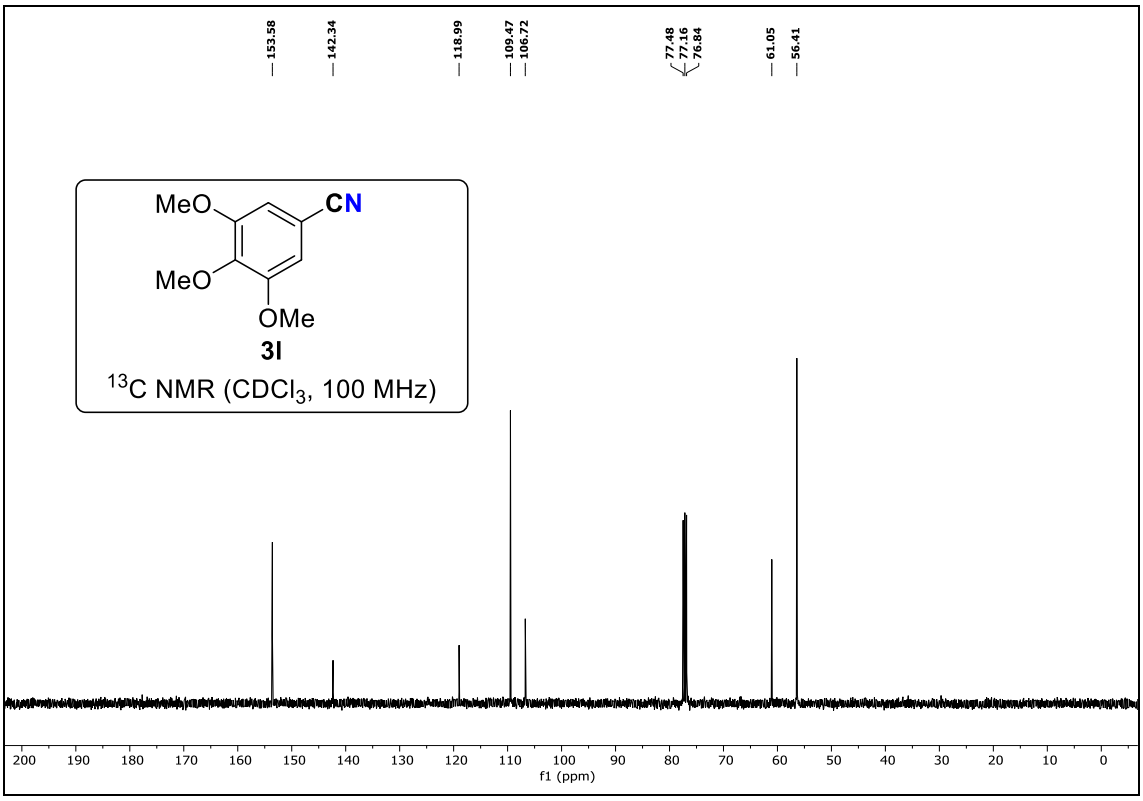

7.260
7.229
7.210
7.079
6.965
6.942
6.189
3.920
CN
HO
OCH3
3j
1H NMR (CDCl3, 400 MHz)
1.00
1.00
1.00
1.00
3.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

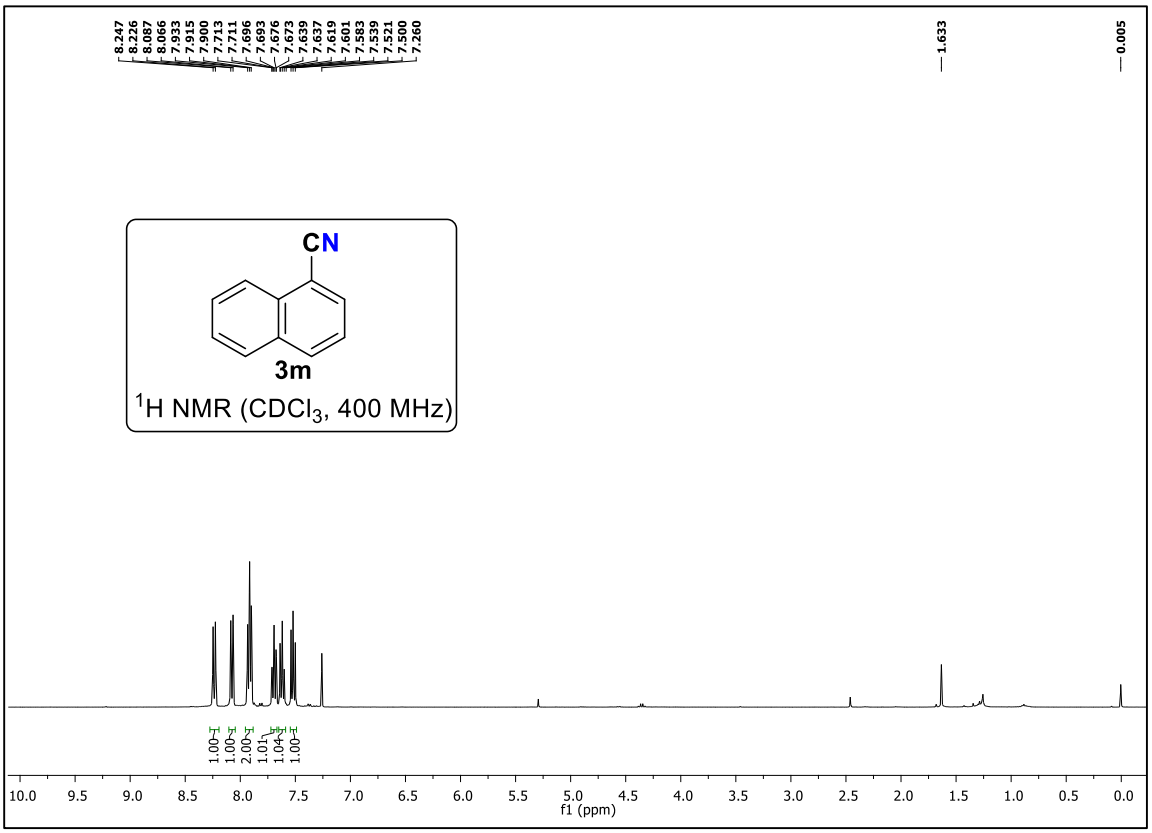

150.04
146.77
127.10
119.37
115.34
113.88
103.35
77.48
77.16
76.84
56.34
CN
HO
OCH3
3j
13C NMR (CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

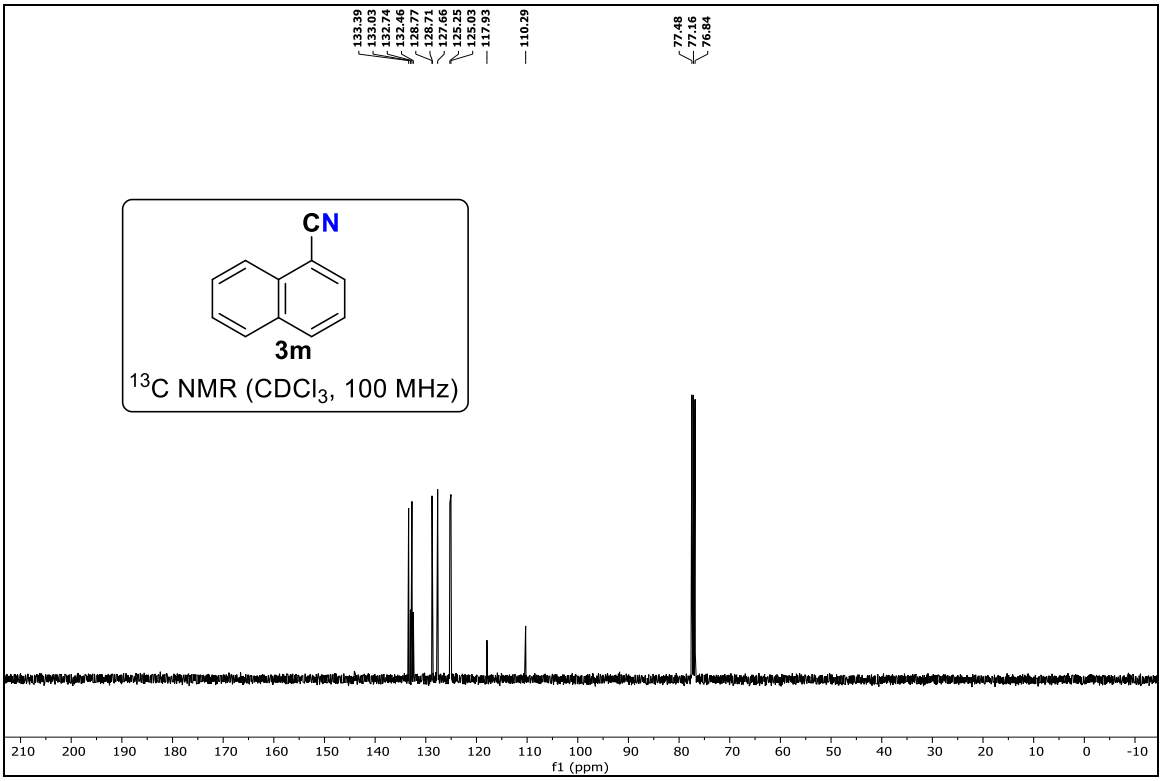

7.303
7.280
7.275
7.260
7.254
7.242
7.062
7.057
6.896
6.875
3.913
3.882
1.236
1.232
0.857
0.839
-0.024
CN
H3CO
OCH3
3k
1H NMR (CDCl3, 400 MHz)
1.39
0.97
0.98
3.00
3.00
f1 (ppm)

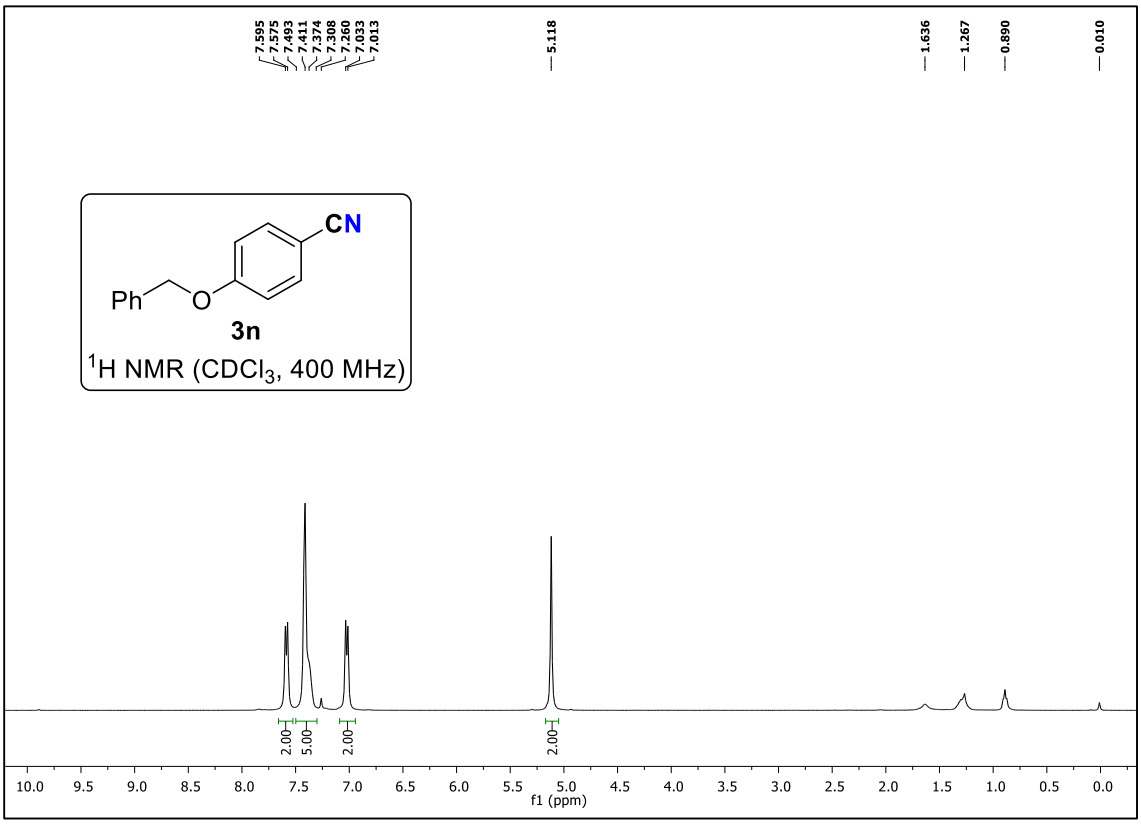

152.960
149.280
126.551
119.305
114.023
111.334
103.978
77.478
77.160
76.842
56.221
56.179
CN
H3CO
OCH3
3k
13C NMR (CDCl3, 100 MHz)
f1 (ppm)

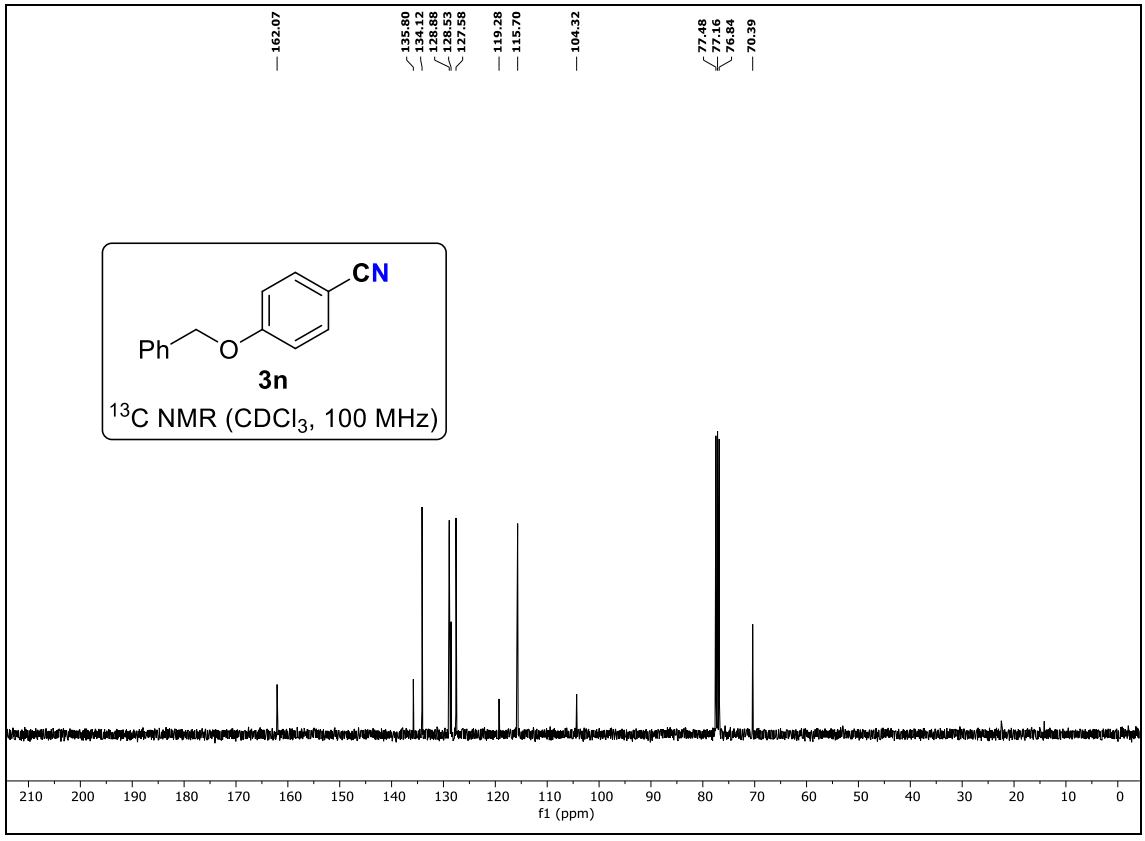

7.260
6.831
3.862
3.843
-0.043
MeO
CN
MeO
OMe
3l
^{1}H NMR (CDCl$_3$, 400 MHz)
2.00
3.00
6.00
f1 (ppm)

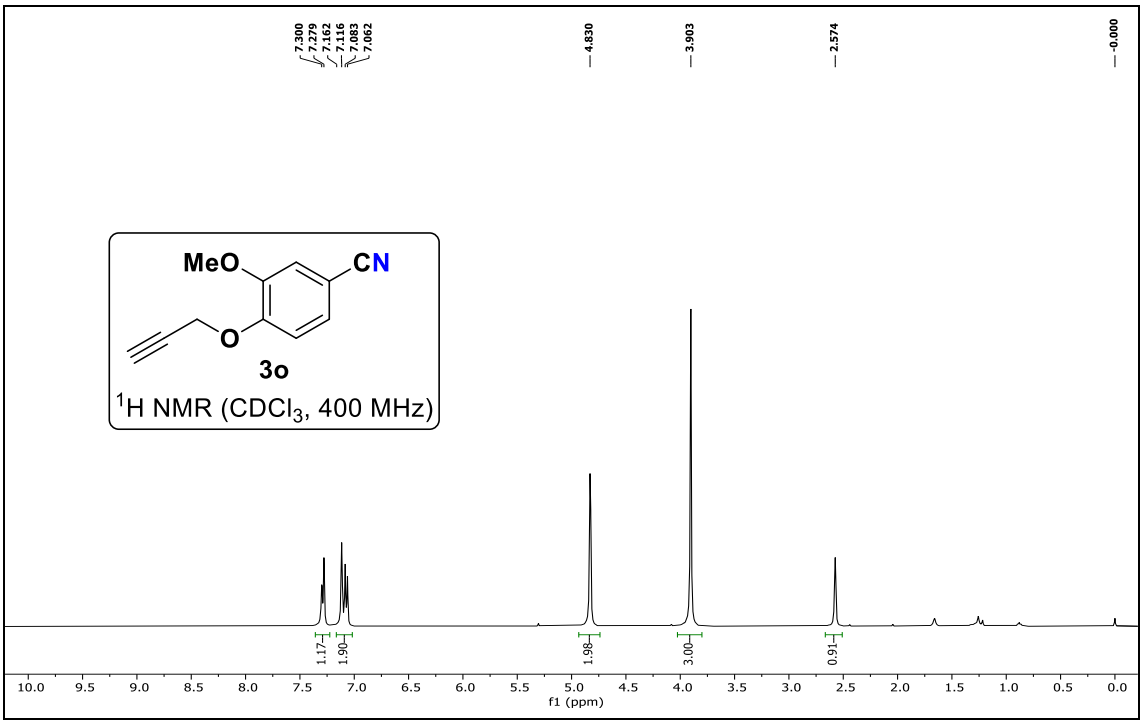

153.58
142.34
118.99
109.47
106.72
77.48
77.16
76.84
61.05
56.41
MeO
CN
MeO
OMe
3l
^{13}C NMR (CDCl$_3$, 100 MHz)
f1 (ppm)

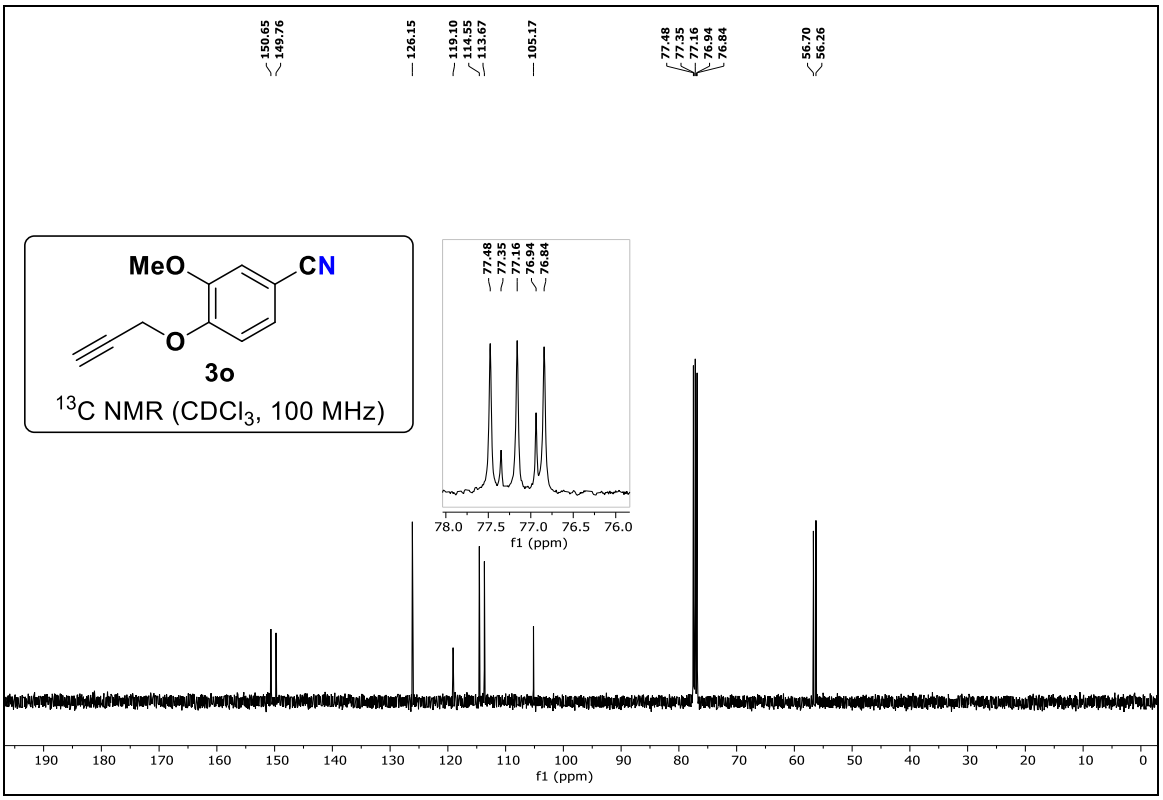

8.247
8.226
8.087
8.066
7.933
7.915
7.900
7.713
7.711
7.696
7.693
7.676
7.673
7.639
7.637
7.619
7.601
7.583
7.539
7.521
7.500
7.260
1.633
0.005
CN
3m
^{1}H NMR (CDCl$_3$, 400 MHz)
1.00
1.00
2.00
1.01
1.04
1.00
f1 (ppm)

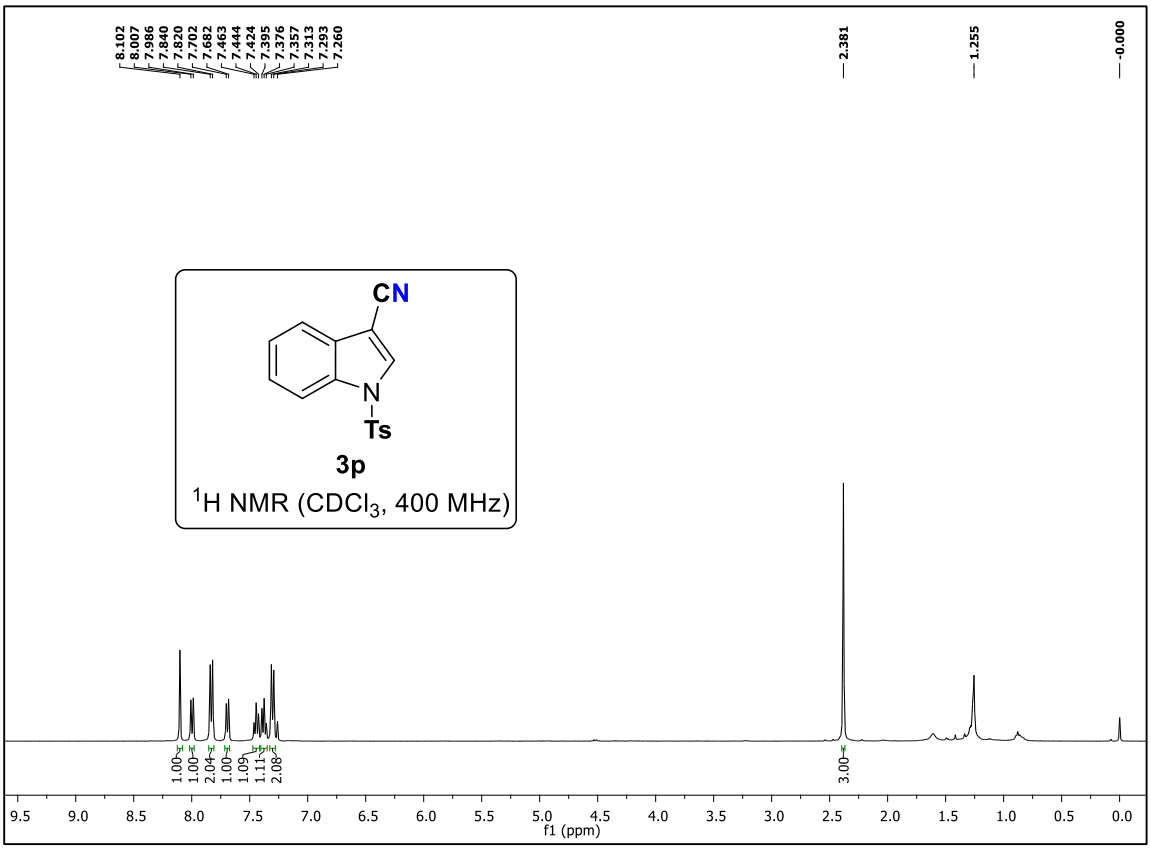

133.39
133.03
132.74
132.46
128.77
128.71
127.66
125.25
125.03
117.93
110.29
77.48
77.16
76.84
CN
3m
^{13}C NMR (CDCl$_3$, 100 MHz)
f1 (ppm)

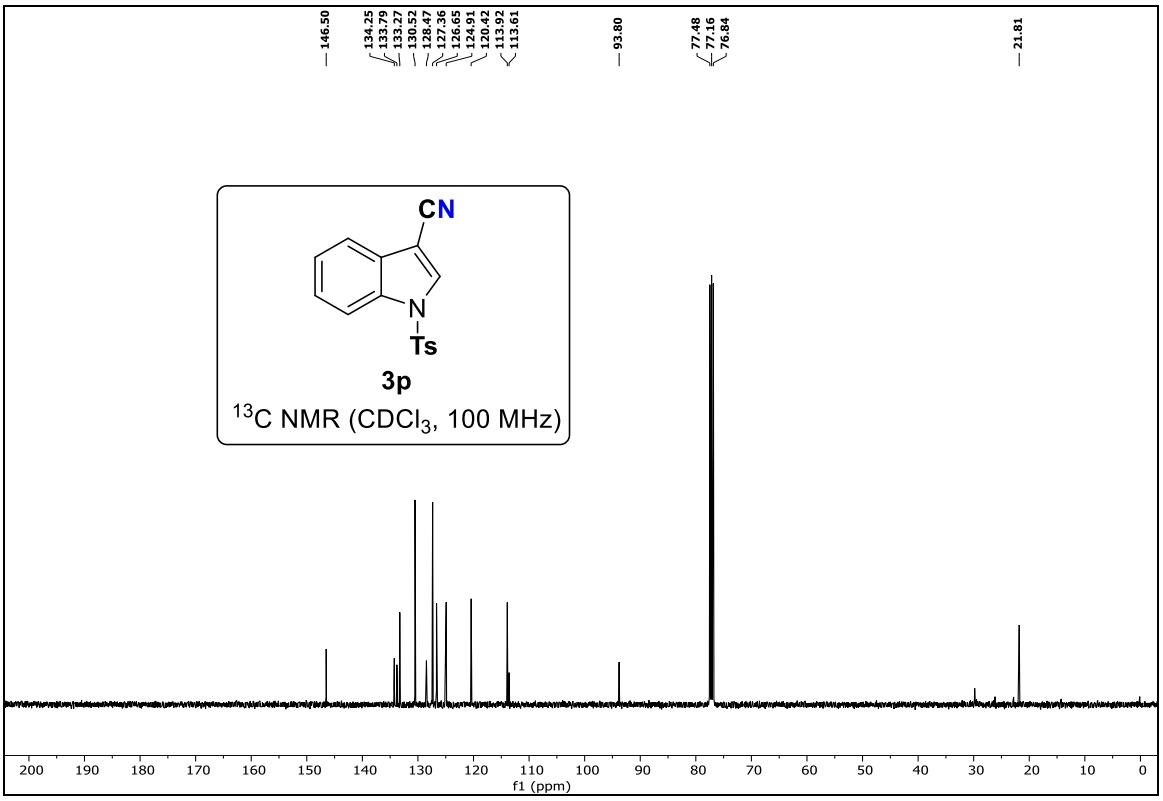

7.595
7.575
7.493
7.411
7.374
7.308
7.260
7.033
7.013
5.118
1.636
1.267
0.890
0.010
CN
Ph
O
3n
^{1}H NMR (CDCl$_3$, 400 MHz)
2.00
5.00
2.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

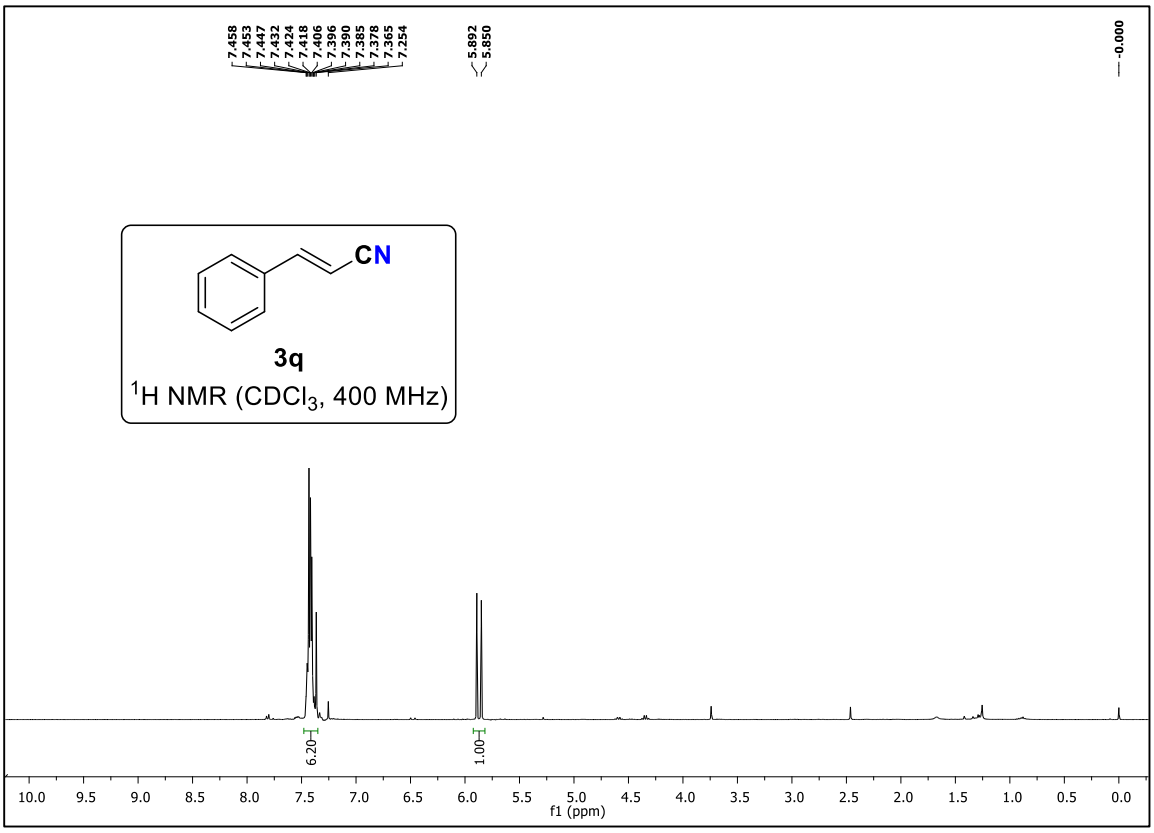

162.07
135.80
134.12
128.88
128.53
127.58
119.28
115.70
104.32
77.48
77.16
76.84
70.39
CN
Ph
O
3n
^{13}C NMR (CDCl$_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

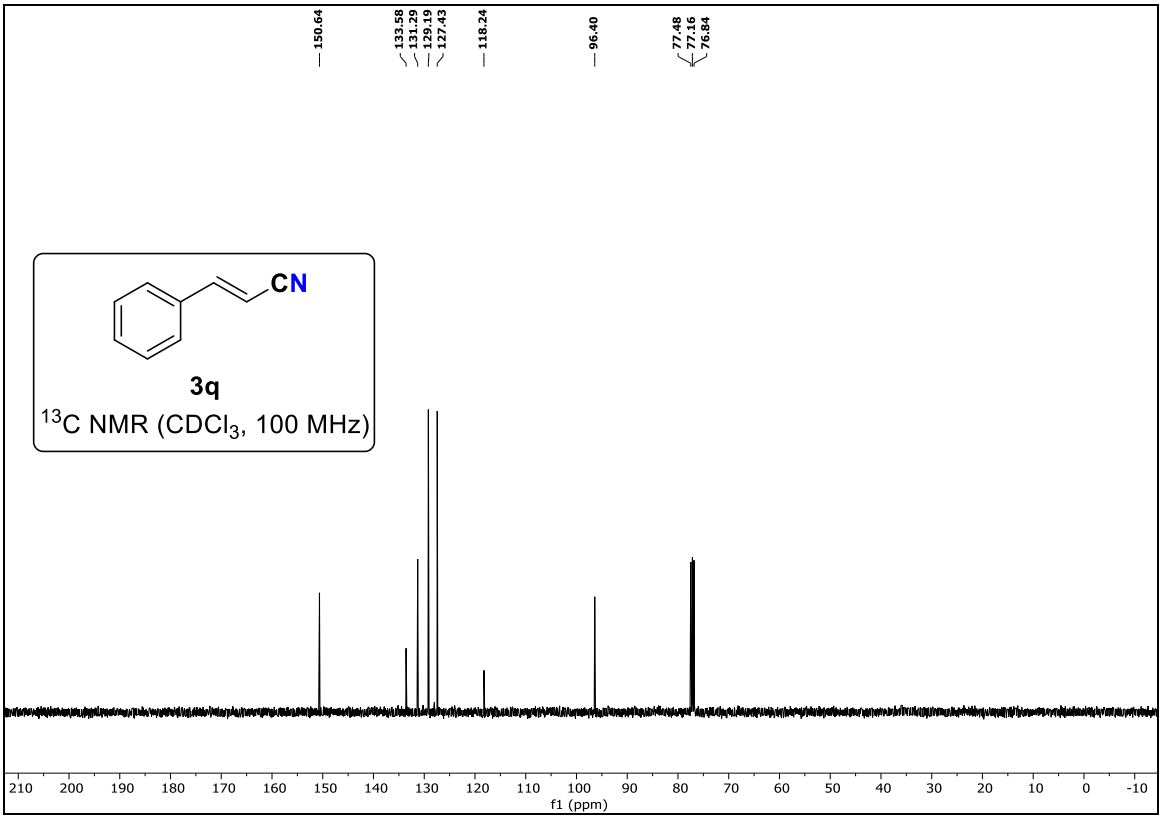

7.300
7.279
7.162
7.116
7.083
7.062
4.830
3.903
2.574
-0.000
MeO
CN
O
3o
^{1}H NMR (CDCl$_3$, 400 MHz)
1.17
1.90
1.98
3.00
0.91
f1 (ppm)

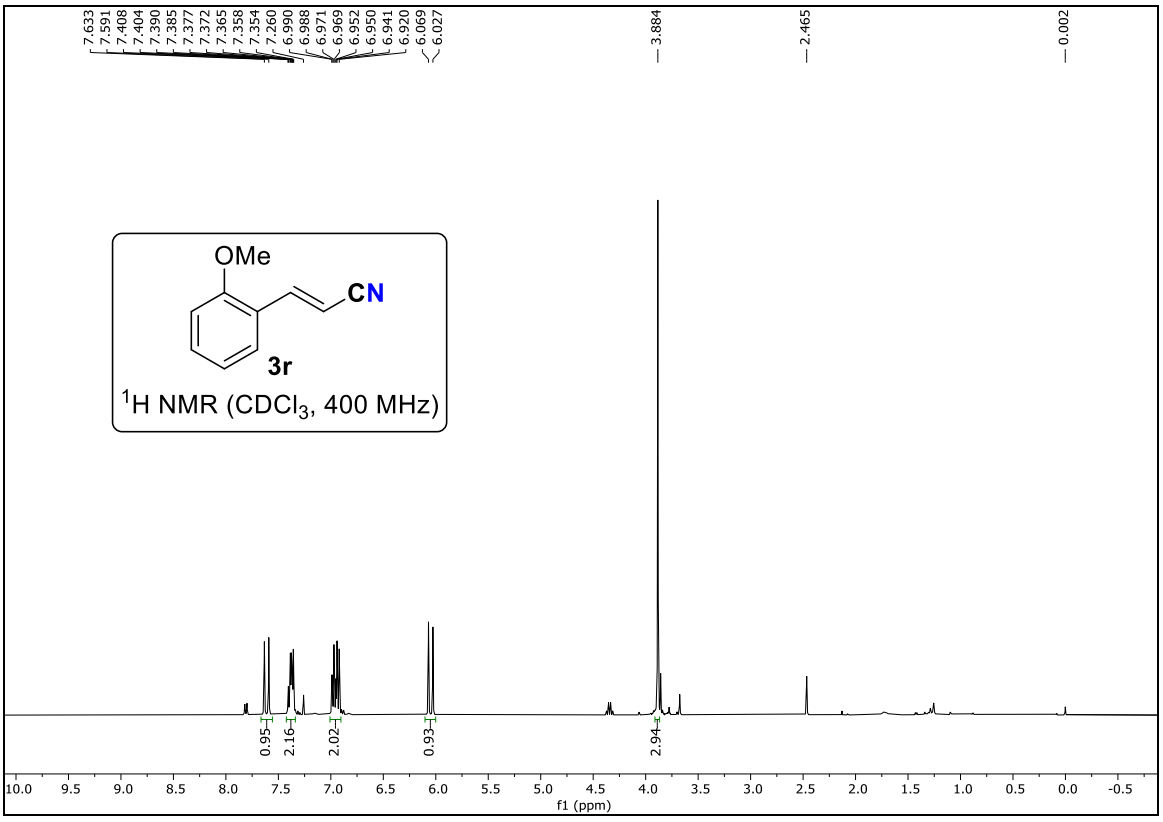

150.65
149.76
126.15
119.10
114.55
113.67
105.17
77.48
77.35
77.16
76.94
76.84
56.70
56.26
MeO
CN
O
3o
^{13}C NMR (CDCl$_3$, 100 MHz)
f1 (ppm)

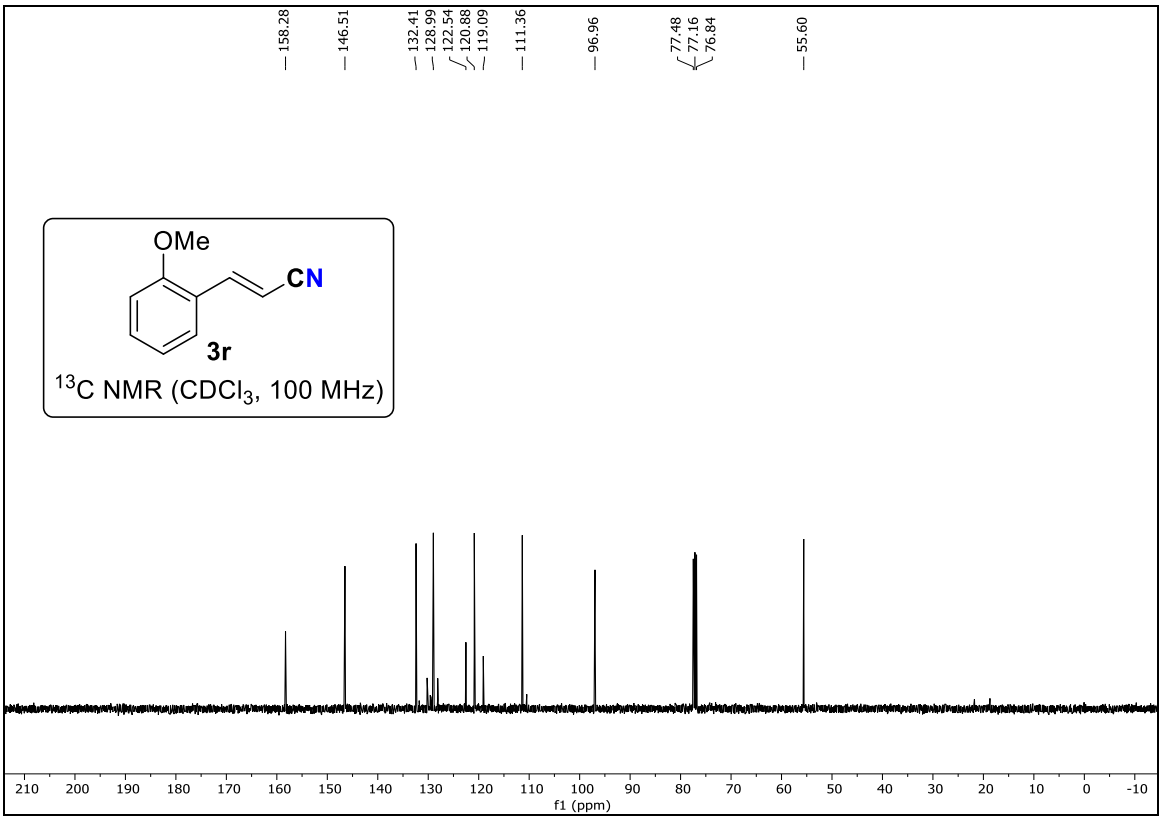

8.102
8.007
7.986
7.840
7.820
7.702
7.682
7.463
7.444
7.424
7.395
7.376
7.357
7.313
7.293
7.260
2.381
1.255
-0.000
CN
N
Ts
3p
^{1}H NMR ($CDCl_3$, 400 MHz)
1.00
1.00
2.04
1.00
1.09
1.11
2.08
3.00
f1 (ppm)

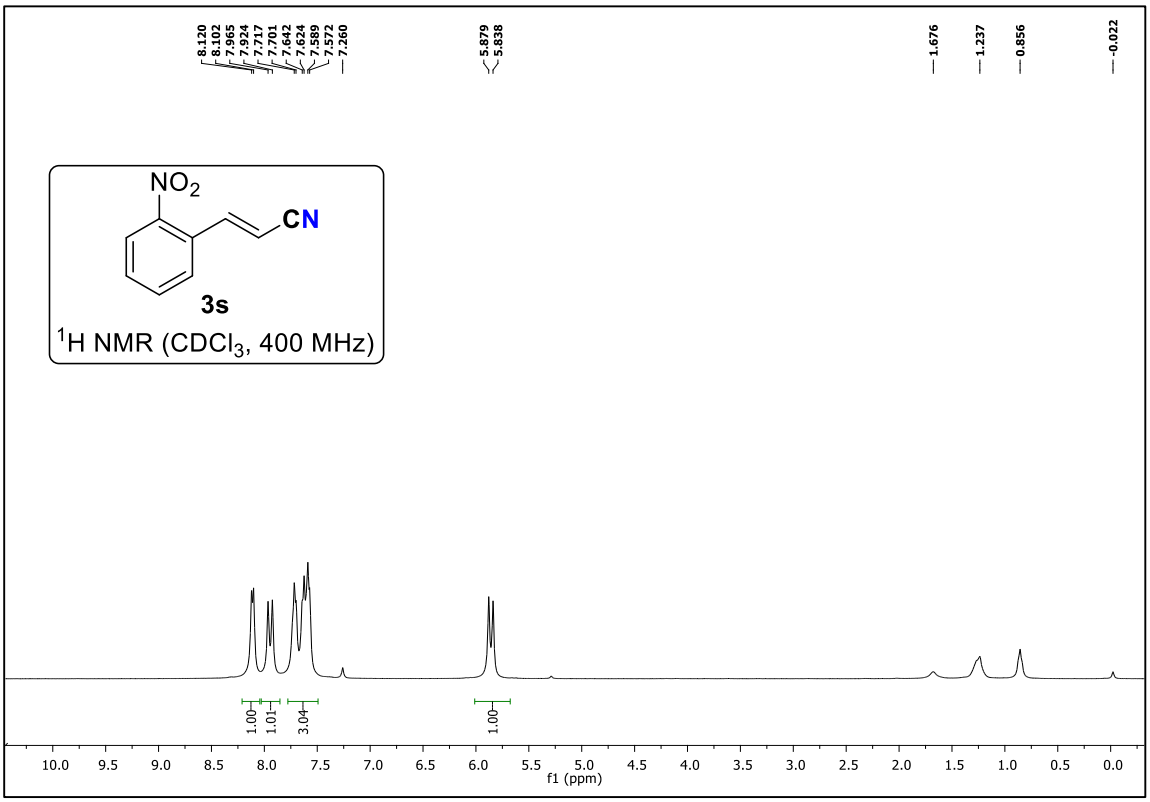

146.50
134.25
133.79
133.27
130.52
128.47
127.36
126.65
124.91
120.42
113.92
113.61
93.80
77.48
77.16
76.84
21.81
CN
N
Ts
3p
^{13}C NMR ($CDCl_3$, 100 MHz)
f1 (ppm)

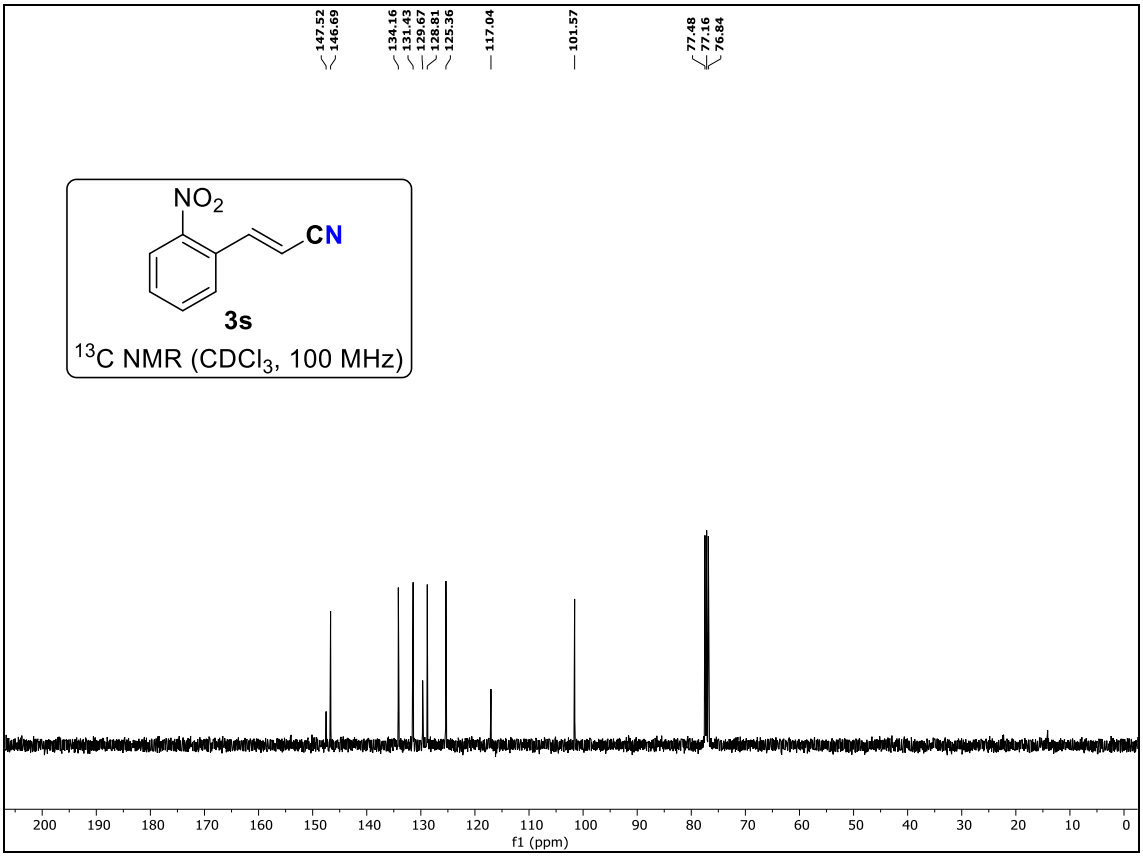

7.458
7.453
7.447
7.432
7.424
7.418
7.406
7.396
7.390
7.385
7.378
7.365
7.254
5.892
5.850
-0.000
CN
3q
^{1}H NMR ($CDCl_3$, 400 MHz)
6.20
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

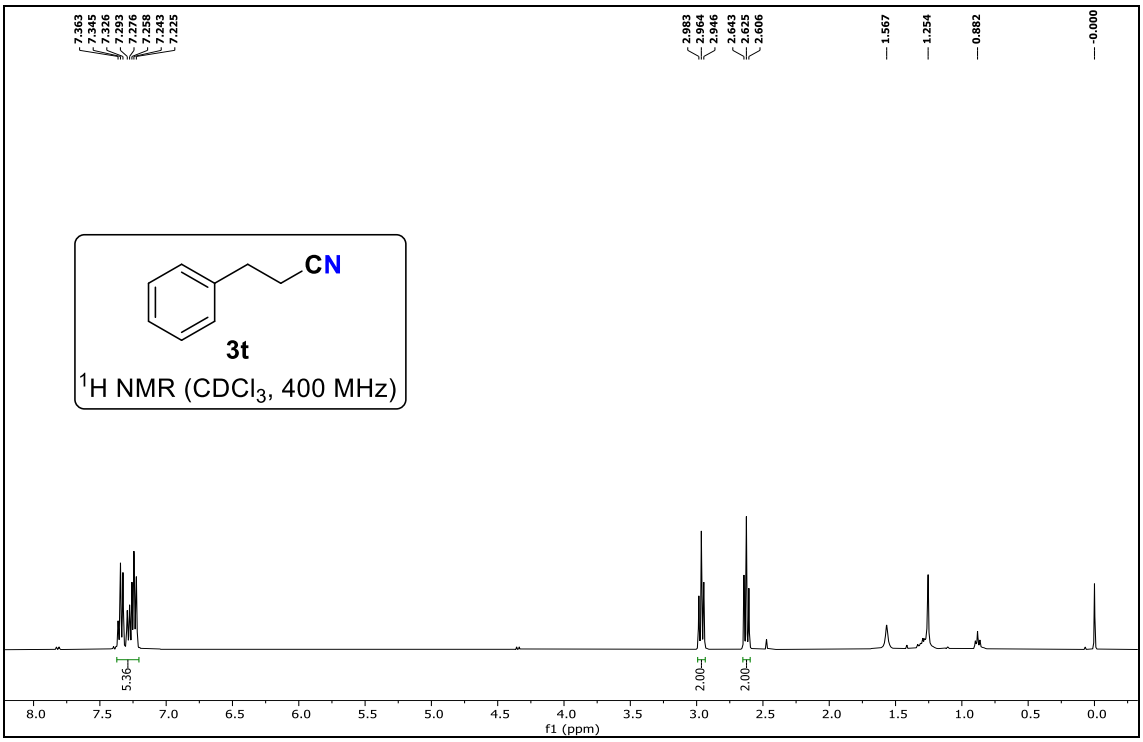

150.64
133.58
131.29
129.19
127.43
118.24
96.40
77.48
77.16
76.84
CN
3q
^{13}C NMR ($CDCl_3$, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

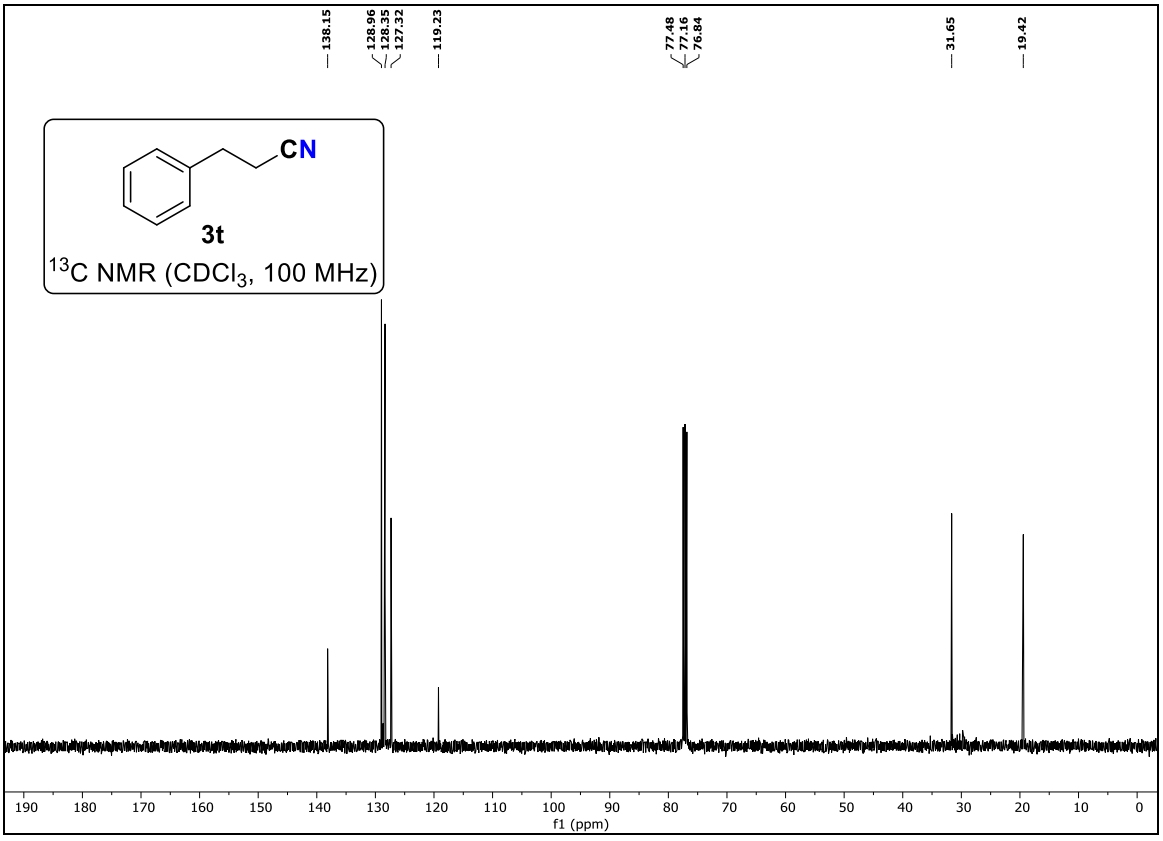

7.633
7.591
7.408
7.404
7.390
7.385
7.377
7.372
7.365
7.358
7.354
7.260
6.990
6.988
6.971
6.969
6.952
6.950
6.941
6.920
6.069
6.027
3.884
2.465
0.002
OMe
CN
3r
1H NMR (CDCl3, 400 MHz)
0.95
2.16
2.02
0.93
2.94
f1 (ppm)

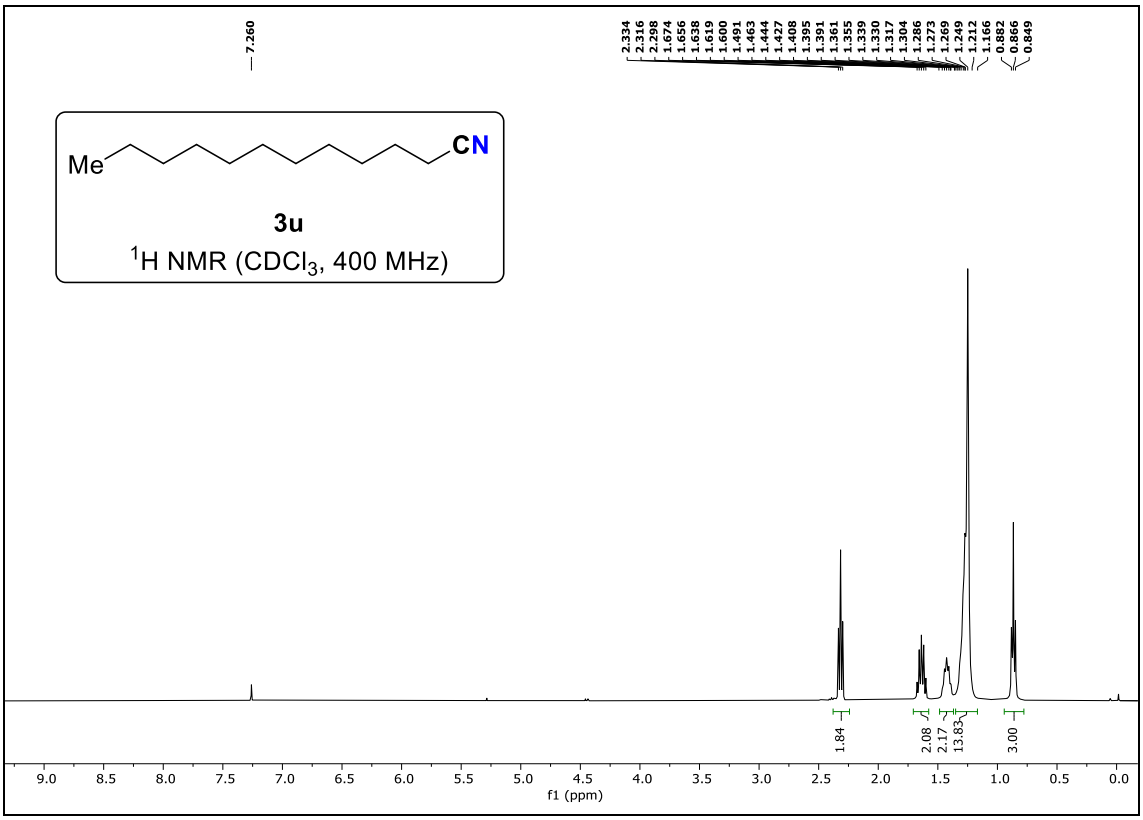

158.28
146.51
132.41
128.99
122.54
120.88
119.09
111.36
96.96
77.48
77.16
76.84
55.60
OMe
CN
3r
13C NMR (CDCl3, 100 MHz)
f1 (ppm)

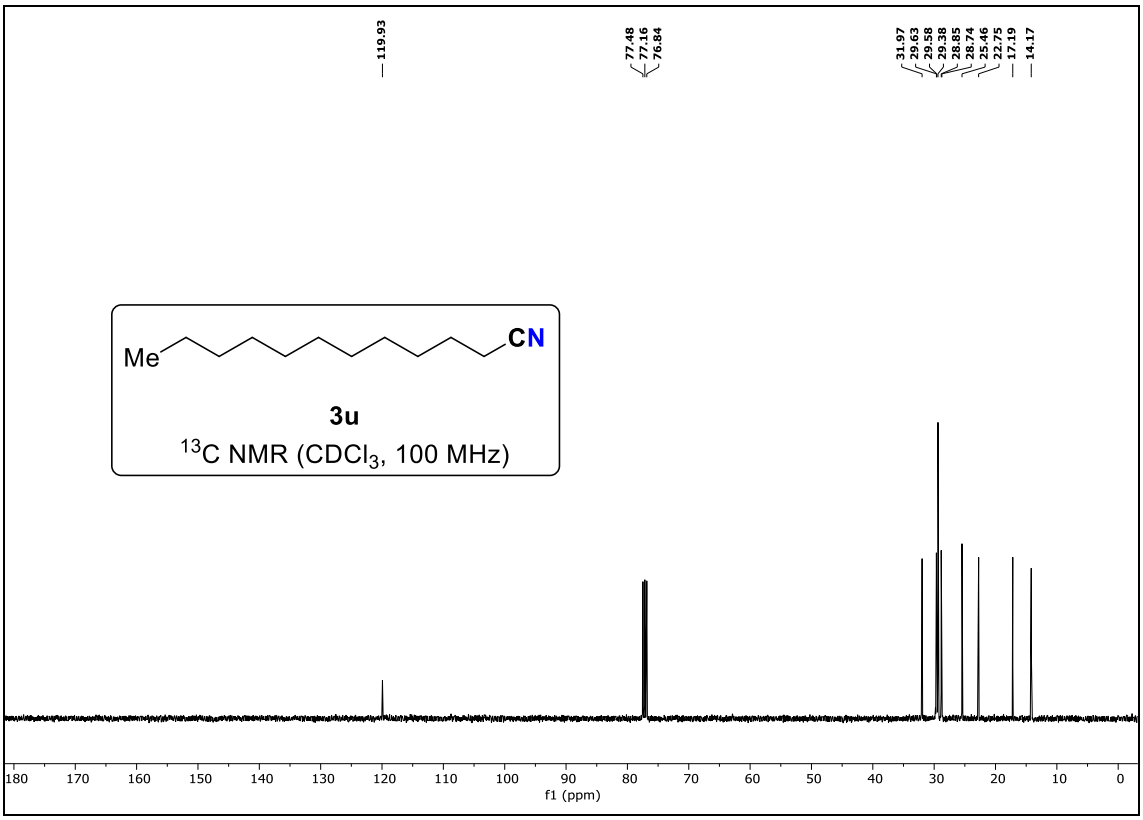

8.120
8.102
7.965
7.924
7.717
7.701
7.642
7.624
7.599
7.572
7.260
5.879
5.838
1.676
1.237
0.856
-0.022
NO2
CN
3s
1H NMR (CDCl3, 400 MHz)
1.00
1.01
3.04
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

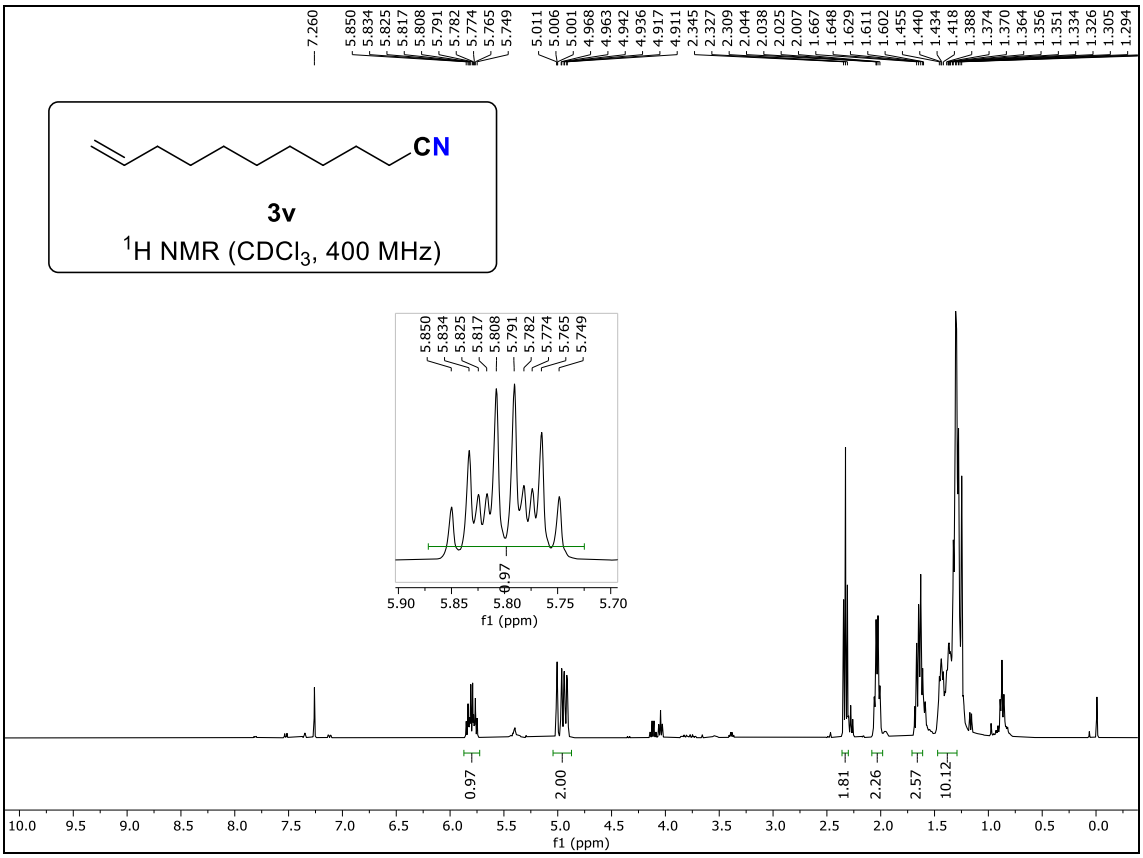

147.52
146.69
134.16
131.43
129.67
128.81
125.36
117.04
101.57
77.48
77.16
76.84
NO2
CN
3s
13C NMR (CDCl3, 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.363
7.345
7.326
7.293
7.276
7.258
7.243
7.225
2.983
2.964
2.946
2.643
2.625
2.606
1.567
1.254
0.882
-0.000
CN
3t
^{1}H NMR (CDCl$_3$, 400 MHz)
5.36
2.00
2.00
f1 (ppm)


138.15
128.96
128.35
127.32
119.23
77.48
77.16
76.84
31.65
19.42
CN
3t
^{13}C NMR (CDCl$_3$, 100 MHz)
f1 (ppm)


7.260
2.334
2.316
2.298
1.674
1.656
1.638
1.619
1.600
1.491
1.465
1.444
1.427
1.408
1.395
1.391
1.361
1.355
1.339
1.330
1.317
1.304
1.286
1.273
1.269
1.249
1.212
1.166
0.882
0.866
0.849
Me
CN
3u
^{1}H NMR ($CDCl_3$, 400 MHz)
1.84
2.08
2.17
13.83
3.00
f1 (ppm)


119.93
77.48
77.16
76.84
31.97
29.63
29.58
29.38
28.85
28.74
25.46
22.75
17.19
14.17
Me
CN
3u
^{13}C NMR ($CDCl_3$, 100 MHz)
f1 (ppm)


7.260
5.850
5.834
5.825
5.817
5.808
5.791
5.782
5.774
5.765
5.749
5.011
5.006
5.001
4.968
4.963
4.942
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4.917
4.911
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2.038
2.025
2.007
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1.351
1.334
1.326
1.305
1.294
CN
3v
^{1}H NMR (CDCl$_3$, 400 MHz)
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f1 (ppm)
0.97
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1.81
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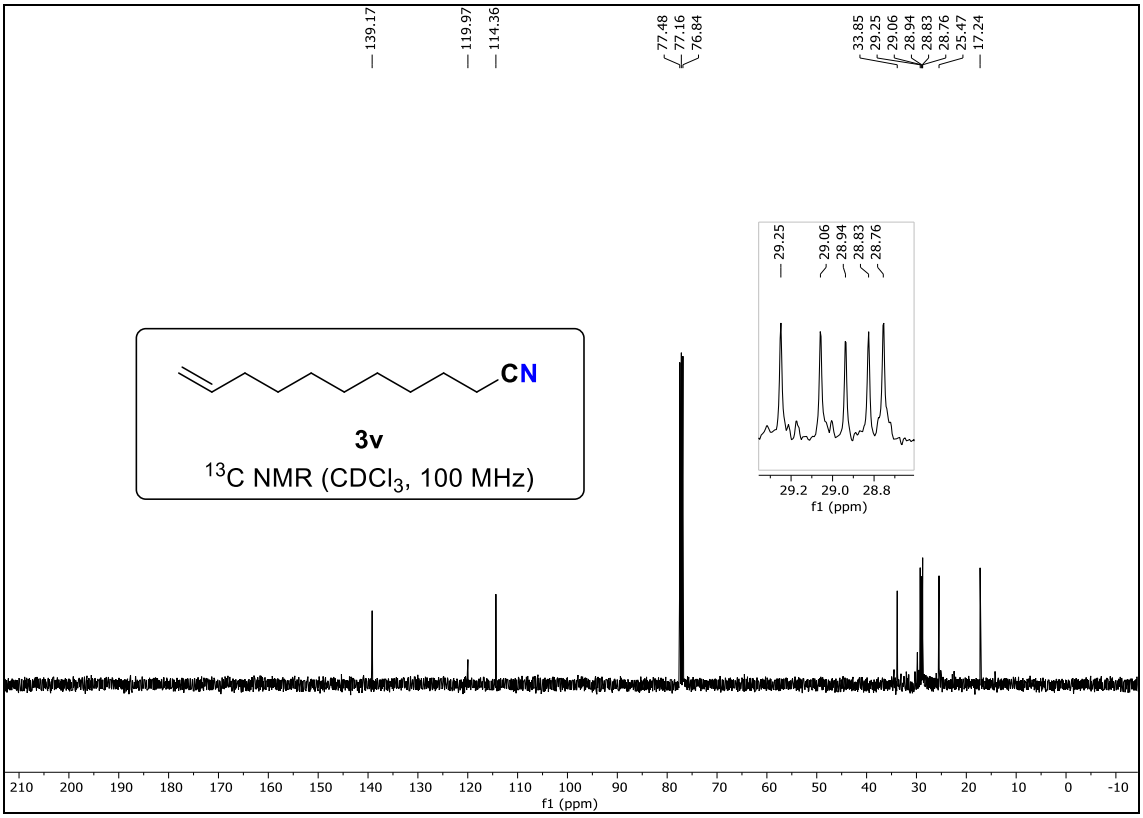
f1 (ppm)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17.24
CN
3v
^{13}C NMR (CDCl$_3$, 100 MHz)
f1 (ppm)
f1 (ppm)

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List of Publications

1. **Zinc(II)-Catalysed Synthesis of Secondary Amides from Ketones *via* Beckmann Rearrangement Using Hydroxylamine-*O*-sulfonic Acid in Aqueous Media.** Saumya Verma, **Puneet Kumar**, Anil K. Khatana, Dinesh Chandra, Ajay K. Yadav, Bhoopendra Tiwari, Jawahar L. Jat *Synthesis* **2020**, *52*, 3272-3276. (Impact Factor = 3.157)
2. **Direct Synthesis of Secondary Amides from Ketones through Beckmann Rearrangement using *O*-(mesitylsulfonyl)hydroxylamine.** Dinesh Chandra, Saumya Verma, Chandra Bhan Pandey, Ajay K. Yadav, **Puneet Kumar**, Bhoopendra Tiwari, Jawahar L. Jat *Tetrahedron Lett.* **2020**, *61*, 151822. (Impact Factor = 2.415)
3. **A Synthetic Overview of Enones Aziridination.** Dinesh Chandra, **Puneet Kumar**, Ajay K. Yadav Jawahar L. Jat, Ganesh Kumar, *ChemistrySelect* **2022** . (Impact Factor = 2.109)
4. **Metal-free synthesis of secondary amides using *N*-Boc-*O*-tosylhydroxylamine as nitrogen source *via* Beckmann rearrangement.** Jawahar L. Jat, Jat, **Puneet Kumar**, Saumya Verma, Dinesh Chandra, Vikram Singh, Bhoopendra Tiwari, *New J. Chem.* **2022**, *46*(31), pp.14782-14785. (Impact Factor = 3.925)
5. **Metal-Free Direct Transformation of Aryl Boronic Acid to Primary Amines. Puneet Kumar**, Saumya Verma, Komal Rathi, Dinesh Chandra, Ved Prakash Verma, Jawahar L. Jat, *Eur. J. Org. Chem.* **2022**, e202200508 (1-4). (Impact Factor = 3.261)
6. **Metal-free transformation of aldehydes into nitriles using TsONHBoc reagent.** (Manuscript submitted).
7. **A Synthetic Overview of Hydroxylamine-*O*-Sulfonic acid** (Manuscript submitted).

List of Conferences and Workshop

Oral Presentations:

1. Presented an oral talk on "Zn(II)-Catalyzed Synthesis of Secondary Amides from Ketones in Aqueous Media", in Virtual International Conference on Chemical Sciences in Sustainable Technology and Development (IC2S2TD-2020), organized by Department of Applied Chemistry, S. V. National Institute of Technology, Surat, Gujarat-India, in association with Department of Chemistry Chung-Ang University Seoul, South Korea, held on 1st-3rt December, 2020.
2. Presented an oral talk on "Synthesis of Secondary Amides from Ketones via Beckmann Rearrangement Using Hydroxylamine-O-Sulfonic Acid as Aminating Agent and Water as Solvent" in International Conference on Recent Trends in Chemical Sciences (RTCS-2020) organized by Indian Chemical Society, Kolkata, West Bengal, during 26-29 December 2020.
3. Presented Online Oral Presentation on, "Direct Approach for Synthesis Secondary Amides from Ketones via Beckmann Rearrangement using O-(mesitylsulfonyl)hydroxylamine" in " The International Virtual Conference on Expanding Frontiers in Chemistry(EFC-21)" held on 11 & 12 November, 2021 Organized by PG Department of Chemistry Arul Anandar College (Autonomous) Karmathur-625514, Madurai District, Tamil Nadu, India.
4. Presented Oral Presentation on, "Zn(II)-Catalyzed Direct Synthesis of Secondary Amides from Ketone via Beckmann rearrangement" in the International Conference on Lucknow Climate Change Conference on Control of Green House Gases at the Source by Physical and Chemical Technologies_2k22 (LCCCCGGSPCT_2K22), 22-24 April 2022, Babasaheb Bhimrao Ambedkar University (A Central University) Lucknow, Uttar Pradesh, India.

Poster Presentations:

1. Synthetic Utilities of O-(substituted)hydroxylamines as Aminating Reagents, Puneet Kumar, Dinesh Chandra, Ajay Kumar Yadav, Saumya Verma and Jawahar L. Jat. National Conference on, "Trends and Innovation in Chemistry" (NCTIC-2019), RNT Groups of Colleges, Kapasan, Dist. Chittorgarh, Rajasthan.

2. Synthetic Applications of O-(substituted) hydroxylamines, Puneet Kumar, Dinesh Chandra, Saumya Verma, Ajay K. Yadav, Jawahar L. Jat*. Global Conference on The Control of Green House Gases at the Source by Physical and Chemical Technology (GCCGHGSPCT-2k19), 22-24 April 2019, Babasaheb Bhimrao Ambedkar University (A Central University) Lucknow, Uttar Pradesh, India.
3. Presented Online Poster Presentation on, "Direct Synthesis of Secondary Amides from Ketones via Beckmann Rearrangement", Puneet Kumar and Jawahar L. Jat. "International Virtual Conference on Frontiers in Chemical Sciences (IVCFCS-2021)" 25th June Organized by Department of Chemistry Mohanlal Sukhadia University Udaipur, Rajasthan, India.
4. Presented Poster Presentation on, "Exploration of O-(Substituted)hydroxylamine as Nitrogen Source in Synthetic Organic Chemistry" in an 5th International Conference on Innovative Approaches (iCiAaT-2021)" jointly-organized by Scientific Education Research Society Meerut 250004 and Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow (U.P). India held on 3rd-5th December, 2021 at Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow (U.P). India.

Workshop:

One week workshop on "Important Techniques for characterization of molecules" held at Faculty of Chemical Sciences, Institute of Natural Sciences and Humanities, Shri Ramswaroop Memorial University, Lucknow from 25thMarch 2019.

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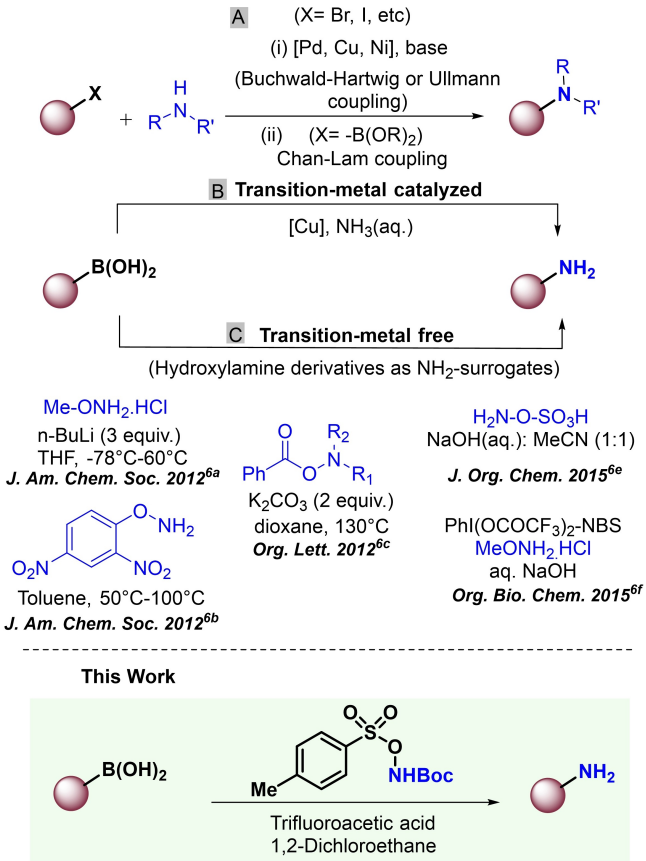
Metal-Free Direct Transformation of Aryl Boronic Acid to Primary Amines

Puneet Kumar,[a] Saumya Verma,[a] Komal Rathi,[b] Dinesh Chandra,[a] Ved Prakash Verma,*[b] and Jawahar L. Jat*[a]

In this work, we report a transition-metal free approach for the construction of primary aromatic amines from aryl boronic acids and esters with *N*-Boc-*O*-tosylhydroxylamine as an amine surrogate. Bench stable TsONHBoc is easy to use and it produces a non-interfering water-soluble by-product. The protocol is operative for both electron-rich and electron-deficient aryl boronic acids under acidic conditions, where the former arenes affords a better yield of the desired product. Even, sterically hindered and halogenated substrates are easily amenable under this reaction condition. The current protocol can be scaled up to produce gram-scale primary aromatic amines.

Introduction

Primary arylamines have acquired a valuable position as key components in numerous natural products, pharmaceuticals, agrochemicals, polymers, and dyes.[1] Due to the great relevance of these compounds to the medicinal field, their preparation has attracted much attention. A conventional synthetic method includes the nitration of aromatic compounds and subsequent metal-catalyzed reduction or catalytic hydrogenation.[2] Alternatively, transition-metal-catalyzed coupling of aryl halides and amines has been extensively used in many synthetic organic transformations.[3] In the context to eliminate strong bases and expensive palladium catalysts, further explorations have been done towards copper-based oxidative amination of arylboronic acids. This method is useful because of the accessibility of several functionalized and stable boronic acids, but provides access to *N*-substituted aromatic amines only.[4] (Scheme 1A). Synthesis of primary aromatic amines was a challenging task till the report of Fu and co-workers, based on copper(I) oxide mediated amination of arylboronic acids and derivatives using aqueous ammonia as amine surrogate (Scheme 1B).[5] In view of metal-free amination, Kürti, and the group described the first metal-free access of primary arylamines from boronic acid and *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH) as nitrogen source (Scheme 1C).[6b] Only a few reports were observed for boronic acids to access primary amines with different aminating agents such as hydroxylamine-*O*-sulphonic acid (HSO_3ONH_2),[6e,h] $MeONH_2.HCl$,[6a,f] aminoazanium of DABCO (H_2N-DABCO)[6i] and others[6d,g]. Indeed, these protocols provide influential access to desired primary amines, however, used $^+NH_2$ reagents (for example DPH) requires 0 °C for storage and liberates toxic, explosive, and interfering by-product (2,4-dinitrophenol). Similarly, hydroxylamine-*O*-sulphonic acid and methoxyamine hydrochloride are hygroscopic and required an excess amount of strong bases (NaOH and *n*-BuLi) while *O*-benzoylhydroxyl-



Scheme 1. Preparation of primary arylamines from aryl halides and arylboronic acid.

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amine derivatives required elevated reaction temperature and are limited to substituted anilines only.[6c]

In view of the limits and potential problems of existing methods, development of a simple method for the direct access of primary amines from aryl boronic acid is meaningful to enrich the synthetic chemist's toolbox. In continuation of our ongoing work on *O*-substituted hydroxylamine derivatives to develop efficient and simple methodologies,[7a–c] we were next interested to develop an efficient, one-pot, mild, and transition-metal-free method using bench stable *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as a nitrogen donor for conversion of aryl boronic acids/derivatives to primary aromatic amines. Recently, Hashmi and the group used this reagent for a metal-free arene C–H amination.[7d] This *N*-Boc protected aminating agent (TsONHBoc) is stable at ambient temperature, easy to handle and generates a non-interfering, water-soluble by-product (TsOH). Also, it is non-hygroscopic, commercially available, and easy to synthesize. These properties enhance the practical use of this simple protocol.

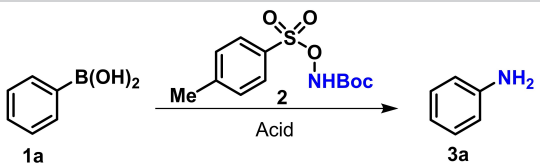
Results and Discussion

In our ongoing work, we observed the *in situ* Boc-deprotection of TsONHBoc reagent in TFE solvent.[8] Following that, we investigated the above result for the conversion of aryl boronic acid to a primary amine. Our initial experiment was started with the amination of phenylboronic acid in TFE solvent, which yielded the desired aniline **3a** in 45% yield (Table 1, Entry 1). Having this encouraging outcome, we hypothesized that an external acid might improve the reaction conversion by the facile deprotection of Boc group in a shorter reaction time and we found that among all the listed acid (Entry 2–4), trifluoroacetic acid turned out to be the best choice with an enhanced yield of the desired product **3a** upto 69% (Table 1, Entry 4). Upon increasing the amount of TFA from 1.5 to 3.0 equiv., the progress of the reaction was enhanced further in less time (Table 1, Entry 5). In addition, screening of solvents identified dichloroethane (DCE) as the best choice to obtain maximum yield (Table 1, entry 7–11).

Having this exciting result, we studied the effect of favorable electron-releasing groups under the present reaction condition. Notably, the substrates bearing methyl (**1b**) and ethoxy (**1c**) group at *o*-position were smoothly transformed to the corresponding amines. In addition, the *p*-methoxy (**1d**) substituent delivered the corresponding amine (**3d**) in excellent yield (Scheme 2).

Di-methoxy (**1e**) and mesitylboronic acid (**1g**) were found compatible under this reaction condition and corresponding amines **3e** and **3g** were isolated with good yield. Similarly, the reaction of 2-methyl-4-methoxyphenylboronic acid (**1f**) proceeded smoothly with a 90% yield of corresponding amine (**3f**). Halogen substituted aromatic anilines are often difficult to

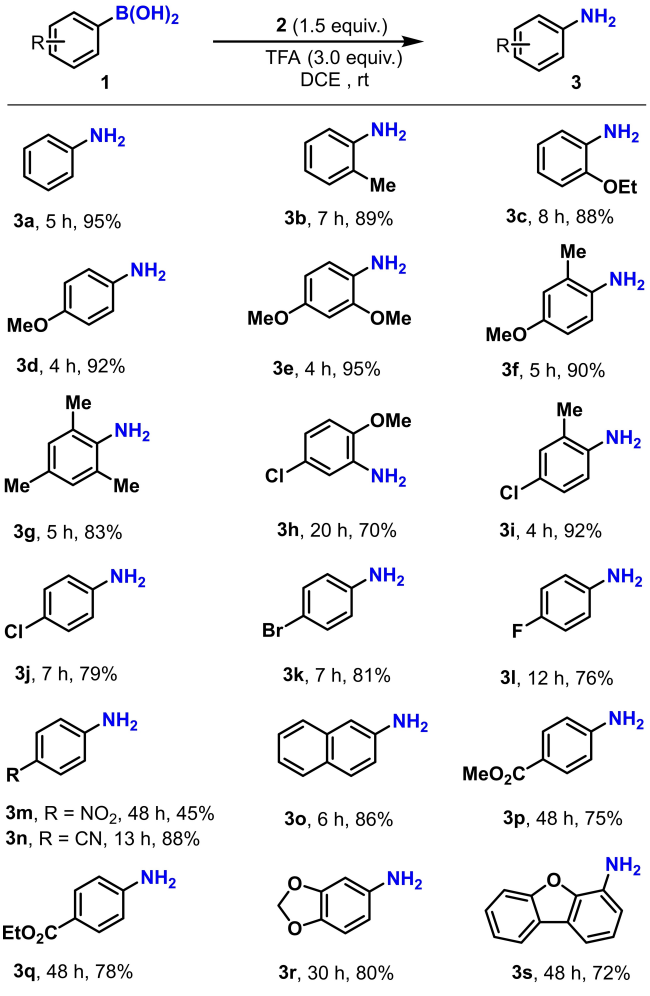
Table 1. Optimization of reaction conditions.[a]



1a 3a

S.No.	Solvent	Additives	Amount [equiv.]	Yield [%][b]
1	TFE	–	–	45
2	TFE	AcOH	1.5	56
3	TFE	$(COOH)_2$	1.5	50
4	TFE	TFA	1.5	69
5[c]	TFE	TFA	3.0	82
6	CH_2Cl_2	TFA	3.0	89
7[d]	DCE	TFA	3.0	95
8	Toluene	TFA	3.0	90
9	CH_3CN	TFA	3.0	30
10	MeOH	TFA	3.0	20
11	DCE	–	–	0

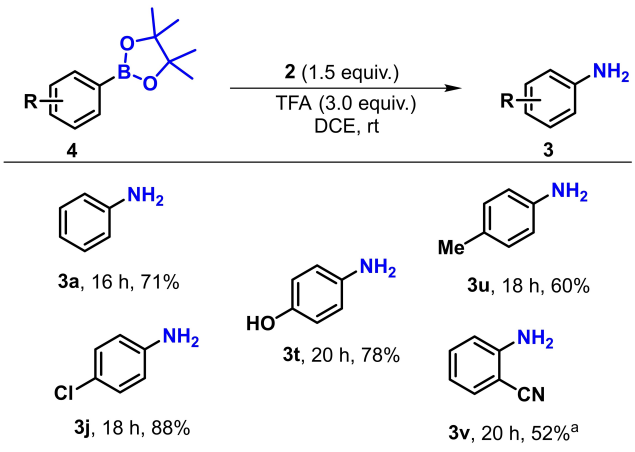
[a] Reaction conditions: 1 (0.5 mmol, 1.0 equiv.), 2 (0.75 mmol, 1.5 equiv.), acid (1.5–3.0 equiv.), Solvents, (CH_2Cl_2, DCE (1,2-dichloroethane), Toluene, CH_3CN, MeOH (1.0 mL), rt, 16 h. [b] Isolated yield. [c–d] Reaction was completed in 6 h and 5 h respectively.



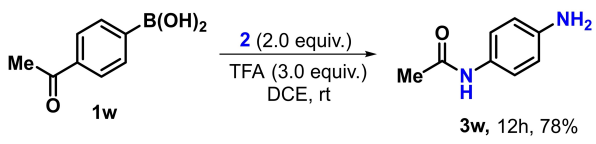
Scheme 2. Substrate scope for the synthesis of primary amines from arylboronic acid. [a] Reaction conditions: 1 (0.5 mmol, 1.0 equiv.), 2 (0.75 mmol, 1.5 equiv.), TFA (1.5 mmol, 3.0 equiv.), DCE (1.0 mL), rt, [b] isolated yield.

prepare by transition-metal-catalyzed amination reaction. Notably, halogen substituents (**1h**–**l**) were tolerated very well under this reaction condition and provided the corresponding amines **3h**–**l** in high yields. On another note, the NO_2 group at the *p*-position provided the respective aniline **3m** in moderate yield (45%) in a longer reaction time and *p*-cyano substituted arylboronic acid smoothly underwent the aryl amination, irrespective of its electronic nature, and provided the related amines **3n** in excellent yield. Naphthyl-2-boronic acid **1o** also provided a good yield of the corresponding amine **3o**. Base sensitive substrates like 4-methoxy and 4-ethoxycarbonylphenylboronic acid **1p**–**q** worked very well and provided very good yields of anilines in a longer time Unfortunately, phenethylboronic acid and cyclohexylboronic acid, did not work under this reaction condition. Heterocyclic substrates like 3,4-(methylenedioxy)phenylboronic acid **1r** and dibenzofuran boronic acid **1s** provided an excellent yield of corresponding amines **3r**–**s**. This promising finding inspired us to explore more applications of the present reaction condition with easily accessible boronate esters. As a start, we selected simple boronate ester **4a** which furnished aniline **3a** in high yield. The investigation of substituted boronate esters showed that electron-rich boronate esters **4t** and **4u**, and electron-deficient substrates **4j&4v** afforded the corresponding anilines in good yields (Scheme 3).

To check the chemoselectivity of this methodology, we treated (4-acetylphenyl) boronic acid **1w** with 1 equivalent of reagent **2**. The ketonic group was converted into the corresponding amide and the boron center remained unreacted.



Scheme 3. Substrate scope for the synthesis of primary amines from arylboronic ester. Yields are reported after isolation. [a] Reaction was performed in Toluene.



Scheme 4. Simultaneous transformation of both ketone and boronic acid functional groups.

After the addition of one more equivalent of reagent **2**, the boronic acid group was transformed into amino group **3w** (Scheme 4).

The favorable results found in mmol scale motivated us to further examine the scalability of this method. This amination reaction has been examined for its practical use by employing gram-scale transformation of phenylboronic acid **1a** to aniline **3a** in quantitative yield (Scheme 5).

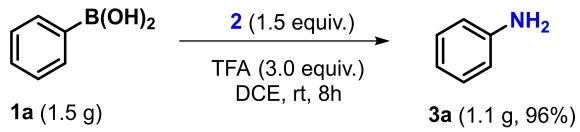
We assumed that the mechanism of this reaction proceeded via 1,2-aryl migration, the same pathway as described earlier by Kurti and the group (Scheme 6).[6b]

Conclusion

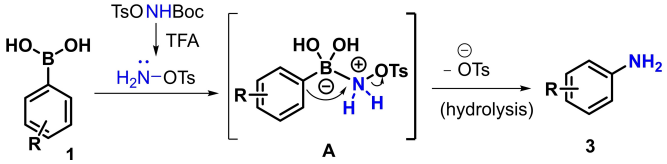
In conclusion, we have developed a metal-free approach to synthesize primary aromatic amines from various functionalized aryl boronic acids and esters using *N*-Boc-*O*-tosylhydroxylamine as an aminating agent. This reaction condition provides good tolerance for both electron-rich and deficient as well as for heterocyclic substrates. *N*-Boc protected aminating agent *in situ* generates the free amino group that overcomes the limitations to use isolated $-NH_2$ reagents which are generally explosive or hygroscopic. This protected aminating agent is stable, economical, and easy to operate. The simplicity and scalability of this procedure make it synthetically useful and practical.

Experimental Section

General procedure for preparation of anilines from boronic acid: To a round-bottom flask equipped with a magnetic stirring bar were added boronic acid **1** (0.5 mmol, 1.0 equiv.) and *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) ***2*** (1.5 equiv.) in DCE solvent (1 mL) at room temperature. To this stirred solution TFA (3 equiv.) was added. The reaction mixture was further stirred at this temperature for the specified duration and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3×5 mL). The organic layer was washed with brine solution (5 mL) and dried over anhydrous Na_2SO_4. The crude product obtained after removal of all of the volatiles was



Scheme 5. Gram-scale synthesis of primary amines from boronic acid.



Scheme 6. Proposed reaction mechanism.

purified by a silica gel column chromatography to afford the pure desired product **3** using EtOAc/hexane as an eluent.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Boronic acid · Boronic ester · *N*-Boc-*O*-tosylhydroxylamine · Metal-free amination · Primary aromatic amine

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Metal-free synthesis of secondary amides using *N*-Boc-*O*-tosylhydroxylamine as nitrogen source *via* Beckmann rearrangement†

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Herein, we report the first direct method for the synthesis of secondary amides from ketones *via* the Beckmann rearrangement using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as the aminating agent. This reagent is expected to play a dual role, first in the formation of the activated oxime intermediate, and then *via* facilitation of the amide formation as a Brønsted acid by the tosylic acid by-product. The metal and additive-free one-step method progresses in TFE solvent through the *in situ* generation of the primary amine reagent ($TsONH_2$), and produces a water-soluble by-product.

Introduction

Secondary amides show fascinating structural subunits in various important bioactive natural products and drug candidates as well as in polymers, dyes, textiles, and agrochemical products (Fig. 1).[1] They also form versatile synthetic intermediates for the preparation of a diverse range of alkaloids, and nitrogen- and oxygen-containing valuable compounds.[2] In addition, *sec*-amides have emerged as a preferred directing group for selective C–H bond activation.[3] As a result, amide bond synthesis is one of the most frequently used synthetic reactions.[4] The trivial method for their preparation *via* the coupling of carboxylic acids and amines has several intrinsic limitations. For example, the requirement of an expensive (and often stoichiometric) reagent for activation of the carboxylic acid, the generation of toxic waste, and poor atom economy limit its wider application in industry.[5]

Ketones are widely available and stable synthones, and they have therefore been explored for the synthesis of amides for a long time. Discovery of the Beckmann rearrangement (BKR) was a milestone in this direction, transforming the preformed ketoximes to amides in an acidic medium.[6] This approach successfully eliminated the major drawbacks associated with the methods that rely on the use of carboxylic acids as the substrates. Nonetheless, this two-step process starting from ketones generally requires harsh reaction conditions (strong acid and high temperature), rendering this procedure incompatible for sensitive substrates. Several improved studies have been reported recently for the Beckman rearrangement under milder conditions.[7] Despite this notable progress, these methods have one or more limitations, like the toxicity of the reagents, high reaction temperatures, limited substrate scopes, the survival of sensitive functional and protecting groups, the requirement for additives, tedious reaction/purification procedures, *etc.* Recently, *O*-substituted hydroxylamines have emerged as powerful nitrogen-transfer reagents. They have found wide application in C–H amination, aziridination, amidation, hydroamination, amination, *etc.*[8] These reagents bring in several advantages over other traditionally used reagents, such as mild reaction conditions, good functional group tolerance, and easy purification, among others. However, their preparation has some inherent limitations, that is, an additional step is needed for *N*-Boc deprotection in a strong acidic medium such as TFA, they can be explosive and highly unstable after deprotection (*e.g.*, $TsONH_2$), they require fresh preparation every time for maximum output, they require storage at 0 °C or below, retention of moisture, they exist in zwitterionic form (*e.g.*, HOSA), they suffer interference from by-products (2,4-dinitrophenol), *etc.*[8d,9] Hence, the development of an efficient and a practical method that eliminates the requirement of the reagent in an unprotected form is highly desirable. Herein, we report the first direct method for the preparation of *sec*-amides from ketones using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as the aminating agent. This single-step method proceeds *via* the *in situ* generation of the active amine reagent in trifluoroethanol (a weakly acidic solvent) at room temperature (Scheme 1).

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2nj02755k

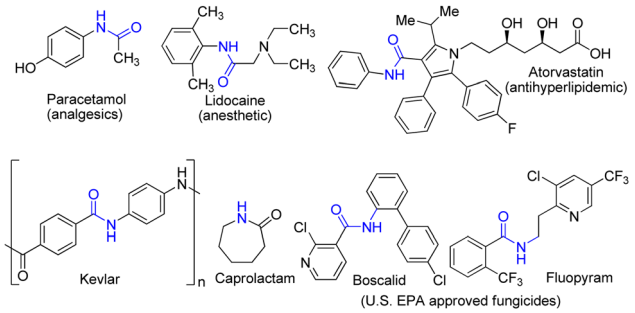
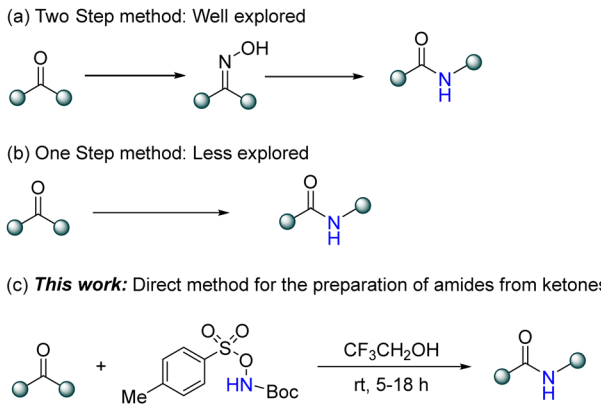


Fig. 1 *sec*-Amide-containing selected pharmaceuticals, polymers and agrochemicals.

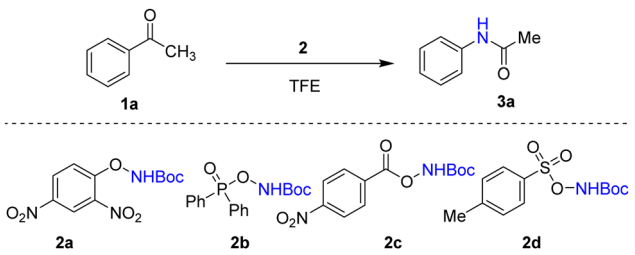


Scheme 1 Preparation of secondary amides from ketones.

Results and discussion

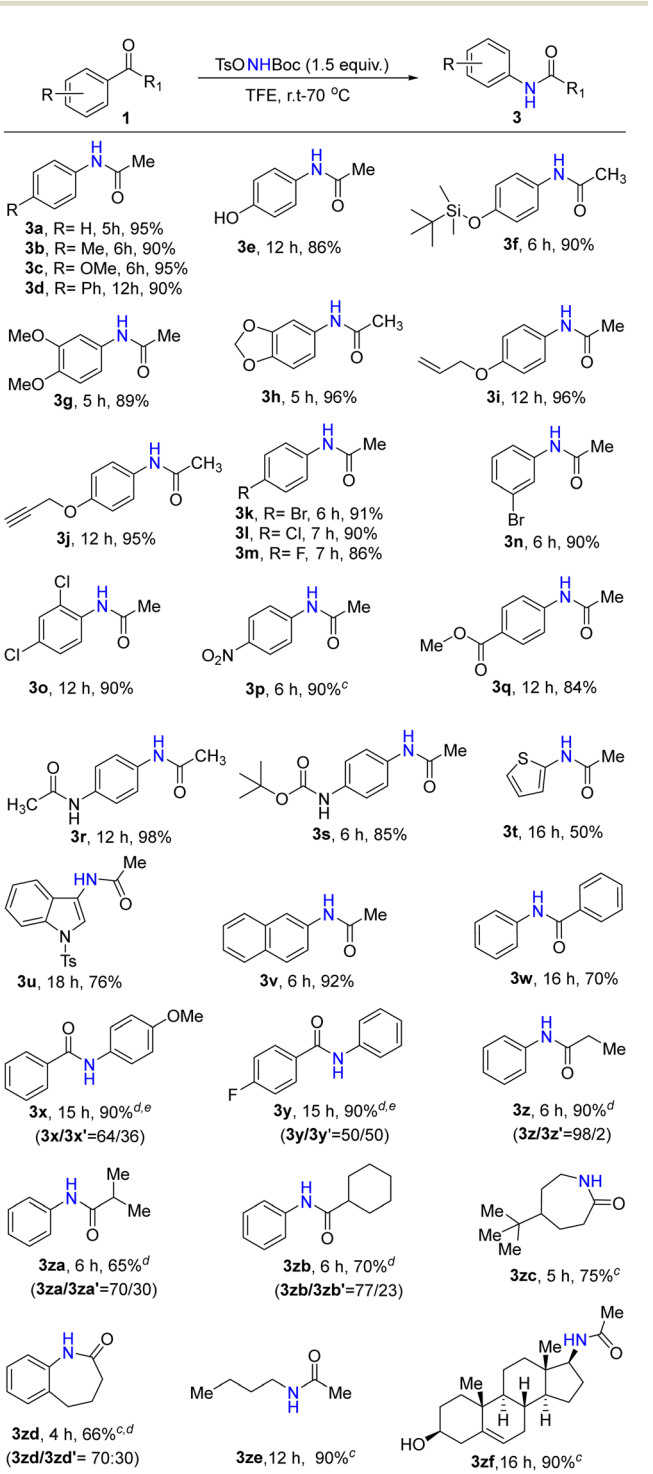
To optimize the reaction conditions, we initiated our studies by screening a series of aminating agents for *in situ* cleavage of the *N*-Boc protecting group in the weakly acidic solvent TFE ($pK_a \approx 12.5$) using acetophenone **1a** as a benchmark substrate (Table 1). *O*-Substituted hydroxylamines (**2a–c**) bearing the 2,4-dinitrophenyl, diphenylphosphoryl or *p*-nitrophenyl group failed to generate the desired amide as the *N*-Boc group remained intact (entries 1–3).

Table 1 Optimization of reaction conditions[a]



Entry	Aminating reagent	Yield[b] (%)
1	**2a**	0
2	**2b**	0
3	**2c**	0
4	**2d**	95
5[c]	**2d**	0

[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), aminating agent **2** (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt. [b] Isolated yield. [c] No reaction was observed in other solvents like MeOH, CH_3CN, CH_2Cl_2, THF, and DMF.



Scheme 2 Preparation of secondary amides.[a,b] [a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), TsONHBoc (**2d**) (0.75 mmol, 1.5 equiv.), TFE (0.5 mL), rt. [b] Isolated yield. [c] Reaction performed at 70 °C. [d] Regioisomers observed, ratio determined *via* ^{1}H NMR of the crude mixture and the major isomer is shown here. [e] Mixture of non-separable regioisomers.

Next, *N*-Boc-*O*-tosylhydroxylamine **2d** was subjected to these reaction conditions and, to our delight, *N*-Boc was cleaved *in situ* and the desired product **3a** was obtained with an excellent yield of 95% (entry 4). As expected, other commonly used solvents like MeOH, CH_3CN, CH_2Cl_2, THF, and DMF were found to be ineffective (entry 5).

To further examine the versatility of this method, we next evaluated different ketones under the optimal reaction conditions (Scheme 2). We initially explored a series of electron-rich substituents on the aryl ring. The substrates with a *para*-substituents like methyl, methoxy or phenyl groups were effortlessly converted to the corresponding products in high yield (**3b–3d**). The presence of a free hydroxyl group or even a highly labile TBS group was well tolerated under the reaction conditions (**3e** and **3f**). Aryl compounds with disubstitution on the ring turned out to be suitable substrates for this transformation (**3g** and **3h**). Ketones embedded with reactive functionalities such as allyloxy or propargyloxy provided amides **3i** and **3j** in 96% and 95% yield, respectively. We next evaluated a series of electron-deficient substrates bearing halogens at different positions on the ring, and in all cases the desired products were obtained in excellent yield (**3k–3o**). Despite being a less favorable substrate for the Beckmann rearrangement, strongly electron-deficient substituents like the nitro group produced **3p** in 90% at an elevated temperature. The presence of an ester, amide or acid-sensitive *N*-Boc group on the ring did not affect the reaction outcome (**3q–3s**). It is noteworthy that highly acid-sensitive groups like TBS and Boc have remained challenging using literature methods. Heteroarylic amides can easily be obtained under the optimized conditions in high efficiency (**3t** and **3u**). The reaction progressed well for the conversion of naphthyl-substituted ketones to **3v** in 92% yield. When diaryl ketones were used, a mixture of products was obtained due to competing migration of the aryl groups (**3x** and **3y**). The use of ketones bearing an aliphatic chain or carbocycle instead of methyl led to the desired products, albeit as a mitxure (**3z–3zb**). Substituted cyclohexanone underwent NH insertion to produce the desired lactam **3zc** in 75% yield at 70 °C. The conditions were found to be optimal even for aliphatic ketones, which were converted smoothly into the desired amide **3ze** in excellent yield. Furthermore, the same procedure was followed for the complex substrate pregnenolone to access the corresponding amide **3zf** in 90% yield.

Conclusions

In summary, we have developed the first direct method for the preparation of secondary amides from ketones using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as the aminating reagent. This reagent advantageously excludes the additional step of *N*-Boc deprotection in a strongly acidic medium, does not require fresh preparation on every use and storage at low temperature. We hope that this improved method will find a good application.

Conflicts of interest

There are no conflicts to declare.

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Metal- and Additive-Free Intermolecular Aziridination of Olefins Using *N*-Boc-*O*-tosylhydroxylamine

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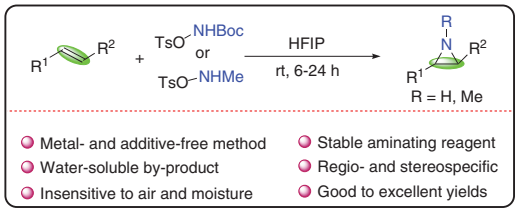

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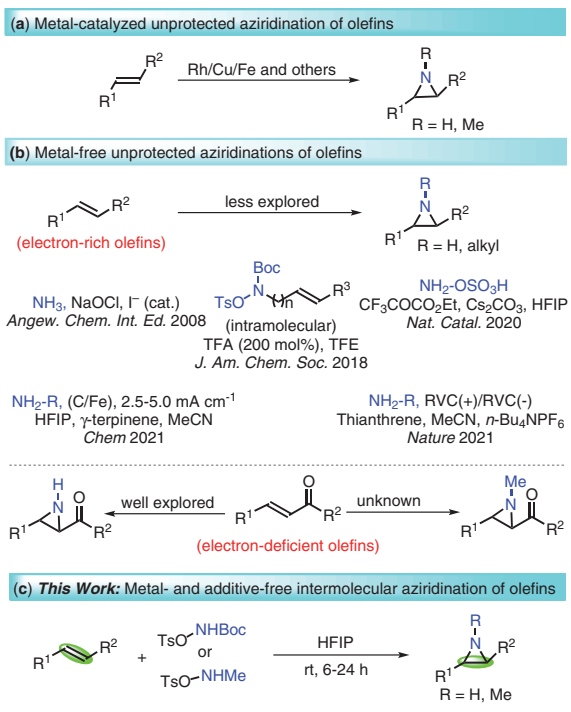
Abstract A metal and additive-free stereospecific direct *N*-H and *N*-Me aziridination of inactivated olefins is disclosed using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as an aminating agent in hexafluoroisopropanol (HFIP). The use of TsONHBoc, which generates the free aminating agent *in situ* under the reaction conditions, has several inherent advantages over other similar agents, such as low cost, easy access, and stability (non-explosiveness) during storage over a longer time.

Key words aziridination, TsONHBoc, metal and additives free, stereospecific, regioselective

The development of improved synthetic methods for the preparation of the smallest saturated azaheterocycles, aziridines, has attracted significant attention in the recent past. They not only form important building blocks but also exist as substructures in many bioactive molecules.[1] For example, aziridines serve as a crucial precursor for many drugs such as (–)-oseltamivir, (+)-lycoricidine, (–)-agelastatin A, etc.[2] Traditionally, they were obtained in a protected/activated form (e. g., *N*-Ts, *N*-Ns, *N*-acyl) through the cyclization of amino- or azido-alcohols, addition of carbenes to imines, or transfer of nitrenes to olefinic bonds.[3] The direct synthesis of non-activated aziridines (*N*-H, *N*-alkyl) from alkenes remained challenging until recently. Initially, the success in this direction was achieved on unactivated olefins using Rh catalyst and hydroxylamine-derived *O*-2,4-dinitrophenylhydroxylamine (DPH), hydroxylamine-*O*-sulfonic acid (HOSA), or *O*-(mesitylsulfonyl)hydroxylamine (MSH) as one of the aminating reagents, reported by the groups of Falck, Kurti, and Jat and Tiwari (Scheme 1a).[4] The expensive Rh-catalyst was later replaced by Cu and Fe catalysts.[5] Accessing useful scaffolds under transition-metal-free conditions offers several unique advantages and therefore remains one of the top priorities in organic synthesis. In this direction, the preliminary breakthrough for aziridines came from the group of Bottaro in 1980 who prepared unprotected aziridines using *O*-tosylhydroxylamine.[6] In 2008, Vos and co-workers reported an iodine-catalyzed aziridination of styrenes using ammonia (Scheme 1b).[7]



Scheme 1 Literature approaches for direct *N*-H and *N*-alkyl aziridination of olefins■■*letters* ***1b-f*** *removed as conditions, not compound numbers; text is clear*■■

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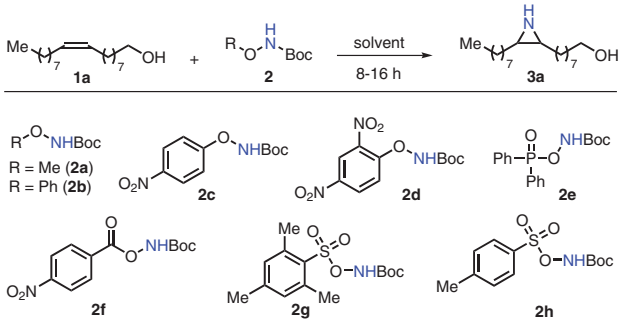
An intramolecular aziridination was achieved through *in situ* deprotection of *O*-Ts and *N*-Boc on aminating reagent tethered olefins in the presence of TFA by Bower and coworkers in 2018 (Scheme 1b).[8] Very recently, the group of Kurti reported an organocatalytic aziridination of olefins involving transient oxaziridines generated from ethyl trifluoropyruvate using HOSA as the aminating agent (Scheme 1b).[9] In addition to these metal-free methods, electrochemical approaches also have been developed mainly for the synthesis of *N*-alkyl aziridines from olefins (Scheme 1b).[10] Despite these magnificent developments, these methods in general have one or the other limitations such as the requirement of expensive metal catalysts, additives, explosive or toxic reagents, limited substrates scope, interference of byproduct, etc. Our literature search did not produce any report on the aziridination of unactivated alkenes that excludes the use of both the metal catalysts as well as additives and hence any such method is highly desirable. In continuation of our research in this area, herein we report an unprecedented metal- and additive-free direct atom-economical method for the aziridination of unactivated alkenes using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) in hexafluoroisopropanol (HFIP) solvent (Scheme 1c). This aminating reagent offers several advantages over its other variants such as: (i) stability on long storage, (ii) straightforward and cost-effective synthetic steps, and (iii) *in situ* generation of the actual aminating reagent in solvents such as TFE and HFIP.

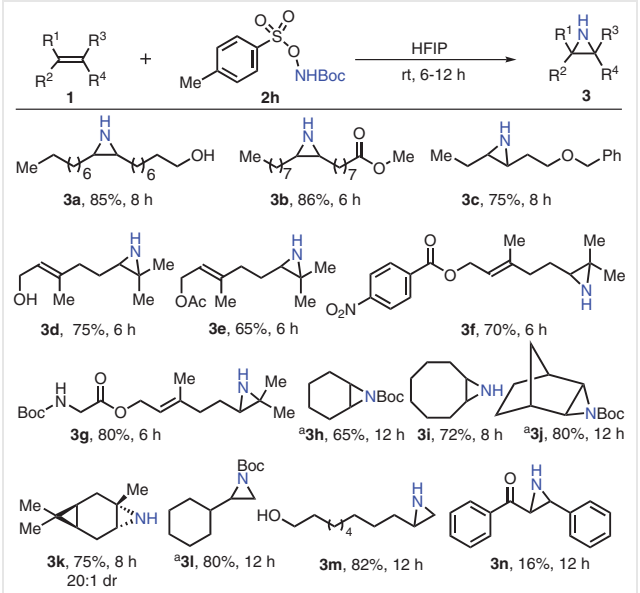
We initiated the reaction condition optimization study by screening various *N*-Boc-protected hydroxylamines **2** using oleyl alcohol (**1a**) as the model substrate (Table 1). As the *in situ* deprotection of *N*-Boc group on the aminating agent was essential for the initiation of the reaction, weakly acidic 2,2,2-trifluoroethanol (TFE) was chosen as the solvent. Among the different reagents used, the *O*-alkyl or *O*-aryl substituted hydroxylamines **2a–d** failed to produce the desired product (entries 1–4). The use of **2** having electron-withdrawing substitution, like the *O*-phosphoryl or *O*-acyl group, did not change the outcome due to the non-cleavage of the *N*-Boc group (entries 5 and 6). To our delight, *N*-Boc-*O*-(mesitylsulfonyl)hydroxylamine (**2g**) underwent the desired deprotection smoothly to provide the corresponding *cis*-unactivated aziridine **3a** in a good yield of 76% (entry 7). Switching to TsONHBoc (**2h**) was found to be the most suitable aminating agent producing **3a** in an excellent yield of 80% (entry 8). The use of slightly higher acidic hexafluoroisopropanol (HFIP, pK_a = 9.3) in place of TFE (pK_a = 12.4) facilitated the deprotection of *N*-Boc group, producing the desired product in a shorter reaction time with an improved yield of 85% (entry 9).

Table 1 Optimization of Reaction Conditions[a]

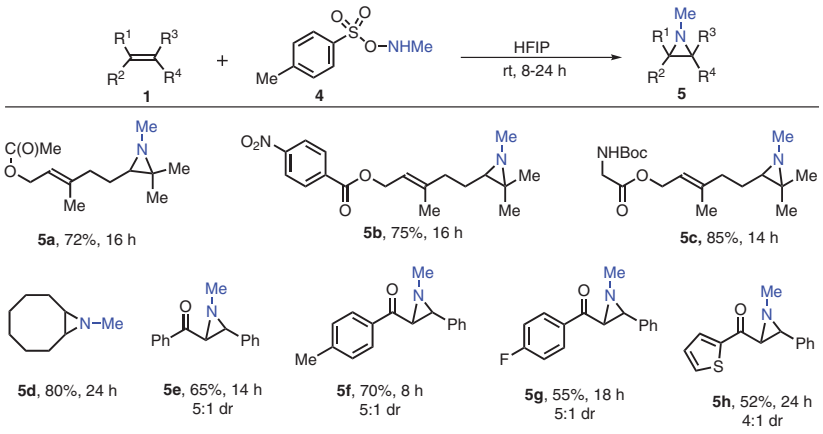


Entry	Aminating agent [**2**]	Solvent	Time [h]	Yield [%][b]
1	**2a**	TFE	16	0
2	**2b**	TFE	16	0
3	**2c**	TFE	16	0
4	**2d**	TFE	16	0
5	**2e**	TFE	16	0
6	**2f**	TFE	16	0
7	**2g**	TFE	16	76
8	**2h**	TFE	16	80
9	**2h**	HFIP	8	85
10[c]	**2h**	HFIP	8	70
11	**2h**	solvents[d]	16	<5

[a] Reaction conditions, unless otherwise presented: **1a** (1.0 equiv.), aminating agent **2** (1.5 equiv.), solvent (0.5 mL), rt.
[b] Isolated yield after silica gel column chromatography.
[c] 1.0 equiv. of **2h** were used.
[d] EtOH, CH_3CN, DMF, THF, $CHCl_3$, CH_2Cl_2 were used. TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoroisopropanol.



Scheme 2 Substrate scope for *N*-H aziridination. *Reaction conditions*: **1** (0.5 mmol), aminating agent **2h** (0.75 mmol), HFIP (0.5 mL), rt. Isolated yields are reported. [a] For the ease of purification, isolated as Boc derivatives. ■■*check times vs procedures*■■

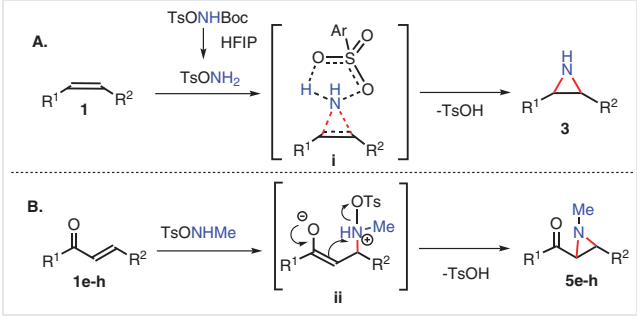


Scheme 3 Substrate scope for *N*-Me aziridination. *Reaction conditions*: **1** (0.5 mmol), aminating agent **4** (0.60 mmol), HFIP (0.5 mL), rt. Isolated yields are reported.

With the optimized conditions in hand, we explored the scope of this aziridination method using a wide range of structurally diverse olefins (Scheme 2). Both *cis*- and *trans*-1,2-disubstituted aliphatic olefins **1a–c** delivered *cis*- and *trans*-configured aziridines **3a–c** as the sole diastereomer in very good yields. Notably, the trisubstituted olefin, geraniol and its derivatives reacted regioselectively at 6,7-olefinic position to produce the corresponding aziridines **3d–g** in good yields. Cyclic alkenes such as cyclohexene, *cis*-cyclooctene, norbornene, and 3-carene transformed into the corresponding aziridines **3h–k** in good to excellent yields. The substrates with terminal alkenes such as vinylcyclohexane (**1l**) and 10-undecen-1-ol (**1m**) underwent smooth aziridination under optimized conditions to produce corresponding aziridines **3l**,**m** in good yields. The aziridines **3h** and **3l** were isolated in Boc-protected form for ease of purification. On the other hand, the activated alkene such as chalcone **1n** provided the aziridine **3n** in 16% yield.

We were next interested to explore this metal and additive free protocol for the direct *N*-Me aziridination of olefins using *N*-methyl-*O*-tosylhydroxylamine (**4**; TsONHMe) as an aminating reagent in HFIP (Scheme 3). Under these conditions, the trisubstituted alkenes produced the corresponding *N*-Me aziridines **5a–c** in good to excellent yields. The cyclic alkene *cis*-cyclooctene was aziridinated to give **5d** with a good yield. The conjugated alkenes were converted smoothly under these conditions to produce aziridines **5e–h** with moderate to good yields and diastereoselectivities. The reaction is expected to follow an aza-Prilezhaev-type mechanism[8a] for unactivated olefins (Scheme 4A) and *via* aza-MIRC pathway for chalcones[8b] (Scheme 4B).

In conclusion, we have established a metal and additive-free protocol for the direct synthesis of *N*-H/*N*-Me aziridines from alkenes using bench stable and cost-effective hydroxylamine derived as the nitrogen source. The reagent TsONHBoc produces non-interfering byproduct (TsOH) that



Scheme 4 Plausible aziridination pathway for non-activated (A) and electron-deficient olefins (B)

could be easily removed by simple aqueous workup. The reaction proceeds through *in situ* deprotection of *N*-Boc in TFE or HFIP solvent. This stereospecific and regioselective reaction tolerates several labile functional groups like alcohol, ether, ester, Boc, *etc*. Therefore, this operationally simple, cost-effective, metal- and additive-free aziridination approach is expected to find a broad synthetic utility in for a large-scale synthesis of unprotected aziridines.

Unless otherwise specified, all reactions were carried out under an open atmosphere in a round-bottom flask. All the commercial olefins were used without further purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (Merck TLC silica gel 60, F_{254}), and the spots were visualized with UV light or by charring the plates dipped in PMA or $KMnO_4$ or Ninhydrin solution. The compounds were purified by flash column chromatography using silica gel (100–400 mesh, neutralized with *t*-$BuNH_2$) with distilled solvents. NMR spectra were acquired on Bruker 400 MHz (^1H at 400 MHz, ^{13}C at 100 MHz), in $CDCl_3$ as the solvent. The residual solvent signals were used as references ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$). High-resolution mass spectrometry (HRMS) was performed on an Agilent 6530 Q-TOF instrument using electrospray ion-

ization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode. TsONHBoc,[11a] TsONHMe,[11b] **1f**,[4c] and **1g**[5b] were prepared following literature procedure.

N-H Aziridination; General Procedure

To a round-bottom flask equipped with a magnetic stirring bar was added olefin **1** (0.5 mmol) and HFIP (0.5 mL). To this stirred solution aminating agent **2h** (1.5 equiv.) was added and the reaction mixture was stirred at rt for the specified time. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine solution (10 mL) and dried (anhyd Na_2SO_4). The organic layer was evaporated under reduced pressure and crude obtained was purified by column chromatography (silica gel neutralized with *t*-$BuNH_2$, EtOAc/hexane).

N-Me Aziridination; General Procedure

To a round-bottom flask equipped with a magnetic stirring bar was added olefin **1** (0.5 mmol) and HFIP (0.5 mL). To this stirred solution aminating agent **4** (0.6 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at rt for the specified time. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine solution (10 mL) and dried (anhyd Na_2SO_4). The organic layer was evaporated under reduced pressure and crude obtained was purified through column chromatography (silica gel neutralized with *t*-$BuNH_2$, EtOAc/hexane).

8-(3-Octylaziridin-2-yl)octan-1-ol (3a)

Following the general *N*-H aziridination procedure, oleyl alcohol (135 mg, 0.502 mmol) and TsONHBoc (216 mg, 0.754 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h. Chromatographic purification of crude product afforded **3a** as colorless syrupy liquid (120.5 mg, 85% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.5 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 6.6 Hz, 2 H), 1.94 (s, 1 H), 1.65–1.49 (m, 4 H), 1.41–1.13 (m, 27 H), 0.86 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.66, 37.83, 35.05, 32.77, 31.83, 29.57, 29.56, 29.52, 29.47, 29.32, 29.23, 28.71, 28.68, 27.99, 27.98, 25.71, 22.62, 14.06.

Methyl (*Z*)-8-(3-Octylaziridin-2-yl)octanoate (3b)

Following the general *N*-H aziridination procedure, methyl oleate (148 mg, 0.50 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 6 h. Chromatographic purification of crude product afforded **3b** as a colorless oil (134 mg, 86% yield) whose spectral data were in accord with the literature values.[4c]

TLC R_f ~ 0.3 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 2.03–1.94 (m, 2 H), 1.69–1.57 (m, 2 H), 1.48–1.19 (m, 25 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

(*E*)-2-(2-(Benzyloxy)ethyl)-3-ethylaziridine (3c)

Following the general *N*-H aziridination procedure, (*E*)-((hex-3-en-1-yloxy)methyl))benzene (95 mg, 0.50 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.6 mL) at rt for 8 h. Chromatographic purification of crude product afforded **3c** as colorless oil (77 mg, 75% yield).

TLC R_f ~ 0.4 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H), 4.52 (s, 2 H), 3.59 (t, *J* = 5.5 Hz, 2 H), 1.83–1.71 (m, 2 H), 1.70–1.60 (m, 2 H), 1.52–1.31 (m, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.36, 128.32, 127.57, 127.51, 73.02, 68.62, 38.93, 34.87, 34.25, 27.21, 11.55.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{13}H_{20}NO]^+$: 206.1539; found: 206.1531.

(*E*)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-en-1-ol (3d)

Following the *N*-H general aziridination procedure, geraniol (77 mg, 0.50 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 6 h. Chromatographic purification of crude product afforded **3d** as clear liquid (63 mg, 75% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.4 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (t, *J* = 6.7 Hz, 1 H), 4.09 (d, *J* = 6.8 Hz, 2 H), 2.56 (brs, 2 H), 2.20–2.02 (m, 2 H), 1.82–1.72 (m, 1 H), 1.64 (s, 3 H), 1.57–1.44 (m, 2 H), 1.22 (s, 3 H), 1.14 (s, 3 H).

(*E*)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-en-1-yl Acetate (3e)

Following the general *N*-H aziridination procedure, geranyl acetate (98 mg, 0.50 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 6 h. Chromatographic purification of crude product afforded **3e** as clear liquid (68 mg, 65% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.3 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (t, *J* = 7.0 Hz, 1 H), 4.52 (d, *J* = 7.1 Hz, 2 H), 2.21–2.01 (m, 2 H), 1.98 (s, 3 H), 1.73–1.66 (m, 1 H), 1.65 (s, 3 H), 1.53–1.43 (m, 2 H), 1.19 (s, 3 H), 1.09 (s, 3 H).

(*E*)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-en-1-yl 4-Nitrobenzoate (3f)

Following the general *N*-H aziridination procedure, geranyl 4-nitrobenzoate■■*OK*?■■ (151 mg, 0.5 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 6 h. Chromatographic purification of crude product afforded **3f** as yellow semisolid (111 mg, 70% yield).

TLC R_f = 0.5 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.8 Hz, 2 H), 8.14 (d, *J* = 8.8 Hz, 2 H), 5.45 (t, *J* = 6.8 Hz, 1 H), 4.83 (d, *J* = 7.1 Hz, 2 H), 2.24–2.04 (m, 2 H), 1.74 (s, 3 H), 1.69 (t, *J* = 6.6 Hz, 1 H), 1.56–1.46 (m, 2 H), 1.18 (s, 3 H), 1.10 (s, 3 H), 0.65 (brs, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.65, 150.43, 142.97, 135.84, 130.68, 123.46, 117.97, 62.67, 42.89, 37.76, 35.58, 28.09, 27.51, 19.71, 16.61.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{23}N_2O_4]^+$: 319.1652; found: 319.1656.

(*E*)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-en-1-yl *N*-(*tert*-Butoxycarbonyl)glycinate (3g)

Following the general *N*-H aziridination procedure, (*E*)-3,7-dimethylocta-2,6-dien-1-yl *N*-(*tert*-butoxycarbonyl)glycinate (156 mg, 0.50 mmol) and TsONHBoc■■*OK?*■■ (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 6 h. Chromatographic purification of crude product afforded **3g** as clear liquid (130 mg, 80% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f ~ 0.5 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (t, *J* = 7.0 Hz, 1 H), 5.21 (brs, 1 H), 4.59 (d, *J* = 7.1 Hz, 2 H), 3.81 (d, *J* = 5.2 Hz, 2 H), 2.20–1.99 (m, 2 H), 1.72–1.66 (m, 1 H), 1.64 (s, 3 H), 1.54–1.42 (m, 2 H), 1.37 (s, 9 H), 1.18 (s, 3 H), 1.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.22, 155.61, 142.22, 118.01, 79.64, 61.82, 42.85, 42.25, 37.48, 35.74, 28.12, 27.63, 27.14, 19.36, 16.28.

***tert*-Butyl 7-Azabicyclo[4.1.0]heptane-7-carboxylate (3h)**

Following the general *N*-H aziridination procedure, cyclohexene (41 mg, 0.5 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h■■*12 h, Sch.2?*■■. The progress of the reaction was monitored by TLC. After complete consumption of olefin, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine solution and then dried (anhyd Na_2SO_4). After removal of Na_2SO_4, the organic layer was evaporated under reduced pressure and the crude obtained was dissolved in DCM (5 mL) and Boc_2O (218 mg, 1.0 mmol) and TEA (178 µL, 1.25 mmol) were added at 0 °C. The reaction mixture was stirred at rt for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine solution and then dried (anhyd Na_2SO_4). The organic layer was evaporated under reduced pressure and crude obtained was purified by column chromatography (silica gel neutralized by *t*-BuNH_2, 10–20% EtOAc/hexane). Aziridine **3h** was obtained as a colorless liquid (64 mg, 65% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.4 (30% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56–2.49 (m, 2 H), 1.91–1.84 (m, 2 H), 1.78–1.70 (m, 2 H), 1.41 (s, 9 H), 1.39–1.31 (m, 2 H), 1.23–1.13 (m, 2 H).

9-Azabicyclo[6.1.0]nonane (3i)

Following the general *N*-H aziridination procedure, *cis*-cyclooctene (55 mg, 0.50 mmol) and TsONHBoc■■*OK?*■■ (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h. Chromatographic purification of crude product afforded **3i** as a clear liquid (45 mg, 72% yield) whose spectral data were in accord with the literature values.[4b]

TLC R_f = 0.4 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12–1.99 (m, 2 H), 1.89 (brs, 2 H), 1.65–1.47 (m, 4 H), 1.44–1.29 (m, 4 H), 1.11–0.93 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.15, 27.42, 27.37, 26.64.

***tert*-Butyl (1*R*,2*S*,4*S*,5*S*)-3-Azatricyclo[3.2.1.0^{2,4}]octane-3-carboxylate (3j)**

Following the general *N*-H aziridination procedure, norbornene (47 mg, 0.5 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h■■*12 h, Sch.2?*■■. The progress of the reaction was monitored by TLC. After complete consumption of olefin, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine solution and then dried (anhyd Na_2SO_4). After removal of Na_2SO_4, the organic layer was evaporated under reduced pressure and crude obtained was dissolved in DCM (5 mL) and Boc_2O (218 mg, 1.0 mmol) and TEA (178 µL, 1.25 mmol) were added at 0 °C. The reaction mixture was stirred at rt for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine solution and then dried (anhyd Na_2SO_4). The organic layer was evaporated under reduced pressure and crude obtained was purified by column chromatography (silica gel neutralized by *t*-BuNH_2, 10–15% EtOAc/hexane). Aziridine **3j** was obtained as a colorless liquid (84 mg, 80% yield) which configuration has been determined by comparing the crude ^{1}H NMR values of *N*-H aziridine.[12]

TLC R_f = 0.5 (20% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 2 H), 2.44 (s, 2 H), 1.49 (s, 2 H), 1.40 (s, 9 H), 1.35–1.29 (m, 1 H), 1.21–1.12 (m, 2 H), 0.73 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.51, 80.67, 39.08, 36.01, 28.10, 28.09, 25.99.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{12}H_{19}NO_2Na$]$^+$: 232.1308; found: 232.1310.

(1*S*,3*S*,5*R*,7*R*)-3,8,8-Trimethyl-4-azatricyclo[5.1.0.0^{3,5}]octane (3k)

Following the general *N*-H aziridination procedure, 3-carene (68 mg, 0.50 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h. Chromatographic purification of crude product afforded **3k** as a yellow liquid (57 mg, 75% yield, 20:1 dr) whose spectral data were in accord with the literature values.[4b]

TLC R_f = 0.4 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (dd, *J* = 15.6, 9.5 Hz, 1 H), 2.01 (dd, *J* = 15.5, 9.4 Hz, 1 H), 1.73 (s, 1 H), 1.58–1.51 (m, 1 H), 1.33 (dd, *J* = 15.5, 3.2 Hz, 1 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.73 (s, 3 H), 0.44 (td, *J* = 9.2, 3.4 Hz, 1 H), 0.33 (td, *J* = 9.2, 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.72, 32.76, 27.97, 24.91, 23.22, 18.20, 16.48, 15.66, 14.84, 13.04.

***tert*-Butyl 2-Cyclohexylaziridine-1-carboxylate (3l)**

Following the general *N*-H aziridination procedure, vinylcyclohexane (55 mg, 0.5 mmol) and TsONHBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h■■*12 h, Sch.2?*■■. The progress of the reaction was monitored by TLC. After complete consumption of olefin, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine solution and dried (anhyd Na_2SO_4). The organic layer was evaporated *in vacuo* and crude obtained was dissolved in DCM (5 mL) and cooled to 0 °C then Boc_2O (218 mg, 1 mmol) and TEA (178 µL, 1.25 mmol) were added. The reaction mixture was stirred at rt for 4 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine solution and dried (anhyd Na_2SO_4). The organic layer was evaporated in *vacuo* and crude obtained was purified by column chroma-

tography (silica gel neutralized by *t*-BuNH$_2$, 10–20% EtOAc/hexane). Aziridine **3l** was obtained as a colorless liquid (90 mg, 80% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.4 (30% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (d, *J* = 6.2 Hz, 1 H), 2.16–2.10 (m, 1 H), 1.94–1.84 (m, 2 H), 1.79–1.61 (m, 4 H), 1.44 (s, 9 H), 1.26–1.01 (m, 6 H).

9-(Aziridin-2-yl)nonan-1-ol (3m)

Following the general *N*-H aziridination procedure, undec-10-en-1-ol (85 mg, 0.50 mmol) and TsONHMBoc (215 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h■■*12 h, Sch.2?*■■. Chromatographic purification of crude product afforded **3m** as colorless thick liquid (76 mg, 82% yield).

TLC R_f = 0.5 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (t, *J* = 6.6 Hz, 2 H), 1.93–1.86 (m, 1 H), 1.79 (brs, 1 H), 1.71 (d, *J* = 5.8 Hz, 1 H), 1.57–1.45 (m, 2 H), 1.44–1.18 (m, 16 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.65, 34.41, 32.88, 30.55, 29.58, 29.48, 27.61, 25.86, 25.17.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{11}H_{24}NO$]$^+$: 186.1852; found: 186.1842.

Phenyl(3-phenylaziridin-2-yl)methanone (3n)

Following the general *N*-H aziridination procedure, (*E*)-chalcone (104 mg, 0.50 mmol) and TsONHBoc (161.25 mg, 0.75 mmol) were stirred in HFIP (0.5 mL) at rt for 12 h. Chromatographic purification of crude product afforded **3n** as a colorless liquid (18 mg, 16% yield) whose spectral data were in accord with the literature values.[4d]

TLC R_f = 0.5 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.8 Hz, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.40–7.28 (m, 5 H), 3.52 (d, *J* = 6.3 Hz, 1 H), 3.18 (d, *J* = 7.7 Hz, 1 H), 2.68 (brs, 1 H).

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl Acetate (5a)

Following the general *N*-Me aziridination procedure, geranyl acetate (98 mg, 0.50 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 16 h. Chromatographic purification of crude product afforded **5a** as colorless oil (81 mg, 72% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.3 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (t, *J* = 6.9 Hz, 1 H), 4.51 (d, *J* = 7.1 Hz, 2 H), 2.31 (s, 3 H), 2.16–2.00 (m, 2 H), 1.96 (s, 3 H), 1.63 (s, 3 H), 1.55–1.42 (m, 2 H), 1.12 (s, 3 H), 1.08 (t, *J* = 6.5 Hz, 1 H), 1.04 (s, 3 H).

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl 4-Nitrobenzoate (5b)

Following the general *N*-Me aziridination procedure, (*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-nitrobenzoate (150 mg, 0.5 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 16 h. Chromatographic purification of crude product afforded **5b** as colorless oil (124 mg, 75% yield) whose spectral data were in accord with the literature values.[5b]

TLC R_f = 0.3 (10% MeOH/DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.6 Hz, 2 H), 8.19 (d, *J* = 8.7 Hz, 2 H), 5.49 (t, *J* = 7.1 Hz, 1 H), 4.89 (d, *J* = 7.1 Hz, 2 H), 2.35 (s, 3 H), 2.24–2.11 (m, 2 H), 1.79 (s, 3 H), 1.59–1.47 (m, 2 H), 1.16 (s, 3 H), 1.08 (s, 3 H), 1.06–1.03 (m, 1 H).

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl *N*-(*tert*-Butoxycarbonyl)glycinate (5c)

Following the general *N*-Me aziridination procedure (*E*)-3,7-dimethylocta-2,6-dien-1-yl *N*-(*tert*-butoxycarbonyl)glycinate (156 mg, 0.50 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 14 h. Chromatographic purification of crude product afforded **5c** as colorless oil (144 mg, 85% yield).

TLC R_f = 0.5 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.32 (t, *J* = 7.1 Hz, 1 H), 5.11 (brs, 1 H), 4.62 (d, *J* = 7.2 Hz, 2 H), 3.85 (d, *J* = 5.4 Hz, 2 H), 2.32 (s, 3 H), 2.18–2.03 (m, 2 H), 1.67 (s, 3 H), 1.52–1.43 (m, 2 H), 1.40 (s, 9 H), 1.13 (s, 3 H), 1.04 (s, 3 H), 1.02–0.98 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.42, 155.77, 142.79, 118.13, 79.94, 62.14, 51.93, 42.51, 39.60, 39.43, 37.79, 28.37, 27.45, 21.75, 18.03, 16.45.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{18}H_{33}N_2O_4$]$^+$: 341.2435; found: 341.2441.

9-Methyl-9-azabicyclo[6.1.0]nonane (5d)

Following the general *N*-Me aziridination procedure *cis*-cyclooctene (110 mg, 1.0 mmol) and TsONHMe (241 mg, 1.2 mmol) were stirred in HFIP (0.5 mL) at rt for 24 h. Chromatographic purification of crude product afforded **5d** as a colorless oil (111 mg, 80% yield).

TLC R_f = 0.4 (50% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.13–2.00 (m, 2 H), 1.60–1.49 (m, 4 H), 1.44–1.29 (m, 6 H), 1.18–1.05 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.75, 44.76, 27.18, 26.58, 25.91.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_9H_{18}N$]$^+$: 140.1434; found: 140.1435.

(1-Methyl-3-phenylaziridin-2-yl)(phenyl)methanone (5e)

Following the general *N*-Me aziridination procedure (*E*)-chalcone (104 mg, 0.5 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 14 h. Chromatographic purification of crude product afforded **5e** as a colorless oil (77 mg, 65% yield, >5:1 dr) whose spectral data were in accord with the literature values.[4d]

TLC R_f = 0.5 (20% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 2 H), 7.64–7.57 (m, 1 H), 7.53–7.47 (m, 2 H), 7.43–7.30 (m, 5 H), 3.59 (d, *J* = 2.3 Hz, 1 H), 3.37 (d, *J* = 2.0 Hz, 1 H), 2.70 (s, 3 H).

(1-Methyl-3-phenylaziridin-2-yl)(*p*-tolyl)methanone (5f)

Following the general *N*-Me aziridination procedure (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (111 mg, 0.5 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 8 h. Chromatographic purification of crude product afforded **5f** as yellowish oil (88 mg, 70% yield, >5:1 dr) whose spectral data were in accord with the literature values.[4d]

TLC R_f = 0.5 (20% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.9 Hz, 2 H), 7.39–7.27 (m, 7 H), 3.59 (d, *J* = 2.1 Hz, 1 H), 3.37 (d, *J* = 1.5 Hz, 1 H), 2.68 (s, 3 H), 2.43 (s, 3 H).

(4-Fluorophenyl)(1-methyl-3-phenylaziridin-2-yl)methanone (5g)

Following the general *N*-Me aziridination procedure (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (113 mg, 0.5 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 18 h. Chromatographic purification of crude product afforded **5g** as yellowish oil (70 mg, 55% yield, 5:1 dr) whose spectral data were in accord with the literature values.[4d]

TLC R_f = 0.5 (20% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.02 (m, 2 H), 7.34–7.26 (m, 3 H), 7.17 (t, *J* = 8.4 Hz, 2 H), 7.02 (t, *J* = 8.5 Hz, 2 H), 3.50 (d, *J* = 2.0 Hz, 1 H), 3.35 (s, 1 H), 2.66 (s, 3 H).

(1-Methyl-3-phenylaziridin-2-yl)(thiophen-2-yl)methanone (5h)

Following the general *N*-Me aziridination procedure (*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (107 mg, 0.5 mmol) and TsONHMe (120.6 mg, 0.6 mmol) were stirred in HFIP (0.5 mL) at rt for 24 h. Chromatographic purification of crude product afforded **5h** as colorless oil (63 mg, 52% yield, 4:1 dr) whose spectral data were in accord with the literature values.[4d]

TLC R_f = 0.4 (20% EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 3.4 Hz, 1 H), 7.71 (d, *J* = 4.9 Hz, 1 H), 7.43–7.30 (m, 5 H), 7.22–7.13 (m, 1 H), 3.53 (d, *J* = 1.9 Hz, 1 H), 3.38 (d, *J* = 2.0 Hz, 1 H), 2.74 (s, 3 H).

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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Direct synthesis of secondary amides from ketones through Beckmann rearrangement using *O*-(mesitylsulfonyl)hydroxylamine

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ABSTRACT

The Beckmann rearrangement is a versatile method for the preparation of secondary amides from ketones *via* oxime intermediates and has been widely used in the synthesis of bioactive natural products and pharmaceuticals. Herein, we have developed a highly efficient direct method for the preparation of secondary amides and lactams from ketones using *O*-(mesitylsulfonyl)hydroxylamine (MSH). The reactions proceed rapidly at room temperature under mild condition without requiring any additive, and tolerate multiple functional groups. A simple aqueous work-up often furnished the products in excellent yield with high purity.

The ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR), comprising of top global pharmaceutical manufacturers, in their 2006 and 2016 meetings, identified the catalytic or sustainable direct preparation of amide functionality as one of the key reactions to be developed [1]. The Beckmann rearrangement of oximes is a very effective method to access amides and lactams, and is an industrial process to prepare the raw materials for polyamides, such as nylon-6 and nylon-12 [2]. It is a versatile method used to incorporate an *N*-atom into cyclic or acyclic ketones. Traditionally, the Beckmann rearrangement requires strongly acidic media (e.g. PCl_5, H_2SO_4) and high temperatures [3]. These reaction conditions can produce large amounts of undesired products and are untenable for sensitive substrates. This limitation could be partly overcome with the advent of milder reagents or catalysts such as cyanuric chloride [4j], BOP-Cl [4i], propyl phosphonic anhydride (T3P) [4d], triphosphagene [4g], triphosgene [4k], tosylchloride [4f], cyclopropenium salt [4e], TFA [4h], $Ca(NTf_2)_2$ [4a], and boronic acid [4b] (Scheme 1a). Despite the development of these reagents, several major limitations persist, such as: (a) the necessary preparation and purification of ketoxime substrates, (b) column chromatographic purification of the products, (c) and expensive solvents or elevated reaction temperature.

Therefore, a direct method devoid of the additional step of oxime substrate preparation is highly desired [5]. To that end Hyodo and co-workers very recently disclosed a direct method for the preparation of amides from ketones *via* transoximation using ethyl *N*-(phenylsulfonyl)oxyacetimidate [6]. This reacts with ketones to produce the corresponding sulfonyloxime, which in the presence of $TsOH{\cdot}H_2O$ and water gives the corresponding amides. Nonetheless, this elegant method requires: (a) Brønsted acid and water as additives, (b) extended reaction times of 24 h, (c) column chromatographic purification. Prior to this, Tamura and co-workers reported a two-step method for the conversion of ketones to amides through the Beckmann rearrangement *via* mesitylene sulfonyloxime using basic alumina in methanol [7]. In view of these limited studies, along with their intrinsic difficulties, an improved method for the direct preparation of secondary amides from ketones is needed.

Results and discussion

As part of an ongoing program to develop efficient reagents and transition metal catalyzed methods, we recently reported the highly regio- and stereo-specific aziridination of unactivated alkenes using MSH [8a] and the $Cu(OTf)_2$-catalyzed Beckmann rearrangement of ketones using hydroxylamine-*O*-sulfonic acid [8c]. We were next interested in developing an efficient, one-pot, mild, and possibly column chromatography-free method for preparing secondary amides directly from ketones using MSH.

We began using acetophenone **1a** as a model substrate and MSH **2** as the aminating agent (Table 1). The Beckmann rearrange-

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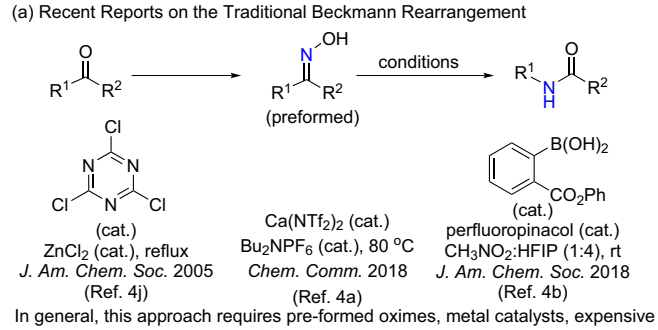
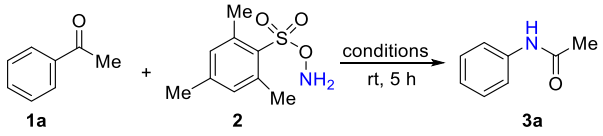


Scheme 1. The Beckmann Rearrangement for the Preparation of Amides.

Table 1
Optimization of the Reaction Conditions.[a]

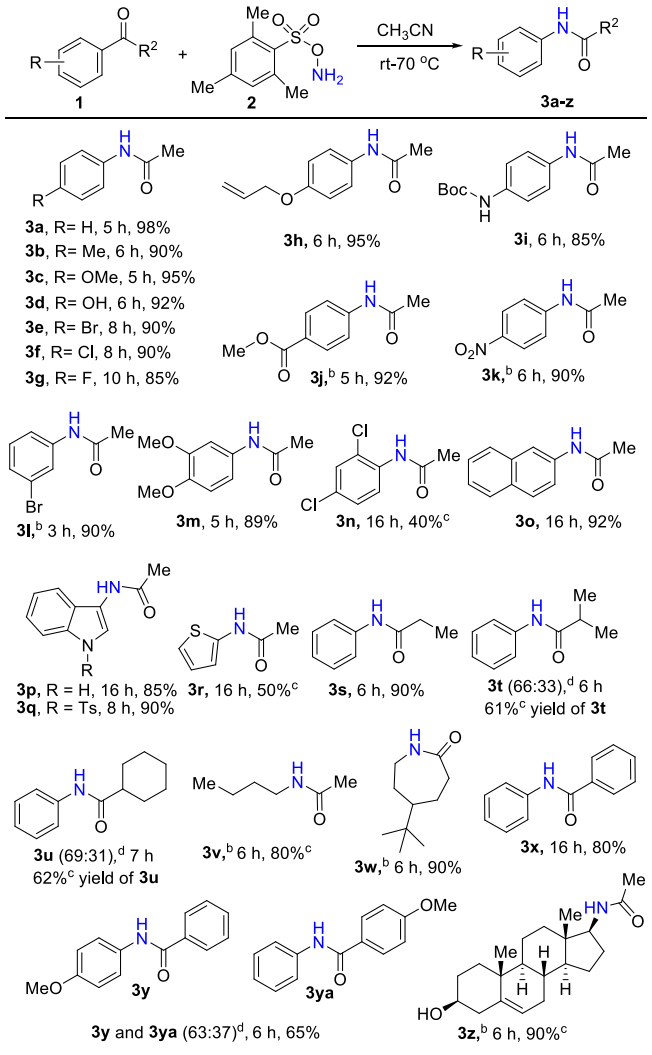


Entry	Additive	Solvent	Yield 3a (%)[b]
1	TFA[c]	TFE	82
2	–	TFE	85
3	–	CH_2Cl_2	87
4	–	THF	81
5	–	MeOH	80
6	**–**	**CH_3CN**	**98**
7[d]	–	CH_3CN	70
8[e]	–	CH_3CN	78
9[f]	–	CH_3CN	85
10	–	H_2O	77
11	–	EtOH	80

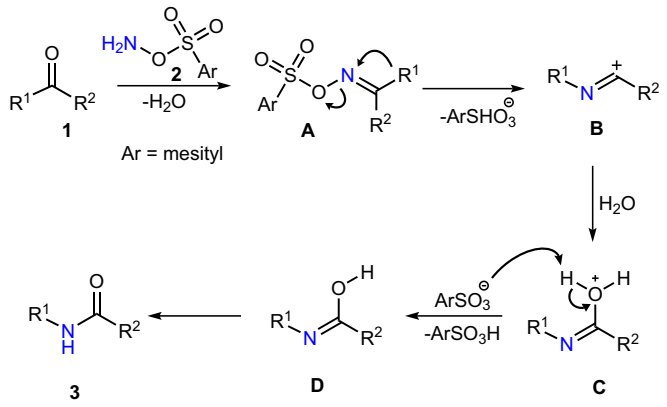
[a] Reagents and conditions unless otherwise stated: **1a** (0.5 mmol), **2** (1.0 mmol), solvent (2 mL), rt.
[b] Isolated yield.
[c] 10 mol% of TFA was used.
[d] 0.5 mmol of MSH was used.
[e] 0.6 mmol of MSH was used.
[f] 0.75 mmol of MSH was used, TFE = 2,2,2-trifluroethanol, TFA = trifluoroacetic acid. (MSH **2** is highly energetic and explosive in nature; in our routine lab work we have prepared moist MSH on up to a 2.0 g scale without any incident although care must be taken while handling it in gram scale)

ment generally gives better yields in an acidic medium and hence the reaction was performed in the presence of 10 mol% of TFA in 2,2,2-trifluoroethanol (TFE). The desired product **3a** was obtained in 82% yield at room temperature after 5 h (Entry 1). Gratifyingly, the reaction proceeded well with a slightly improved yield in the absence of TFA (Entry 2). Further, we examined the effect of different solvents. Acetonitrile turned out to be the optimal solvent giving the desired product in 98% yield (Entry 6). Lowering the MSH loading led to a diminished yield (Entries 7, 8 and 9). It is worth noting that the product could be isolated with high purity after washing the crude product (which was obtained after basic aqueous workup) with *n*-hexanes and no further purification was required.

With the optimized condition in hand, we investigated the substrate scope for this MSH-mediated Beckmann rearrangement (Scheme 2). For these studies, *para*-substituted acetophenones containing both electron-donating (Me, OH, OMe) as well as electron-withdrawing substituents (Br, Cl, F) were valuable substrates for the reaction and the products were obtained in excellent yields after a *n*-hexane wash of the crude products (**3a**–**3g**). The reactions with electron-rich derivatives were slightly faster compared to the electron-deficient acetophenones. An unprotected phenolic group was also tolerated (**3d**). The *para*-*O*-allyl-substituted acetophenone also provided the corresponding amide **3h** in excellent yield**.** Methyl 4-acetylbenzoate **1j** and *p*-nitroacetophenone **1k** were converted into the corresponding amides **3j** and **3k** at 70 °C. In these



Scheme 2. Substrate Scope of the Ketones[a]. [a]Reagents and conditions: **1** (0.5 mmol), **2** (1.0 mmol), CH_3CN (2 mL), rt. [b]Reaction temperature of 70 °C. [c]Column chromatography was required. [d]Ratio of non-separable regioisomers.



Scheme 3. Proposed Mechanism.

cases the reaction stopped at mesitylenesulfonyloxime intermediate **A** (Scheme 3) at room temperature.

Products **3h**, **3i** and **3j** bearing acid sensitive alkene, *N*-Boc, and ester functionalities highlight the functional group tolerance compared to literature methods that require strong acidic conditions. *meta*-Substituted, as well as disubstituted acetophenones, also reacted well to afford the desired products in good to excellent yields (**3l**–**3n**). Other aromatic rings such as naphthyl, indolyl, and thiophenyl were tolerated giving the corresponding amides in good to excellent yields (**3o**–**3r**). Propiophenone also furnished exclusively the phenyl migrated product (**3s**). On the other hand, when α-branched or cycloalkyl-phenylketones were used, a separable mixture of regioisomers was formed due to the comparable migratory aptitude of the aryl and branched alkyl groups (**3t** and **3u**). Gratifyingly, aliphatic cyclic and acyclic ketones were also smoothly converted into the corresponding amides and lactams, albeit at elevated temperatures (**3v** and **3w**). Whereas benzophenone reacted well to give amide in good yield, the unsymmetrical benzophenone offered a mixture of products due to the comparable migrating properties of the two aryl groups (**3x** and **3y**). Even a complex ketone such as pregnenolone gave the respective amide (**3z**) in 90% yield.

A plausible mechanism is described in Scheme 3. Ketone **1** reacts with MSH **2** to give mesitylenesulfonyloxime intermediate **A** which undergoes Beckmann rearrangement *via* a concerted 1,2-intramolecular shift to form intermediate **B** [5g], followed by nucleophilic attack of H_2O to give **C**. Deprotonation of **C** provides **D**, which further tautomerizes into the corresponding amide **3**.

In conclusion, we have developed a direct method for the synthesis of secondary amides and lactams from a variety of ketones using MSH. This method is operationally simple and does not require acid or any other additive. Labile or reactive functional groups such as ester, alcohol, phenolic-OH, Boc, halo, and alkenes were tolerated under our optimized reaction conditions. The various secondary amides were obtained in good to excellent yields. The products were isolated in high purity after aqueous work-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151822.

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Synthesis S. Verma et al. Special Topic

Zinc(II)-Catalyzed Synthesis of Secondary Amides from Ketones via Beckmann Rearrangement Using Hydroxylamine-*O*-sulfonic Acid in Aqueous Media

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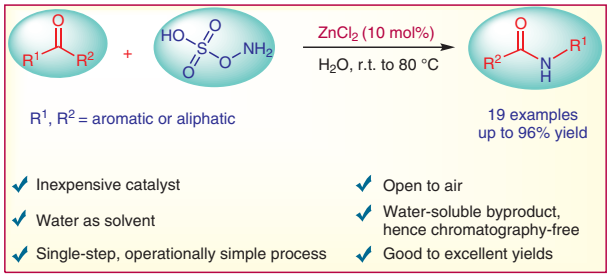

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Abstract A zinc(II)-catalyzed single-step protocol for the Beckmann rearrangement using hydroxylamine-*O*-sulfonic acid (HOSA) as the nitrogen source in water was developed. This direct method efficiently produces secondary amides under open atmosphere in a pure form after basic aqueous workup. It is environmentally benign and operationally simple.

Key words zinc(II) chloride, hydroxylamine-*O*-sulfonic acid (HOSA), ketones, Beckmann rearrangement, amides

Secondary amides play a pivotal role as a basic structural unit in numerous pharmaceuticals, bioactive natural products, polymers, dyes, and other functional materials (Figure 1).[1] They also serve as versatile building blocks for organic synthesis. For instance, the transformation of amides to different heterocyclic compounds is a well sought-after method for the preparation of medicinal agents and alkaloids.[2]

Conventionally, secondary amides are prepared from carboxylic acids and amines.[3] This trivial method typically requires the activation of the carboxylic acid functionality using a stoichiometric amount of reagents that eventually lead to a poor atom economy and release of a huge quantity of toxic waste. These serious limitations have severely impacted its industrial applications.[3a,e] Developing catalytic variations has led to substantial improvements, but with other limitations.[3c] In 1886, Beckmann and co-workers developed an altogether different approach, known as the Beckmann rearrangement, to prepare amides from ketones in two steps, using preformed oximes.[4] Nevertheless, the harsh reaction conditions (high temperature and strong acidic media) have largely precluded its application to sensitive substrates. Since then, tremendous advances have been made to surmount these shortcomings, leading to several interesting methods with relatively milder conditions from ketoximes (Scheme 1a).[5] Good progress has been made in recent years towards the development of direct methods using ketones instead of preformed ketoximes.[6] Nevertheless, these methods also suffer from some limitations, such as the use of toxic solvents, expensive reagents, or catalysts, high temperatures, and/or longer reaction

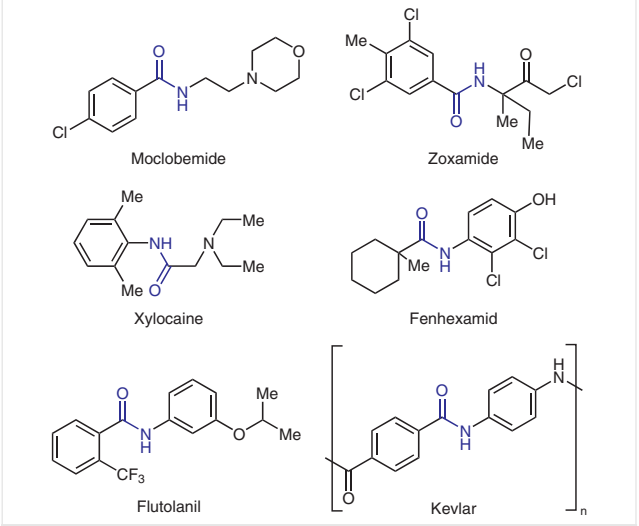

Figure 1 Examples of pharmacologically active molecules and polymers consisting of secondary amide functionalities

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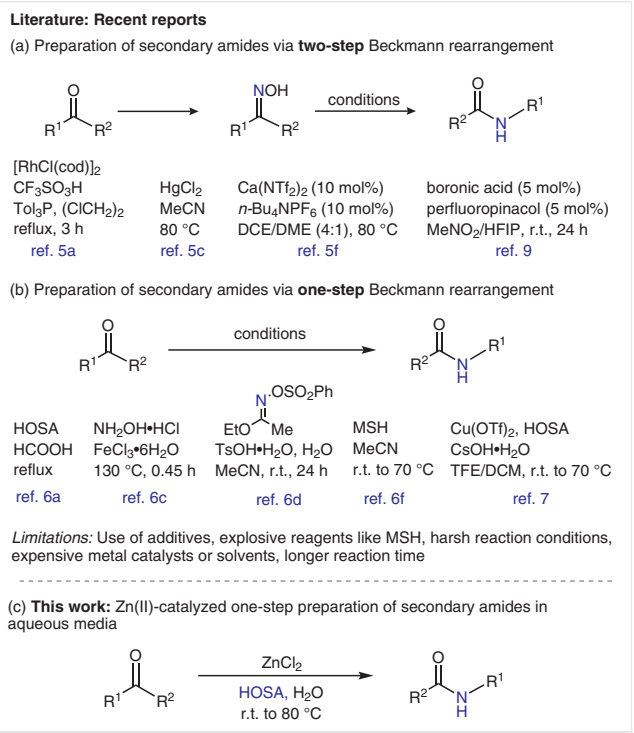
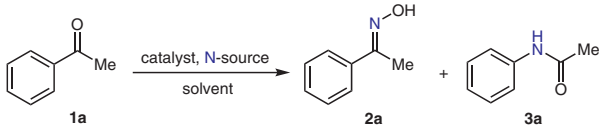
times (Scheme 1b). In 1979, Olah et al. synthesized secondary amides from ketones using commercially available hydroxylamine-*O*-sulfonic acid (HOSA), with formic acid as the solvent, at reflux temperature.[6a] This method was suitable only for cyclic ketones and required the use of strongly acidic solvent under reflux conditions. Recently, we reported a copper(II) triflate catalyzed single-step synthesis of secondary amides directly from ketones using hydroxylamine-*O*-sulfonic acid (HOSA) as the nitrogen source.[7] Although this provided several advantages over literature methods, it required the use of (a) expensive $Cu(OTf)_2$ catalyst, solvent (TFE), and additive (CsOH) and (b) column chromatography for purification. Therefore, an environmentally benign method, free from these limitations, is highly desired. Herein, we describe a Zn(II)-catalyzed synthesis of secondary amides from ketones using HOSA as the nitrogen source and water as the solvent (Scheme 1c). Much to our delight, the desired products could be obtained in pure form just after aqueous workup followed by a simple wash with *n*-hexane solvent, without requiring column chromatography.



Scheme 1 Preparation of secondary amides

We initiated the reaction conditions optimization studies by adopting acetophenone **1a** as a model substrate and hydroxylamine-*O*-sulfonic acid (HOSA) as the nitrogen source, as it is commercially available, water-soluble, and generates a non-interfering water-soluble byproduct (Table 1).[8] Initially, we screened solvents of varying polarity, such as 2,2,2-trifluoroethanol (TFE), acetonitrile, methanol, tetrahydrofuran, water, and ethanol without any catalyst at room temperature (entries 1–6).

Table 1 Optimization of Reaction Conditions[a]



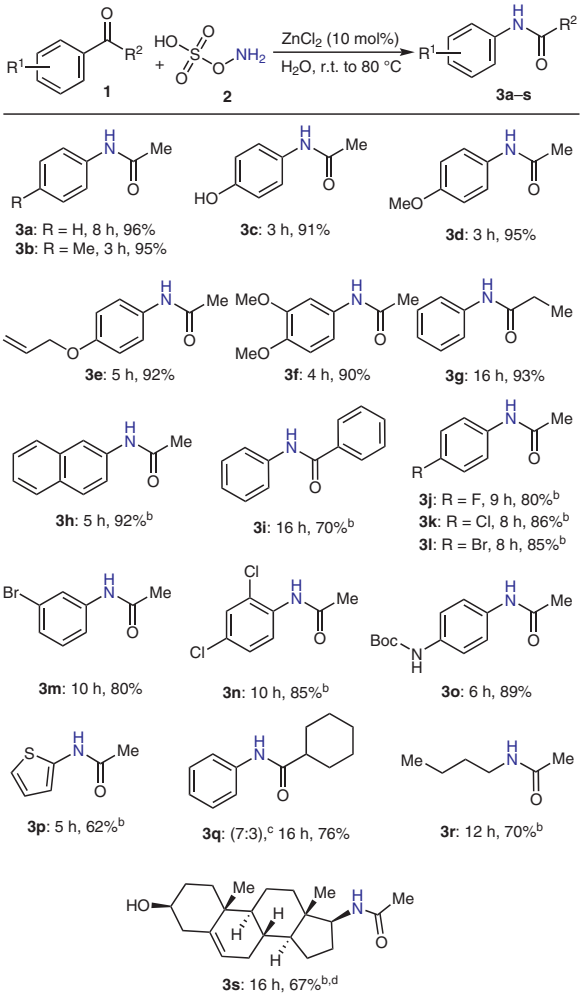
Entry	Solvent	Nitrogen source	Catalyst	Yield (%)[b]	
				2a	**3a**
1	TFE	HOSA	–	50	30
2	MeCN	HOSA	–	30	0
3	MeOH	HOSA	–	50	25
4	THF	HOSA	–	40	20
5	H_2O	HOSA	–	20	70
6	EtOH	HOSA	–	50	20
7	H_2O	HOSA	$FeSO_4$	10	70
8	H_2O	HOSA	$Fe(acac)_3$	10	65
9	H_2O	HOSA	$FeCl_2$	0	60
10	H_2O	HOSA	$Cu(OTf)_2$	10	80
11	H_2O	HOSA	$ZnCl_2$	0	96
12[c]	H_2O	HOSA	$ZnCl_2$	0	80
13[d]	H_2O	HOSA	$ZnCl_2$	10	80
14	H_2O	$NH_2OH{\cdot}HCl$	$ZnCl_2$	10	0
15[e]	H_2O	$NH_2OH{\cdot}HCl$	$ZnCl_2$	15	0

[a] Reaction conditions: **1a** (1.0 equiv), nitrogen source (1.5 equiv), catalyst (10 mol%), solvent (2 mL), r.t.
[b] Isolated yields.
[c] HOSA (1.0 equiv) was used.
[d] $ZnCl_2$ (5 mol%) was used.
[e] $NaHCO_3$ (2.0 equiv) was added at r.t.

To our delight, water proved to be the best choice, giving the desired product **3a** in 70% isolated yield (Table 1, entry 5). To further enhance the product yield, we screened commercially available inexpensive catalysts (entries 7–11). $ZnCl_2$ was observed to be the optimal catalyst that delivered the amide **3a** in an excellent yield of 96% (entry 11). It is worth mentioning that $ZnCl_2$ is cost-effective and readily accessible when compared to previously used expensive catalysts, and the reaction proceeds at room temperature, compared to an elevated/reflux temperature as in previous reports.[7] Attempts to reduce the loading of either HOSA or $ZnCl_2$ diminished the yield (entries 12 and 13). Furthermore, switching to another nitrogen source such as hydroxylamine hydrochloride did not provide any satisfactory result (entries 14 and 15). Remarkably, the product could be accessed in its pure form after a routine workup; column chromatographic purification was not needed.

With these optimized conditions in hand, we next investigated the substrate scope of the reaction (Scheme 2). Ketones with electron-donating substituents (e.g., Me, OH, OMe) at the *para* position of the aryl ring reacted smoothly at room temperature to furnish the corresponding secondary amides in excellent yields (**3b–d**). In a similar manner, the *para*-*O*-allyl substituted acetophenone afforded the desired product **3e** in 92% isolated yield. Gratifyingly, disubstituted acetophenones as well as propiophenone were also good substrates, providing the corresponding amides **3f** and **3g** in remarkable yields of 90% and 93%, respectively. In contrast, a naphthyl ketone and benzophenone required an elevated reaction temperature for the complete conversion to produce the corresponding products **3h** and **3i** in 92% and 70% isolated yields, respectively. We next examined electron-deficient ketones. Acetophenones substituted with electron-withdrawing groups on the aryl rings, such as Cl, F, and Br at *para* and *meta* positions, reacted smoothly at 80 °C to give the expected products **3j–m** in 80–86% yield. These conditions were suitable even for the conversion of a dihalo-substituted ketone (**3n**, 85% yield). The acid-sensitive *N*-Boc substrate also furnished the desired amide **3o** at room temperature without losing the Boc group. Pleasingly, a thienyl ketone was smoothly converted into the corresponding product **3p**. Cyclohexyl phenyl ketone was monitored under these reaction conditions, ending up producing a separable mixture of regiomers of **3q** (7:3), due to a competing migratory aptitude of the phenyl and cyclohexyl groups. The aliphatic acyclic ketone hexan-2-one could also be transformed into the corresponding amide **3r** at 80 °C. Gratifyingly, an encouraging result was obtained in the case of the complex ketone pregnenolone, which delivered the corresponding amide **3s** in a good yield.

In summary, we have developed an efficient and practical approach for the synthesis of secondary amides from ketones via the Beckmann rearrangement using HOSA as the nitrogen source in aqueous media. This single-step synthetic method is cost-effective, operationally simple, and environmentally benign.



Scheme 2 Substrate scope of the reaction. [a] *Reagents and conditions*: same as Table 1, entry 11, unless otherwise mentioned. [b] Reaction temperature 80 °C. [c] Ratio of separable regiomers; major isomer shown. [d] Reaction performed in H_2O/dioxane (2:1).

Reactions, unless otherwise stated, were carried out with magnetic stirring open to the atmosphere in oven-dried glassware. Reagents were used as received, unless otherwise noted. TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}) and was visualized with UV light and/or charring after dipping in PMA or $KMnO_4$ solution. The compounds were purified by triturating the crude reaction mixture under hexane. ^{1}H NMR spectra of samples in $CDCl_3$ or DMSO-d_6 as solvent were recorded at 400 MHz. Chemical shifts are reported relative to residual undeuterated solvent as an internal reference (^{1}H: δ = 7.26 for $CDCl_3$, δ = 2.50 for DMSO-d_6).

Secondary Amides from Ketones; General Procedure

To a stirring solution of $ZnCl_2$ (0.05 mmol, 10 mol%) in H_2O (2 mL) at r.t. in an open round-bottom flask, ketone **1** (0.5 mmol, 1.0 equiv) was added, followed by HOSA (1.5 equiv). The reaction mixture was stirred at the indicated temperature and for the duration indicated in Scheme 2. After completion, the reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq Na_2CO_3 (3 × 5 mL). The organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude product obtained after removal of all volatiles in vacuo was washed with *n*-hexane to remove some minor nonpolar impurities.

N-Phenylacetamide (3a)[9]

Yield: 65 mg (96%); white solid; mp 114–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (br s, 1 H), 7.50 (d, *J* = 7.6 Hz, 2 H), 7.30 (t, *J* = 7.9 Hz, 2 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 2.16 (s, 3 H).

N-(*p*-Tolyl)acetamide (3b)[10]

Yield: 72 mg (95%); white solid; mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.1 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 2.31 (s, 3 H), 2.15 (s, 3 H).

***N*-(4-Hydroxyphenyl)acetamide (3c)**[9]

Yield: 68 mg (91%); brown solid; mp 169–171 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.66 (br s, 1 H), 9.16 (br s, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 6.68 (d, *J* = 8.6 Hz, 2 H), 1.98 (s, 3 H).

***N*-(4-Methoxyphenyl)acetamide (3d)**[9]

Yield: 78 mg (95%); white solid; mp 130–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 2.14 (s, 3 H).

***N*-[4-(Allyloxy)phenyl]acetamide (3e)**[11]

Yield: 88 mg (92%); white solid; mp 94–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.03 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1 H), 5.39 (d, *J* = 17.2 Hz, 1 H), 5.27 (d, *J* = 10.6 Hz, 1 H), 4.49 (d, *J* = 5.0 Hz, 2 H), 2.12 (s, 3 H).

***N*-(3,4-Dimethoxyphenyl)acetamide (3f)**[13]

Yield: 88 mg (90%); white solid; mp 126–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (br s, 1 H), 7.29 (s, 1 H), 6.86 (d, *J* = 8.7 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 3.84 (s, 6 H), 2.14 (s, 3 H).

***N*-Phenylpropionamide (3g)**[15]

Yield: 69 mg (93%); off white solid; mp 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.8 Hz, 2 H), 7.32 (t, *J* = 7.9 Hz, 2 H), 7.17 (br s, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 2.39 (q, *J* = 7.6 Hz, 2 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

***N*-(2-Naphthyl)acetamide (3h)**[10]

Yield: 85 mg (92%); brown solid; mp 133–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.90 (br s, 1 H), 7.77–7.73 (m, 3 H), 7.48–7.37 (m, 3 H), 2.21 (s, 3 H).

***N*-Phenylbenzamide (3i)**[9]

Yield: 69 mg (70%); white solid; mp 165–166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.6 Hz, 2 H), 7.82 (br s, 1 H), 7.65 (d, *J* = 8.1 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 2 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H).

***N*-(4-Fluorophenyl)acetamide (3j)**[9]

Yield: 61 mg (80%); Yellowish solid; mp 154–155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (br s, 1 H), 7.46–7.43 (m, 2 H), 6.99 (t, *J* = 8.5 Hz, 2 H), 2.15 (s, 3 H).

***N*-(4-Chlorophenyl)acetamide (3k)**[12]

Yield: 72 mg (86%); white solid; mp 177–179 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 9.2 Hz, 2 H), 2.17 (s, 3 H).

***N*-(4-Bromophenyl)acetamide (3l)**[9]

Yield: 91 mg (85%); white solid; mp 167–170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 5 H), 2.16 (s, 3 H).

***N*-(3-Bromophenyl)acetamide (3m)**[5c]

Yield: 86 mg (80%); white solid; mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.47 (br s, 1 H), 7.40 (d, *J* = 7.9 Hz, 1 H), 7.24–7.14 (m, 2 H), 2.17 (s, 3 H).

***N*-(2,4-Dichlorophenyl)acetamide (3n)**[14]

Yield: 87 mg (85%); brown solid; mp 144–145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.8 Hz, 1 H), 7.57 (br s, 1 H), 7.37 (s, 1 H), 7.24 (d, *J* = 8.9 Hz, 1 H), 2.23 (s, 3 H).

***tert*-Butyl (4-Acetamidophenyl)carbamate (3o)**[9]

Yield: 112 mg (89%); white solid; mp 159–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.9 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 7.16 (br s, 1 H), 6.45 (br s, 1 H), 2.15 (s, 3 H), 1.51 (s, 9 H).

***N*-(2-Thienyl)acetamide (3p)**[9]

Yield: 44 mg (62%); brown solid; mp 144–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H), 6.88–6.82 (m, 1 H), 6.65 (d, *J* = 3.5 Hz, 1 H), 2.20 (s, 2 H).

***N*-Phenylcyclohexanecarboxamide (3q)**[9]

Yield: 78 mg (76%); white solid; mp 145–148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.9 Hz, 2 H), 7.32–7.26 (m, 2 H), 7.08 (t, *J* = 7.3 Hz, 1 H), 2.29–2.16 (m, 1 H), 2.01–1.90 (m, 2 H), 1.89–1.77 (m, 2 H), 1.75–1.63 (m, 1 H), 1.61–1.47 (m, 2 H), 1.39–1.17 (m, 3 H).

***N*-Butylacetamide (3r)**[16]

Yield: 40 mg (70%); clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (br s, 1 H), 3.14–3.09 (m, 2 H), 1.87 (s, 3 H), 1.44–1.33 (m, 2 H), 1.31–1.18 (m, 2 H), 0.82 (t, *J* = 7.3 Hz, 3 H).

***N*-[(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-3-Hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]acetamide (3s)**[9]

Yield: 110 mg (67%); white solid; mp 230–232 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38–5.32 (m, 1 H), 5.28 (d, *J* = 8.5 Hz, 1 H), 3.99–3.78 (m, 1 H), 3.59–3.46 (m, 1 H), 2.35–2.06 (m, 3 H), 2.03–1.95 (m, 1 H), 1.98 (s, 3 H), 1.90–1.78 (m, 2 H), 1.75–1.62 (m, 2 H), 1.61–1.16 (m, 9 H), 1.16–1.02 (m, 3 H), 1.01 (s, 3 H), 0.70 (s, 3 H).

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Supporting Information

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Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using O-(Sulfonyl)hydroxylamine Reagents Thesis Submitted to Babasaheb Bhimrao Ambedkar University (A Central University) Lucknow For The Degree Of Doctor of Philosophy In Chemistry Submitted By Puneet Kumar (M. Sc., NFSC-UGC SRF) Enrolment Number: 1100/18 Under the Supervision of Dr. Jawahar Lal Jat Assistant Professor Department of Chemistry School of Physical & Decision Sciences Babasaheb Bhimrao Ambedkar University (A Central University) Vidya Vihar, Raebareli Road, Lucknow-226025, Uttar Pradesh (India) August, 2022

Chapter 1 A General Overview on nitrogen-containing compounds (Secondary amides, Anilines, and Nitriles) and O-(substituted)hydroxylamines: Introduction and Motivation of Present Work Secondary amides, anilines and nitriles moieties are present in various naturally occurring bioactive compounds. They are also used as a versatile synthetic intermediates in organic chemistry. O-(subtituted)hydroxylamines serve as a useful aminating reagent. Recently, these reagents have been used in C-H, N-amination, aziridination, amidation and cyanation etc. In this chapter, we have described the importance and general synthetic routes and applications of secondary amides, anilines and nitriles followed by emerging synthetic applications of O- (substituted)hydroxylamine reagents.