tert-Butyl Nitrite Mediated Domino Synthesis of *N*-Heterocycles via C–H Bond Functionalization

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted By

Prasenjit Sau

Roll No. 156122014

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781039, Assam, India

January, 2019

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DEDICATED TO

MY PARENTS AND FAMILY

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Prof. Bhisma K. Patel.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

January, 2019
IIT Guwahati

Prasenjit Sau

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Prasenjit Sau has been working under my supervision since July 2015 as a regular registered Ph.D. student. His thesis entitled "***tert-Butyl Nitrite Mediated Domino Synthesis of N-Heterocycles via C–H Bond Functionalization***" is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis to submit for the Ph.D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

January, 2019

Prof. Bhisma K. Patel
(Thesis Supervisor)
Department of Chemistry
IIT Guwahati

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Prasenjit Sau

SYNOPSIS

The contents of this thesis have been divided into four chapters based on the results of experimental works performed during the course of the research period. The introductory chapter of the thesis presents an overview of *tert*-butyl nitrite mediated C–H functionalization reactions and other newer strategies leading to the formation of C–C and C–heteroatom bonds under metal and metal-free conditions. All the other chapters emphasize on C–C, C–O and C–N bond forming reactions under metal and metal-free conditions using strategies like C–H functionalizations, cross dehydrogenative coupling, one pot sequential and rearrangement reactions.

Chapter II demonstrates *tert*-butyl nitrite mediated domino synthesis of isoxazolines and isoxazoles from terminal aryl alkenes and alkynes.

Chapter III illustrates three sequential C–N bond formation: *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[1,2-*a*]quinolines / imidazo[2,1-*a*]isoquinolines.

Chapter IV describes *tert*-butyl nitrite mediated greener synthesis of 1,2,4-oxadiazol-5(4H)-ones from terminal aryl alkenes.

CHAPTER I. An Overview of *tert*-Butyl Nitrite Mediated C–H Functionalization Reactions

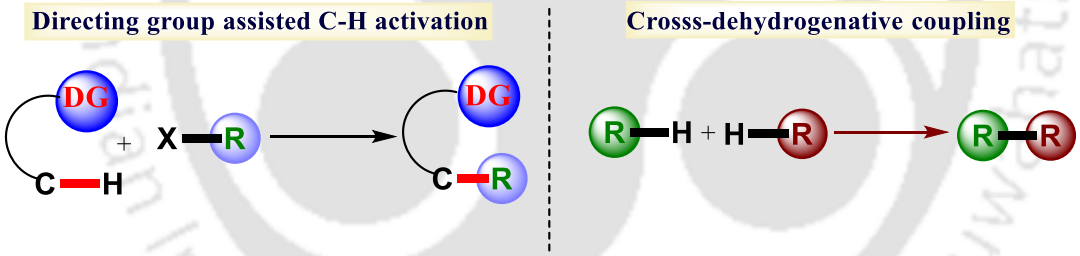
This chapter includes the brief understanding of C–H functionalization, their advantages, challenges and applications in organic synthesis. It mainly focused on *tert* butyl nitrite mediated various C–H functionalization reactions *viz.* nitrosation, nitration, oximation, diazotization, oxidation, and construction of *N*-heterocycles.

C–H functionalization is an important synthetic strategy, extensively used in both industry and academics for the construction of C–C and C–heteroatom bonds. Traditional organic synthesis based on the exchange of one functional group (FG) with another. Thus, the requirement of pre-functionalized starting materials in traditional approaches, adds additional steps towards the formation of anticipated product, is a major concern in terms of both atom-economic and environmental. On the other hand, C–H functionalization strategy exclude pre-functionalized starting materials and lead to

direct functionalization of relatively inert C–H bonds, which facilitated the construction of divers array of complex molecules in single operations.

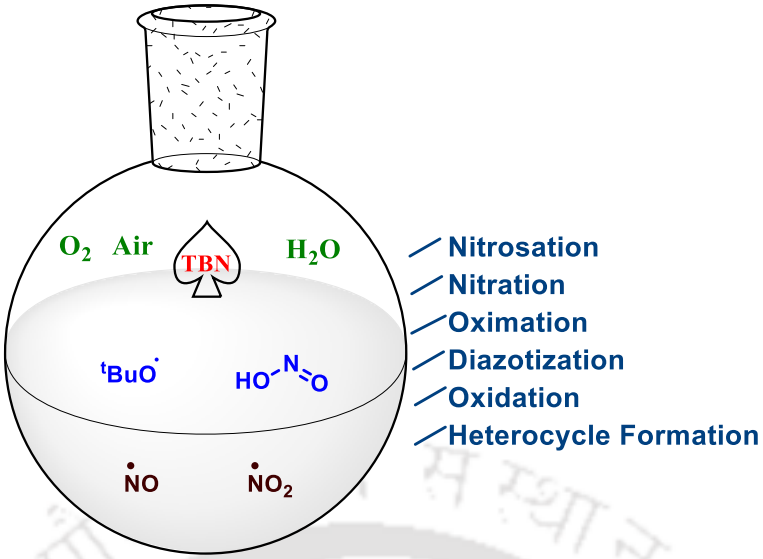
Though there are several advantages of direct C–H bond functionalization reactions but it also suffer from some limitations such as controlling the chemo–, regio– and stereoslectivity in a complex organic molecule is quite challenging. These challenges of selectivity in C–H bond functionalization can overcome mainly by three strategies: (i) directing group assisted C–H bond functionalization (ii) cross dehydrogenative coupling (CDC) and (iii) methodologies which are based on the combination of these two.

In directing group assisted C–H bond functionalization need a heteroatom (*viz.* O, S. N) which can co-ordinate with the metal and bring it to the close proximity of the desired C–H bond which is the subject of functionalization. On the other hand CDC is the formation of C–C/C-X bonds from the coupling of two different C–H bonds or the coupling of C–H and X–H (X = heteroatoms) bonds. Sometimes in advance synthesis chemists use the combination of these two strategies: (a) substrate directed C–H bond functionalization and (b) cross dehydrogenative coupling for the transformation of C–H bonds to C–C and C–heteroatom bonds (scheme I.1)



Scheme I.1. *(a) Substrate directed C–H bond functionalization; (b) cross dehydrogenative coupling*

In C-H bond functionalizations reactions, *tert*-butyl nitrite (TBN) a metal free reagent play important role for construction of varieties of complex molecules. *tert*-Butyl nitrite mediated C–H functionalizations reactions mostly occurs via radical pathaway. Under thermal condition TBN decomposes to produce NO and NO_2 radicals which trigger a variety of C–H functionalization reactions *viz.* nitrosation, nitration, oximation, diazotization, Oxidation, and construction of heterocycles. So the research in this area raise rapidly.



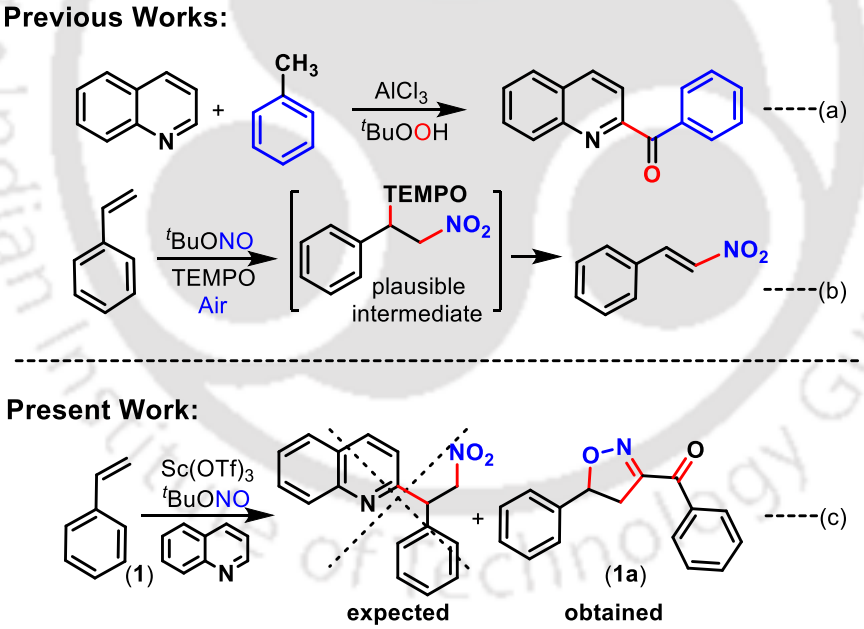
CHAPTER II. *tert*-Butyl Nitrite Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes

This chapter describes *tert*-butyl nitrite mediated domino synthesis of isoxazolines and isoxazoles from terminal aryl alkenes and alkynes. An unprecedented consecutive three C–H functionalizations of two styrenes are involved during this isoxazoline synthesis. In this radical mediated reaction one half of the aryl alkene is converted into intermediate 2-nitro ketone which serve as a 1,3-dipolarophile and undergo cycloaddition with the other half of unreacted aromatic terminal alkene. The use of alkyne in lieu of alkene leads to the formation of isoxazole under an identical reaction condition.

Alkenes are simple organic molecules which have been widely applied in organic synthesis for the construction of a diverse array of complex molecules. One of the finest approaches to build such molecules in a single operation is via the direct 1,2-difunctionalization of alkenes. In this context, both intra and intermolecular hetero difunctionalization of alkenes have acquired significant attention. In contrast to intermolecular processes intramolecular difunctionalizations are more selective and thermodynamically favorable. Despite that, the transition metal catalyzed intermolecular difunctionalizations *viz.* carbohalogenation, dihydroxylation, oxyarylation, oxyamination, aminofluorination, aminocyanation, hydroalkylation, carboboration, and other difunctionalization are well explored. However, intermolecular difunctionalization of olefins using C–H functionalization strategy remain fewer in numbers. In this context,

an intermolecular Fe(II)-catalyzed carbonylation-peroxidation, *p*-toluenesulfonic acid (*p*TsOH) catalyzed oxidative keto-peroxidation, copper or cobalt catalyzed alkylation-peroxidation and copper catalyzed cycloalkylation-peroxidation of olefins have been reported.

Recently, our group has developed a Lewis acid ($AlCl_3$) catalyzed cross-dehydrogenative coupling between electron-deficient *N*-heterocycles (quinoline, isoquinoline and quinoxaline) and alkylbenzenes for the synthesis of C1 or C2 aroylated *N*-heterocycles (Scheme II.1). In the presence of $AlCl_3$ catalyst electron-deficient *N*-heterocycles acts as a radical acceptor, which trapped the *in situ* generated aroyl radical ($ArCO^{\cdot}$) obtained from alkyl benzene by the action of peroxide (TBHP). During the nitration of alkenes using *tert*-butyl nitrite as a nitrating agent follows a radical pathway where the *in situ* generated alkyl radical is trapped by the radical scavenger TEMPO (Scheme II.1). Now a query arises if an alkene is treated with *tert*-butyl nitrite in the presence of quinoline in lieu of TEMPO, will it offer a similar 1,2-difunctionalized product (Scheme II.1).



Scheme II.1. *C–H Functionalization of alkene to isoxazoline*

With this assumption, we treated styrene (**1**) with quinoline (1 equiv), *tert*-butyl nitrite (^{t}BuONO) (**a**, 2.0 equiv) and $AlCl_3$ catalyst (5 mol%) in 1,2-dichloroethane (DCE) at 80 ^{o}C. A new product was isolated (55%), spectroscopic analysis of which confirmed the structure to be phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**) (Scheme

II.1). The synthesis of isoxazolines involving three C–H functionalization of two styrenes is unprecedented in the literature. The newly formed product is devoid of any quinoline moiety however, in its absence the yield was dropped to 12% thereby suggesting its possible involvement as a base. Isoxazolines, are an important class of heterocycle that have attracted considerable attention in the field of anticancer research. Some of the important isoxazoline scaffolds exhibiting potent anticancer properties are 3,5-diaryl-isoxazoline linked 2,3-dihydroquinazolinone hybrids, arylisoxazoline containing anthranilic diamides, 3,5-diaryl-isoxazoline linked pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) conjugates and dibenzo[b,f]azepine tethered isoxazoline.

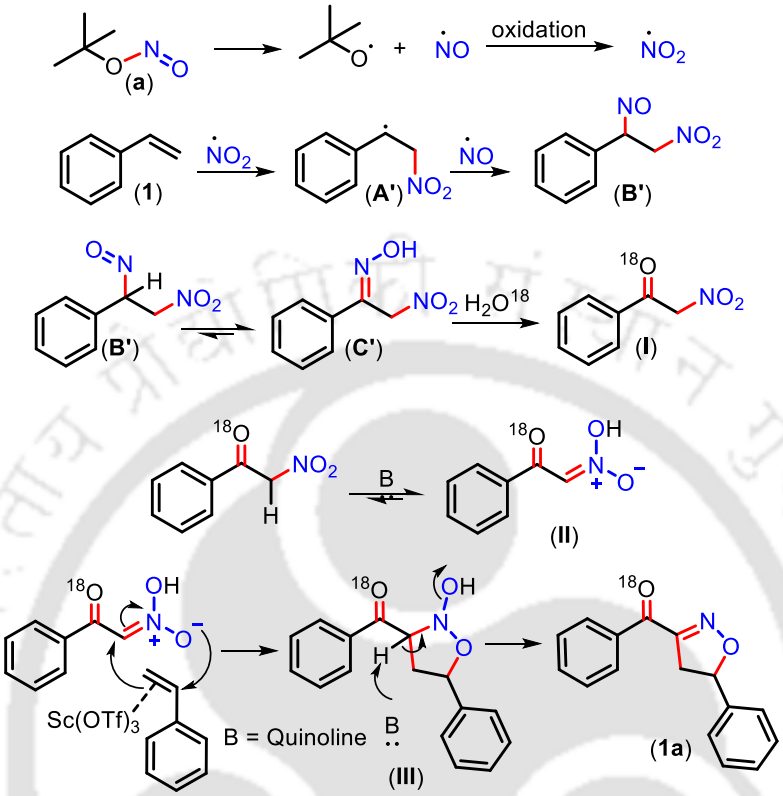
We then look forward to improving the self-coupling of aryl alkene via C–H functionalization leading to the formation of isoxazoline by varying other reaction parameters. After screening various reaction conditions, it was observed that the use of styrene (0.4 mmol), ^{t}BuONO (2.0 equiv), $Sc(OTf)_3$ (5 mol%) and quinoline (0.5 equiv) gave the best yield for this transformation.

The above optimized condition was then implemented to explore the scope and generality of the process. It was found that both alkenes and alkynes were well tolerated in this transformation to afford their corresponding isoxazolines and isoxazoles.

Based on the literature reports, intermediates detected by HRMS study and from the controlled experiments carried out a plausible mechanism have been proposed (Scheme II.2). The heterolytic cleavage of *tert*-butyl nitrite produces a $NO^{\cdot}$ radical which is converts to a NO_2 radical under the aerobic reaction condition. The nitro radical ($NO_2^{\cdot}$) then attacks at the terminal carbon of the olefin to generate a nitroalkane radical intermediate (**A'**). The nitroalkane radical (**A'**) thus generated couples with another $NO^{\cdot}$ radical to give a C-nitroso intermediate (**B'**). In the presence of base the C-nitroso intermediate (**B'**) rearranges to a α-nitrooxime (**C'**), which is hydrolyzed from the moisture present in the solvent/open atmosphere to 2-nitroacetophenon (**I**). The intermediate 2-nitroacetophenone tautomerized to a 1,3-dipolar intermediate (**II**) in the presence of base. The unreacted styrene serves as the dienophile and undergoes cycloaddition with the 1,3-dipolar intermediate (**II**) to give intermediate (**III**). Here $Sc(OTf)_3$ acts as a Lewis acid catalyst to enhance the reactivity of alkene towards cycloaddition reaction. Finally, loss of a water molecule from the intermediate (**III**) leads to the formation of final isoxazoline product (**1a**). Intermediates (**C′**), (**I**), (**II**) and (**III**) have been detected by the HRMS analysis of the reaction mixture at various time

intervals. A similar mechanism for the formation of isoxazole from terminal alkyne can be proposed.

Scheme II.2. *Proposed mechanism for isoxazoline synthesis*



In conclusion, *tert*-butyl nitrite serves as a convenient N–O source to convert alkenes or alkynes into intermediate 2-nitro ketone in DCE. The intermediate so generated reacts with the unreacted alkenes or alkynes via a 1,3-dipolar cycloaddition to afford isoxazolines or isoxazoles in the presence of quinoline and $Sc(OTf)_3$ catalyst. In this domino process, C–C, C–O, C=N and C=O bonds are constructed simultaneously. A radical mechanism has been proposed, where the cleavage of *tert*-butyl nitrite produce a NO radical. The NO radical is oxidized to NO_2 radical and a sequential addition of these radicals to styrene produce a C-nitroso intermediate which is hydrolyzed to a 2-nitroacetophenone. The 2-nitroacetophenone so generated is tautomerize to a 1,3-dipolar intermediate which undergo cycloaddition with unreacted alkene to generate isoxazoline via loss of a water molecule. An analogous mechanism has been proposed involving alkynes for the generation of isoxazoles.

CHAPTER III: Three Sequential C–N Bond Formation: *tert*-Butyl Nitrite as a N1 Synthon in a Three Component Reaction Leading to Imidazo[1,2-*a*]quinolines / Imidazo[2,1-*a*]isoquinolines

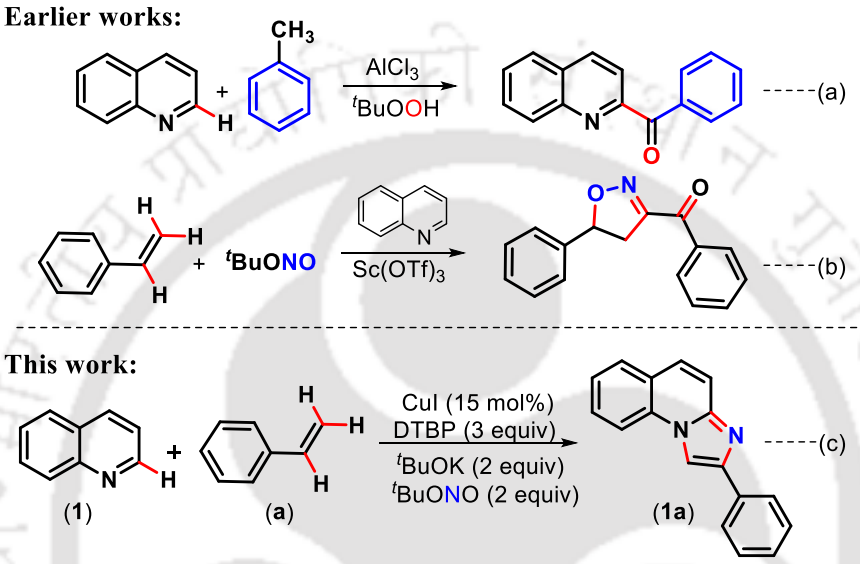
This chapter described *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[1,2-*a*]quinolines/imidazo[2,1-*a*]isoquinolines. *tert*-Butyl nitrite serves the dual role of an oxidant as well as a N1 synthon in a multi-component reaction involving quinolines/isoquinolines and styrenes. Herein two sp^2 C–H's functionalization of styrenes and one of quinolines/isoquinolines leads to the formation of fused quinolines/isoquinolines via three sequential C–N bond formation.

Further functionalization and late stage functionalization of biologically important organic frameworks amplifies its activity towards pharmaceutical and medicinal chemistry. Quinolines and isoquinolines are integral part in many natural products and building blocks of several pharmaceuticals. The functionalized derivatives of those *viz*. imidazo[1,2-*a*]quinoline and imidazo[2,1-*a*]isoquinoline exhibit effective biological activities such as inhibitors of Shiga Toxin, hypertensive, antiallergic, contraceptive and antiasthmatic anxiolytic.

Various functionalizations of quinolines and isoquinolines has been documented in the literature *viz*. alkylation, halogenation, sulfonation, trifluoromethylation etc. Of late, C–H functionalization is an alternative strategy to create complex structural frameworks from small organic molecules. Consequently, the C–H functionalization protocols have been applied to quinoline and isoquinoline moieties. In this regard, Liu *et al*. demonstrated a novel route for the synthesis of C1-benzyl and benzoyl substituted isoquinolines through a direct oxidative C–H functionalization of isoquinolines using alkyl benzene as the coupling partner. Our group has also developed a Lewis acid catalyzed C1 or C2 arylation of isoquinolines and quinolines (Scheme III.1) using methylarenes as the aroyl surrogates.

On the other hand direct 1,2-difunctionalization of alkenes with or without the involvement of sp^2 C–H bonds have played a vital role in building complex molecules. Bis-functionalization of olefins such as dihydroxylation, hydroalkylation, oxyamination, carbohalogenation, oxyarylation, aminofluorination, aminocyanation, nitration, carboboration, and others are well documented in the literature. Our group has recently

reported an efficient synthesis of isoxazolines via 1,2-difunctionalization of styrene in the presence of quinoline (as a base), *tert*-butyl nitrite as the N–O source in the presence of catalyst $Sc(OTf)_3$ (Scheme III.1). Taking cues from these radical mediated reactions, especially, nitration of alkenes using *ter*t-butyl nitrite and C1 or C2 aroylation of *N*-heterocycles, we envisaged a double functionalization of styrene and a concomitant C2 functionalization of quinoline or a C1 functionalization of isoquinoline leading to the synthesis of fused heterocycles.



Scheme III.1. *Strategies for C–H functionalization of N-heterocycles with alkyl benzene and styrenes*

By judiciously choosing the catalyst and other reaction parameters it was possible to fuse styrene onto both quinoline and isoquinoline moieties in the presence of *tert*-butyl nitrite (TBN) (Scheme III.1). Our initial investigation started using quinoline (0.25 mmol), styrene (0.625 mmol), $Cu(OTf)_2$ (10 mol%), Cs_2CO_3 (2 equiv) and *tert*-butyl nitrite (2 equiv) in 1,2-dichloroethane (DCE) at 80 °C. Interestingly, the reaction resulted in the formation of a new product (**1a**, 41%), spectroscopic analysis confirmed its structure to be 2-phenylimidazo[1,2-*a*]quinoline (**1a**). In this structure the incorporation of a new N atom is associated with the formation of three C–N bonds. We believe that TBN to be the possible source of additional nitrogen atom in this product. So far TBN has been exploited mainly as a source of NO and NO_2 radicals. Besides this it has been employed as a nitrogenating agent in the formation of nitriles from alkylbenzene and terminal aryl alkenes. Prior to this report there is only one illustration where TBN has been used as a N1 synthon in the synthesis of cinnolines from 2-vinyl aniline. In spite of

the recent surge in the use of TBN, we feel it is an underutilized reagent, thus exploring alternative pattern of reactivity would open novel avenues for synthetic chemists. Herein, we disclose a copper catalyzed three-component synthesis of *N*-fused heterocycles involving quinoline/isoquinoline, styrene and TBN as the N1 synthon via three sequential C–N bond formations.

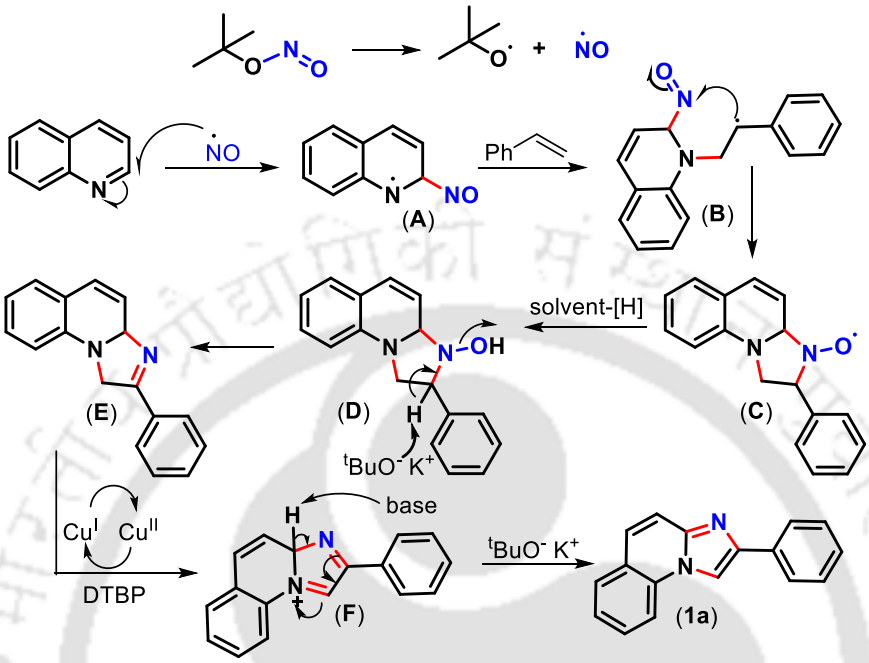
Encouraged by the above unprecedented three component reaction, further optimization were carried out by varying various reaction parameters using styrene (**a**) and quinoline (**1**) as the coupling partners in the presence of ^{t}BuONO. After screening of various reaction parameters, the optimized condition for this transformation is the use of quinoline (0.25 mmol), styrene (0.625 mmol), CuI (15 mol%), ^{t}BuOK (0.5 mmol), *tert*-butyl nitrite (0.5 mmol) and DTBP (0.75 mmol) at 80 ^{o}C in DCE solvent.

The above optimized condition was then implemented to explore the scope and generality of the process. It was found that both the quinoline and isoquinoline derivatives are successfully coupled with a series aromatic alkenes and afforded their corresponding products.

In order to elucidate a plausible mechanism, an experiment was performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3 equiv) under otherwise identical condition. Retardation in the desired product (**1a**, <5%) formation suggest the radical nature of the reaction. Based on the intermediates detected by the HRMS analysis of the reaction mixture at various time intervals and from the literature reports, a plausible mechanism has been proposed for this transformation (Scheme III.2). The heterolytic cleavage of *tert*-butyl nitrite generates a NO$^{\cdot}$ radical which attacks at the more electrophilic C2 position of quinoline to generate a radical intermediate (**A**). The nitrogen radical intermediate (**A**) then attacks at the terminal carbon of the styrene to form a benzylic radical species (**B**), which underwent an intramolecular radical coupling with the adjacent NO group to give a radical intermediate (**C**). The *N*-oxide radical intermediate (**C**) abstract a prtoton from the solvent DCE to form a *N*-hydroxy intermediate (**D**). A base (^{t}BuOK) mediated dehydration of which resulted in the formation of intermediate (**E**). In the presence of CuI and DTBP, the intermediate (**E**) generates an iminium carbocation (**F**) via two sequential single electron transfer (SET) process. Finally loss of a proton from intermediate (**F**) leads to the formation of the desired product (**1a**). Intermediacy of (**B**), (**C**) and (**F**) have been detected by the HRMS analysis of reaction mixtures at various

time intervals. Formation of intermediates (B) and (C) are further confirmed by radical trapping experiments. A similar mechanism is expected to operate for isoquinoline (**4**) leading to 2-phenylimidazo[2,1-*a*]isoquinoline (**4a**).

Scheme III.2. *Proposed mechanism for imidazo[1,2-a]quinolines synthesis*



In conclusion, selective C1 or C2 functionalizations of isoquinolines or quinolines with concurrent *bis*-functionalization of styrenes in the presence of *tert*-butyl nitrite and Cu catalyst leads to the construction of imidazo[2,1-*a*]isoquinolines or imidazo[1,2-*a*]quinolines. In this radical mediated reaction *tert*-butyl nitrite serve as a N1 synthon and assist in the simultanious installation of three new C–N bonds. This is an excellent illustration of novel reactivity of *tert*-butyl nitrite thereby, expending its utility towards the synthesis of complex molecules.

CHAPTER IV: *tert*-Butyl Nitrite Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(4H)-ones from Terminal Aryl Alkenes

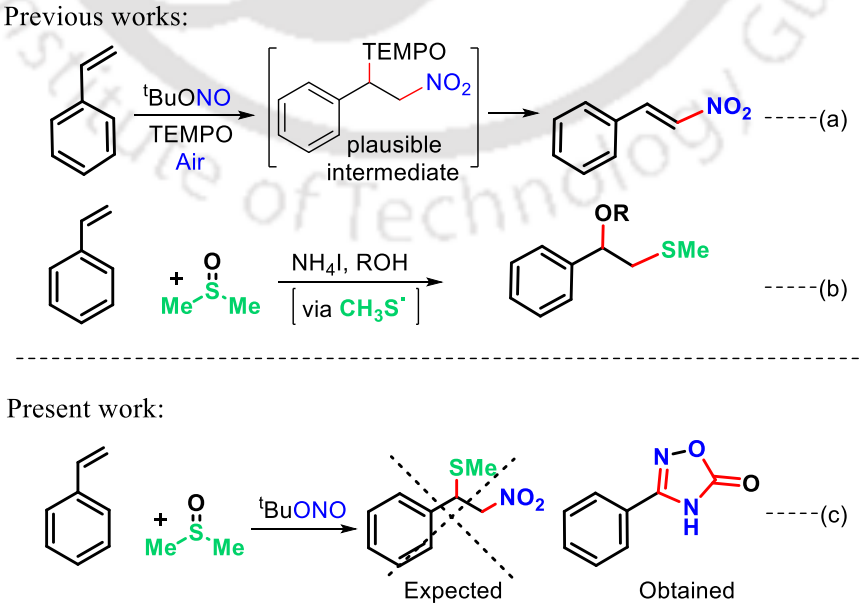
This chapter described *tert*-butyl nitrite mediated vinyl bond cleavage/cyclizations of aromatic alkenes lead to the formations of 3-phenyl-1,2,4-oxadiazol-5(4H)-ones. An unprecedented consecutive three C–H functionalization of styrene and formation of new three C–N and two C–O bonds are involved during this 1,2,4-oxadiazol-5(4H)-ones synthesis.

Nitrogen-containing heterocyclic framework are ubiquitous in many naturally occurring and synthetic compounds exhibiting remarkable biological and medicinal

properties. These heterocycles have engrossed the synthetic chemists to develop newer methodologies for their synthesis. Among the *N*-containing heterocycles, 1,2,4-oxadiazol-5(4H)-one form the integral part of many natural products and pharmaceutically and biologically active molecules. Their derivatives serve as inhibitors of S-Nitrosoglutathione reductase (GSNOR), in vitro and in vivo angiotensin II (AII) receptor antagonistic activities, selective noncompetitive antagonists for the homomeric kainate receptor subtype GluR5 and inhibition of secretory phospholipase A_2. Thus, considerable attention has been devoted to exploit new routes and especially one-pot strategies toward these *N*- heterocycle and their derivatives.

In this regard, only few methods are available for the construction of 3-phenyl-1,2,4-oxadiazol-5(4H)-one. However, all the existing strategies involve the condensation of amidoximes with carboxylic acid esters or Carbonyldiimidazole. Nevertheless, these strategies often require synthesis of amidoximes, which often needs additional reaction steps, thus affects the efficiency. Therefore, it would be highly desirable to develop an efficient simple method for the total synthesis of 3-phenyl-1,2,4-oxadiazol-5(4H)-one and its derivatives.

Of late direct C–H bond functionalization process has emerged as a valuable tool in organic synthesis, providing more sustainable synthetic methodologies with minimum steps and waste. Among the various C−H bond functionalizations, the functionalization of alkenes using *tert*-butyl nitrite, are powerful shortcut for the construction of a diverse array of complex molecules in a single operation.



Scheme IV.1. *C–H Functionalization of alkene to 1,2,4-oxadiazol*

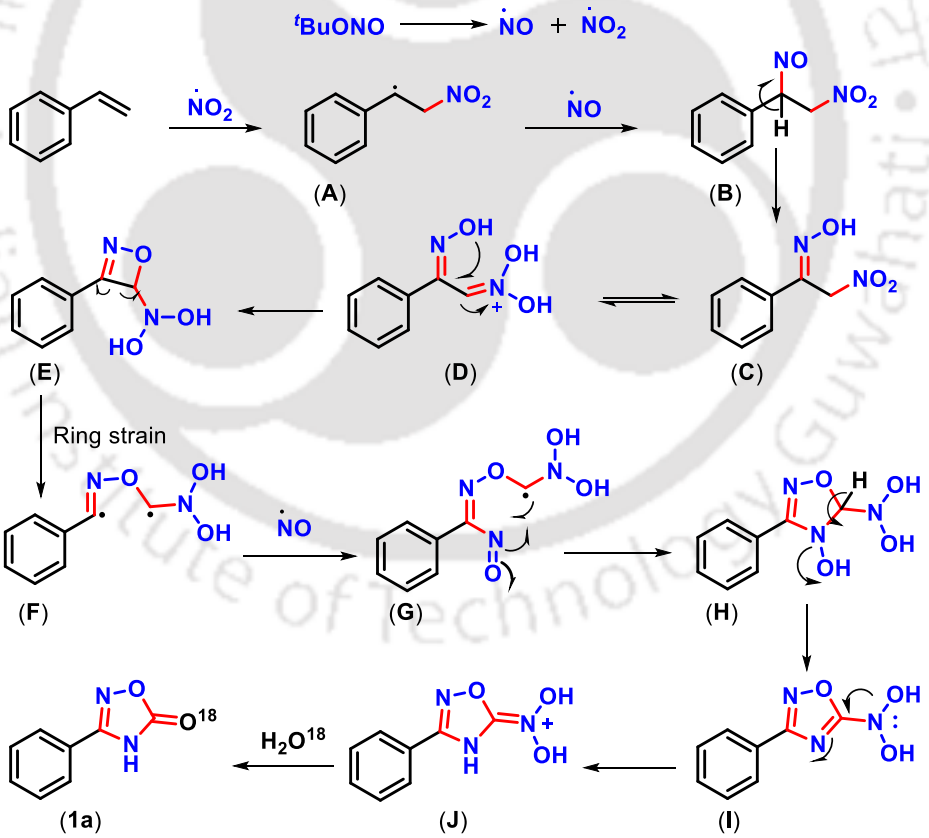
Recently, Maiti *et al.* reported the nitration of alkenes using *tert*-butyl nitrite as a nitrating agent. The reaction proceeds via a radical pathway where the *in situ* generated nitroalkane radical intermediate is trapped by the radical scavenger TEMPO [Scheme IV.1. (a)]. During the oxysulfenylation of alkenes utilizing ammonium iodide, DMSO and alcohols, follows a radical pathway in which generation of methylthiyl radical (MeS•) took place from DMSO [Scheme IV.1. (b)]. In the light of these consideration we were inquisitive to see the reaction of alkene with *tert*-butyl nitrite in the presence of DMSO in lieu of TEMPO, will it offer similar difunctionalized product or a completely different reactivity may drive the formation of some other product? [Scheme IV.1. (c)] With this assumption, we commenced our preliminary studies by reacting styrene (**1**) with *tert*-butyl nitrite (^{t}BuONO) (**a**, 3.0 equiv) and $Sc(OTf)_3$ catalyst (10 mol%) in DMSO at 80 ^oC. Interestingly, the reaction resulted in the formation of a new product (47%), spectroscopic analysis of which confirmed the structure to be 3-phenyl-1, 2, 4-oxadiazol-5(4H)-one (**1a**) [Scheme IV.1 (c)]. The product structure reveals that synthesis of 1,2,4-oxadiazol is realized via the cleavage of a vinylic C–C bond and with the simultaneous construction of three C–N and two C–O bonds. Here in this oxadiazol moiety, the incorporation of two N atom occurs from TBN through the oxidative functionalization of C(sp2)–H bonds. Herein, we disclose a *tert*-butyl nitrite mediated simple and straightforward synthesis of oxadiazol architectures from terminal alkenes under metal and additive free conditions. The importance and scope of the present chemistry is threefold: (1) To the best of our knowledge, such one-pot green synthesis of 1,2,4-oxadiazol using only terminal alkene and *tert*-butyl nitrite is unprecedented in the literature. (2) Construction of oxadiazol from biologically demanding terminal alkenes generate potential opportunity for easy access of many biologically active compounds. (3) The mechanistic study indicates that the initial NO and NO_2 radical addition and following the alkene bond cleavage/cyclization's of aromatic alkenes lead to the formations of 1,2,4-oxadiazol-5(4H)-ones.

Encouraged by the above *tert*-butyl nitrite mediated C–H functionalization of aromatic alkenes, further optimizations were carried out by varying various reaction parameters. After screening of various reaction parameters, the optimized condition for this transformation is the use of styrene (0.25 mmol), *tert*-butylnitrite (1 mmol) at 80 ^oC in DMSO solvent.

The above optimized condition was then implemented to explore the scope and generality of the process. It was found aromatic alkenes were well tolerated in this transformation to afford their corresponding 1,2,4-oxadiazol-5(4H)-ones.

To find out the source of keto oxygen in product (**1a**), the reaction of styrene (**1**) was performed in the presence of H_2O^{18} under otherwise identical condition. Incorporation of an ^{18}O labeled product suggests that water might be the source of oxygen in the keto group. In order to elucidate a plausible mechanism a reaction was carried out in presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv) under otherwise identical condition. Obstruction in the desired product (**1a**, <3%) formation suggest the radical nature of the reaction. Based on literature reports and the intermediates detected by the HRMS analysis of the reaction mixture at various time intervals, a plausible mechanism has been proposed for this transformation (Scheme IV.2).

Scheme IV.2. *Proposed mechanism for 3-phenyl-1,2,4-oxadiazol-5(4H)-one synthesis*



Heterolytic cleavage of *tert*-butyl nitrite generates a NO· radical which is converts to a NO_2 radical under the aerobic reaction condition. The nitro radical (NO_2·) then attacks at the more reactive terminal carbon of the styrene to generate a nitroalkane radical intermediate (**A**). The in situ generated radical intermediate (**A**) couples with another NO

radical to give a C-nitroso intermediate (**B**). Then C-nitroso intermediate (**B**) rearranges to produce α-nitrooxime (**C**), which is tautomerized to give another intermediate (**D**). The intermediate (**D**) undergoes an intramolecular cyclization reactions which leads to the formation of an unstable four membered ring (**E**). Because of ring strain the four membered ring undergoes a ring opening reactions to generate intermediate (**F**). This reactive radical intermediate (**F**), then couple with NO radicals, followed by a radical cyclization resulted in the formation of intermediate (**H**). Dehydration of intermediate (**H**) generates an intermediate (**I**). Finally the intermediate (**I**) tautomerize to another intermediate (**J**) which is hydrolyzed from the moisture present in the solvent/open atmosphere to give the desired product (**1a**). Almost all intermediates has been detected by the HRMS analysis of reaction mixtures at various time intervals.

In conclusion, we have developed an efficient metal free protocol to synthesize 3-phenyl-1,2,4-oxadiazol-5(4H)-ones from aromatic terminal alkenes using *tert*-butyl nitrite only. Herein three sp^2 C–H' functionalisations of styrene and formation of new three C–N and two C–O bonds are involved during this 1,2,4-oxadiazol-5(4H)-ones synthesis.

CONTENTS

Chapter III Three Sequential C–N Bond Formation: *tert*-Butyl Nitrite as a N1 Synthon in a Three Component Reaction Leading to Imidazo[1,2-*a*]quinolines / Imidazo[2,1-*a*]isoquinolines

Chapter IV *tert*-Butyl Nitrite Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(4H)-ones from Terminal Aryl Alkenes

CHAPTER I

An Overview of tert-Butyl Nitrite Mediated C–H Functionalization Reactions

CHAPTER I

An Overview of *tert*-Butyl Nitrite Mediated C–H Functionalization Reactions

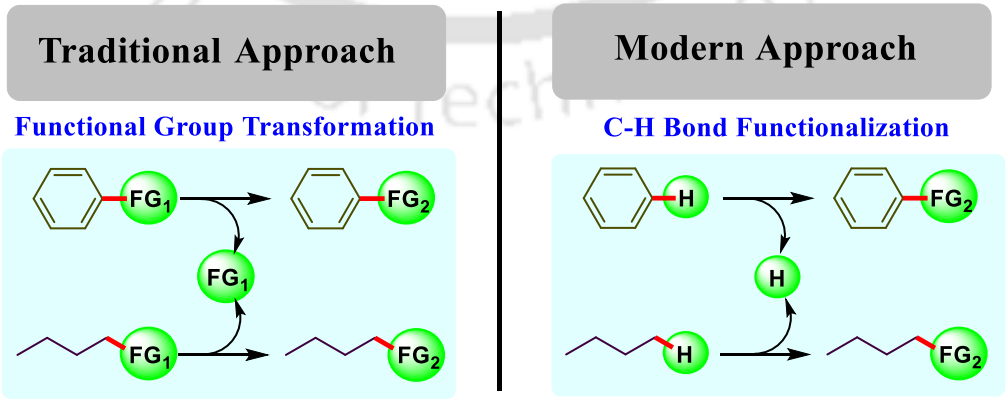
I.1. Introduction

Over the past decades, cross-coupling chemistry have significantly improved the strategies for the construction of carbon–carbon and carbon–heteroatom bonds in both industry as well as academia.[1] The advance cross-coupling strategies are successfully implemented for the synthesis of commercially important products.[2] Despite the tremendous progress made in this area, it suffers from significant drawbacks such as:

(i) This strategy is based on the exchange of one functional group (FG) with another. In order to install a new functional group needs pre-functionalized starting materials (Scheme I.1.1).Thus, the overall process decreases both its efficiency and atom economy and also adds extra step and cost to the transformation.

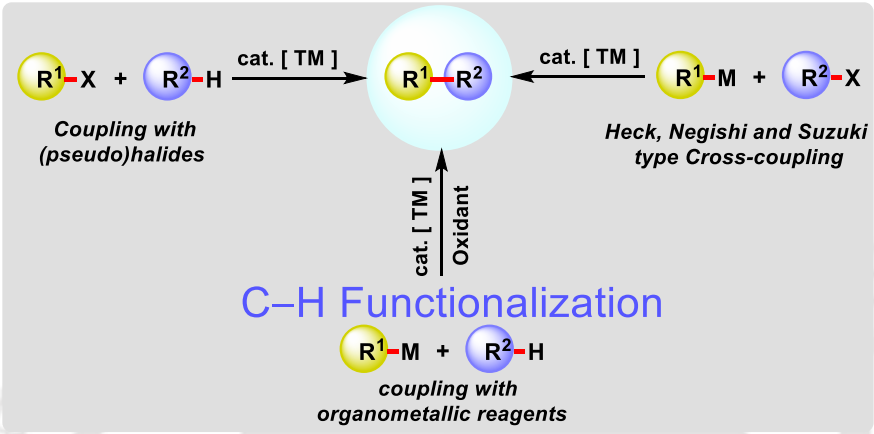
(ii) Use of stoichiometric organometallic reagents, thereby producing the chemical waste in the overall transformations.

These issues can be overcome using an advance strategy called C-H functionalization[3] which leads to the direct cleavage of un-activated carbon–hydrogen (C–H) bonds (Scheme I.1.1). This strategy excludes the requirement of pre-functionalized starting materials and is reliable as it is highly step and atom-economic. Hence C-H functionalizations represent an ideal tool in organic synthesis to provide new synthetic routes with minimum steps and waste.



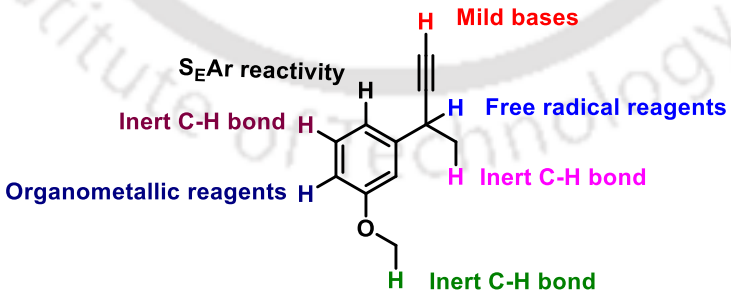
Scheme I.1.1. *Traditional approach vs C–H bond functionalization*

During the past years, extensive research on transition metal catalyzed C–H activation process have greatly upgraded our understanding of how to cleave and functionalize inert C–H bonds effectively. In 2010, R. F. Heck, E. Negishi and A. Suzuki were awarded with Noble Prize in chemistry for their significant contribution to the development of palladium-catalyzed cross-coupling reactions. Metals such as copper, palladium, ruthenium, rhodium, iridium, cobalt, iron, rhenium and nickel are mainly used in metal catalyzed C–H functionalization process (scheme I.1.2).[4]



Scheme I.1.2. *Developing algorithm in organic synthesis*

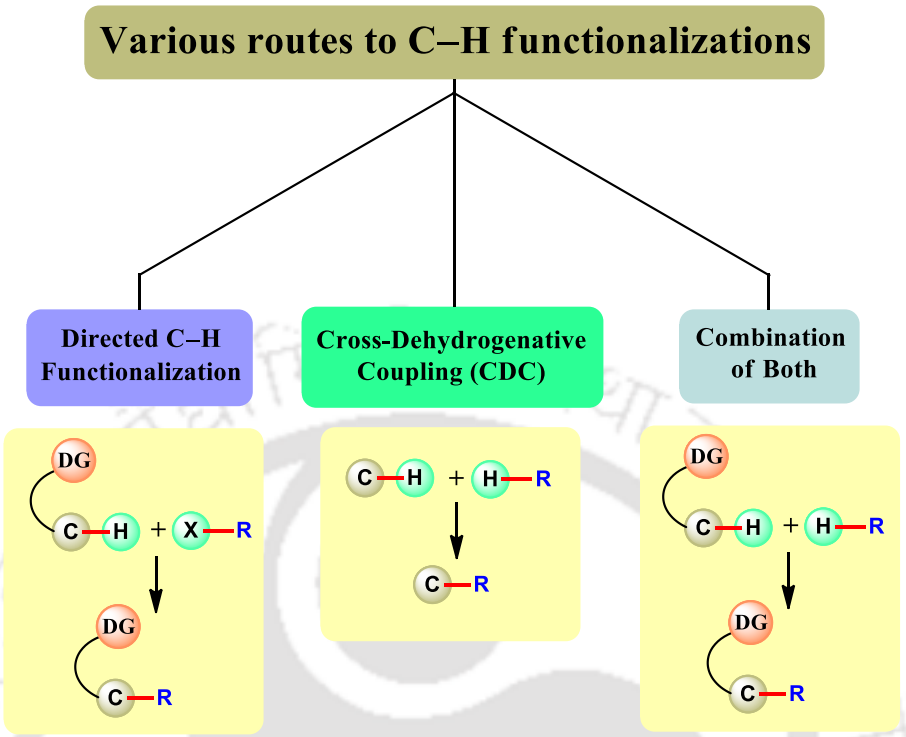
Functionalization of selective C–H bond among the available other C–H bonds and controlling the chemo–, regio– and stereoslectivity in a complex organic molecule is quite challenging (Scheme I.1.3). Hence the skill to selectively target a number of different C–H bonds in a complex organic scaffold permits direct access to multiple analogues from a common structural pioneer.



Scheme I.1.3. *Reactivity of a variety of C-H bonds*

These challenges of selectivity in C–H bond functionalization can be overcome mainly by three strategies: (i) directing group assisted C–H bond functionalization,[5] (ii)

cross dehydrogenative coupling (CDC)[6] and (iii) methodologies which are based on the combination of these two (Scheme I.1.4).



***Scheme I.1.4**. Various approaches to C–H functionalizations*

The directing group assisted C–H bond functionalization requires a group containing heteroatoms[7] such as nitrogen (N), oxygen (O) and sulfur (S) which can chelate the metal ion and bring it to the close proximity of the desired C–H bond which is the subject of functionalization (positional selectivity). The transition metals generally forms either a five or a six-member chelated metallacycle which is a resourceful intermediate for the construction of new C–C or C–X (X = heteroatoms) bonds via functionalization of both sp^2 and sp^3 C–H bonds. Though these strategies have several advantages but it suffer from some limitations.

Advantages:

- ✓ Direct the metal to activate the close proximity of the desired C–H bond and effectively increase the concentration of the metal catalyst at the site of interest.
- ✓ Improvement of reactivity and regioselectivity.

Limitations:

- ✓ Involves extra synthetic steps such as installation and removal of directing group (in many cases directing group remain integral part of the substrate).

The formation of C–C bonds from the coupling of two different C–H bonds or the coupling of C–H and X–H (X = heteroatoms) bonds is called "cross-dehydrogenative coupling" (CDC). Cross dehydrogenative coupling (CDC) is more attractive as it does not require any directing groups or pre-functionalization of starting materials. A variety of metal catalysts like Cu, Fe, Pd, Ru, Rh and Ir etc. are employed for CDC reactions.[8] There are also examples of CDC reactions which proceed in the absence of metal catalysts.[9] Generally a CDC reaction proceeds in the presence of a hydrogen acceptor such as inorganic peroxides for example hydrogen peroxide (H_2O_2), potassium persulphate ($K_2S_2O_8$), sodium persulphate ($Na_2S_2O_8$), ammonium persulphate ($(NH_4)_2S_2O_8$) and organic peroxides such as *tert*-butyl hydrogen peroxide (TBHP), *tert*-butyl nitrite (^{t}BuONO), benzoyl peroxide (BPO), di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS). Some advantages and limitations of these strategy are

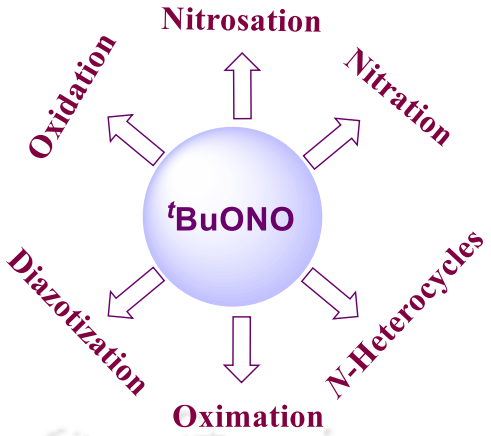
Advantages:

- ✓ No need of any directing groups or pre-functionalization of starting materials.
- ✓ Ambient reaction conditions.
- ✓ High degree of C–H bond functionalization.

Limitations:

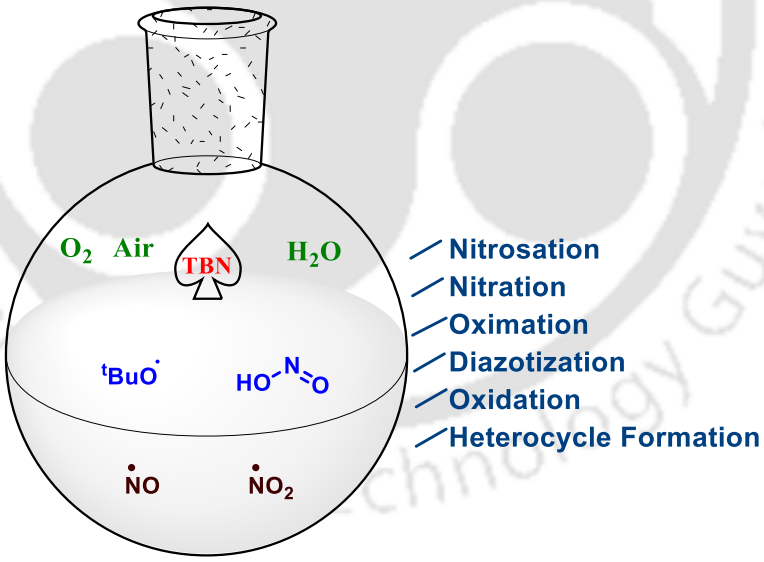
- ✓ Regioselectivity issues as the functionalization can occur at any of the C–H's.
- ✓ Lacking of chemoselectivity due to over functionalizations.

Further in the field of C–H bond functionalization, especially in CDC reactions, *tert*-butyl nitrite, a metal free reagents play a vital role for the contraction of *N*-containing diverse array of complex molecules. *tert*-Butyl nitrite (TBN) has numerous advantages in synthetic chemistry as it is inexpensive, readily accessible, good solubility in all organic solvents, easy handling, moreover, it provides only *tert*-butanol (^{t}BuOH) as the nontoxic side product. *tert*-Butyl nitrite mediated C–H functionalization reactions mostly occurs via radical pathaway. Under thermal condition, the heterolytic cleavage of *tert*-butyl nitrite generates a NO• radical which is converted to a NO_2• radical in an aerobic reaction condition. The generation of NO• and NO_2• radicals trigger a variety of C–H functionalization reactions *viz.* nitrosation, nitration, oximation, diazotization, oxidation, and construction of *N*-heterocycles (Scheme I.1.5).



***Scheme I.1.5**. tert-Butyl nitrite mediated various organic transformations*

Further, *tert* butyl nitrite (TBN) has its inherent ability to react with molecular oxygen and initiate aerobic transformations, especially the aerobic oxidation of various C–H bonds, which are important strategies applied in various C–H functionalization/cyclization reactions. In addition, since analogues of TBN, show higher and different reactivity under different conditions, therefore further modification and investigation surely open up more opportunities for applications in organic chemistry.



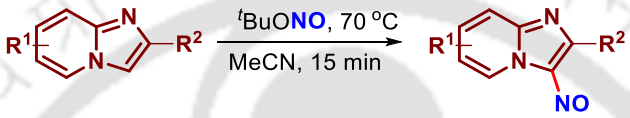
I.2. Representative examples of *tert*-butyl nitrite mediated C–H bond functionalization

I.2.1. Nitrosation:

Nitroso group containing frameworks are abundant in many naturally occurring and synthetic compounds exhibiting interesting biological activities and functional

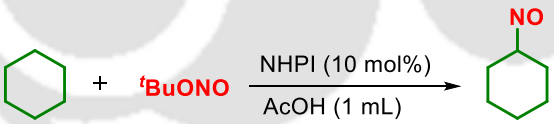
properties.[10] Some of the important nitroso compounds shows potent anticancer properties, also used in the treatment of cardiovascular diseases, central nervous disorders, and physiological disorders.[11] Therefore synthesis of nitroso compounds is a fascinating research area for synthetic chemist. Some examples of *tert*-butyl nitrite mediated nitrosation reactions via C–H bond functionalization is shown below.

Hajra and co-workers demonstrated a straight forward method for the construction of nitrosoimidazo[1,2-*a*]pyridines using TBN under mild reaction conditions. This reaction proceeds, via selective C–H bonds nitrosation of imidazo[1,2-*a*]pyridine ring at C3 position (Scheme I.2.1.1).[12]



Scheme I.2.1.1. *C–H bond nitrosation of imidazo[1,2-a]pyridines*

In 2004, Ishii group reported a novel and efficient method for nitrosation of cyclohexane by the action of *tert*-butyl nitrite in presence of *N*-Hydroxyphthalimide (NHPI) as the catalyst (Scheme I.2.1.2). Advantages of this protocol over conventional methods, are: (i) halogen free, (ii) reaction without photo-irradiation, (iii) high recovery of the catalyst, and (iv) good product selectivity.[13]

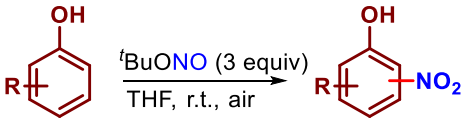


Scheme I.2.1.2. *Nitrosation of cyclohexane*

I.2.2. Nitration:

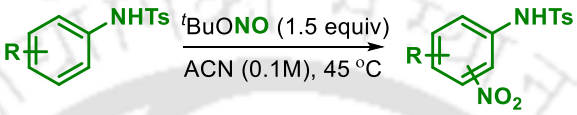
Nitro compounds are the basic subunits of many biologically active compounds. Hence, the construction of nitro compounds via C–H bond functionalizations using *tert*-butyl nitrite is an important strategy in organic synthesis. Few examples of such nitration reactions are represented below.

In 2009, Savinov *et al.* reported a chemo-selective nitration of phenols using *tert*-butyl nitrite under catalyst-free conditions (Scheme I.2.2.1). The mechanistic investigation revealed that the heterolytic cleavage of TBN generates nitrogen dioxide radicals involved in this nitration.[14]



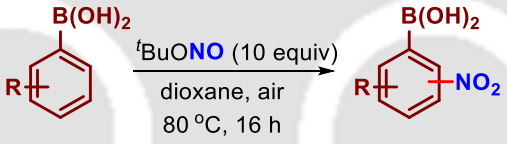
Scheme I.2.2.1. *tert Butyl nitrite mediated nitration of phenol*

Arns group developed a novel method for the nitration of aromatic sulfonamides using TBN as the nitrating agent (Scheme I.2.2.2). The major advantage of this protocol is high degree of chemo-selectivity and produced only mono-nitro derivatives of aromatic sulfonamides.[15]



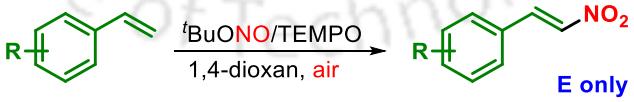
Scheme I.2.2.2. *Nitration of aromatic sulphonamides*

Wu, Beller, and co-workers reported an efficient nitration of phenylboronic acids using excess TBN under metal-free conditions (Scheme I.2.2.3). Substrates possessing both electron-donating and withdrawing groups are well tolerated under this transformation to afford their corresponding nitroarenes.[16]



Scheme I.2.2.3. *Nitration of phenylboronic acids using TBN*

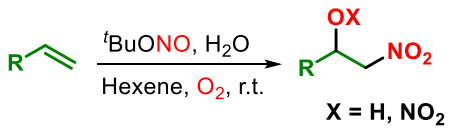
Stereoselective nitration of olefin using *tert*-butyl nitrite under metal-free conditions has been achieved by Maiti *et al.* (Scheme I.2.2.4). This transformation exhibits excellent E-selectivity.[17]



Scheme I.2.2.4. *Nitration of olefin under metal-free conditions*

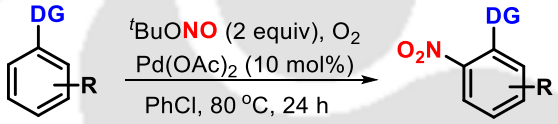
Taniguchi and co-workers stated an efficient protocol for the oxidative nitration of alkenes using a combination of *tert*-butyl nitrite and molecular oxygen to give β-nitro alcohols and their derivatives (Scheme I.2.2.5).[18] In this transformation, water causes gradual hydrolysis of ^{t}BuONO to generate nitrous acid (HNO_2) which is subsequently

decomposed to gives NO_2 and NO radicals. The *in situ* generated NO_2 radical is trapped by terminal alkene to produce nitro-alkane radical intermediate which captures a molecular oxygen, followed by hydrolysis to give β-nitro alcohols.



Scheme I.2.2.5. *Oxidative radical nitrations of alkenes*

In 2015, Jiao group described a Pd-catalyzed aerobic oxidative C–H nitration of arenes using readily available *tert*-butyl nitrite (TBN). The directing group mediated ortho C–H nitration of arene occurs through the formation of palladacycle intermediate in presence of molecular oxygen (Scheme I.2.2.6).[19]

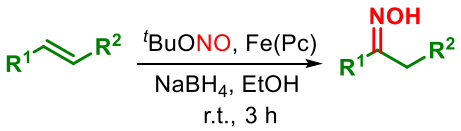


Scheme I.2.2.6. *Pd-catalyzed C–H nitration*

I.2.3. Oximation:

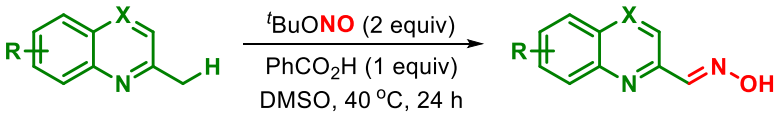
Oximes are important class of organic compounds having significant biological as well as industrial used *viz.* anti-skinning agents in paint, blocking agents in the polymer industry and many biological activities including anti-allergic and anti-inflammatory.[20] In this regard *tert*-butyl nitrite is very useful reagent for the direct synthesis of oximes under mild reaction conditions. Some examples of such reaction are shown below.

In 2009, Beller and co-workers have revealed the oximation of internal alkenes using *tert*-butyl nitrite, $NaBH_4$ and iron catalyst (Scheme I.2.3.1). *tert*-Butyl nitrite acts as a NO radical source which reacts with styrene in presence of iron catalyst and $NaBH_4$, leading to a nitroso intermediate; tautomerization of this intermediate gives the corresponding oxime.[21]



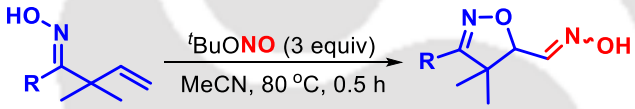
Scheme I.2.3.1. *Iron-catalyzed oximation of alkenes*

Yang *et al*. described a Brønsted acid catalyzed benzylic C–H bond functionalization of 2-alkylazaarenes using nitroso compounds as an acceptor of nucleophilic addition (Scheme I.2.3.2). Here in this transformation *tert*-butyl nitrite act as nitroso source, reacted smoothly with 2-alkylazaarenes to afford azaarene-2-oximes in high yields.[22]



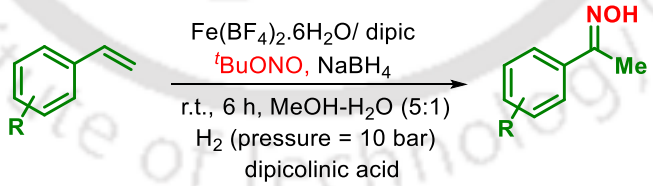
Scheme I.2.3.2. *Brønsted acid catalyzed benzylic C–H bond oximation of azaarenes*

Han *et al.* reported a novel method for the oxyoximation of β,γ-unsaturated ketoximes using TBN which not only act as the iminoxyl radical initiator but as a carbon radical trap (Scheme I.2.3.3). The formation of iminoxyl radical intermediate was confirmed by a TEMPO trapping experiment.[23]



Scheme I.2.3.3. *Oxyoximation of β,γ-unsaturated ketoximes*

Maiti, Lahiri and co-workers developed an efficient protocol for the conversion of styrene derivatives to their respective oximes (Scheme I.2.3.4).[24] This transformation occurs in the presence of $Fe(BF_4)_2{\cdot}6H_2O$/2,6 pyridinedicarboxylic acid and $^tBuONO/NaBH_4$ under H_2 pressure (10 bar) in MeOH–H_2O (5 : 1).



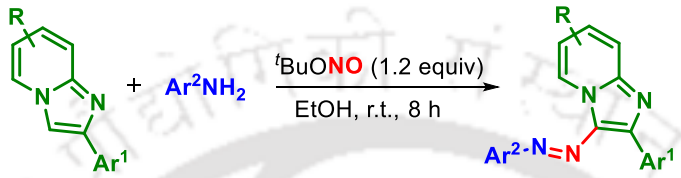
Scheme I.2.3.4. *Iron catalyzed oximation of olefins*

I.2.4. Diazotization:

In traditional synthesis of arenediazonium salts, generally nitrous acid ($NaNO_2$/HCl) is used. However, the use of acidic conditions, poor functional group tolerance and formation of undesirable side products have restricted its further application. In this regard, *tert*-butyl nitrite, as a mild and easy to handle chemical, can be used to generate

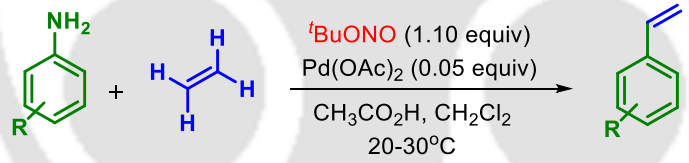
arenediazonium salts *in situ* without any acidic conditions. Few example of such reactions are shown below.

A ^{t}BuONO mediated synthesis of azoimidazoheterocycles have been accomplished through the coupling between imidazoheterocycles and anilines under mild reaction condition (Scheme I.2.4.1). This reaction proceeds via the formation of a diazonium intermediate from aniline in presence of ^{t}BuONO which subsequently reacted with imidazopyridine selectively at the 3-postion to give the desired product.[25]



Scheme I.2.4.1. *TBN mediated synthesis of azoimidazoheterocycles*

Beller *et al.* demonstrated the olefination of aniline with simple ethylene at room temperature through a tandem diazotization Heck reaction (Scheme I.2.4.2). Aniline in the presence of *tert*-butyl nitrite generates diazonium intermediate which may undergo coupling reactions with ethylene using Pd-catalyst to afford aromatic olefins.[26]

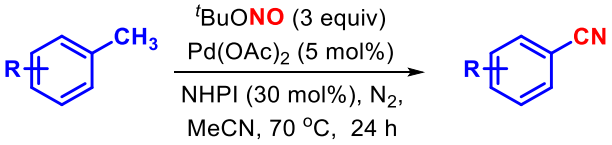


Scheme I.2.4.2. *Tandem diazotization heck reactions for the synthesis of olefins*

I.2.5. Oxidation:

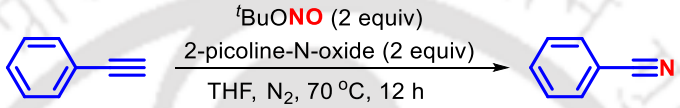
tert-Butyl nitrite, a metal free reagent serves the dual role of an oxidant as well as a nitrogen source in various organic reactions. Some example of *tert*-butyl nitrite mediated oxidation reactions are represented below.

In 2013, Wang and co-workers reported a novel strategy for the direct synthesis of aromatic nitriles from the corresponding methyl arenes (Scheme I.2.5.1). These reactions have been accomplished using palladium catalyst in the presence of TBN as the nitrogen source.[27]



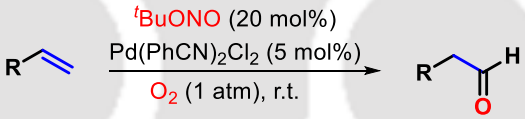
Scheme I.2.5.1. *Palladium (II)-catalyzed oxidation of the benzyl C–H bond*

Lupton, Maiti, and Dutta established a new protocol for the installation of a cyano group through the cleavage of terminal alkynes. This is the first example where TBN was employed as a powerful nitrogenating agent for terminal alkynes to produce nitriles (Scheme I.2.5.2).[28]



Scheme I.2.5.2. *Synthesis of aromatic nitriles from alkynes*

Kang and co-workers reported an aldehyde-selective aerobic Wacker−Tsuji oxidation at room temperature assisted by *tert*-butyl nitrite as a simple organic redox co-catalyst (Scheme I.2.5.3).[29]

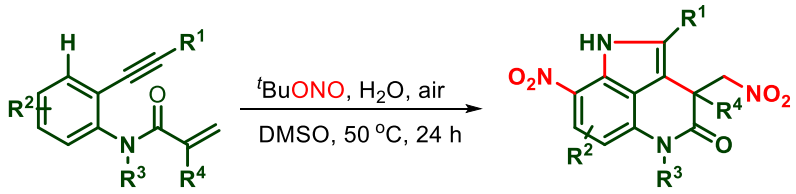


Scheme I.2.5.3. *Oxidation of terminal olefin to aldehyde*

I.2.6. Construction of heterocycles:

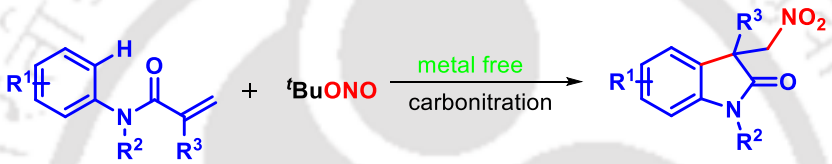
tert-Butyl nitrite plays the vital role for the construction of *N*-heterocycles through the generation of NO and NO_2 radicals respectively under aerobic reaction condition. Construction of various *N*-heterocycle using *tert*-butyl nitrite is shown below.

Li *et al*. described the direct synthesis of pyrrolo[4,3,2-de]quinolinone scaffold through a cascade nitration/cyclization reaction of *N*-methyl-*N*-(2-(phenylethynyl)phenyl)methacrylamide with ^{t}BuONO and H_2O (Scheme I.2.6.1).[30]



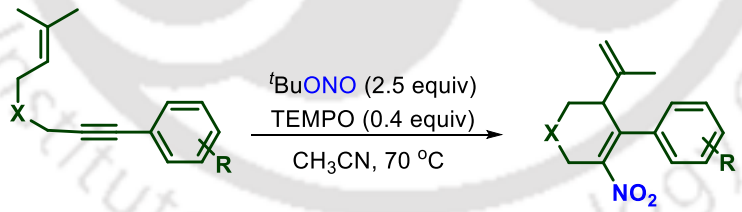
Scheme I.2.6.1. *Cascade nitration/cyclization of 1,7-enynes*

Nitro-carbocyclization of activated alkenes to nitro oxindoles via cascade C–N and C–C bond formation have been achieved by Jiao *et al*. The mechanistic studies revealed that under a thermal condition, TBN generates NO and NO_2 radicals which on addition to the activated alkene, followed by nitro-carbocyclization lead to the formation nitro oxindoles (Scheme I.2.6.2).[31]



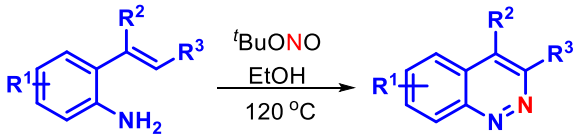
Scheme I.2.6.2. *Metal-free nitro-carbocyclization of activated alkenes*

Liang group developed a novel method for one step nitration and cyclization of 1,6-enynes using readily available *tert*-butyl nitrite (TBN). In this domino process, two C–C bonds and one C–N bonds are constructed simultaneously (Scheme I.2.6.3).[32]



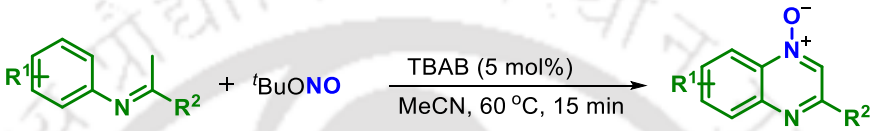
Scheme I.2.6.3. *Cyclization of 1,6-enynes using tert-butyl nitrite*

Yan *et al.* demonstrated a novel route to synthesize substituted cinnolines from 2-vinylanilines and TBN via tandem oxidation/cyclization reactions (Scheme I.2.6.4).[33] During the synthesis of cinnolines, *tert*-butyl nitrite serves the dual role of an oxidant as well as a N_1 synthon.



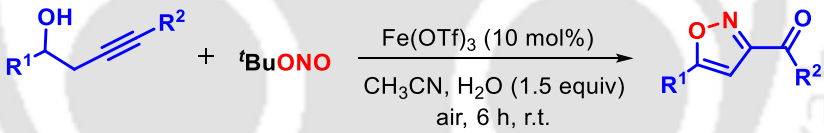
Scheme I.2.6.4. *The synthesis of substituted cinnolines*

An efficient and practical approach for the synthesis of quinoxaline *N*-oxides was achieved by Jiao *et al.* using commercially available *tert*-butyl nitrite as the NO radical source. The reaction involves the cleavage of one C(sp^2)-H bond and two C(sp^3)-H bonds for the construction of multiple C–N bonds (Scheme I.2.6.5).[34]



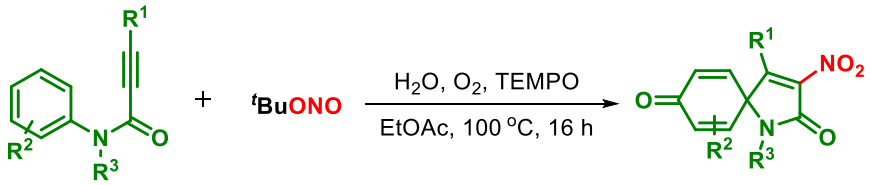
Scheme I.2.6.5. *Synthesis of quinoxaline N-oxides via the cleavage of three C–H bonds*

Liang and co-workers synthesized di-substituted isoxazoles using homopropargylic alcohol, ^{t}BuONO, H_2O, and iron catalyst. During this transformations, oxidation of one C–H bond and construction of one C=N and C=O bond occur to yield di-substituted isoxazoles (Scheme I.2.6.6).[35]



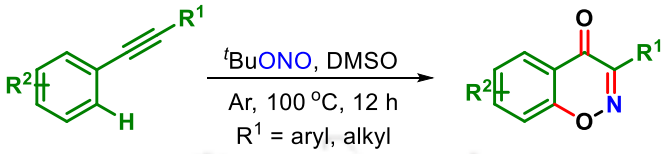
Scheme I.2.6.6. *Synthesis of disubstituted isoxazoles*

The nitrative spirocyclization of internal alkynes using ^{t}BuONO was demonstrated by Song and Li groups as represented in Scheme I.2.6.7. The mechanistic study of this transformation shown that the reaction proceeds via a radical pathway using TEMPO [(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl] as the radical initiator and ^{t}BuONO combined with water as the nitro source.[36]



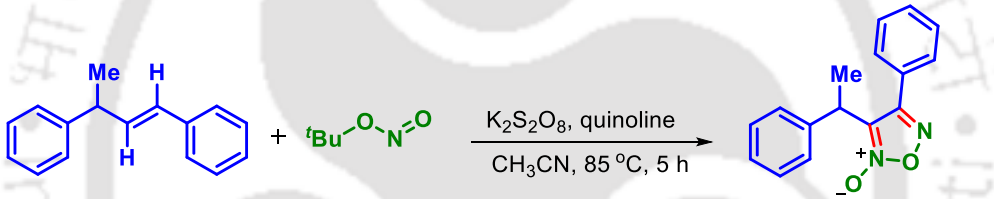
Scheme I.2.6.7. *Nitrative spirocyclization of N-arylpropiolamides*

Li and co-workers reported a radical-mediated [4+2] annulation reaction of aryl alkynes with ^{t}BuONO for the synthesis of benzo[*e*][1,2]oxazin-4-ones (Scheme I.2.6.8).[37] Importantly, this transformation allows the incorporation of two O atoms in the final skeleton and the ^{18}O-labeling experiment confirmed that two oxygen atoms in the product are from water.



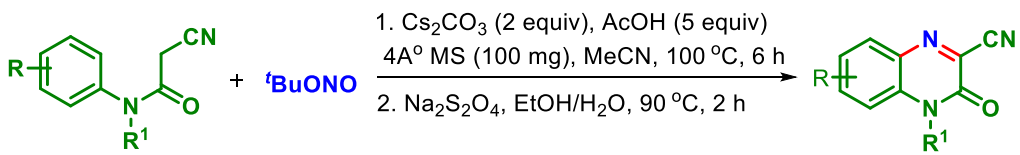
Scheme I.2.6.8. *Radical-mediated [4+2] annulation reaction of arylalkynes*

Recently, our group has demonstrated a new and efficient method for the construction of 1,2,5-oxadiazole-*N*-oxides (furoxans) from internal alkenes using *tert*-butyl nitrite (TBN), quinoline and $K_2S_2O_8$ (Scheme I.2.6.9).[38] During this transformation, *tert*-butyl nitrite is serving as a NO_2 cum NO synthon.



Scheme I.2.6.9. *tert-Butyl nitrite mediated functionalization of olefins*

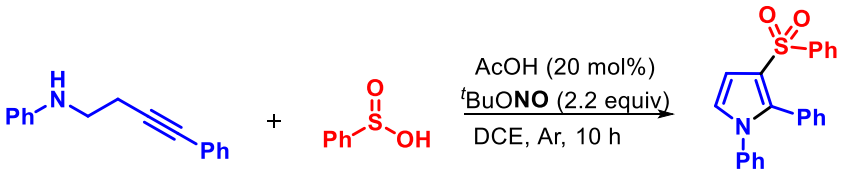
Zhang *et al.* established an efficient method for the synthesis of quinoxalin-2-ones *via* a one-pot tandem nitrosation/cyclization of *N*-aryl cyanoacetamides with *tert*-butyl nitrite (Scheme I.2.6.10).[39] Herein two sp^3 C–H's and one sp^2 C–H cleavage of *N*-aryl cyanoacetamides leads to the formation of fused quinoxalin-2-ones *via* two sequential C–N bond formation.



Scheme I.2.6.10. *One-pot synthesis of quinoxalinones via tandem nitrosation/cyclization*

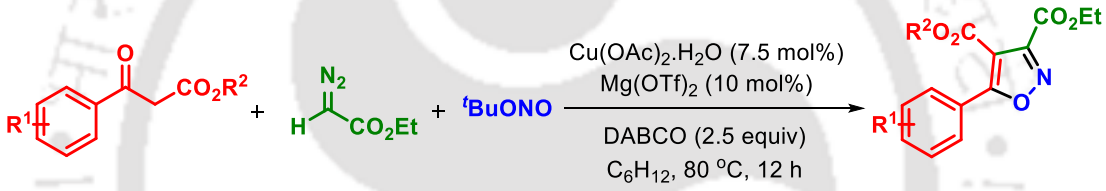
tert-Butyl nitrite promoted tandem addition/cyclization of alkynylamines with sulfinic acids to synthesize substituted sulfonyl pyrroles was accomplished by Yan and co-

workers. This is an oxidative intermolecular sulfonamination of alkynes where *tert*-butyl nitrite serves as an oxidant (Scheme I.2.6.11).[40]



Scheme I.2.6.11. *One-pot synthesis of sulfonyl pyrroles*

Wan, Bao and co-workers introduced a new route to synthesize isoxazole derivatives from *β*-keto esters, diazo regents and *tert*-butyl nitrite catalyzed by a copper catalyst (Scheme I.2.6.12).[41] This reaction proceeds through the generation of nitrile oxides from copper carbene and *tert*-butyl nitrite, followed by [3 + 2] cycloaddition with β-keto esters to afford isoxazoles.



Scheme I.2.6.12. *Copper catalyzed synthesis of isoxazoles*

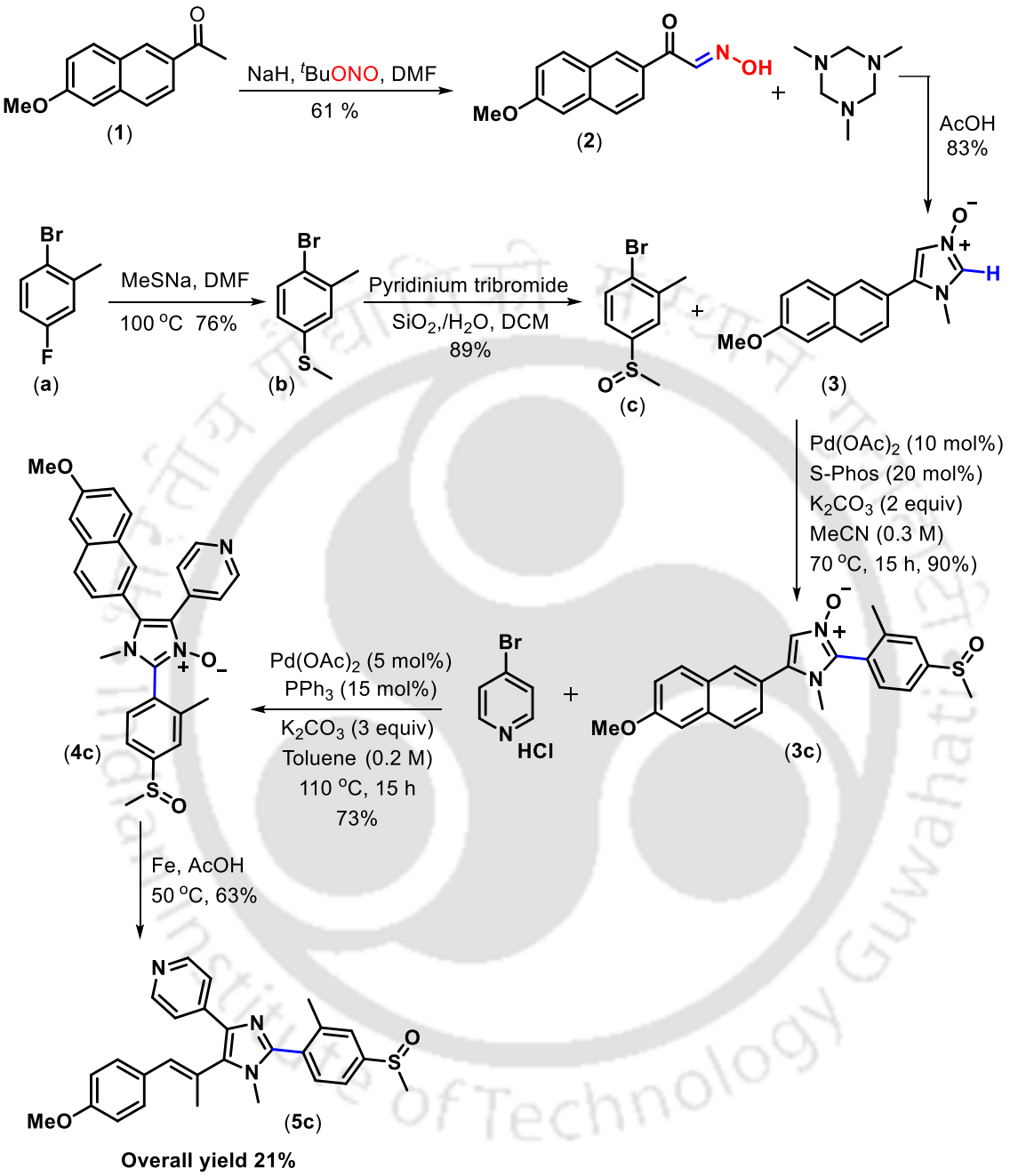
I.3. C–H Functionalization: a new paradigm for total synthesis

The existing knowledge in the field of C–H functionalization has empowered its use as a reliable tool for natural product synthesis. Herein mentioned below is one example of total synthesis showcasing creative and ingenious incorporation of C–H functionalization as a strategic plan compared to the traditional methods, enlightening a new paradigm in strategic synthetic design.

I.3.1. Total synthesis of Tie2 tyrosine kinase inhibitor:

Tie2 Tyrosine Kinase inhibitor is a highly bioactive compound used for the treatment of advanced breast cancer and gleevec for chronic myelogenous leukemia and gastrointestinal stromal tumors. In this regard, Fagnou and co-worker[42] developed a novel strategy for the total synthesis of Tie2 tyrosine kinase inhibitor. Synthesis of this drug molecule have two major C–H functionalization steps (Scheme I.3.1). The first C–H functionalization step involves cleavage of sp^3 C–H bond of 1-acetonaphthone in presence

of oxidant *tert*-butyl nitrite and later is Pd-catalyzed sp^2 C–H functionalization of imidazole *N*-oxide (**3**).



Scheme I.3.1. *Total synthesis of Tie2 tyrosine kinase inhibitor*

I.4. Conclusion:

In conclusion, *tert*-butyl nitrite mediated C–H functionalization process have greatly improved our understanding of how to cleave and functionalize inert C–H bonds effectively. We believe that C–H functionalization using *tert*-butyl nitrite is still young

and it can open huge opportunities for synthetic chemist to build diverse array of complex molecules in a single operation.

I.5. References:

(1) (a) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 6954. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev*. **2008**, *108*, 3054. (c) Corbet, J. P.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651. (d) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev*. **2008**, *37*, 1108. (e) Würtz, S.; Glörius, F. *Acc. Chem. Res*. **2008**, *41*, 1523. (f) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed*. **2003**, *43*, 5400.

(2) (a) Carruthers, W.; Coldham, I. in *Modern Methods of Organic Synthesis*, Cambridge University Press, Cambridge, **2004**, 45. (b) Huryn, D. M. in *Comprehensive Organic Synthesis*, Vol. 1 (Eds.: Trost, B. M.; Fleming, I.), Pergamon, Oxford, **1991**, 49. (c) Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem*. **2002**, *653*, 288.

(3) (a) Dyker, G. *Handbook of C–H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, **2005**. (b) Yu, J.-Q.; Shi, Z.-J. *C–H Activation*; Springer: Berlin, Germany, **2010**. (c) *Activation and Functionalization of C–H Bond*; Goldberg, K. I.; Goldman, A. S., Eds.; ACS Symposium Series 885; American Chemical Society: Washington, DC, **2004**. (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res*. **2008**, *41*, 1013. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2009**, *48*, 5094. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun*. **2010**, *46*, 677. (g) Gunay, A.; Theopold, K. H. *Chem. Rev*. **2010**, *110*, 1060. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev*. **2011**, *111*, 1293. (j) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315. (k) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215. (l) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev*. **2011**, *111*, 1780. (m) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev*. **2012**, *41*, 5588.

(4) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev*. **2011**, *111*, 1293. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 10236. (e) Zhu, C.; Wang, R.; Falck, J. R. *Chem.-Asian J*. **2012**, *7*, 1502. (f) White, M. C. *Science* **2012**, *335*, 807. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res*. **2012**, *45*, 788. (h) Wencel-Delord, J.; Glorius, F. *Nat. Chem*. **2013**, *5*, 369. (i) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc*. **2009**, *131*, 3466. (j) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.

(5) (a) Dyker, G. *Angew. Chem., Int. Ed*. **1999**, *38*, 1698. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (d) Ashenhurst, J. A. *Chem. Soc. Rev*. **2010**, 39, 540. (e) Cheuermann, C. J. *Chem. Asian J*. **2010**, *5*, 436.

(6) (a) Li, C.-J. *Acc. Chem. Res*. **2009**, *42*, 335. (b) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (c) Ashenhurst, J. A. *Chem. Soc. Rev*. **2010**, 39, 540. (d) Cheuermann, C. J. *Chem. Asian J*. **2010**, *5*, 436. (e) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem*. **2013**, 5769. (f) Girad, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2.

(7) (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc*. **2002**, *124*, 1586. (b) Yang, S. D.; Li, B. J.; Wan, X. B.; Shi, Z. J. *J. Am. Chem. Soc*. **2007**, *129*, 6066. (c) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc*. **2006**, *128*, 78. (d) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 9542. (e) Ackermann, L.; Pospech, J. *Org. Lett*. **2011**, *13*, 4153

(8) (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev*. **2015**, *115*, 1622. (b) Patel, P.; Chang, S. *Org. Lett*. **2014**, *16*, 3328. (c) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc*. **2010**, *132*, 9602.

(9) (a) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219. (b) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (c) Thome, I.; Bolm C. *Org. Lett.* **2012**, *14*, 1892. (d) Yu, W. Z.; Chen, F.; Cheng, Y. A.; Yeung, Y.-Y. *J. Org. Chem.* **2015**, *80*, 2815. (e) Narayan, R.; Matcha, K.; Antonchick, A. P. *Chem. -Eur. J.* **2015**, *21*, 1.

(10) (a) Loeppky, R. N.; Outram, J. R. *N-Nitroso Compounds: Occurrence and Biological Effects*; IARC Scientific Publishers: Lyon, **1982**. (b) *Nitrosamines and Related N-Nitroso Compounds:Chemistry and Biochemistry, ACS Symposium Series No. 553*; Loeppky, R. N.; Michejda, C. J., Eds.; American Chemical Society: Washington DC, **1994**.

(11) (a) Wang, P. G.; Cai, T. B.; Taniguchi, N. *Nitric Oxide Donor, For Pharmaceutical and Biological Applications*; Wiley-VCH: Weinheim, **2005**. (b) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091

(12) Monir, K.; Ghosh, M.; Jana, S.; Mondal, P.; Majee, A.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 8717.

(13) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Angew. Chem., Int. Ed*. **2004**, *43*, 1120.

(14) Koley, D.; Colón, O.-C.; Savinov, S.-N. *Org. Lett*. **2009**, *11*, 4172.

(15) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun*. **2013**, *49*, 514.

(16) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun*. **2011**, *47*, 12462.

(17) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett*. **2013**, *15*, 3384.

(18) Yajima, A.; Ishibashi, H.; Taniguchi, T. *Adv. Synth. Catal*. **2011**, *353*, 2643.

(19) Liang, Y.-F.; Li, X.-Y.; Wang, X.-Y.; Yan, Y.-P.; Feng, P.; Jiao, N. *ACS Catal*. **2015**, *5*, 1956.

(20) (a) Bodor, N.; Koussi, A. El.; Kano, M.; Nakamura, T. *J. Med. Chem*. **1988**, *31*, 100. (b) Katagi, T.; Kataoka, H.; Takahashi, K.; Fujioka, T.; Kunitomo, M.; Yamaguchi, Y.; Fujiwara, M.; Inoi, T. *Chem. Pharm. Bull*. **1992**, *40*, 2419. (c) Katagi, T.; Kataoka, H.; Konishi, Y.; Takata, Y.; Kitano, S.; Yamaki, M.; Inoi, T.; Yamamoto, K.; Yamamoto, S.; and Yamagata, Y. *Chem. Pharm. Bull*. **1996**, *44*, 145. (d) Kataoka, H.; Horiyama, S.; Yamaki, M.; Oku, H.; Ishiguro, K.; Katagi, T.; Takayama, M.; Semma, M.; Ito, Y. *Biol. Pharm. Bull*. **2002**, *25*, 1436. (e) Nilsson, A. M.; Bergstrom, M. A.; Luthman, K.; Nilsson, J. L. G.; Karlberg, A. T. *Food Chem. Toxicol*. **2005**, *43*, 1627.

(21) Prateeptongkum, S.; Jovel, I.; Jackstell, R.; Vogl, N.; Weckbeckerb, C.; Beller, M. *Chem. Commun*. **2009**, *15*, 1990.

(22) Gao, X.; Zhang, F.; Deng, G.-J.; Yang, L. *Org. Lett.* **2014**, *16*, 3364.

(23) Peng, X.-X.; Deng, Y.-J.; Yang, X.-L.; Zhang, L.; Yu, W.; Han, B. *Org. Lett.* **2014**, *16*, 4650.

(24) Ray, R.; Chowdhury, A. D.; Maiti, D.; Lahiri, G. K. *Dalton Trans*. **2014**, *43*, 38.

(25) Chakraborty, A.; Jana, S.; Kibriya, G.; Dey, A.; Hajra, A. *RSC Adv.* **2016**, *6*, 34146.

(26) Fischer, H.; Kuhlein, K.; Beller, M. *Tetrahedron Lett*. **1994**, *35*, 8773.

(27) Shu, Z.-B.; Ye, Y.-X.; Deng, Y.-F.; Zhang, Y.; Wang, J.-B. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573.

(28) Dutta, U.; Lupton, D. W.; Maiti, D. *Org. Lett.* **2016**, *18*, 860.

(29) Ning, X.-S; Wang, M.-M.; Yao, C.-Z.; Chen, X.-M.; Kang, Y.-B. *Org. Lett*. **2016**, *18*, 2700.

(30) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Qian, P.-C.; Li, J.-H. *Angew. Chem., Int. Ed*. **2014**, *53*, 9017.

(31) Shen, T.; Yuan, Y.-Z.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554.

(32) Hao, X.-H.; Gao, P.; Song, X.-R.; Qiu, Y.-F.; Jin, D.-P.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun*. **2015**, *51*, 6839.

(33) Pang, X.; Zhao, L.; Zhou, D.; He, P. Y.; An, Z.; Ni, J. X.; Yan, R. *Org. Biomol. Chem*. **2017**, *15*, 6318.

(34) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495.

(35) Gao, P.; Li, H. X.; Hao, X. H.; Jin, D. P.; Chen, D. Q.; Yan, X. B.; Wu, X. X.; Song, X. R.; Liu, X. Y.; Liang, Y. M. *Org. Lett*. **2014**, *16*, 6298.

(36) Yang, X.-H.; Ouyang, X.-H.; Wei, W.-T.; Song, R.-J.; Li, J.-H. *Adv. Synth. Catal*. **2015**, *357*, 1161.

(37) Yang, X.-H.; Song, R.-J.; Li, J.-H. *Adv. Synth. Catal*. **2015**, *357*, 3849.

(38) Mir, B. A.; Singh, S. J.; Kumar, R.; Patel, B. K. *Adv. Synth. Catal*. **2018**, *360*, 3801.

(39) Wang, F.; Hu, B.-L.; Liu, L.; Tu, H.-Y.; Zhang, X.-G. *J. Org. Chem*. **2017**, *82*, 11247.

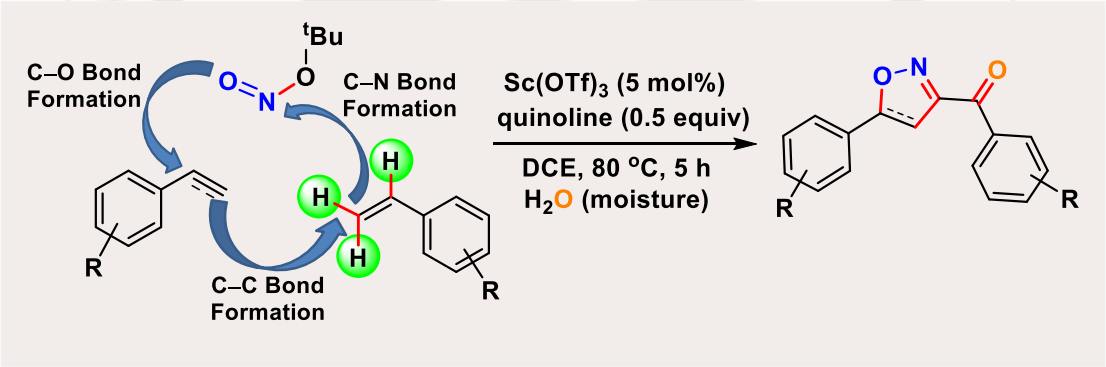
(40) Qi, Z.; Jiang, Y.; Wang, Y.; Yan, R. *J. Org. Chem*. **2018**, *83*, 8636.

(41) Chen, R.; Ogunlana, A. A.; Fang, S.; Long, W.; Sun, H.; Bao, X.; Wan, X. *Org. Biomol. Chem.* **2018**, *16*, 4683.

(42) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

CHAPTER II

tert-Butyl Nitrite Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes



ABSTRACT: *A sequential construction of C–C, C–O, C=N and C=O bonds from alkenes leading to the direct synthesis of isoxazolines in the presence of tert-butyl nitrite, quinoline and Sc(OTf)$_3$ catalyst in DCE at 80 °C has been accomplished. An unprecedented consecutive three C–H functionalizations of two styrenes are involved during this isoxazoline synthesis. In this radical mediated reaction one half of the aryl alkene is converted into intermediate 2-nitro ketone which serve as a 1,3-dipolarophile and undergo cycloaddition with the other half of unreacted aromatic terminal alkene. The use of alkyne in lieu of alkene leads to the formation of isoxazole under an identical reaction condition.*

J. Org. Chem. 2017, *82*, 6358

CHAPTER II

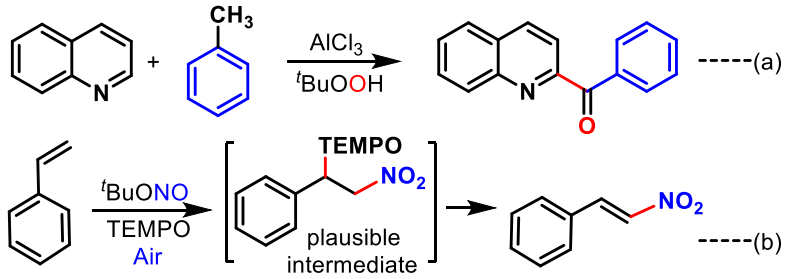
tert-Butyl Nitrite Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes

II.1. Introduction

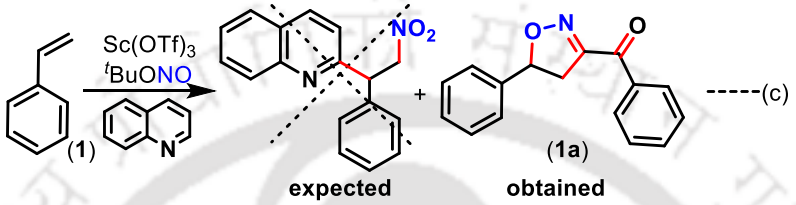
Alkenes are simple organic molecules which have been widely applied in organic synthesis for the construction of a diverse array of complex molecules. One of the finest approaches to build such molecules in a single operation is via the direct 1,2-difunctionalization of alkenes. In this context, both intra and intermolecular hetero functionalization of alkenes have acquired significant attention. In contrast to intermolecular processes intramolecular difunctionalizations are more selective and thermodynamically favourable. Despite that, the transition metal catalyzed intermolecular difunctionalizations *viz.* carbohalogenation,[1] dihydroxylation,[2] oxyarylation,[3] oxyamination,[4] aminofluorination,[5] aminocyanation,[6] hydroalkylation,[7] carboboration,[8] and other difunctionalization[9] are well explored. However, intermolecular difunctionalization of olefins using C–H functionalization strategy remain fewer in numbers. In this context, an intermolecular Fe(II)-catalyzed carbonylation-peroxidation,[10] *p*-toluenesulfonic acid (*p*TsOH) catalyzed oxidative keto-peroxidation,[11] copper or cobalt catalyzed alkylation-peroxidation[12] and copper catalyzed cycloalkylation-peroxidation[13] of olefins have been reported.

Recently, our group has developed a Lewis acid ($AlCl_3$) catalyzed cross-dehydrogenative coupling between electron-deficient *N*-heterocycles (quinoline, isoquinoline and quinoxaline) and alkylbenzenes for the synthesis of C1 or C2 aroylated *N*-heterocycles [Scheme II.1.1 (a)].[14] In the presence of $AlCl_3$ catalyst electron-deficient *N*-heterocycles acts as a radical acceptor, which trapped the *in situ* generated aroyl radical ($ArCO^{\cdot}$) obtained from alkyl benzene by the action of peroxide (TBHP). During the nitration of alkenes using *tert*-butyl nitrite as a nitrating agent follows a radical pathway where the *in situ* generated alkyl radical is trapped by the radical scavenger TEMPO [Scheme II.1.1 (b)].[15a] Now a query arises if an alkene is treated with *tert*-butyl nitrite in the presence of quinoline in lieu of TEMPO, will it offer a similar 1,2-difunctionalized product (Scheme II.1.1).

Previous works:



Present work:



Scheme II.1.1. *C–H Functionalization of alkene to isoxazoline*

With this assumption, we treated styrene (**1**) with quinoline (1 equiv), *tert*-butyl nitrite (^{t}BuONO) (**a**, 2.0 equiv) and $AlCl_3$ catalyst (5 mol%) in 1,2-dichloroethane (DCE) at 80 ^oC. A new product was isolated (55%), spectroscopic analysis of which confirmed the structure to be phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**) [Scheme II.1.1 (c)].[16a] The synthesis of isoxazolines involving three C–H functionalization of two styrenes is unprecedented in the literature. The newly formed product is devoid of any quinoline moiety however, in its absence the yield was dropped to mere 12% (Table II.3.1) thereby suggesting its possible involvement as a base. Isoxazolines, are an important class of heterocycle that have attracted considerable attention in the field of anticancer research.[17] Some of the important isoxazoline scaffolds exhibiting potent anticancer properties are 3,5-diaryl-isoxazoline linked 2,3-dihydroquinazolinone hybrids,[17a] arylisoxazoline containing anthranilic diamides,[17b] 3,5-diaryl-isoxazoline linked pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) conjugates[17c] and dibenzo[b,f]azepinetethered isoxazoline[17d] (Figure II.1.1)

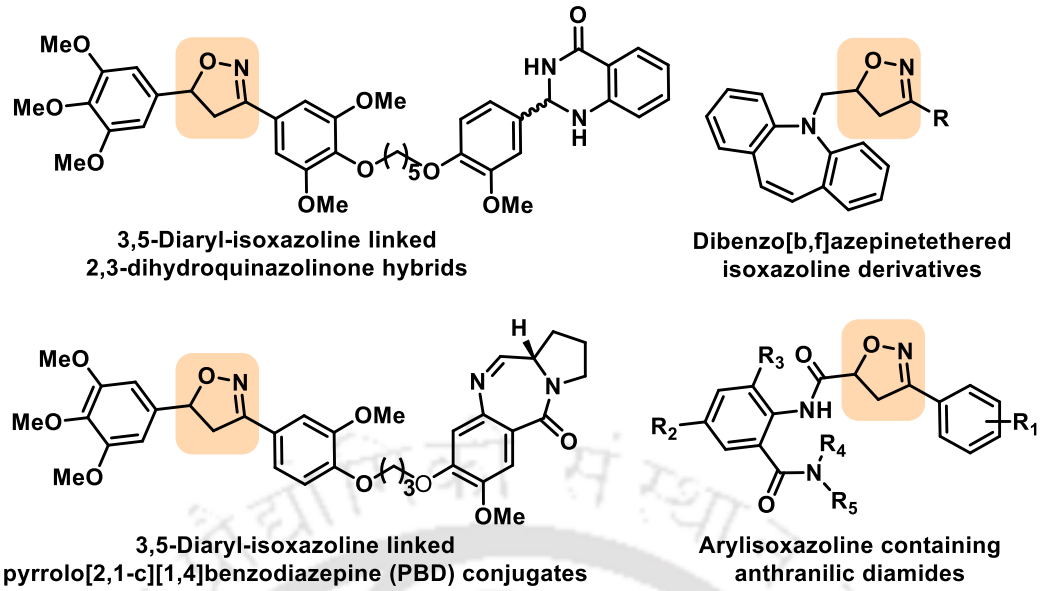
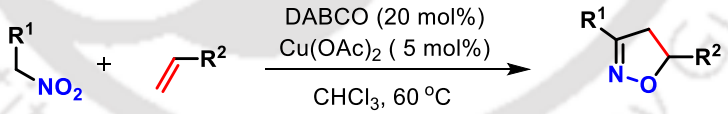


Figure II.1.1. *Representative anticancer isoxazolines*

II.2. Strategies for the synthesis of isoxazolines or isoxazoles

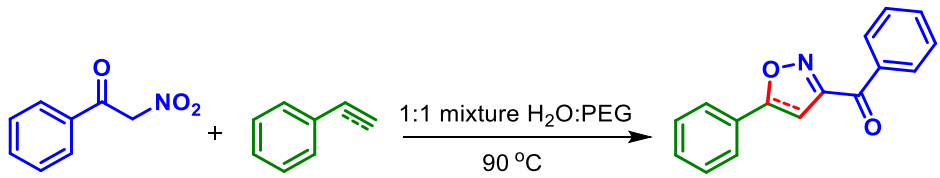
Due to the enormous utility of isoxazolines or isoxazoles in both biological and synthetic fields, several methods thus implemented for the synthesis of isoxazolines or isoxazoles *via* C–H functionalization are enlisted below.

Machetti *et al.* developed a novel route for the synthesis of 4,5-dihydroisoxazoles via the reaction of primary nitro compounds with olefins in presence of [Cu]/NMP catalyst as shown in scheme II.2.1.[18]



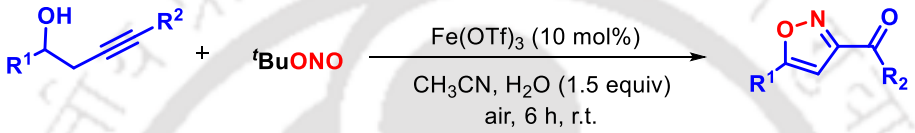
Scheme II.2.1. *Synthesis of 4,5-dihydroisoxazoles*

Pal's research group has shown the synthesis of isoxazoles or isoxazolines derivatives from α-nitroketones using terminal alkynes or alkenes (Scheme II.2.2).[19] Here in this reaction 2-nitro ketone takes part in 1,3-dipolar cycloaddition reaction with alkene/alkyne to give corresponding isoxazoles or isoxazolines derivatives.



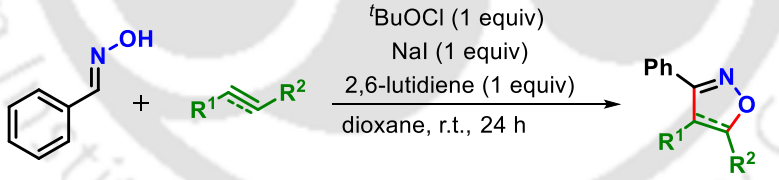
Scheme II.2.2. *Synthesis of isoxazoles and isoxazolines using α-nitroketones*

Iron-catalyzed synthesis of di-substituted isoxazoles from homopropargylic alcohol using ^{t}BuONO, and H_2O was demonstrated by Liang *et al.* (Scheme II.2.3).[20] During this transformation, oxidation of one C–H bond and construction of one each of C=N and C=O bonds occur to produce di-substituted isoxazoles.



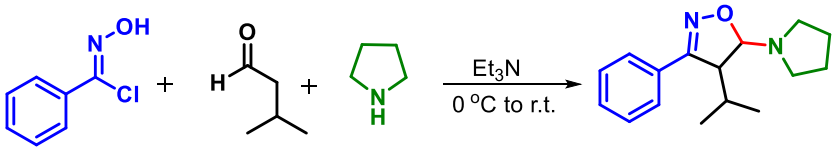
Scheme II.2.3. *Synthesis of disubstituted isoxazoles*

^{t}BuOCl and base promoted synthesis of isoxazolines / isoxazoles via the reaction of oximes with internal alkenes/alkynes was established by Takeda groups. During this reaction generation of nitrile oxide occurs from aryl-oximes by the action of electrophilic iodine compound, and ^{t}BuOCl, which on reaction with alkene/alkyene lead to the synthesis of corresponding isoxazolines / isoxazoles (Scheme II.2.4).[21]



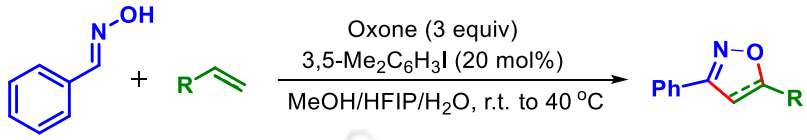
Scheme II.2.4. *Cycloaddition of benzaldoxime using ^{t}BuOCl*

Wang and co-worker described a novel route for the construction of highly substituted dihydroisoxazole through an enamine-promoted [3+2] cycloaddition reaction, between aldehydes and *N*-hydroximidoyl chlorides in the presence of triethylamine (Scheme II.2.5).[22]



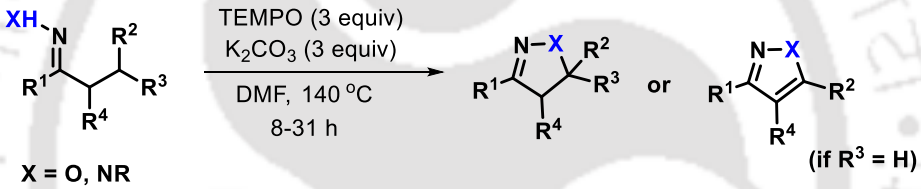
Scheme II.2.5. *Synthesis of 3,4-disubstituted isoxazoles*

Zhdankin group reported the hypervalent iodine catalyzed synthesis of isoxazolines / isoxazoles through the oxidative cyclization reaction of aldoxime with alkene / alkynes (Scheme II.2.6). [23] The mechanistic study revealed that the reaction proceeds via initial formation of nitrile oxides from aldoxime, which react with alkenes and alkynes to give corresponding isoxazolines and isoxazoles.



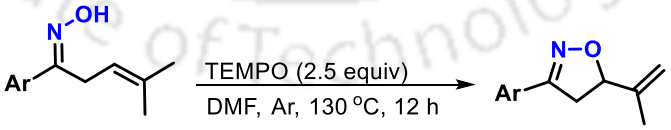
Scheme II.2.6. *Catalytic heterocyclization of aldoximes with alkynes or alkene*

Chiba *et al.* demonstrated a TEMPO-mediated synthesis of substituted isoxazoles and pyrazoles skeletons involving C–H bond oxidation of oximes and hydrazones under transition-metal-free conditions (Scheme II.2.7).[24]



Scheme II.2.7. *Synthesis of substituted isoxazole and pyrazole skeletons*

Han's group established an efficient, metal-free, and regioselective approach for the construction of isoxazoline/cyclic nitrone-featured methylenes by the reaction of β,γ- and γ,δ-unsaturated ketoximes with TEMPO via iminoxyl radical mediated cyclization, followed by β-hydrogen elimination (Scheme II.2.8).[25]



Scheme II.2.8. *Regioselective synthesis of isoxazoline*

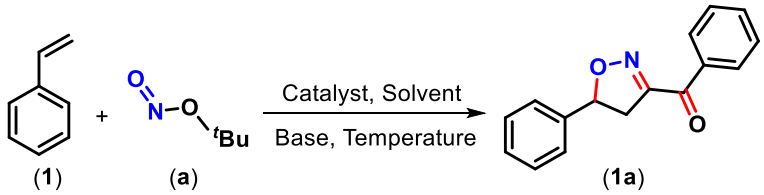
II.3. Present work

In the light of the aforementioned protocols, the present method for the construction of isoxazoline using styrene, quinoline and *tert*-butyl nitrite is unprecedented in literature.

Optimization of reaction conditions:

As mentioned earlier an initial trial was executed using styrene (**1**) with quinoline (1 equiv), *tert*-butyl nitrite (^{t}BuONO) (**a**, 2.0 equiv) and $AlCl_3$ catalyst (5 mol%) in 1,2-dichloroethane (DCE) at 80 ^oC. A new product was isolated (55%), spectroscopic analysis of which confirmed the structure to be phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**). We then look forward to improving the self-coupling of aryl alkene via C–H functionalization leading to the formation of isoxazoline by varying other reaction parameters. Non polar solvents such as *p*-xylene (45%), toluene (43%), chlorobenzene (52%), and cyclohexane (50%), and polar aprotic solvents such as DMF (34%), and DMSO (<5%) were all found to be less efficient compared to DCE (55%), (Table II.3.1, entries 3-8). Other Lewis acid catalysts such as $FeCl_3$ (51%) and $FeCl_2$ (55%) provided comparable yield of (**1a**), but $Cu(OTf)_2$ completely failed to give the desired product (Table II.3.1, entries 9–11). When $Sc(OTf)_3$ (5 mol%) was employed in lieu of other catalysts under otherwise identical conditions gave the best yield of 66% (Table II.3.1, entry 12). No substantial improvement in the yield (68%) was observed when the catalyst loading was increased up to 10 mol% (Table II.3.1, entry 13). Replacing the base quinoline to DBU (54%), DABCO (50%), pyridine (41%) and DMAP (30%) all gave lower yield of (**1a**) (Table II.3.1, entries 14–17). The presence of $Sc(OTf)_3$ is essential for this transformation, which is perhaps serving the role of a Lewis acid catalyst to enhance the reactivity of alkene, because in its absence the reaction just provided 22% yield of (**1a**) (Table II.3.1, entry 18). Both increasing (110 ^oC) and decreasing temperature (60 ^oC) reduced the product yield (Table II.3.1, entries 19 and 20). The product yield remained unaltered even when the quantity of quinoline was reduced to 0.5 equiv. After screening various reaction conditions, it was observed that the use of styrene (0.4 mmol), ^{t}BuONO (2.0 equiv), $Sc(OTf)_3$ (5 mol%) and quinoline (0.5 equiv) gave the best yield for this transformation (Table II.3.1, entry 21).

Table II.3.1. *Optimization of the reaction conditions*[a]



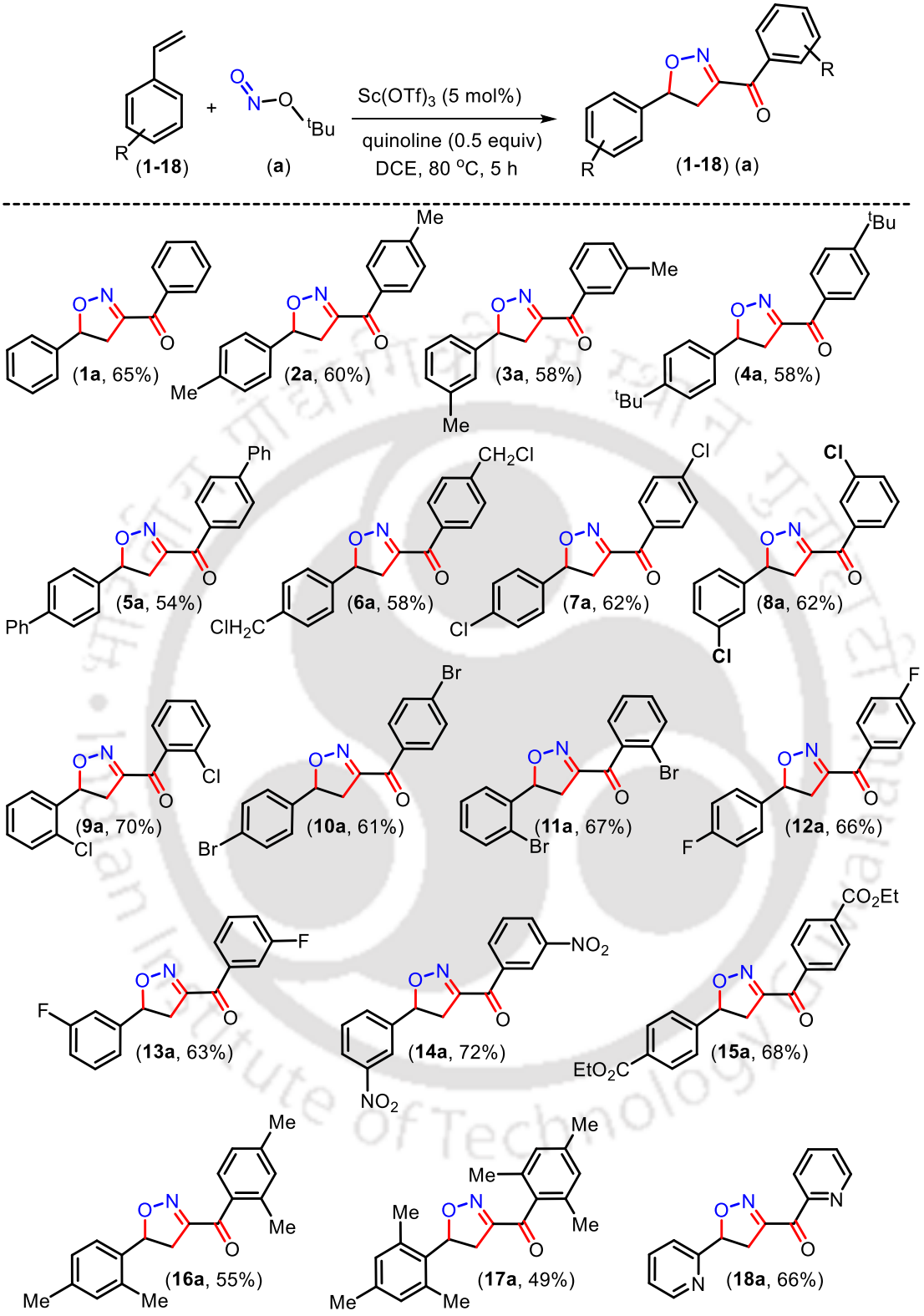
entry	catalyst (mol%)	Solvent	Base	yield %[b]
1	$AlCl_3$ (5.0)	DCE	quinoline	55
2	$AlCl_3$ (5.0)	DCE	-	12
3	$AlCl_3$ (5.0)	*p*-xylene	quinoline	45
4	$AlCl_3$ (5.0)	Toluene	quinoline	43
5	$AlCl_3$ (5.0)	PhCl	quinoline	52
6	$AlCl_3$ (5.0)	cyclohexane	quinoline	50
7	$AlCl_3$ (5.0)	DMF	quinoline	34
8	$AlCl_3$ (5.0)	DMSO	quinoline	<5
9	$FeCl_3$ (5.0)	DCE	quinoline	51
10	$FeCl_2$ (5.0)	DCE	quinoline	55
11	$Cu(OTf)_2$ (5.0)	DCE	quinoline	0
12	$Sc(OTf)_3$ (5.0)	DCE	quinoline	66
13	$Sc(OTf)_3$ (10.0)	DCE	quinoline	68
14	$Sc(OTf)_3$ (5.0)	DCE	DBU	54
15	$Sc(OTf)_3$ (5.0)	DCE	DABCO	50
16	$Sc(OTf)_3$ (5.0)	DCE	Pyridine	41
17	$Sc(OTf)_3$ (5.0)	DCE	DMAP	30
18	-	DCE	quinoline	22
19	$Sc(OTf)_3$(5.0)	DCE	quinoline	39[c]
20	$Sc(OTf)_3$(5.0)	DCE	quinoline	56[d]
21	**$Sc(OTf)_3$(5.0)**	**DCE**	**quinoline**	**65**[e]

[a]Reaction conditions: Styrene (**1**) (0.4 mmol) and *tert*-butylnitrite (**a**) (0.8 mmol) at 80 °C. [b]Yield after 5 h. [c]Temperature110 °C. [d]Temperature 60 °C. [e]Quinoline 0.5 equiv.

Substrate scope for synthesis of isoxazolines:

Encouraged by this unprecedented self-coupling of styrenes we further implemented this strategy to other substrates. Styrenes containing moderately electron-donating groups such as *p*-Me (**2**), *m*-Me (**3**), *p*-^{t}Bu (**4**), *p*-Ph (**5**) and *p*-CH_2Cl (**6**) all provided their corresponding isoxazolines (**2a**, 60%), (**3a**, 58%), (**4a**, 58%), (**5a**, 54%) and (**6a**, 58%) in moderate yields (Scheme II.3.1). Styrenes having moderately electron-withdrawing substituents such as *p*-Cl (**7**), *m*-Cl (**8**), *o*-Cl (**9**), *p*-Br (**10**) *o*-Br (**11**) *p*-F (**12**), and *m*-F (**13**), yielded their corresponding isoxazolines (**7a**), (**8a**), (**9a**), (**10a**), (**11a**), (**12a**) and (**13a**) in the range of 61−70% (Scheme II.3.1).

Scheme II.3.1. *Substrate scope for synthesis of isoxazolines*[a,b]

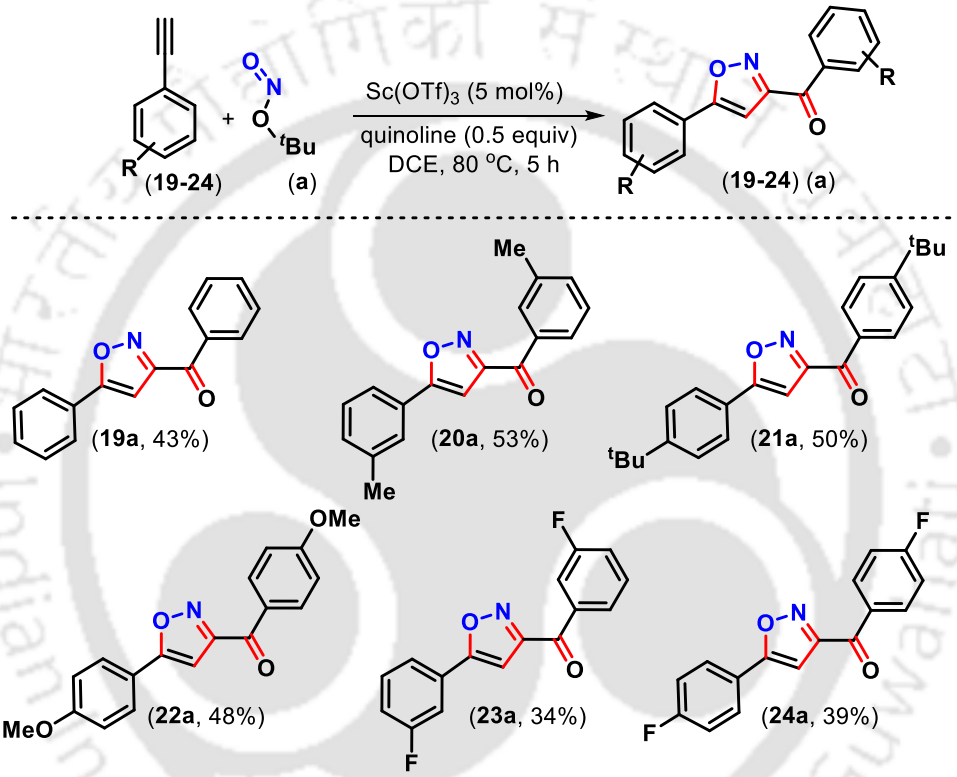


[a]Reaction conditions: alkene (**1-18**) (0.4 mmol), Quinoline (0.2 mmol) and *tert*-butyl nitrite (**a**) (0.8 mmol) at 80 °C in DCE. [b] Yield after 5 h.

However, styrene containing strongly electron-withdrawing substituents such as *m*-nitro (**14**) and *p*-CO_2Et (**15**) both provided their desired product in similar yields (**14a**,

72%) and (**15a**, 68%). 2,4-Dimethyl (**16**) and 2,4,6-trimethyl (**17**) substituted styrenes also reacted successfully affording their corresponding isoxazolines (**16a**, 55%) and (**17a**, 49%) respectively. Hetero-aromatic olefin (**18**) was well tolerated in this transformation giving its product **18a** in 66% yield. No substantial differences in the yield of the products were observed for substrates possessing either electron-donating or electron-withdrawing substituents. This may be due to the high reactivity of the reaction intermediates leading to product in this multi-step process.

Scheme II.3.2. *Substrate scope for synthesis of isoxazoles*[a,b]



[a]Reaction conditions: alkyne (**19-23**) (0.5 mmol), Quinoline (0.5 equiv) and *tert*-butyl nitrite (**a**) (1 mmol) at 80 °C in DCE. [b]Yield after 5 h.

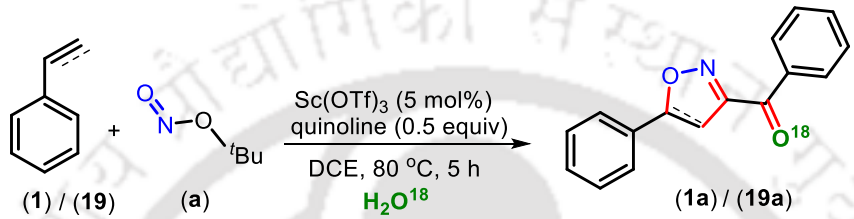
Substrate scope for synthesis of isoxazoles:

We envisaged, that the reaction of terminal alkyenes with *tert*-butyl nitrite is expected to give similar 2-nitroketone intermediate, which is expected to undergo a 1,3-dipolar cycloaddition with the unreacted alkyne, serving as the dienophile. This strategy was tested with different alkynes *viz.* phenylacetylene (**19**), 3-methylphenylacetylene (**20**), 4-*tert*-butylphenylacetylene (**21**), 4-methoxyphenylacetylene (**22**), 3-flurophenylacetylene (**23**) and 4-flurophenylacetylene (**24**) under the exact experimental condition to that of styrene (Scheme II.3.2). Interestingly, all the substrates yielded their corresponding isoxazoles (**19a**), (**20a**), (**21a**), (**22a**), (**23a**) and (**24a**) in the range of 34-53% (Scheme II.3.2) rather

than isoxazoline derivatives. This result is not surprising since in the case of terminal aryl alkyne the unreacted part serving as the dienophile while the other half forms 2-nitro ketone intermediate which acts as the 1,3-dipolarophile.

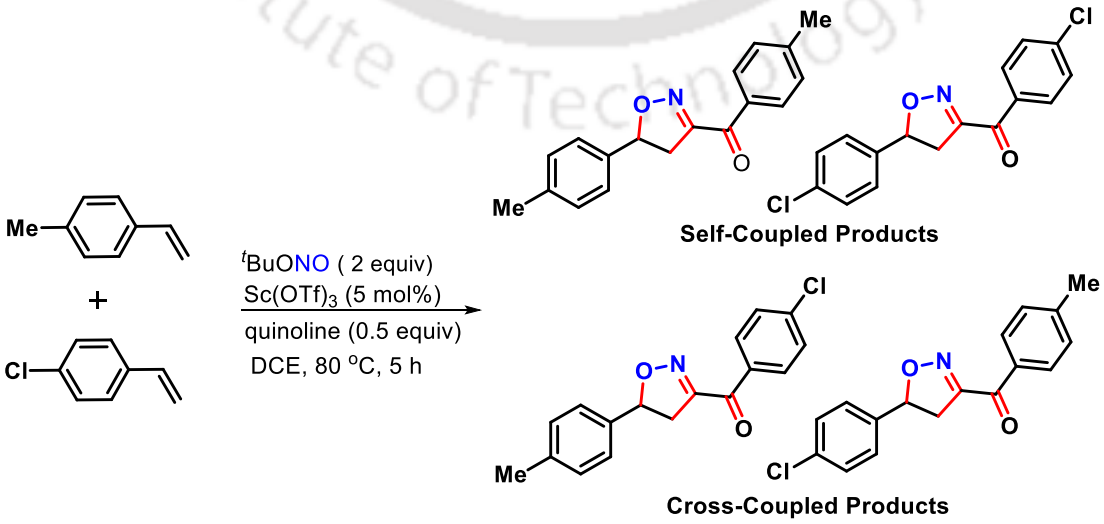
To ascertain the source of keto oxygen in product (**1a**), the reaction of styrene (**1**) was performed in the presence of H_2O^{18} under otherwise identical condition. Incorporation of an ^{18}O labelled product suggests that water might be the source of oxygen in the keto group (Scheme II.3.3).

Scheme II.3.3. *H_2O^{18} labelled experiment*



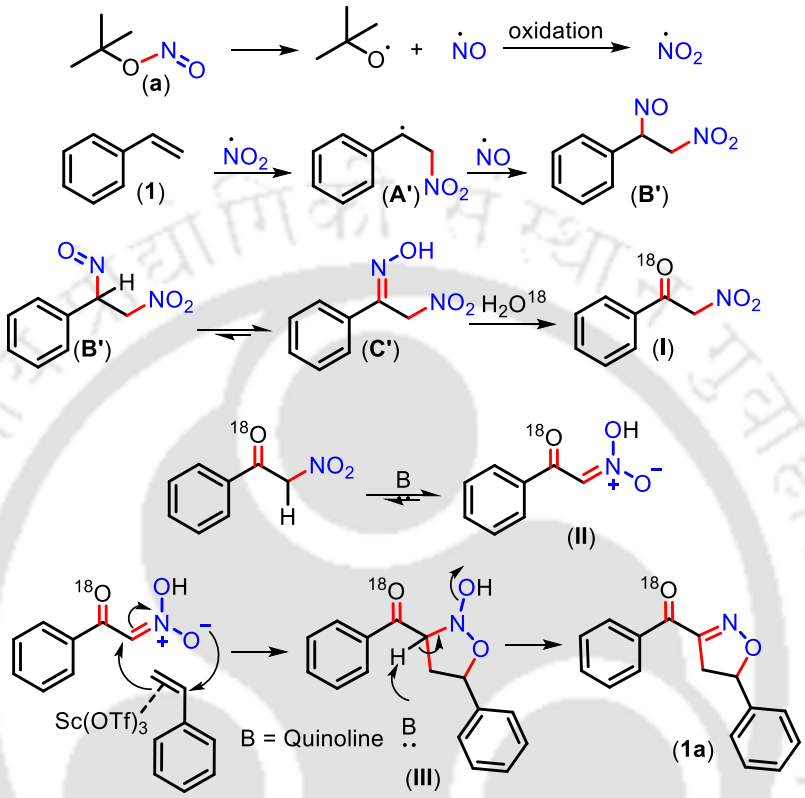
When the reaction was performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv) no desired product was observed however it form a TEMPO adduct along with the formation of β-nitro styrene. This result is consistent with the finding of Maiti *et.al*.[15a] thereby confirming the radical nature of the reaction. To ascertain the intermolecular nature of the coupling an equimolar mixture of two different styrenes *viz*. *p*-Me (**2**) and *p*-Cl (**7**) were reacted under the present experimental condition. Detection of four different isooxazolines (Scheme II.3.4) from the ^1H NMR (Figure II.5.4) and HRMS analysis (Figure II.5.5) confirms the intermolecular cross coupling of the process.

Scheme II.3.4. *Crossover experiment*



Based on the literature reports, intermediates detected by HRMS study and from the controlled experiments carried out a plausible mechanism have been proposed (Scheme II.3.5).

Scheme II.3.5. *Proposed mechanism for isoxazoline synthesis*



The heterolytic cleavage of *tert*-butyl nitrite produces a NO˙ radical which is converts to a NO_2 radical under the aerobic reaction condition.[26] The nitro radical (NO_2˙) then attacks at the terminal carbon of the olefin to generate a nitroalkane radical intermediate (**A'**). The nitroalkane radical (**A'**) thus generated couples with another NO˙ radical to give a C-nitroso intermediate (**B'**). In the presence of base the C-nitroso intermediate (**B'**) rearranges to a α-nitrooxime (**C'**), which is hydrolyzed from the moisture present in the solvent/open atmosphere to 2-nitroacetophenon (**I**).[27] The intermediate 2-nitroacetophenone tautomerized to a 1,3-dipolar intermediate (**II**) in the presence of base. The unreacted styrene serves as the dienophile and undergoes cycloaddition with the 1,3-dipolar intermediate (**II**) to give intermediate (**III**).[16] Here $Sc(OTf)_3$ acts as a Lewis acid[28] catalyst to enhance the reactivity of alkene towards cycloaddition reaction. Finally, loss of a water molecule from the intermediate (**III**) leads to the formation of final isoxazoline

product (**1a**). Intermediates (**C′**), (**I**), (**II**) and (**III**) have been detected by the HRMS analysis of the reaction mixture at various time intervals (Figure II.3.1).

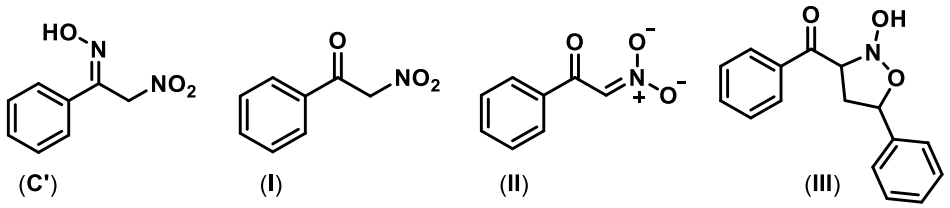


Figure II.3.1. *Intermediates detected by the HRMS analysis*

This mechanism successfully accounts for the formation of all the four isoxazololine products (Scheme II.3.4). Two independent 1,3-dipolar intermediates would be generated from two different styrenes (**2** and **7**). Each of this 1,3-dipolar intermediate would couple with the unreacted styrenes (**2** and **7**) independently to give four possible products (Scheme II.3.4). A similar mechanism for the formation of isoxazole from terminal alkyne can be proposed.

In conclusion, *tert*-butyl nitrite serves as a convenient N–O source to convert alkenes or alkynes into intermediate 2-nitro ketone in DCE. The intermediate so generated reacts with the unreacted alkenes or alkynes via a 1,3-dipolar cycloaddition to afford isoxazolines or isoxazoles in the presence of quinoline and $Sc(OTf)_3$ catalyst. In this domino process, C–C, C–O, C=N and C=O bonds are constructed simultaneously. A radical mechanism has been proposed, where the cleavage of *tert*-butyl nitrite produce a NO radical. The NO radical is oxidized to NO_2 radical and a sequential addition of these radicals to styrene produce a C-nitroso intermediate which is hydrolyzed to a 2-nitroacetophenone. The 2-nitroacetophenone so generated is tautomerize to a 1,3-dipolar intermediate which undergo cycloaddition with unreacted alkene to generate isoxazoline via loss of a water molecule. An analogous mechanism has been proposed involving alkynes for the generation of isoxazoles.

II.4. Experimental section

II.4.1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the

internal standard for ^{1}H NMR (400 and 600 MHz) and in for ^{13}C NMR (100 and 150 MHz) $CDCl_3$ as the internal standard. MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

II.4.2. General procedure for the synthesis of phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (1a) from styrene (1) and *tert*-butyl nitrite (a):

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added styrene (**1**) (42 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), and 1, 2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9.9:0.1) to give pure phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**) (33 mg, yield 65%). The identity and purity of the product ware confirmed by spectroscopic analysis.

II.4.3. General procedure for the synthesis of phenyl(5-phenylisoxazol-3-yl)methanone (19a) from phenyl acetylene (19) and *tert*-butyl nitrite (a):

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added Phenyl acetylene (**19**) (51 mg, 0.5 mmol), quinoline (33 mg, 0.25 mmol), *tert*-butyl nitrite (**a**) (103 mg, 1 mmol), $Sc(OTf)_3$ (12 mg, 0.025 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9.9:0.1) to give pure Phenyl(5-phenylisoxazol-3-yl)methanone (**19a**) (27 mg, yield 43%). The identity and purity of the product ware confirmed by spectroscopic analysis.

II.4.4. Cross over experiment using two styrenes:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added *p*-Me styrene (**2**) (24 mg, 0.2 mmol), *p*-Cl styrene (**7**) (28 mg, 0.2 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol),

and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C for 5 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9.9:0.1) to get rid of the non-polar impurities. The identities of the products were confirmed by ^{1}H spectra (Figure II.5.4) and HRMS spectrum (Figure II.5.5).

II.4.5. H_2O^{18} Labelling experiment for the formation of isoxazoline (1a) from styrene:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added sequentially styrene (**1**) (42 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (**a**) (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), H_2O^{18} (8 mg, 0.4 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C. After completion of the reaction (5 h) the crude product was admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The identity of the ^{18}O labeled product was confirmed by HRMS (Figure II.5.6) and $^{13}C\{^{1}H\}$ NMR (Figure II.5.7).

II.4.5. H_2O^{18} Labelling experiment for the formation of isoxazole (19a) from phenylacetylene:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added sequentially phenyl acetylene (41 mg, 0.4 mmol), quinoline (26 mg, 0.2 mmol), *tert*-butyl nitrite (82 mg, 0.8 mmol), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), H_2O^{18} (8 mg, 0.4 mmol), and 1,2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C. After completion of the reaction (5 h) the crude product was admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The identity of the ^{18}O labeled product was confirmed by HRMS (Figure II.5.8).

II.5. Mechanistic investigation:

II.5.1. ESI-MS study for the detection of reaction intermediates during the synthesis of phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (1a) from styrene (1) and *tert*-butyl nitrite (a) at different time interval:

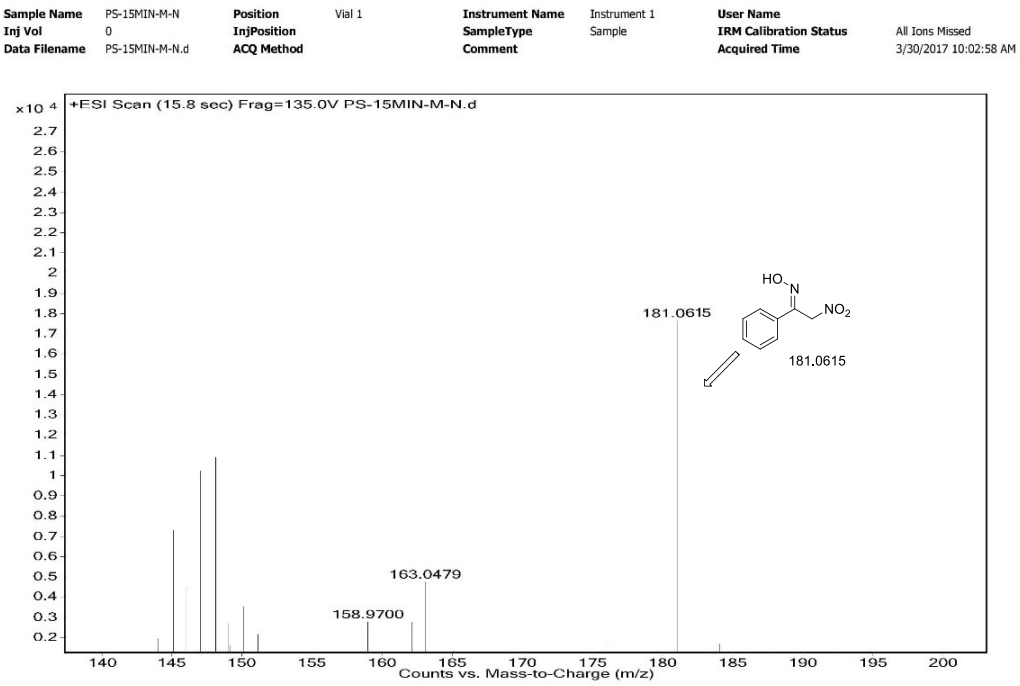


Figure II.5.1. *HRMS spectrum of reaction mixture after 15 minute*

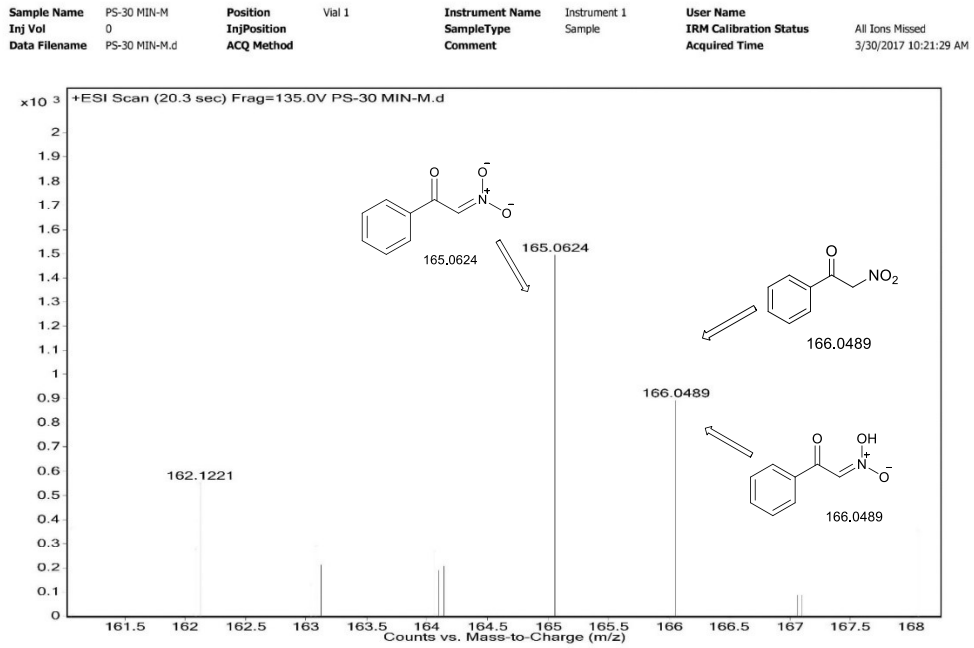


Figure II.5.2. *HRMS spectrum of reaction mixture after 30 minute*

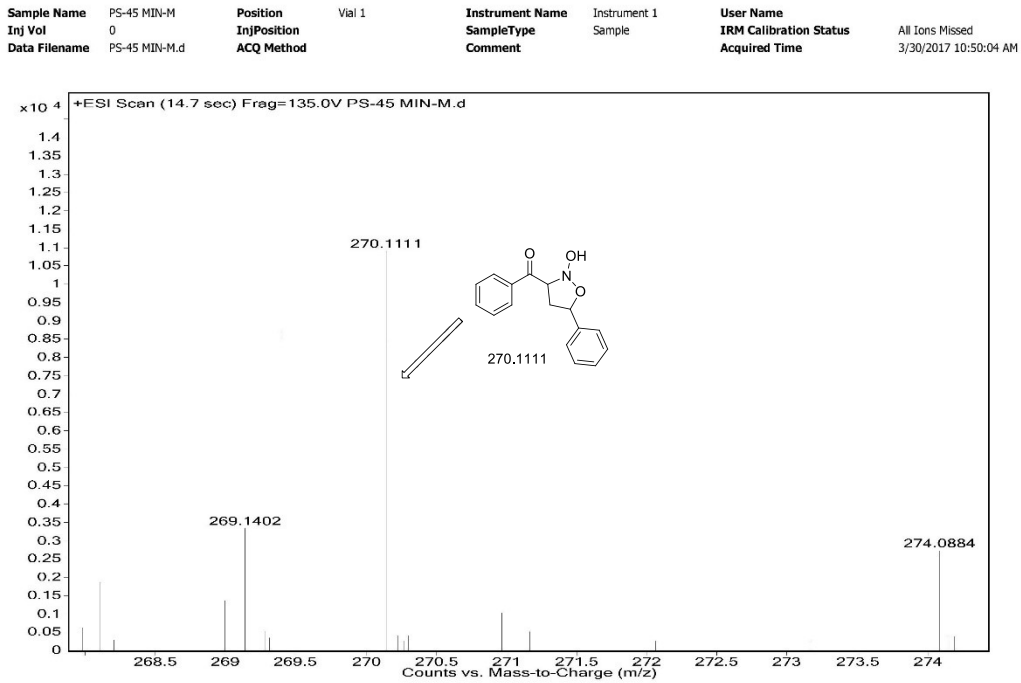


Figure II.5.3. *HRMS spectrum of reaction mixture after 45 minute*

II.5.2. Cross over experiment using two styrenes:

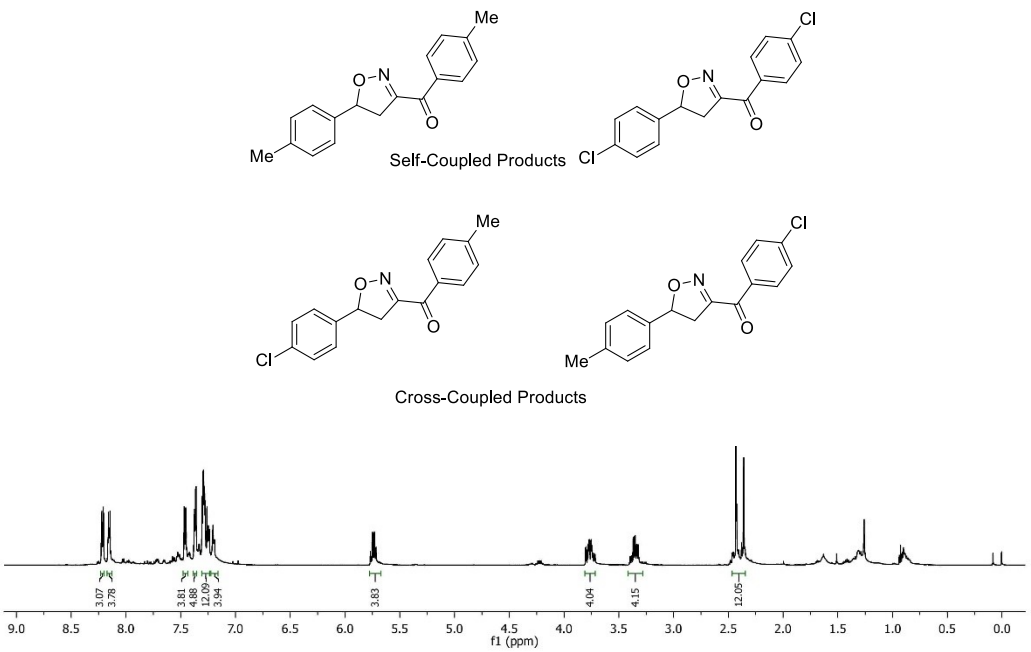


Figure II.5.4. *^{1}H Spectra of cross-experiments products*

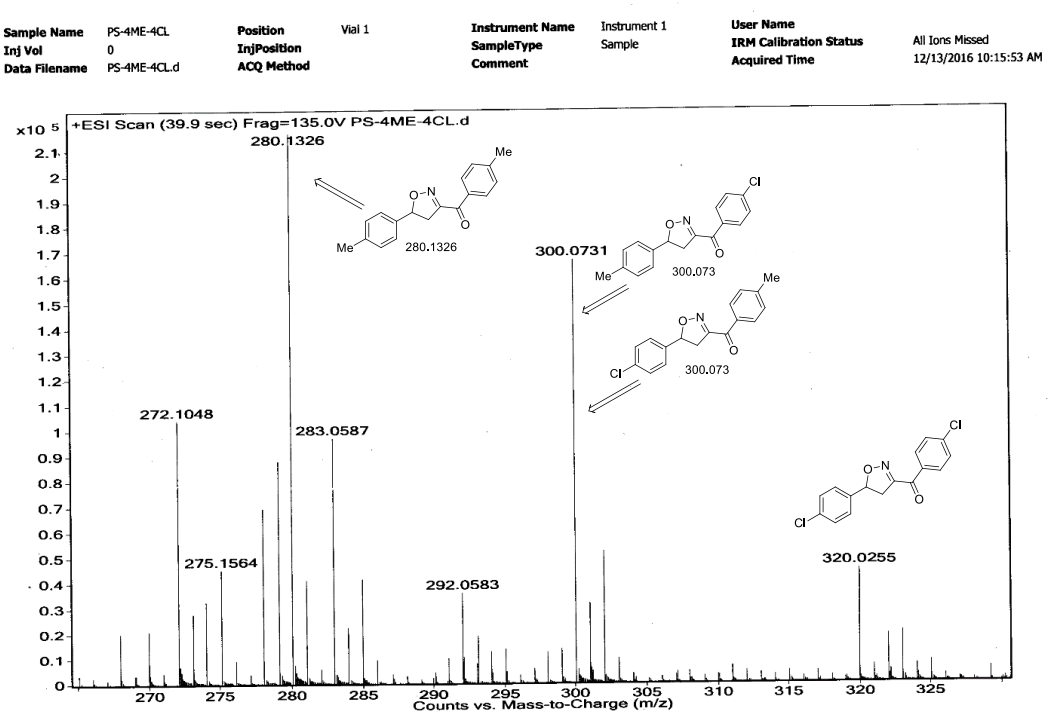


Figure II.5.5. *HRMS spectrum of cross-experiments products*

II.5.3. ESI-MS and $^{13}C\{^{1}H\}$ NMR for the H_2O^{18} labelled experiment for the formation of isoxazoline (1a) from styrene

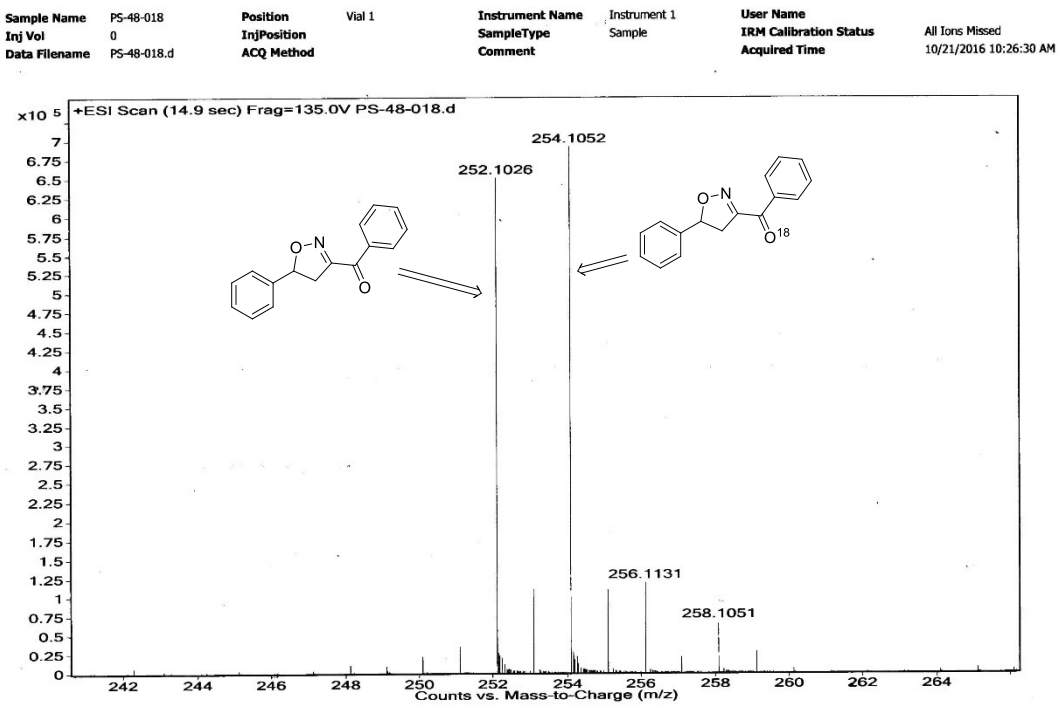


Figure II.5.6. *HRMS spectrum of ^{18}O labelled (**1a**)*

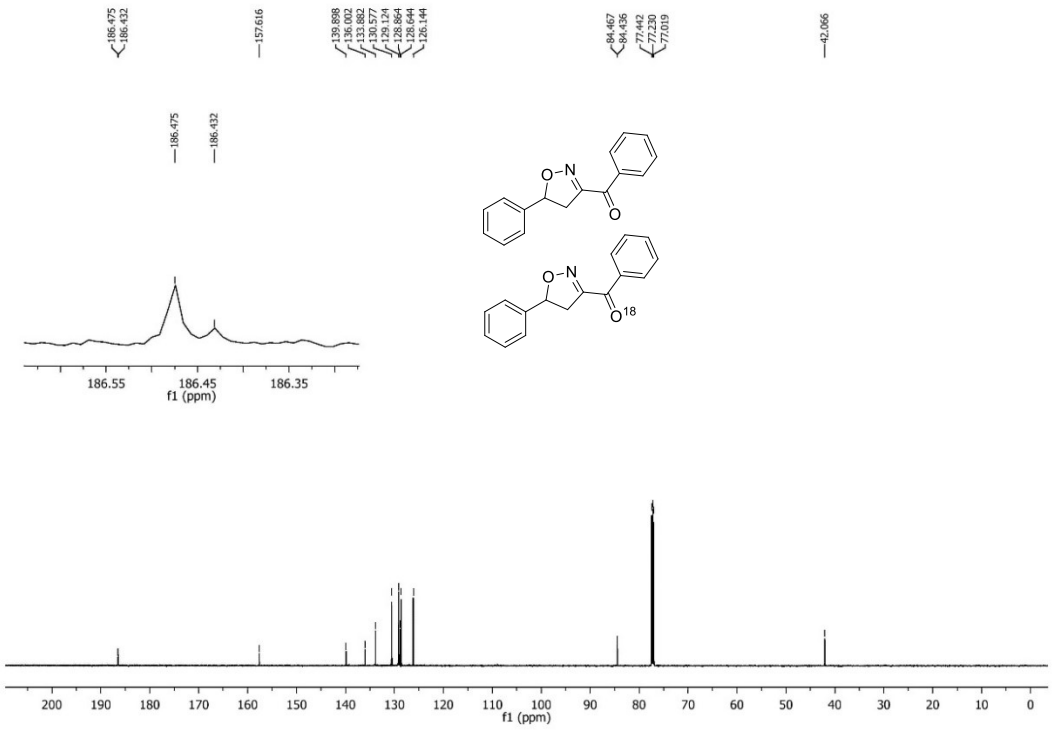


Figure II.5.7. *$^{13}C\{^{1}H\}$ NMR spectrum of ^{18}O labelled (**1a**)*

II.5.4. ESI-MS studies for H_2O^{18} labelled experiment for phenyl acetylene

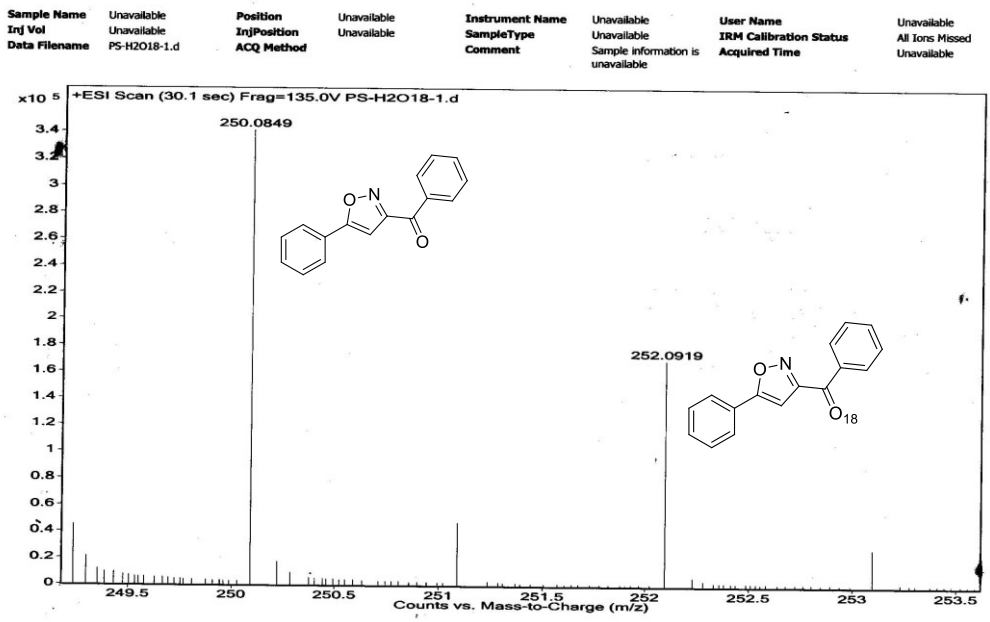


Figure II.5.8. *HRMS spectrum of ^{18}O labelled* ***(19a)***

II.6. References

(1) (a) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150. (b) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419.

(2) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471.

(3) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6877.

(4) Xie, Y.; Hu, J.; Xie, P.; Qian, B.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 18327.

(5) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856.

(6) Miyazaki, Y.; Ohta, N.; Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014**, *136*, 3732.

(7) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592.

(8) Kageyuki, I.; Osaka, I.; Takaki, K.; Yoshida, H. *Org. Lett*. **2017**, *19*, 830.

(9) Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *J. Org. Chem*. **2016**, *81*, 4020.

(10) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

(11) Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klussmann, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 8737.

(12) Cheng, J.-K.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 42.

(13) Banerjee, A.; Santra, S. K.; Mishra, A.; Khatun, N.; Patel, B. K. *Org. Biomol. Chem*. **2015**, *13*, 1307.

(14) Ali, W.; Behera, A.; Guin, S.; Patel, B. K. *J. Org. Chem*. **2015**, *80*, 5625.

(15) (a) Maity, S.; Togati, N.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384. (b) Dutta, U.; Maity, S.; Kancherla, R.; Maiti, D. *Org. Lett.* ***2014***. *16*. 6302.

(16) (a) Chary, R. G.; Reddy, G. R.; Ganesh, Y. S. S.; Prasad, K. V.; Raghunadh, A.; Krishna, T.; Mukherjee, S.; Pal, M. *Adv. Synth. Catal*. **2014**, *356*, 160. (b) Cecchi, L.; Sarlo, F. D.; Machetti, F. *Eur. J. Org. Chem.,* **2006**, 4852. (c) Cecchi, L.; Sarlo, F. D.; Machetti, F. *Chem. Eur. J.* **2008**, *14*, 7903. (d) Gao, P.; Li, H. X.; Hao, X. H.; Jin, D. P.; Chen, D. Q.; Yan, X. B.; Wu, X. X.; Song, X. R.; Liu, X. Y.; Liang, Y. M. *Org. Lett*. **2014**, *16*, 6298.

(17) (a) Kamal, A.; Bharathi, E. V.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Reddy, M. K.; Viswanath, A.; Reddy, T. L.; Shaik, T. B.; Pushpavalli, S. N. C. V. L.; Bhadra, M. P. *Eur. J. Med. Chem.* **2011**, *46*, 691. (b) Shi, L.; Hu, R.; Wei, Y.; Liang, Y.; Yang, Z.; Ke, S. *Eur. J. Med. Chem.* **2012**, *54*, 549. (c) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E.V.; Azhar, M. A.; Sultana, F.; Pushpavalli, S. N. C. V. L.; Pal-Bhadra, M.; Juvekar, A.; Sen, S.; Zingde, S. *Eur. J. Med. Chem.* **2010**, *45*, 3924. (d) Sadashiva, M. P.; Basappa.; Swamy, S. N.; Li, F.; Manu, K. A.; Sengottuvelan, M.; Prasanna, D. S.; Kumar, N. C. A.; Sethi, G.; Sugahara, K.; Rangappa, K. S. *BMC Chem. Biol.* **2012**, *12*, 1.

(18) Cecchi, L.; Sarlo, F. D.; Machetti, F. *Chem. Eur. J.* **2008**, *14*, 7903.

(19) Chary, R. G.; Reddy, G. R.; Ganesh, Y. S. S.; Prasad, K. V.; Raghunadh, A.; Krishna, T.; Mukherjee, S.; Pal, M. *Adv. Synth. Catal*. **2014**, *356*, 160.

(20) Gao, P.; Li, H. X.; Hao, X. H.; Jin, D. P.; Chen, D. Q.; Yan, X. B.; Wu, X. X.; Song, X. R.; Liu, X. Y.; Liang, Y. M. *Org. Lett*. **2014**, *16*, 6298.

(21) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966.

(22) Jia, F. Q.; Benjamin, S. M. P.; Huang, J.; Du, Z.; Zheng, X.; Zhang, K.; Conney, H. A.; Wang, J. *Synlett.* **2013**, *24*, 79.

(23) Yoshimura, A.; Middleton, R. K.; Todora, D. A.; Kastern, J. B.; Koski, R. S.; Maskaev, V. A.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010.

(24) Zhu, X.; Wang, Y.F.; Ren, W.; Zhang, F.L.; Chiba S. *Org. Lett.* **2013**, *15*, 3214.

(25) Chen, F.; Yang, X. L.; Wu, Z. W.; Han, B. *J. Org. Chem*. **2016**, *81*, 3042.

(26) (a) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal*. **2011**, *353*, 2643. (b) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun*. **2013**, *49*, 514. (c) Taniguchi,

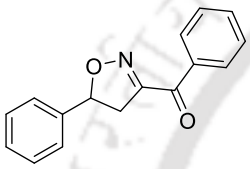
T.; Sugiura, Y.; Hatta, T.; Yajima, A.; Ishibashi, H. *Chem. Commun.* **2013**, *49*, 2198. (d) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun*. **2011**, *47*, 12462. (e) Galliker, B.; Kissner, R.; Nauser, T.; Koppenol, W. H. *Chem. Eur. J*. **2009**, *15*, 6161.

(27) Chumnanvej, N.; Katrun, P.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Kuhakarn, C. *Chin. J. Chem.* **2016**, *34*, 830.

(28) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996,** *61,* 4560.

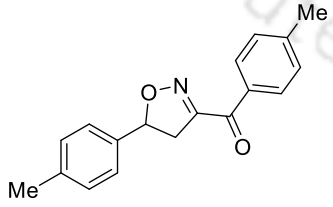
II.7. Spectral data

*Phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (**1a**)*:



Gummy; yield 33 mg, 65%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 2H, J = 7.2 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 7.8 Hz), 7.42–7.35 (m, 5H), 5.79 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 3.80 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.4 Hz), 3.40 (dd, 1H, J_1 = 8.8 Hz, J_2 = 9.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.4, 157.6, 139.8, 135.9, 133.9, 130.5, 129.1, 128.8, 128.6, 126.1, 84.4, 42.0; IR (KBr, cm^{-1}) 3063, 3029, 2957, 2926, 2851, 1651, 1598, 1580, 1572, 1494, 1448, 1360, 1250, 1154, 1077, 901, 851, 791, 756; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1019; Found 252.1025.

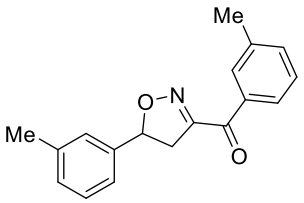
*p-Tolyl(5-(p-tolyl)-4,5-dihydroisoxazol-3-yl)methanone (**2a**)*:



Gummy; yield 33 mg, 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.6 Hz), 7.27–7.25 (m, 2H), 7.20 (d, 2H, J = 8.0 Hz), 5.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 3.75 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 3.38 (dd, 1H, J_1 = 8.8 Hz, J_2 = 8.8 Hz), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.1, 157.7, 144.9, 138.7, 136.9, 133.4, 130.7, 129.7, 129.4, 126.2, 84.4, 42.0, 21.9, 21.4; IR (KBr, cm^{-1}) 3025, 2952, 2923, 2856, 1647, 1606, 1577, 1516, 1450, 1358, 1253, 1185, 1118, 1036, 902,

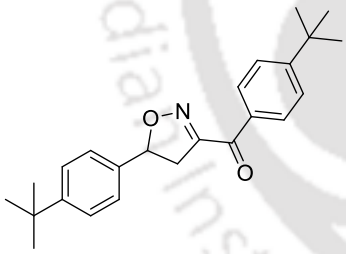
852, 831, 813, 788, 741; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332; Found 280.1330.

*m-Tolyl(5-(m-tolyl)-4,5-dihydroisoxazol-3-yl)methanone (**3a**)*:



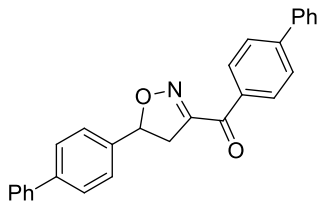
Gummy; yield 31.5 mg, 58%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05–8.03 (m, 2H), 7.43 (d, 1H, J = 7.2 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.18–7.15 (m, 3H), 5.74 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.77 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.39 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 186.7, 157.7, 139.8, 138.9, 138.4, 136.0, 134.7, 130.9, 129.6, 128.9, 128.5, 127.9, 126.8, 123.2, 84.5, 42.1, 21.6, 21.5; IR (KBr, cm^{-1}) 3023, 2957, 2924, 2855, 1650, 1601, 1575, 1488, 1459, 1426, 1358, 1259, 1213, 1134, 1040, 921, 787, 732, 699, 670; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332; Found 280.1342.

*(4-(tert-Butyl)phenyl)(5-(4-(tert-butyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (**4a**)*:



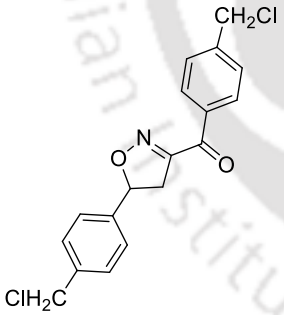
Gummy; yield 42 mg, 58%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.18 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.4 Hz), 5.75 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.75 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.40 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz), 1.35 (s, 9H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 186.2, 157.74, 157.72, 151.9, 136.8, 133.4, 130.5, 126.0, 125.7, 84.3, 41.9, 35.4, 34.8, 31.5, 31.3; IR (KBr, cm^{-1}) 2963, 2926, 2899, 2868, 1647, 1605, 1577, 1559, 1462, 1410, 1363, 1268, 1254, 1198, 1108, 1017, 905, 851, 763, 724; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{30}NO_2$ 364.2271; Found 364.2270.

*[1,1'-Biphenyl]-4-yl(5-([1,1'-biphenyl]-4-yl)-4,5-dihydroisoxazol-3-yl)methanone (**5a**)*:



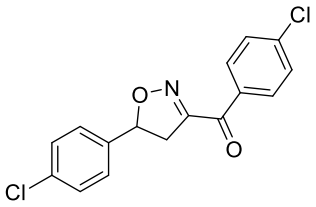
White solid; yield 43 mg, 54%; mp 193.4–195.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.37 (d, 2H, J = 8.4 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.65 (dd, 4H, J_1 = 7.8 Hz, J_2 = 4.2 Hz), 7.60 (d, 2H, J = 7.8 Hz), 7.50 (d, 2H, J = 7.2 Hz), 7.46 (q, 4H, J = 6.4 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 7.5 Hz), 5.85 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.85 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.48 (dd, 1H, J_1 = 9.0 Hz, J_2 = 8.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 185.9, 157.8, 146.6, 141.9, 140.7, 140.0, 138.8, 134.7, 131.2, 129.2, 129.1, 128.6, 127.9, 127.8, 127.5, 127.34, 127.3, 126.7, 84.3, 42.1; IR (KBr, cm^{-1}) 3054, 3029, 2919, 2851, 1647, 1603, 1578, 1559, 1485, 1405, 1157, 1006, 905, 851, 836, 763, 753, 738, 689; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{22}NO_2$ 404.1645; Found 404.1650.

*(4-(Chloromethyl)phenyl)(5-(4-(chloromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (**6a**)*:



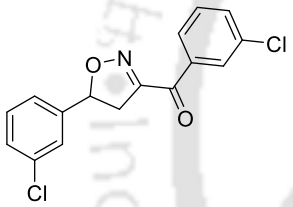
White solid; yield 40 mg, 58%; mp. 109.6–112.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.25 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 7.8 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 5.79 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 3.79 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.38 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 185.6, 157.6, 143.2, 140.0, 138.2, 135.7, 131.0, 129.4, 128.7, 126.5, 84.1, 45.8, 45.5, 42.0; IR (KBr, cm^{-1}) 2965, 2923, 2851, 1640, 1607, 1578, 1564, 1444, 1357, 1286, 1256, 1109, 941, 919, 834, 765, 704, 668, 576, 530; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}Cl_2NO_2$ 348.0553; Found 348.0559.

*(4-Chlorophenyl)(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**7a**)*:



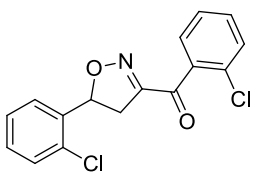
Gummy; yield 40 mg, 62%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, 2H, J = 8.9 Hz), 7.46 (d, 2H, J = 8.9 Hz), 7.37 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.6 Hz), 5.76 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 3.78 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.4 Hz), 3.34 (dd, 1H, J_1 = 8.8 Hz, J_2 = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.8, 157.5, 140.6, 138.2, 134.8, 131.9, 129.7, 129.3, 129.0, 127.5, 83.8, 41.9; IR (KBr, cm^{-1}) 2952, 2924, 2851, 1646, 1584, 1493, 1433, 1401, 1367, 1293, 1274, 1258, 1157, 1039, 1014, 937, 902, 845, 829, 807, 745, 719, 684; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240; Found 320.0242.

*(3-Chlorophenyl)(5-(3-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**8a**)*:



Gummy; yield 40 mg, 62%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.22 (s, 1H), 8.15 (d, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 8.4Hz), 7.44 (t, 1H, J = 7.8Hz), 7.36–7.33 (m, 3H), 7.24–7.23 (m, 1H), 5.77 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 3.79 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.36 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.8, 157.4, 141.7, 137.2, 135.1, 134.9, 133.9, 130.5, 130.4, 129.9, 129.1, 128.7, 126.2, 124.2, 83.7, 41.9; IR (KBr, cm^{-1}) 3068, 2952, 2925, 2854, 1653, 1576, 1566, 1479, 1426, 1361, 1276, 1248, 1094, 1160, 1079, 919, 784, 733, 692; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240; Found 320.0247.

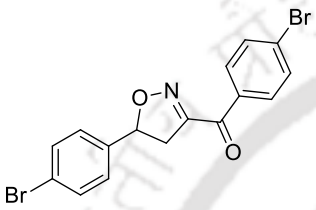
*(2-Chlorophenyl)(5-(2-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**9a**)*:



Gummy; yield 45 mg, 70%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.54 (d, 1H, J = 7.8 Hz), 7.47–7.43 (m, 3H), 7.42 (d, 1H, J = 7.5 Hz), 7.38–7.36 (m, 1H), 7.32–7.28 (m, 2H), 6.15 (dd, 1H, J_1 = 7.8 Hz, J_2 = 3.6 Hz), 3.90 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.23 (dd, 1H, J_1 = 7.8 Hz, J_2 = 10.2 Hz); ^{13}C{^{1}H}

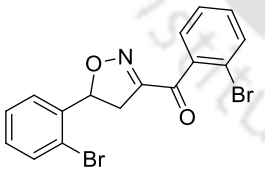
NMR ($CDCl_3$, 150 MHz) δ 188.2, 158.1, 137.8, 137.3, 132.5, 132.4, 132.0, 131.5, 130.5, 130.0, 129.8, 127.5, 126.8, 126.6, 82.8, 40.4; IR (KBr, cm^{-1}) 3066, 2923, 2849, 1672, 1651, 1578, 1471, 1435, 1369, 1310, 1273, 1245, 1161, 1128, 1056, 1036, 933, 910, 882, 855, 755, 742, 691; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Cl_2NO_2$ 320.0240; Found 320.0236.

*(4-Bromophenyl)(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**10a**)*:



Gummy; yield 50 mg, 61%; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.6 Hz), 5.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 3.78 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 3.34 (dd, 1H, J_1 = 8.8 Hz, J_2 = 9.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 185.0, 157.5, 138.7, 134.5, 132.3, 132.03, 132.0, 129.5, 127.8, 122.9, 83.8, 41.9; IR (KBr, cm^{-1}) 2952, 2924, 2853, 1640, 1578, 1559, 1489, 1409, 1396, 1361, 1274, 1256, 1153, 1104, 1072, 1010, 941, 919, 904, 842, 824, 793, 744, 679; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Br_2NO_2$ 409.9210; Found 409.9215.

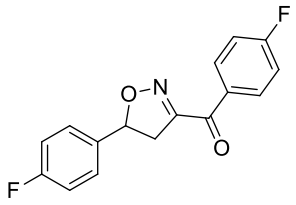
*(2-Bromophenyl)(5-(2-bromophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**11a**)*:



Gummy; yield 55 mg, 67%; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.64 (d, 1H, J = 7.8 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.45 (d, 1H, J = 7.8 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.36 (q, 2H, J = 7.0 Hz), 7.21 (t, 1H, J = 7.7 Hz), 6.11 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.2 Hz), 3.93 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.21 (dd, 1H, J_1 = 7.8 Hz, J_2 = 9.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 188.9, 157.8, 139.5, 139.3, 133.6, 133.2, 132.4, 130.0, 129.9, 128.1, 127.4, 126.8, 121.1, 120.2, 84.8, 40.6; IR (KBr, cm^{-1}) 2956, 2924, 2853, 1672, 1576, 1467, 1434, 1368, 1307, 1270, 1243, 1162, 1119, 1047, 1026, 930, 909, 858, 745, 739, 681,

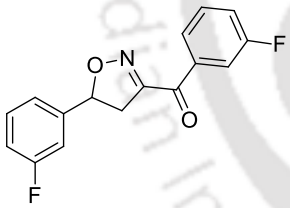
668, 644; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Br_2NO_2$ 409.9210; Found 409.9220.

*(4-Fluorophenyl)(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**12a**)*:



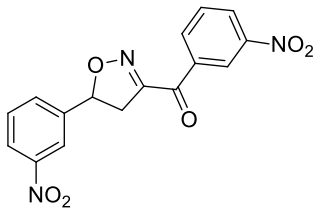
Gummy; yield 38 mg, 66%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.33–8.31 (m, 2H), 7.35–7.33 (m, 2H), 7.16 (t, 2H, J = 8.7 Hz), 7.09 (t, 2H, J = 8.7 Hz), 5.76 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.77 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 3.36 (dd, 1H, J_1 = 9.0 Hz, J_2 = 8.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 184.6, 167.3, 165.6, 163.9, 162.2, 157.6, 135.57, 135.55, 133.41, 133.35, 132.2, 132.18, 128.1, 128.0, 116.2, 116.1, 115.9, 115.8, 83.9, 42.1; IR (KBr, cm^{-1}) 3073, 2957, 2924, 2846, 1642, 1598, 1559, 1511, 1439, 1411, 1358, 1299, 1287, 1239, 1156, 1098, 1013, 939, 902, 853, 816, 754; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}F_2NO_2$ 288.0831; Found 288.0825.

*(3-Fluorophenyl)(5-(3-fluorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**13a**)*:



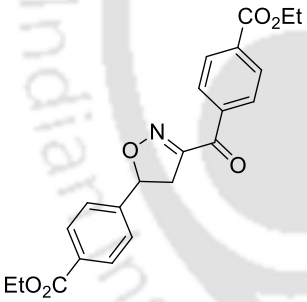
Gummy; yield 36 mg, 63%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.07 (d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 9.4 Hz), 7.50–7.46 (m, 1H), 7.39–7.36 (m, 1H), 7.34–7.31 (m, 1H), 7.13 (d, 1H, J = 7.8 Hz), 7.09–7.04 (m, 2H), 5.79 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 3.80 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.37 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 184.8, 164.1, 163.6, 162.5, 161.9, 157.4, 142.4, 137.6, 130.9, 130.8, 130.4, 130.3, 126.5, 126.4, 121.63, 121.61, 121.1, 120.9, 117.4, 117.2, 115.9, 115.8, 113.2, 113.0, 83.7, 42.0; IR (KBr, cm^{-1}) 2958, 2923, 2851, 1653, 1587, 1484, 1444, 1362, 1260, 1214, 927, 893, 807, 741, 692, 672, 522; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}F_2NO_2$ 288.0831; Found 288.0836.

*(3-Nitrophenyl)(5-(3-nitrophenyl)-4,5-dihydroisoxazol-3-yl)methanone (**14a**)*:



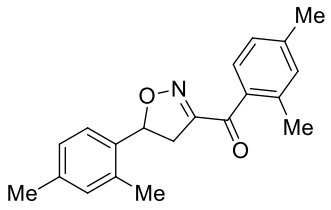
Greay solid; yield 49 mg, 72%; mp 92.3–95.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.08 (s, 1H), 8.60 (d, 1H, J = 7.8 Hz), 8.47 (d, 1H, J = 7.8 Hz), 8.25–8.22 (m, 2H), 7.72 (t, 2H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.8 Hz), 5.94 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.91 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.6 Hz), 3.43 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 183.7, 157.4, 148.8, 141.7, 136.8, 136.1, 132.0, 130.4, 129.9, 128.1, 125.5, 123.9, 122.5, 121.2, 83.4, 41.8; IR (KBr, cm^{-1}) 3124, 3083, 3043, 1653, 1612, 1590, 1534, 1477, 1346, 1256, 1094, 1002, 930, 906, 886, 834, 811, 737, 706, 684, 652; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}N_3O_6$ 342.0721; Found 342.0719.

*Ethyl 4-(3-(4-(ethoxycarbonyl)benzoyl)-4,5-dihydroisoxazol-5-yl)benzoate (**15a**)*:



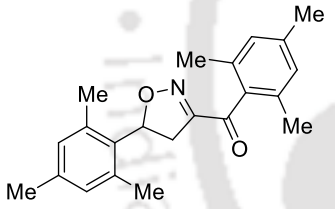
Gummy; yield 54 mg, 68%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.28 (d, 2H, J = 8.4 Hz), 8.14 (d, 2H, J = 8.4 Hz), 8.07 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 7.8 Hz), 5.85 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 4.41 (q, 2H, J = 6.4 Hz), 4.38 (q, 2H, J = 6.4.Hz), 3.83 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 3.37 (dd, 1H, J_1 = 9.0 Hz, J_2 = 9.0 Hz), 1.42 (t, 3H, J = 6.9 Hz), 1.39 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 185.5, 166.2, 165.9, 157.5, 144.5, 139.0, 134.9, 131.0, 130.4, 129.7, 125.9, 84.0, 61.7, 61.4, 42.0, 14.5, 14.47; IR (KBr, cm^{-1}) 3064, 2995, 2979, 2928, 2900, 2848, 1718, 1653, 1613, 1572, 1475, 1444, 1409, 1367, 1284, 1255, 1194, 1126, 1112, 1019, 945, 872, 863, 762, 727; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_6$ 396.1442; Found 396.1451.

*(2,4-Dimethylphenyl)(5-(2,4-dimethylphenyl)-4,5-dihydroisoxazol-3-yl)methanone(**16a**)*:



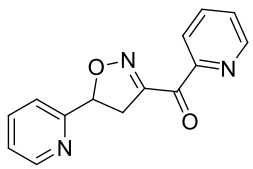
Gummy; yield 34 mg, 55%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, 1H, J = 8.4 Hz), 7.02–7.01 (m, 2H), 6.99–6.96 (m, 3H), 5.87 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 3.67 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.4 Hz), 3.15 (dd, 1H, J_1 = 8.4 Hz, J_2 = 9.0 Hz), 2.36 (s, 3H), 2.30 (s, 3H), 2.25 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 189.8, 158.5, 142.6, 138.8, 138.3, 135.1, 134.6, 132.5, 131.8, 131.3, 127.3, 126.2, 125.2, 82.8, 40.6, 21.7, 21.2, 20.9, 19.4; IR (KBr, cm^{-1}) 3020, 2955, 2924, 2855, 1653, 1612, 1578, 1559, 1500, 1452, 1379, 1311, 1288, 1252, 1236, 1036, 929, 879, 843, 821, 757; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; Found 308.1647.

*Mesityl(5-mesityl-4,5-dihydroisoxazol-3-yl)methanone (**17a**)*:



Gummy; yield 33 mg, 49%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.89 (s, 4H), 6.27 (t, 1H, J = 12.6 Hz), 3.66 (dd, 1H, J_1 = 12.6 Hz, J_2 = 5.4 Hz), 3.29 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.4 Hz), 2.31 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 167.5, 156.2, 140.7, 138.8, 136.9, 135.3, 135.2, 130.8, 130.6, 128.6, 128.5, 126.9, 84.3, 37.7, 21.4, 21.0, 20.2, 19.98, 19.85; IR (KBr, cm^{-1}) 3008, 2960, 2923, 2854, 1612, 1579, 1452, 1379, 1311, 1251, 1036, 978, 953, 934, 878, 850, 834; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{26}NO_2$ 336.1958; Found 336.1968.

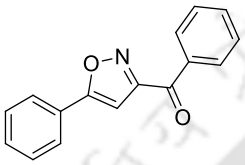
*Pyridin-2-yl(5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl)methanone (**18a**)*:



Gummy; yield 33 mg, 66%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.60–8.57 (m, 2H), 8.41–8.39 (m, 1H), 7.94 (t, 1H, J = 8.1 Hz), 7.73 (t, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.8 Hz), 7.47 (t, 1H, J = 6.3 Hz), 7.25–7.23 (m, 1H), 5.78 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.2 Hz), 3.95 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6.6

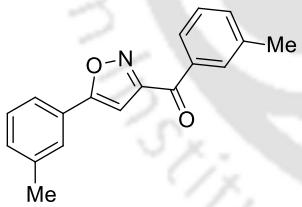
Hz), 3.81 (dd, 1H, J_1 = 7.2 Hz, J_2 = 10.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 159.7, 156.9, 150.3, 149.6, 146.2, 144.4, 138.3, 137.5, 125.32, 125.28, 123.3, 120.9, 82.3, 42.5; IR (KBr, cm^{-1}) 2924, 2853, 1640, 1591, 1569, 1468, 1436, 1384, 1287, 1262, 1152, 1095, 1049, 1006, 894, 849, 790, 749, 668; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}N_3O_2$ 254.0924; Found 254.0934.

*Phenyl(5-phenylisoxazol-3-yl)methanone (**19a**)*:



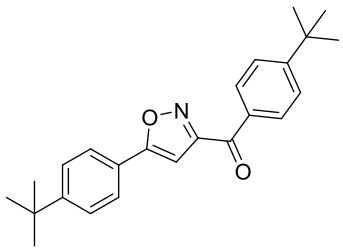
White solid; yield 27 mg, 43%; mp 78.4–82.9 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.36–8.34 (m, 2H), 7.87–7.85 (m, 2H), 7.68–7.66 (m, 1H), 7.56–7.50 (m, 5H), 7.06 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 186.1, 171.0, 162.7, 135.9, 134.3, 130.96, 130.92, 129.4, 128.8, 126.9, 126.2, 100.5; IR (KBr, cm^{-1}) 2953, 2923, 2853, 1655, 1577, 1449, 1244, 1146, 1041, 1028, 848, 894, 824, 769, 681, 676, 617; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}NO_2$ 250.0863; Found 250.0860.

*m-Tolyl(5-(m-tolyl)isoxazol-3-yl)methanone (**20a**)*:



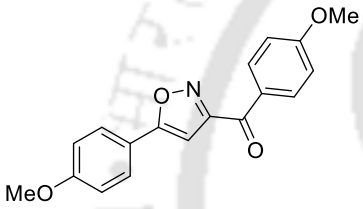
Gummy; yield 37 mg, 53%; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.15 (d, 1H, J = 7.8 Hz), 8.13 (s, 1H), 7.67 (s, 1H), 7.65 (d, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.30 (d, 1H, J = 7.8 Hz), 7.02 (s, 1H), 2.46 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 186.3, 171.2, 162.7, 135.1, 131.7, 131.2, 129.3, 128.7, 128.2, 126.8, 123.4, 100.4, 21.64, 21.61; IR (KBr, cm^{-1}) 2923, 2853, 1665, 1602, 1574, 1444, 1378, 1319, 1290, 1262, 1207, 1158, 1140, 1095, 1055, 941, 841, 811, 793, 751, 701, 678; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}NO_2$ 278.1176; Found 278.1180.

*(4-(tert-Butyl)phenyl)(5-(4-(tert-butyl)phenyl)isoxazol-3-yl)methanone (**21a**)*:



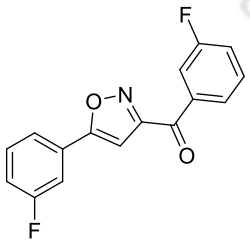
Gummy; yield 45 mg, 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.8 Hz), 7.57–7.52 (m, 4H), 7.00 (s, 1H), 1.372 (s, 9H), 1.365 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 185.7, 171.0, 162.7, 158.1, 154.4, 133.4, 130.9, 126.30, 126.29, 126.0, 125.8, 124.2, 99.9, 35.5, 35.2, 31.3, 31.2; IR (KBr, cm^{-1}) 2958, 2923, 2853, 1659, 1606, 1465, 1444, 1363, 1255, 1106, 1017, 897, 856, 777; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{28}NO_2$ 362.2115; Found 362.2111.

*(4-Methoxyphenyl)(5-(4-methoxyphenyl)isoxazol-3-yl)methanone (**22a**)*:



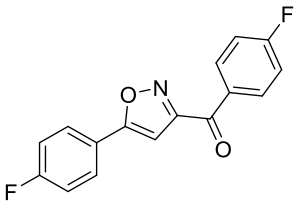
White solid; yield 37 mg, 48%; mp 127.8–130.5 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 2H, J = 8.8 Hz), 7.78 (d, 2H, J = 8.8 Hz), 7.01–6.99 (m, 4H), 6.89 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.4, 170.7, 164.6, 162.9, 161.6, 133.4, 128.9, 127.8, 119.8, 114.7, 114.1, 99.2, 55.8, 55.6; IR (KBr, cm^{-1}) 2940, 2837, 1658, 1580, 1469, 1190, 895, 737; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}NO_4$ 310.1074; Found 310.1070.

*(3-Fluorophenyl)(5-(3-fluorophenyl)isoxazol-3-yl)methanone (**23a**)*:



Gummy; yield 24 mg, 34%; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.19 (d, 1H, J = 7.8 Hz), 8.07–8.05 (m, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.57–7.48 (m, 3H), 7.39–7.36 (m, 1H), 7.22–7.19 (m, 1H), 7.08 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 183.1, 169.9, 164.4, 164.1, 162.5, 161.9, 161.6, 131.3, 131.2, 130.6, 130.5, 128.6, 126.84, 126.81, 122.04, 122.0, 121.6, 121.3, 118.2, 117.9, 117.7, 117.5, 113.4, 113.2, 101.2; IR (KBr, cm^{-1}) 3145, 1655, 1610, 1506, 1450, 1190, 895, 750, 680; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{10}F_2NO_2$ 286.0674; Found 286.0670.

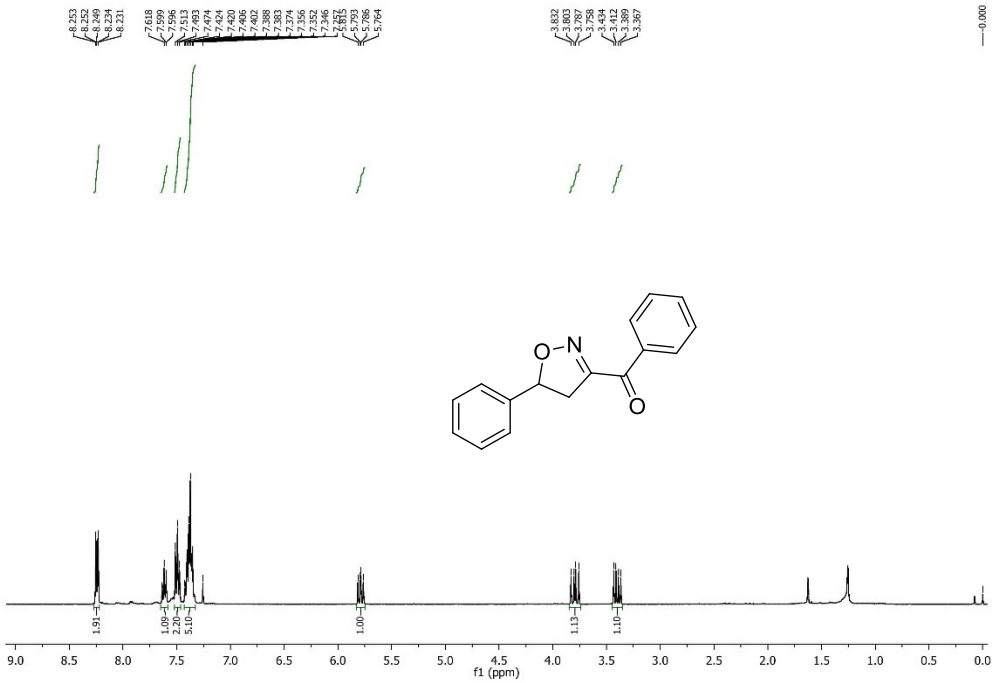
*(4-Fluorophenyl)(5-(4-fluorophenyl)isoxazol-3-yl)methanone (**24a**)*:



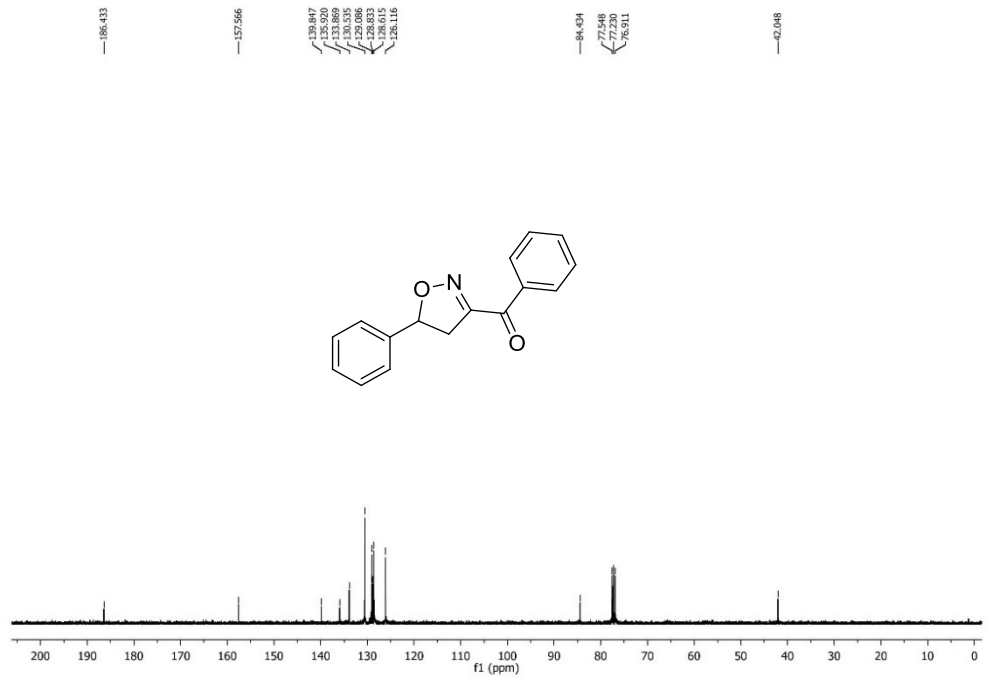
Gummy; yield 28 mg, 39%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44–8.41 (m, 2H), 7.86–7.82 (m, 2H), 7.23–7.18 (m, 4H), 6.99 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 184.1, 170.1, 167.9, 165.6, 165.4, 163.1, 162.6, 133.8, 133.7, 133.6, 132.22, 132.19, 128.4, 128.3, 123.2, 123.1, 116.8, 116.6, 116.5, 116.2, 115.9, 100.27, 100.25; IR (KBr, cm^{-1}) 3135, 2924, 2850, 1654, 1613, 1507, 1446, 1253, 1240, 1162, 942, 838, 771; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{10}F_2NO_2$ 286.0674; Found 286.0680.

II.8. Spectra

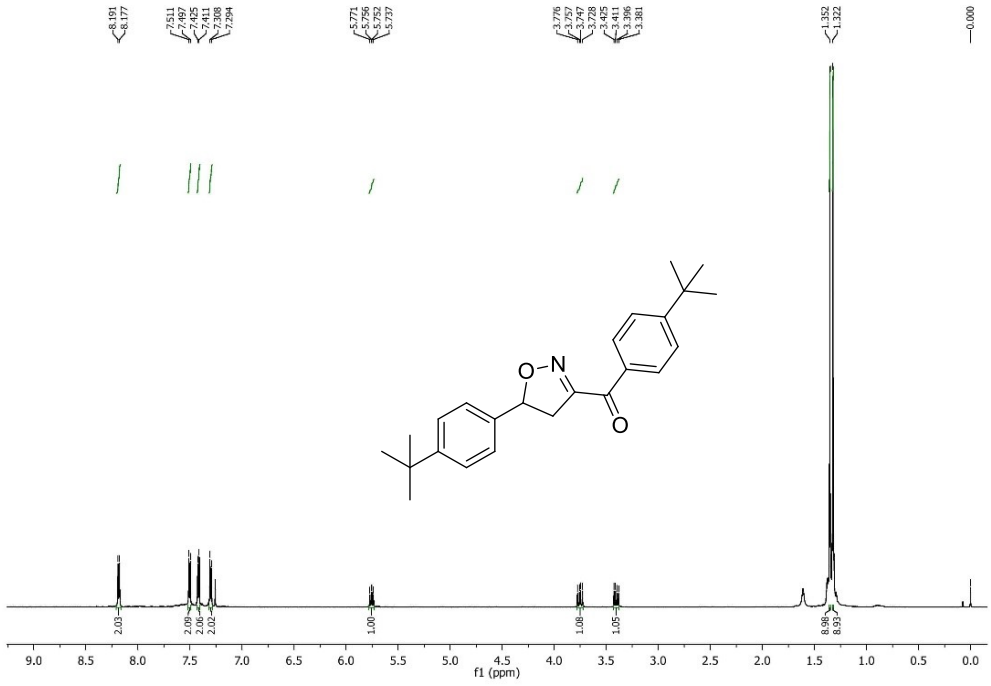
Phenyl (5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (1a): ^{1}H NMR ($CDCl_3$, 400 MHz)



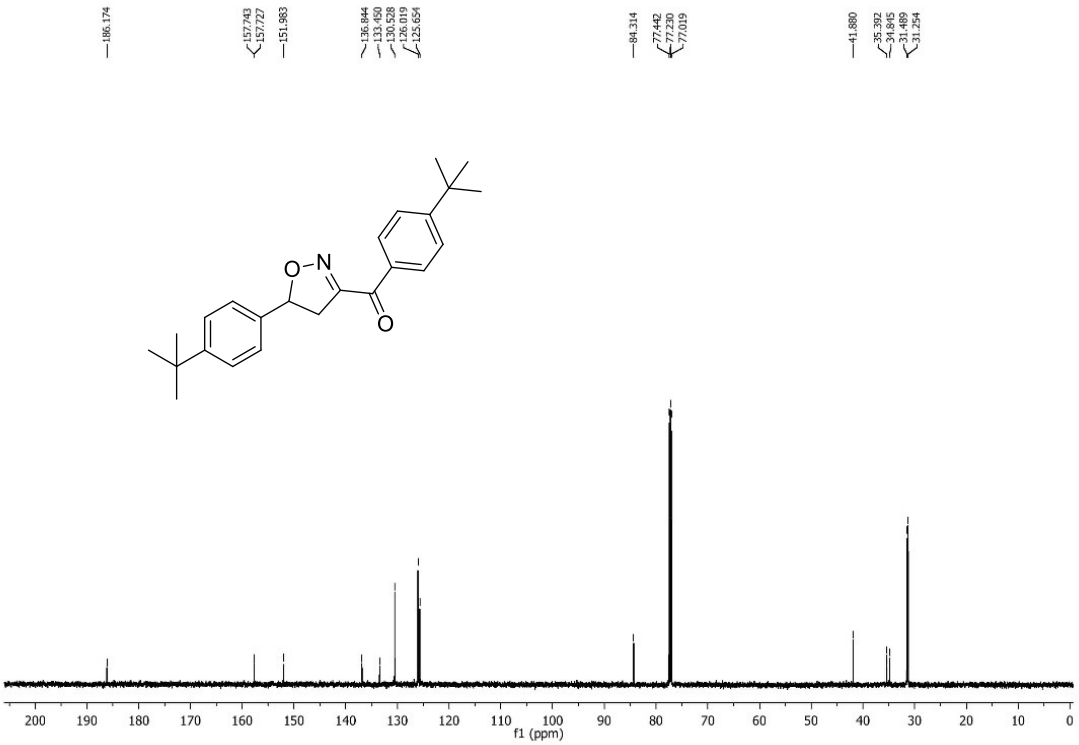
Phenyl (5-phenyl-4,5-dihydroisoxazol-3-yl)methanone (1a): $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)



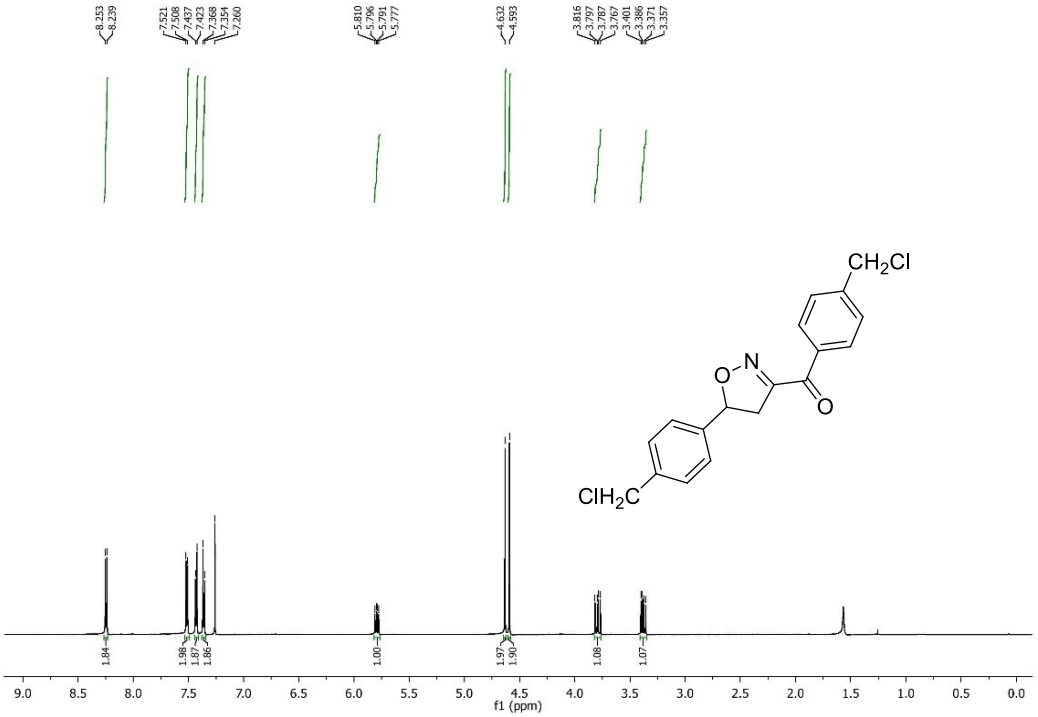
(4-(*tert*-Butyl)phenyl)(5-(4-(*tert*-butyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (4a): ^{1}H NMR ($CDCl_3$, 600 MHz)



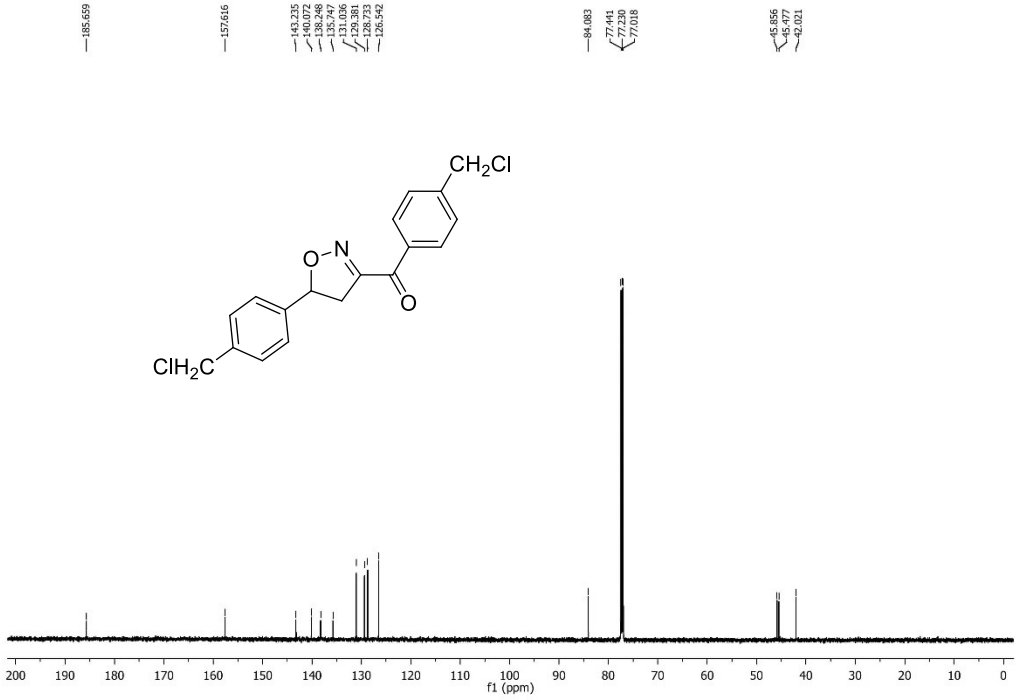
(4-(*tert*-Butyl)phenyl)(5-(4-(*tert*-butyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (4a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



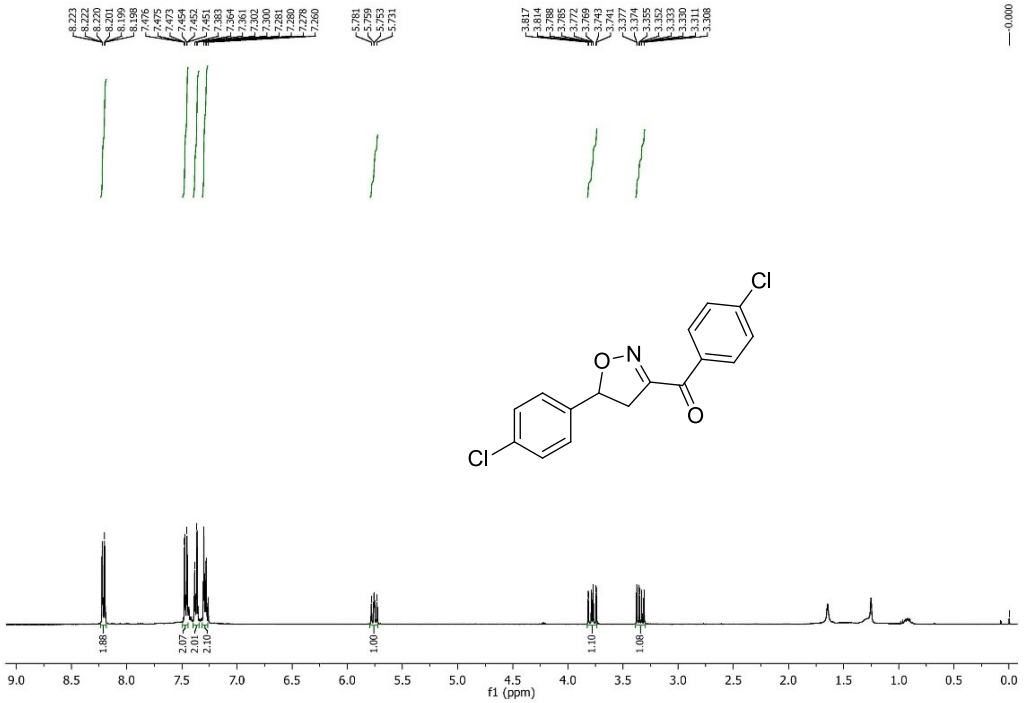
(4-(Chloromethyl)phenyl)(5-(4-(chloromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (6a):^{1}H NMR ($CDCl_3$, 600 MHz)



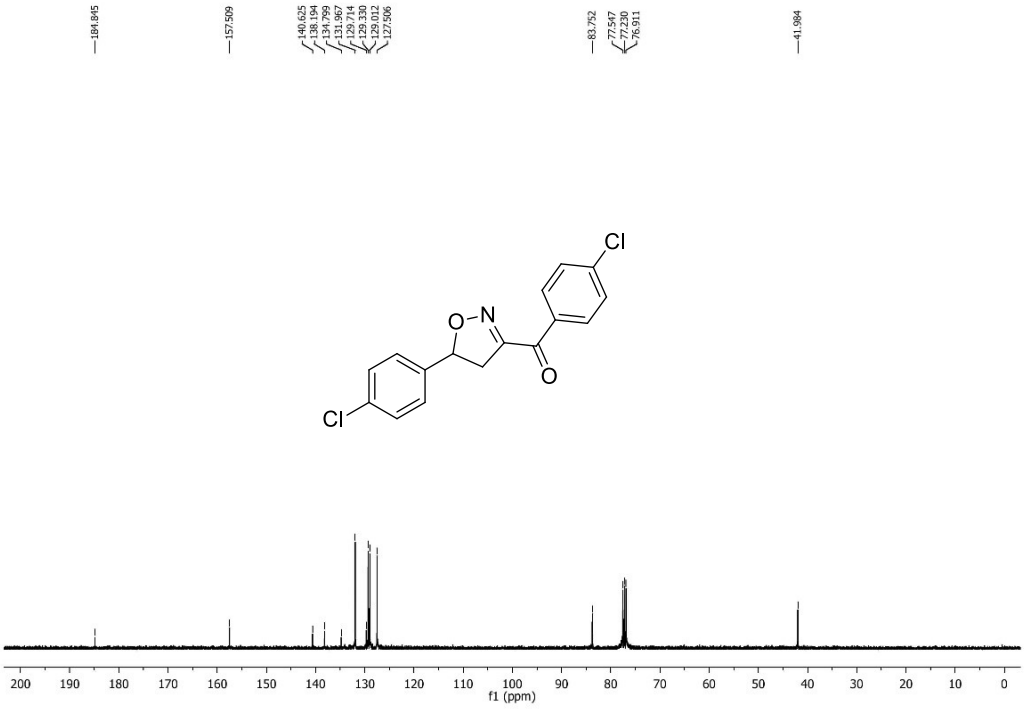
(4-(Chloromethyl)phenyl)(5-(4-(chloromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)methanone (6a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



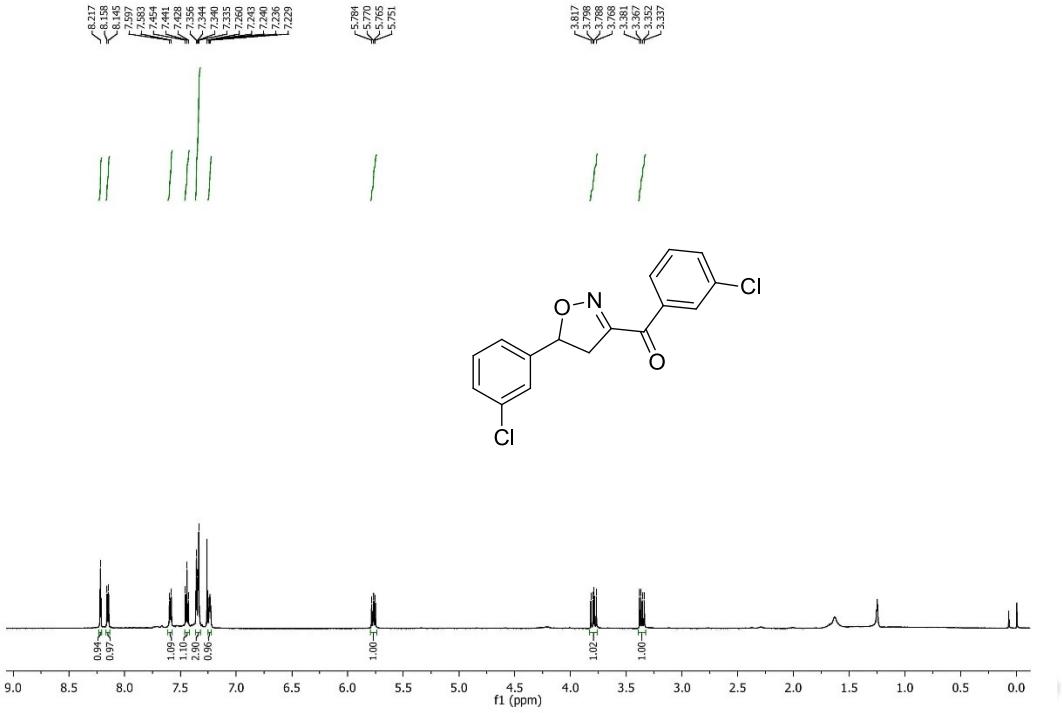
(4-Chlorophenyl)(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (7a): ^{1}H NMR ($CDCl_3$, 400 MHz)



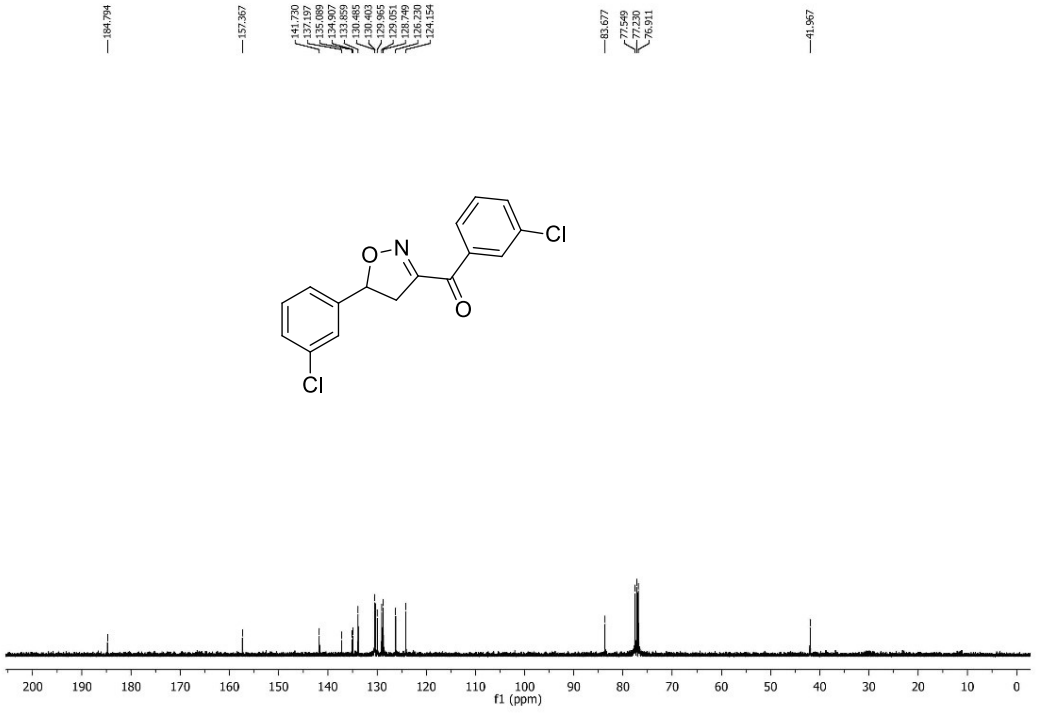
(4-Chlorophenyl)(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (7a): $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)



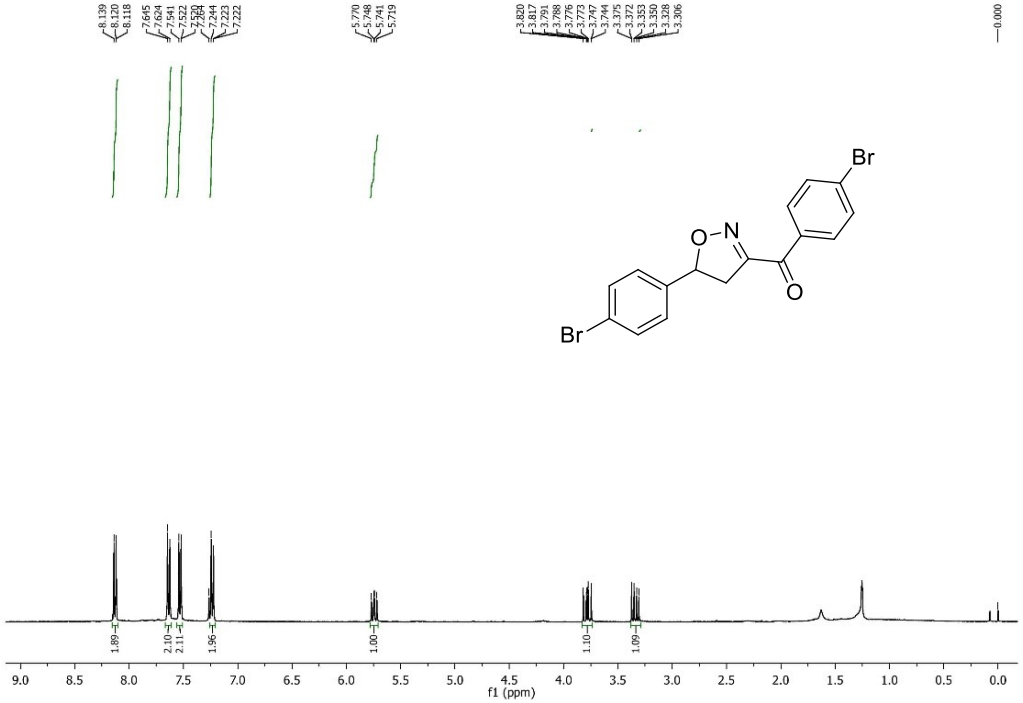
(3-Chlorophenyl)(5-(3-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (8a): ^{1}H NMR ($CDCl_3$, 600 MHz)



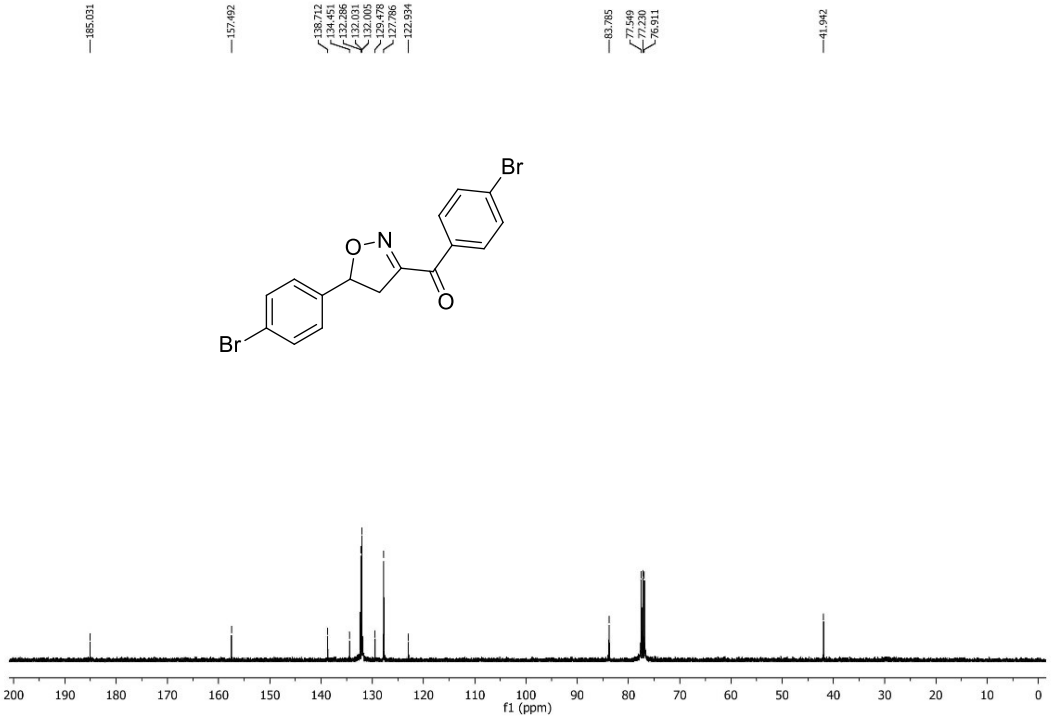
(3-Chlorophenyl)(5-(3-chlorophenyl)-4,5-dihydroisoxazol-3-yl)methanone (8a): ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



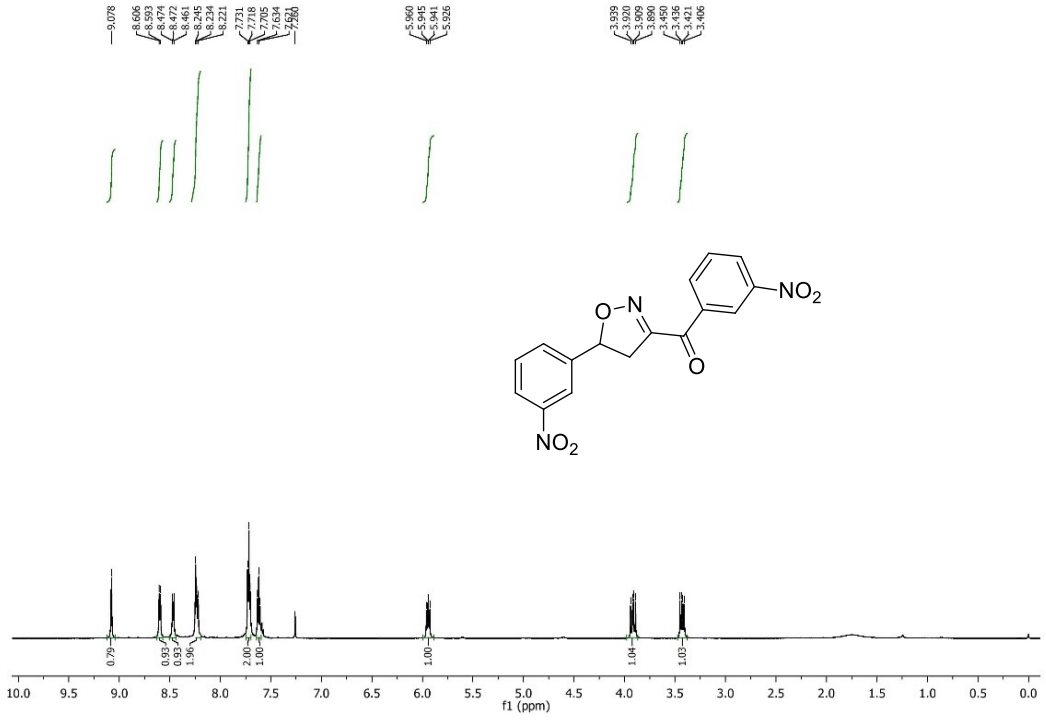
(4-Bromophenyl)(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)methanone (10a): ^{1}H NMR ($CDCl_3$, 400 MHz)



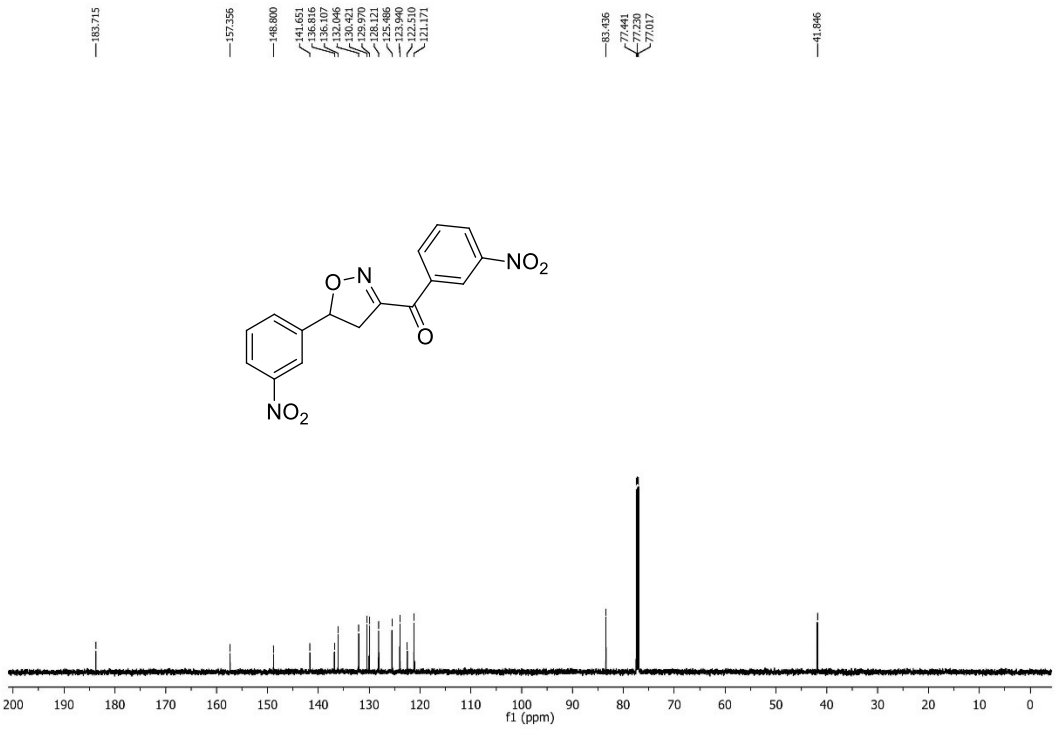
(4-Bromophenyl)(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)methanone (10a): $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)



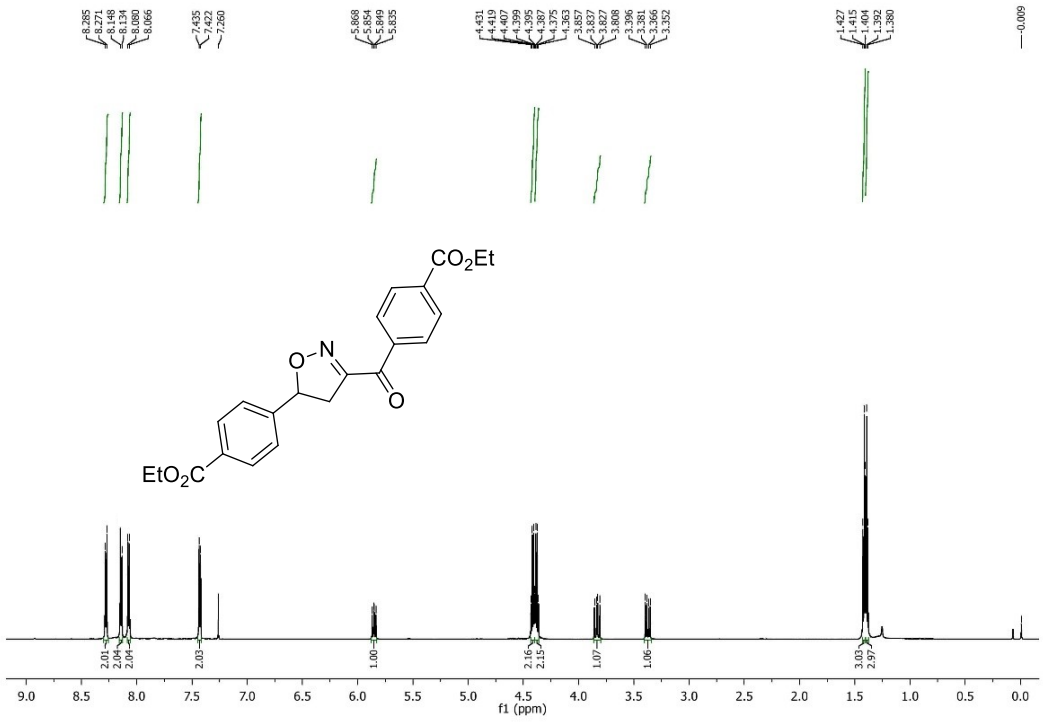
(3-Nitrophenyl)(5-(3-nitrophenyl)-4,5-dihydroisoxazol-3-yl)methanone (14a): ^{1}H NMR ($CDCl_3$, 600 MHz)



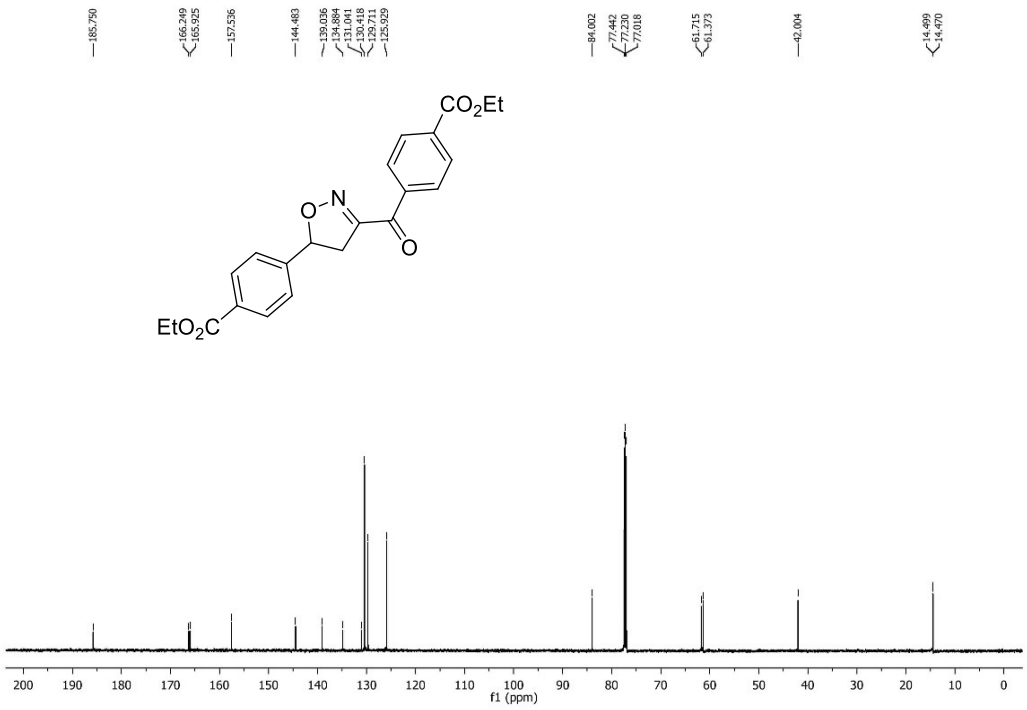
(3-Nitrophenyl)(5-(3-nitrophenyl)-4,5-dihydroisoxazol-3-yl)methanone (14a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



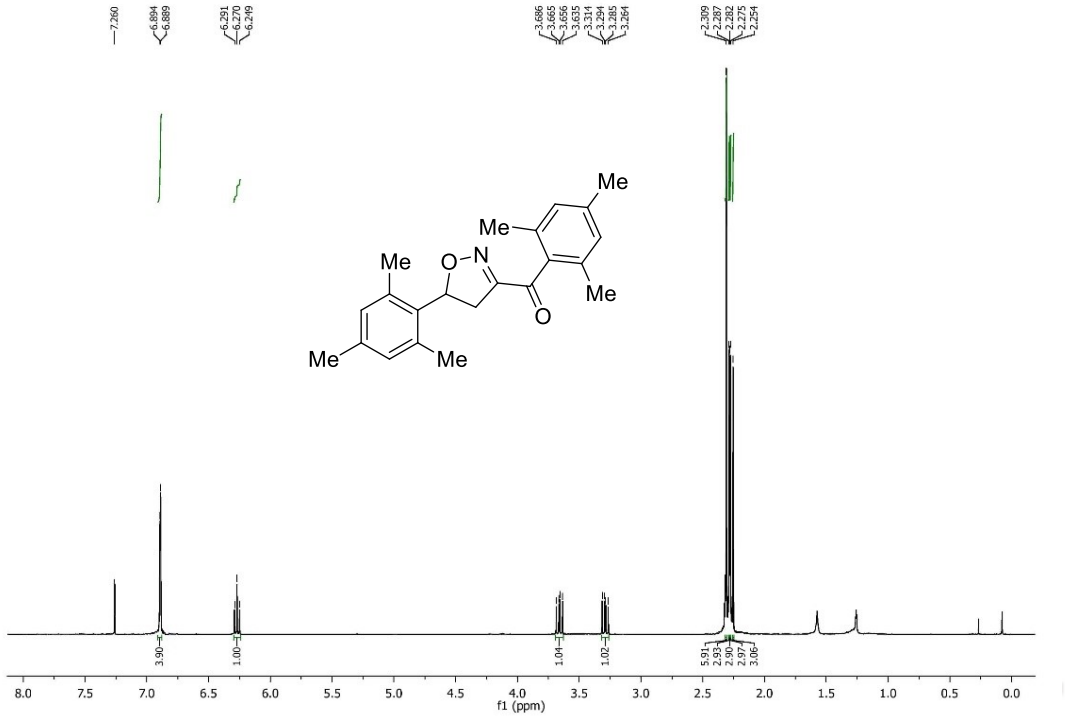
Ethyl 4-(3-(4-(ethoxycarbonyl)benzoyl)-4,5-dihydroisoxazol-5-yl)benzoate (15a): ^{1}H NMR ($CDCl_3$, 600 MHz)



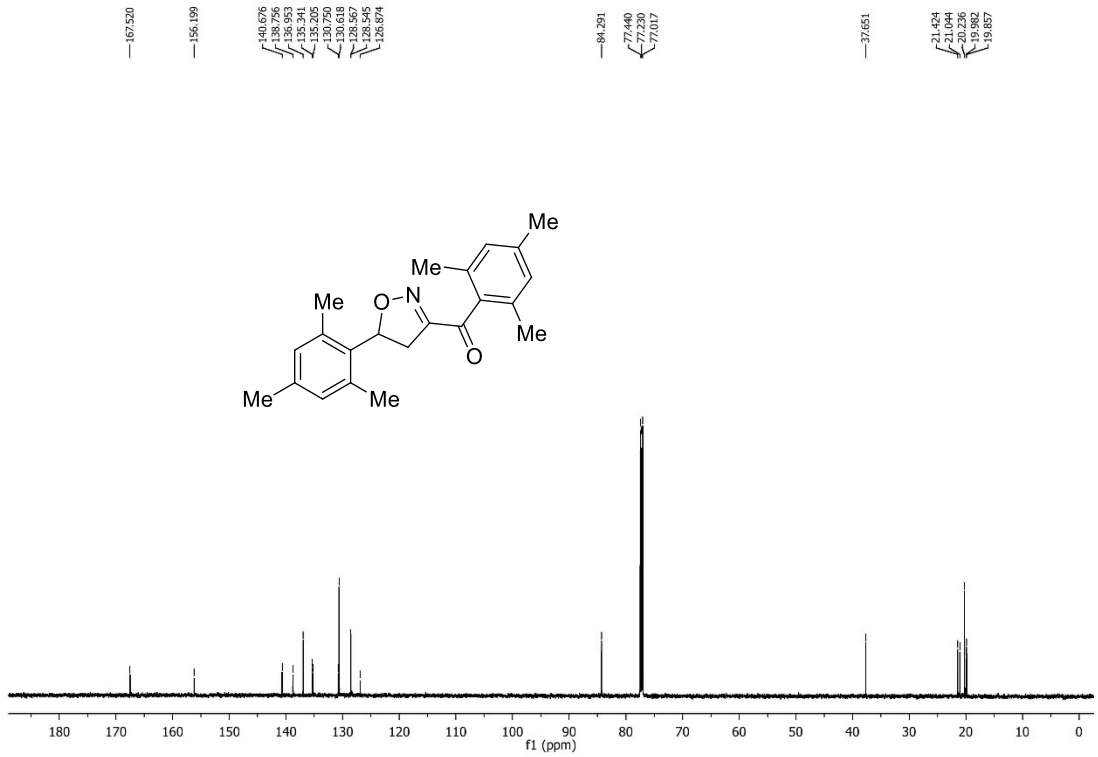
Ethyl 4-(3-(4-(ethoxycarbonyl)benzoyl)-4,5-dihydroisoxazol-5-yl)benzoate (15a): ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



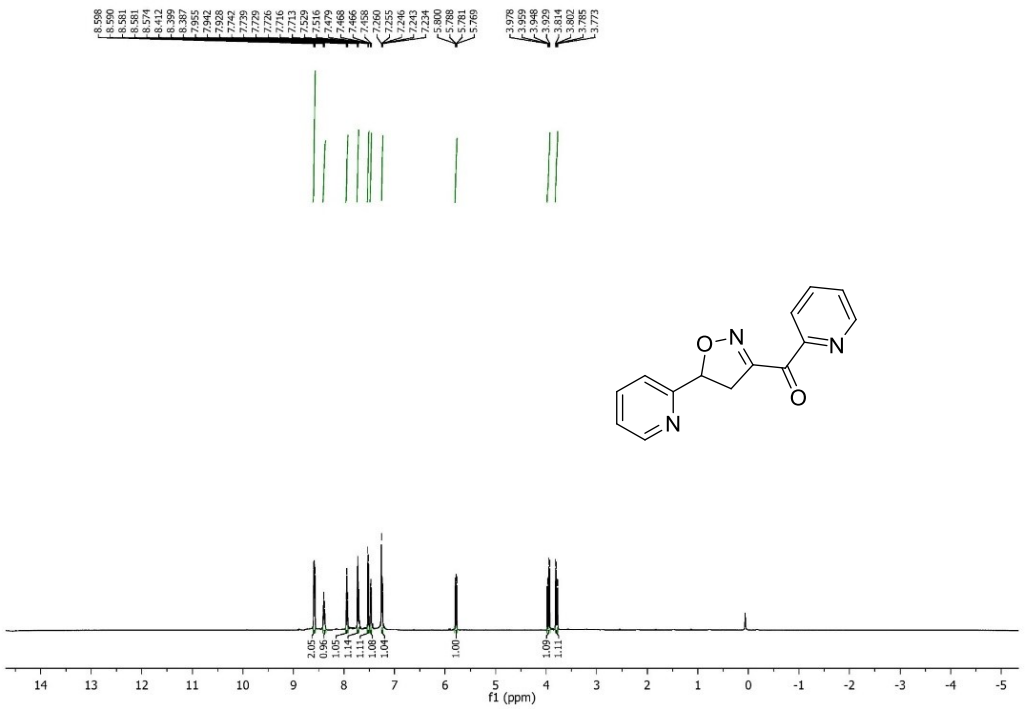
Mesityl(5-mesityl-4,5-dihydroisoxazol-3-yl)methanone (17a): ^{1}H NMR ($CDCl_3$, 600 MHz)



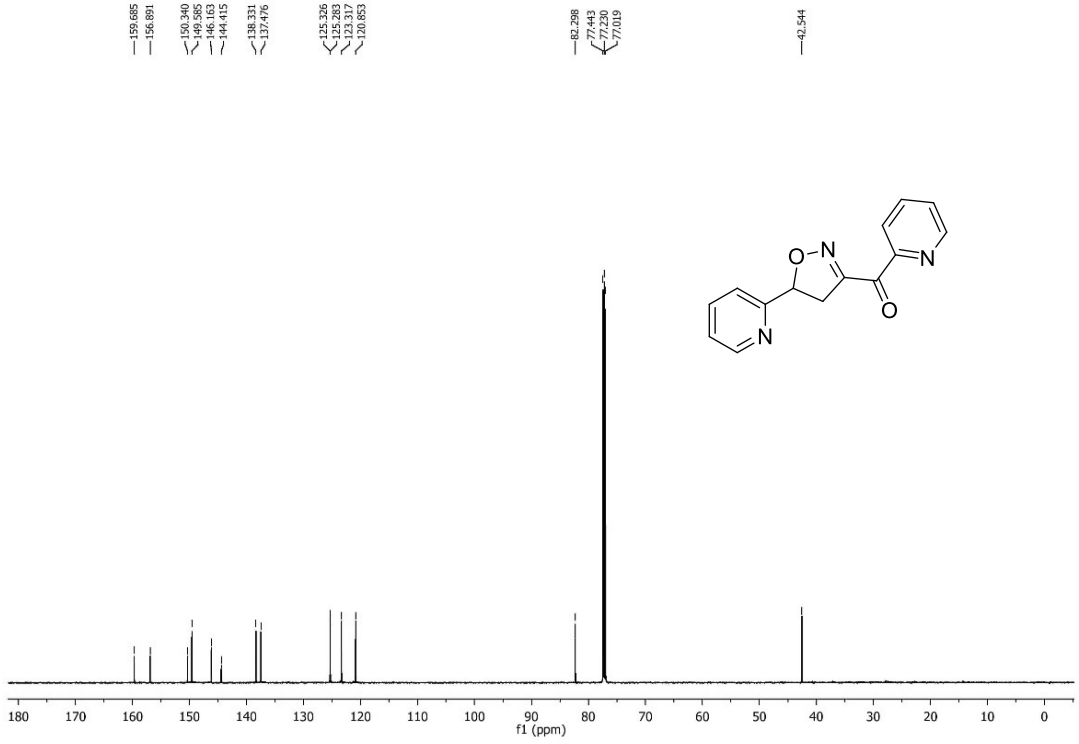
Mesityl(5-mesityl-4,5-dihydroisoxazol-3-yl)methanone (17a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



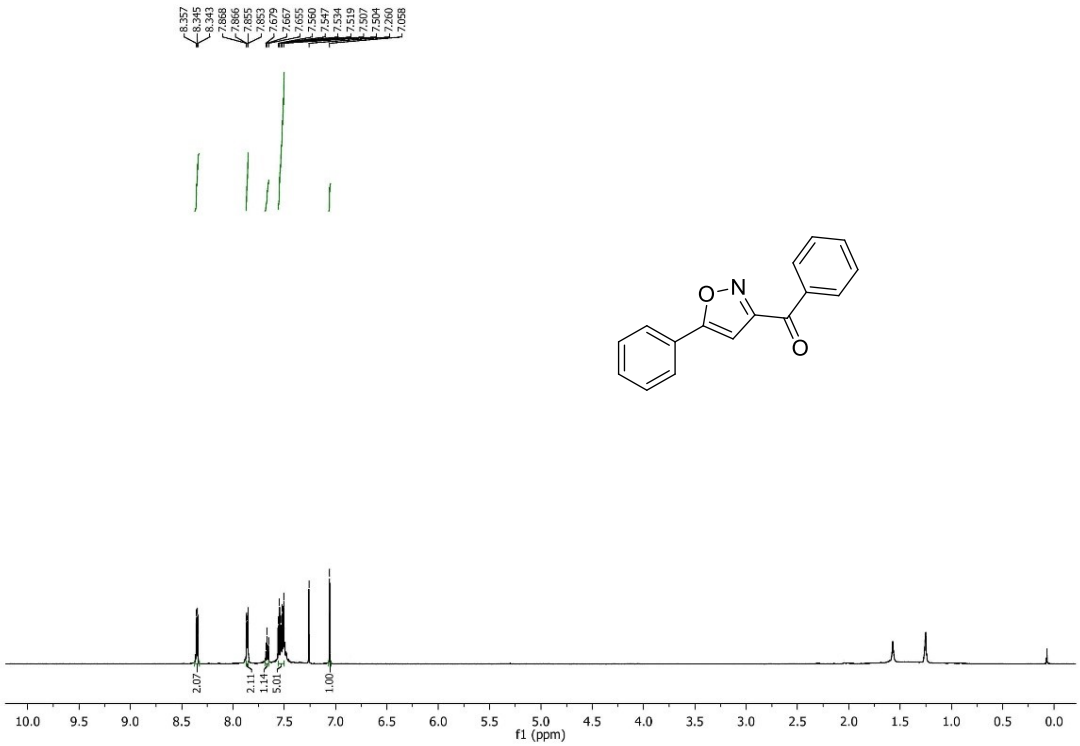
Pyridin-2-yl(5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl)methanone (18a): ^{1}H NMR ($CDCl_3$, 600 MHz)



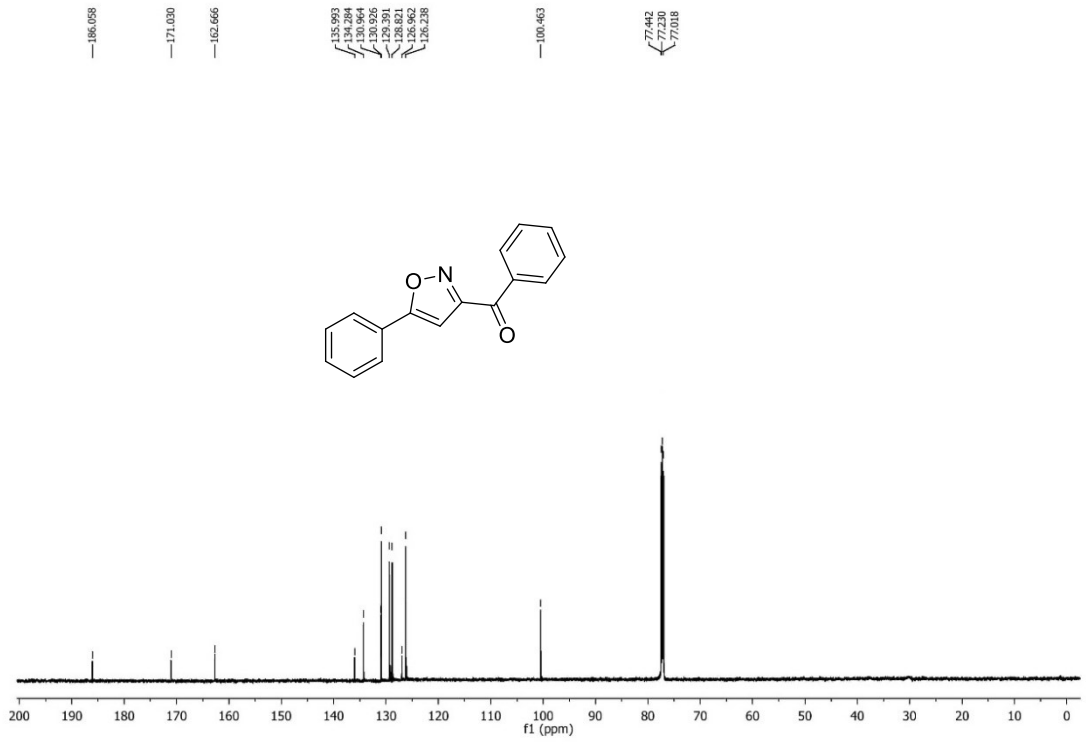
Pyridin-2-yl(5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl)methanone (18a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



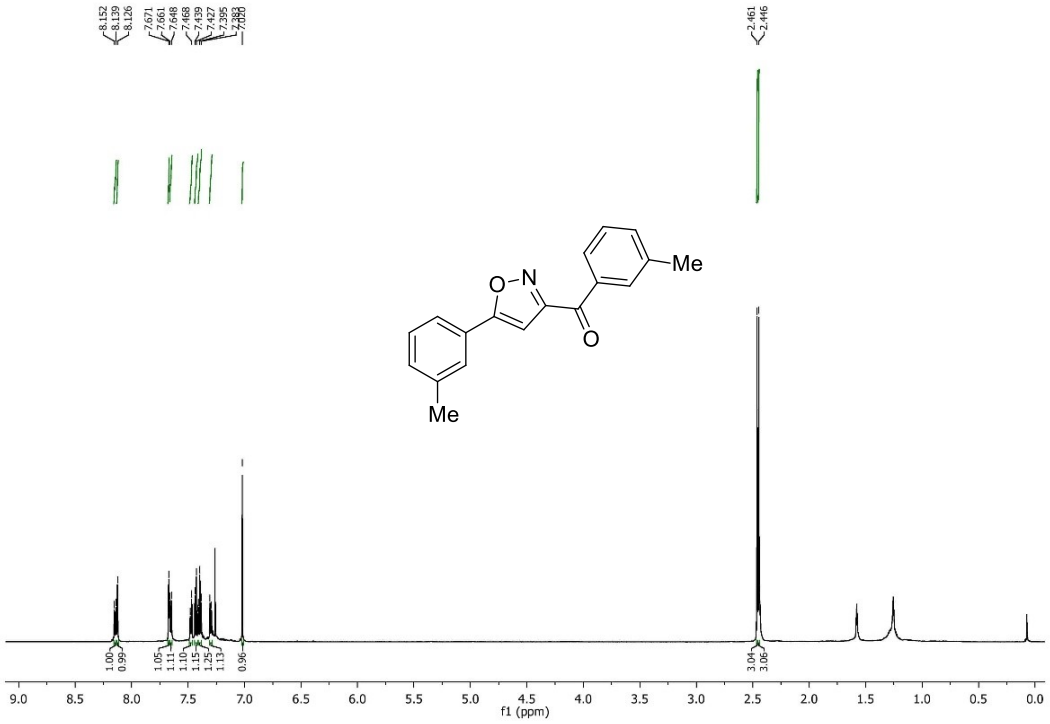
Phenyl(5-phenylisoxazol-3-yl)methanone (19a): ^{1}H NMR ($CDCl_3$, 600 MHz)



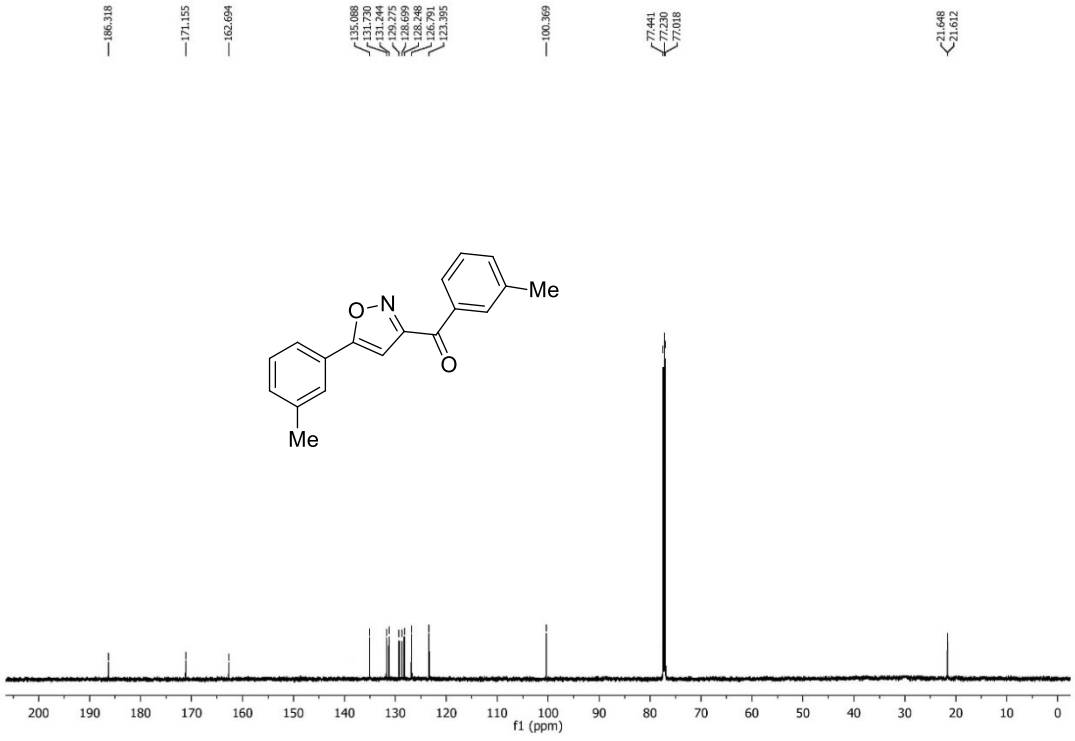
Phenyl(5-phenylisoxazol-3-yl)methanone (19a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



_m_-Tolyl(5-(_m_-tolyl)isoxazol-3-yl)methanone (20a): ^{1}H NMR ($CDCl_3$, 600 MHz)

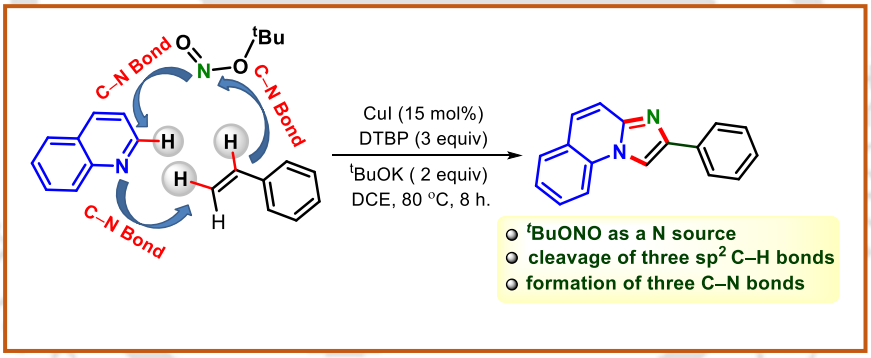


_m_-Tolyl(5-(_m_-tolyl)isoxazol-3-yl)methanone (20a): ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz)



CHAPTER III

Three Sequential C–N Bond Formation: tert-Butyl Nitrite as a N1 Synthon in a Three Component Reaction Leading to Imidazo[1,2-a]quinolines / Imidazo[2,1-a]isoquinolines



ABSTRACT: *tert-Butyl nitrite serves the dual role of an oxidant as well as a N1 synthon in a multi-component reaction involving quinolines/isoquinolines and styrenes. Herein two sp^2 C–H's functionalization of styrenes and one of quinolines/isoquinolines leads to the formation of fused quinolines/isoquinolines via three sequential C–N bond formation.*

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CHAPTER III

Three Sequential C–N Bond Formation: *tert*-Butyl Nitrite as a N1 Synthon in a Three Component Reaction Leading to Imidazo[1,2-*a*]quinolines / Imidazo[2,1-*a*]isoquinolines

III.1. Introduction

Further functionalization and late stage functionalization of biologically important organic frameworks amplifies its activity towards pharmaceutical and medicinal chemistry. Quinolines and isoquinolines are integral part in many natural products and building blocks of several pharmaceuticals.[1] The functionalized derivatives of those *viz*. imidazo[1,2-*a*]quinoline (**I**, **II** and **IV**) and imidazo[2,1-*a*]isoquinoline (**III**) exhibit effective biological activities such as inhibitors of Shiga Toxin, hypertensive, antiallergic, contraceptive and antiasthmatic anxiolytic (Figure III.1.1).[2]

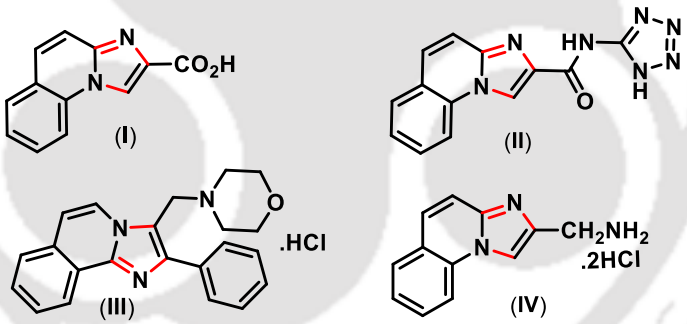
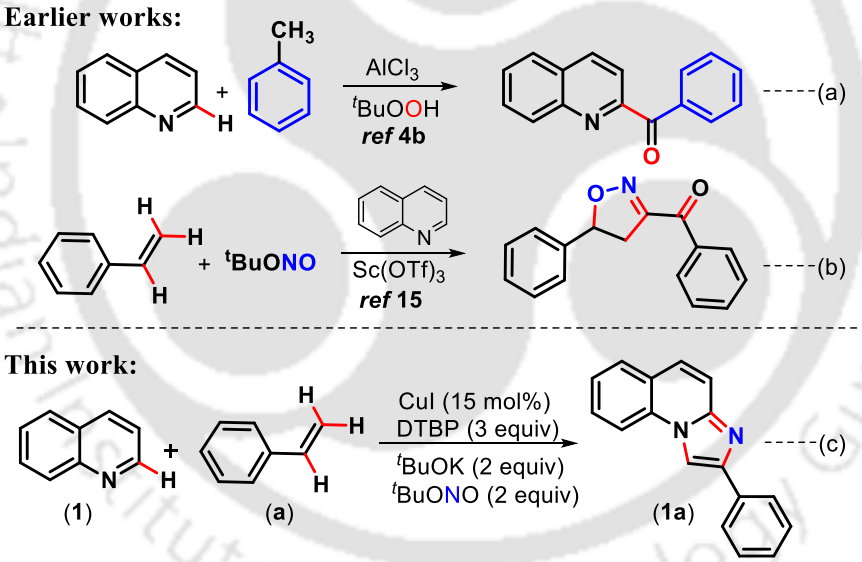


Figure III.1.1. *Representative biologically active imidazo[1,2-a]quinolines and imidazo[2,1-a]isoquinolines*

Various functionalizations *viz*. alkylation,[3a,b] halogenation,[3c] sulfonation,[3d] trifluoromethylation [3e-g] of quinolines and isoquinolines has been documented in the literature. Of late, C–H functionalization is an alternative strategy to create complex structural frameworks from small organic molecules. Consequently, the C–H functionalization protocols have been applied to quinoline and isoquinoline moieties. In this regard, Liu *et al*. demonstrated a novel route for the synthesis of C1-benzyl and benzoyl substituted isoquinolines through a direct oxidative C–H functionalization of isoquinolines using alkyl benzene as the coupling partner.[4a] Our group has also

developed a Lewis acid catalyzed C1 or C2 arylation of isoquinolines and quinolines [Scheme III.1.1 (a)] using methylarenes as the aroyl surrogates.[4b]

On the other hand, direct 1,2-difunctionalization of alkenes with or without the involvement of sp^2 C–H bonds have played a vital role in building complex molecules. Bis-functionalization of olefins such as dihydroxylation,[5] hydroalkylation,[6] oxyamination,[7] carbohalogenation,[8] oxyarylation,[9] aminofluorination,[10] aminocyanation,[11] nitration,[12] carboboration,[13] and others[14] are well documented in the literature. Our group has recently reported an efficient synthesis of isoxazolines *via* 1,2-difunctionalization of styrene in the presence of quinoline (as a base), *tert*-butyl nitrite as the N–O source in the presence of catalyst $Sc(OTf)_3$ [Scheme III.1.1 (b)].[15] Taking cues from these radical mediated reactions, especially, nitration of alkenes[12] using *tert*-butyl nitrite and C1 or C2 aroylation of *N*-heterocycles,[4] we envisaged a double functionalization of styrene and a concomitant C2 functionalization of quinoline or a C1 functionalization of isoquinoline leading to the synthesis of fused heterocycles.



Scheme III.1.1. *Strategies for C–H functionalization of N-heterocycles with alkyl benzene and styrene*

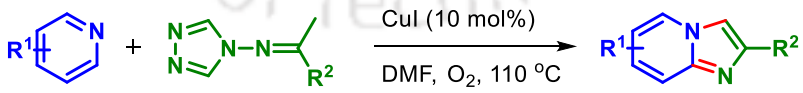
By judiciously choosing the catalyst and other reaction parameters it was possible to fuse styrene onto both quinoline and isoquinoline moieties in the presence of *tert*-butyl nitrite (TBN) [Scheme III.1.1 (c)]. Our initial investigation started using quinoline (0.25 mmol), styrene (0.625 mmol), $Cu(OTf)_3$ (10 mol%), Cs_2CO_3 (2 equiv) and *tert*-butyl nitrite (2 equiv) in 1,2-dichloroethane (DCE) at 80 °C. Interestingly, the reaction resulted in the formation of a new product (**1a**, 41%), spectroscopic analysis confirmed its

structure to be 2-phenylimidazo[1,2-*a*]quinoline (**1a**).[16] In this structure, the incorporation of a new N-atom is associated with the formation of three C–N bonds. We believe that TBN to be the possible source of additional nitrogen atom in this product. So far TBN has been exploited mainly as a source of NO and NO_2 radicals.[12,20] Besides this, it has been employed as a nitrogenating agent in the formation of nitriles from alkylbenzene[17a] and terminal aryl alkenes.[17b] Prior to this report there is only one illustration where TBN has been used as a N1 synthon in the synthesis of cinnolines from 2-vinyl aniline.[17c] In spite of the recent surge in the use of TBN, we feel it is an underutilized reagent, thus exploring alternative pattern of reactivity would open up novel avenues for synthetic chemists. Herein, we disclose a copper catalyzed three-component synthesis of *N*-fused heterocycles involving quinoline/isoquinoline, styrene and TBN as the N1 synthon *via* three sequential C–N bond formations.

III.2. Strategies for the synthesis of imidazo[1,2-*a*]quinolines or imidazo[1,2-*a*]pyridines

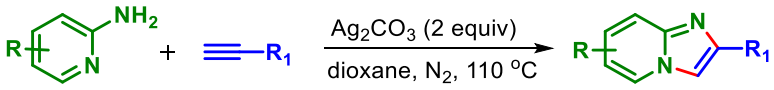
Nitrogen-containing heterocyclic frameworks are abundant in many naturally occurring and synthetic compounds exhibiting interesting biological activities and functional properties. These heterocycles have engrossed the synthetic chemists to develop newer methodologies for their synthesis. Among the nitrogen-fused heterocycles, imidazo[1,2-*a*]quinoline and imidazo[1,2-*a*]pyridine are the integral part of many natural products and pharmaceutically and biologically active molecules. Thus, considerable attention has been paid for the synthesis of these heterocycles.

A copper-catalyzed synthesis of imidazopyridines *via* the aerobic oxidative C–H functionalization of substituted pyridines with *N*-(alkylidene)-4*H*-1,2,4-triazol-4 amines has been accomplished by Fu group (Scheme III.2.1).[18]



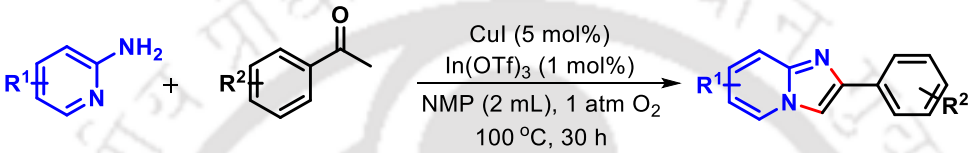
Scheme III.2.1. *Synthesis of imidazo[1,2-a]pyridines*

Lei and co-worker described a novel route for the construction of heteroaromatic imidazo[1,2-*a*]pyridines through the C–H/N–H cross coupling of 2-aminopyridines with terminal alkynes. The oxidative C–H/N–H cross coupling proceeds in the presence of Ag_2CO_3 acting as oxidant, for this transformation (Scheme III.2.2).[19]



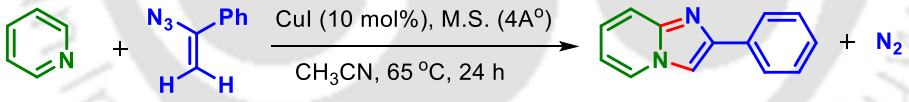
Scheme III.2.2. *Silver-mediated C–H/N–H oxidative cross-coupling/cyclization*

In 2013, Su *et al*. demonstrated an efficient method for the synthesis of imidazoheterocycles by the reaction of 2-aminopyridine and acetophenone (Scheme III.2.3).[20] This aerobic oxidative transformation proceeds through a catalytic Ortoleva−King reaction in presence of CuI and $In(CF_3SO_3)_3$ as catalyst and O_2 as the oxidant.



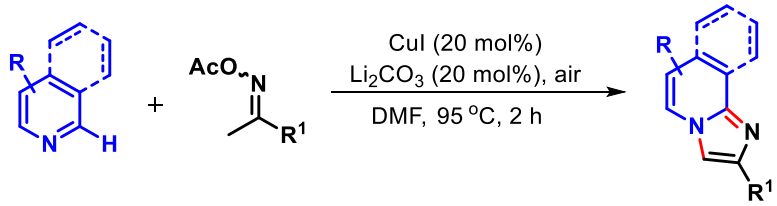
Scheme III.2.3. *CuI-Catalyzed aerobic oxidative reaction of 2-aminopyridines with arylketones*

Recently Adimurthy group reported a copper catalyzed oxidative C(sp2)−H functionalization of both pyridines and vinyl azides, leading to the synthesis of 2-phenylimidazoimidazo[1,2-*a*]pyridines (Scheme III.2.4).[21] From the mechanistic studies, it is concluded that the reaction proceeds both *via* radical as well as ionic pathways.



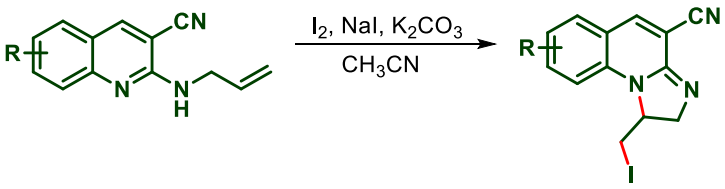
Scheme III.2.4. *Copper-catalyzed C–H functionalization of pyridines*

A new synthetic approach for the synthesis of imidazo[1,2-*a*]pyridines was accomplished through the Cu–catalyzed coupling reactions of pyridine with keto-oxime esters (Scheme III.2.5).[22] This strategy may open up new routes for construction of complex molecules through direct conversion of unactivated pyridine.



Scheme III.2.5. *Copper-catalyzed synthesis of imidazo[1,2-a]quinolines*

Singh's research group has shown the synthesis of imidazo[1,2-*a*]quinolines derivatives from 2-allylaminoquinolines using I_2-NaI reagent (Scheme III.2.6). The reaction proceeds *via* iodocyclization reaction of 2-allylaminoquinolines.[23]



Scheme III.2.6. *Synthesis of imidazo[1,2-a]quinolines*

III.3. Present work

In the light of the aforementioned protocols, the present method for the construction of imidazo[1,2-*a*]quinolines using styrene, quinoline and *tert*-butyl nitrite is unprecedented in literature.

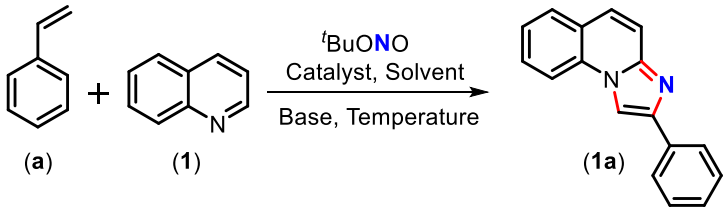
Optimization of reaction conditions:

As has been mentioned earlier, an initial trial reaction was performed using quinoline (0.25 mmol), styrene (0.625 mmol), $Cu(OTf)_3$ (10 mol%), Cs_2CO_3 (2 equiv) and *tert*-butylnitrite (2 equiv) in 1,2-dichloroethane (DCE) at 80 °C. Interestingly, the reaction resulted in the formation of a new product (**1a**, 41%).

Encouraged by the above unprecedented three component reaction, further optimizations were carried out by varying various reaction parameters using styrene (**a**) and quinoline (**1**) as the coupling partners in the presence of ^{t}BuONO. Initially, a variety of non-polar solvents such as *p*-xylene (31%), toluene (29%) and chlorobenzene (36%) and polar aprotic solvents such as DMF (21%) and DMSO (0%) were tested (Table III.3.1, entries 2–6). However, all the solvents tested were found to be less effective compared to DCE (41%) (Table III.3.1, entry 1). Other Cu(I) and Cu(II) salts such as $Cu(OAc)_2$ (33%), $CuCl_2$ (35%) and CuCl (39%) (Table III.3.1, entries 7–9) gave poor yields compared to $Cu(OTf)_2$ (43%) whereas, CuBr and CuI provided improved yields of 45% and 49% respectively (Table III.3.1, entries 10 and 11). With CuI as the suitable catalyst, other inorganic (K_2CO_3 and KO^{t}Bu) and organic (DMAP and DBU) bases were screened. Inorganic bases K_2CO_3 (43%) (Table III.3.1, entry 12) gave lower yield compared to Cs_2CO_3 whereas, KO^{t}Bu furnished an improved yield of 53% (Table III.3.1, entry 13). However, no encouraging results could be obtained using organic bases such as DMAP (31%) and DBU (29%) (Table III.3.1, entries 14 and 15). When the reaction

was carried out in the absence of Cu-catalyst no product formation was detected (Table III.3.1, entry 16), suggesting the involvement of copper salt in facilitating the reaction, possible *via* the formation of an iminium carbocation.[24] When the reaction was performed in the absence of base under otherwise identical condition, resulted in a suppressed yield (27%) of (**1a**) (Table III.3.1, entry 17). These results suggest the involvement of both catalyst and base in this multi-component reaction. In a pursuit to improve the yield, further reactions were carried out in the presence of oxidants. Interestingly, the use of various oxidants such as di-*tert*-butyl peroxide (61%), DDQ (56%), $K_2S_2O_8$ (55%), *tert*-butyl peroxybenzoate (53%) significantly improved the product yield, with DTBP being the most effective (Table III.3.1, entries 18–21). Increasing the catalyst loading to 15 mol% improved the yield up to 66% (Table III.3.1, entry 22). No noticeable enhancement in the yield (68%) was observed when the catalyst loading was increased up to 20 mol% (Table III.3.1, entry 23). There was no enhancement in the yield (66%) when the additive (DTBP) loading was increased to 4 equiv. (Table III.3.1, entry 24) however the yield of the product decreased to 62% when the quantity of additive (DTBP) was reduced to 2 equiv (Table III.3.1, entry 25). Reaction carried out both at higher 100 ^oC (53%) or lower 60 ^oC (40%) temperature was detrimental to the product formation. (Table III.3.1, entries 26 and 27). After screening of various reaction parameters, the optimized condition for this transformation is the use of quinoline (0.25 mmol), styrene (0.625 mmol), CuI (15 mol%), ^{t}BuOK (0.5 mmol), *tert*-butyl nitrite (0.5 mmol) and DTBP (0.75 mmol) at 80 ^oC in DCE solvent (Table III.3.1, entry 22).

Table III.3.1. *Optimization of the reaction conditions*[a]

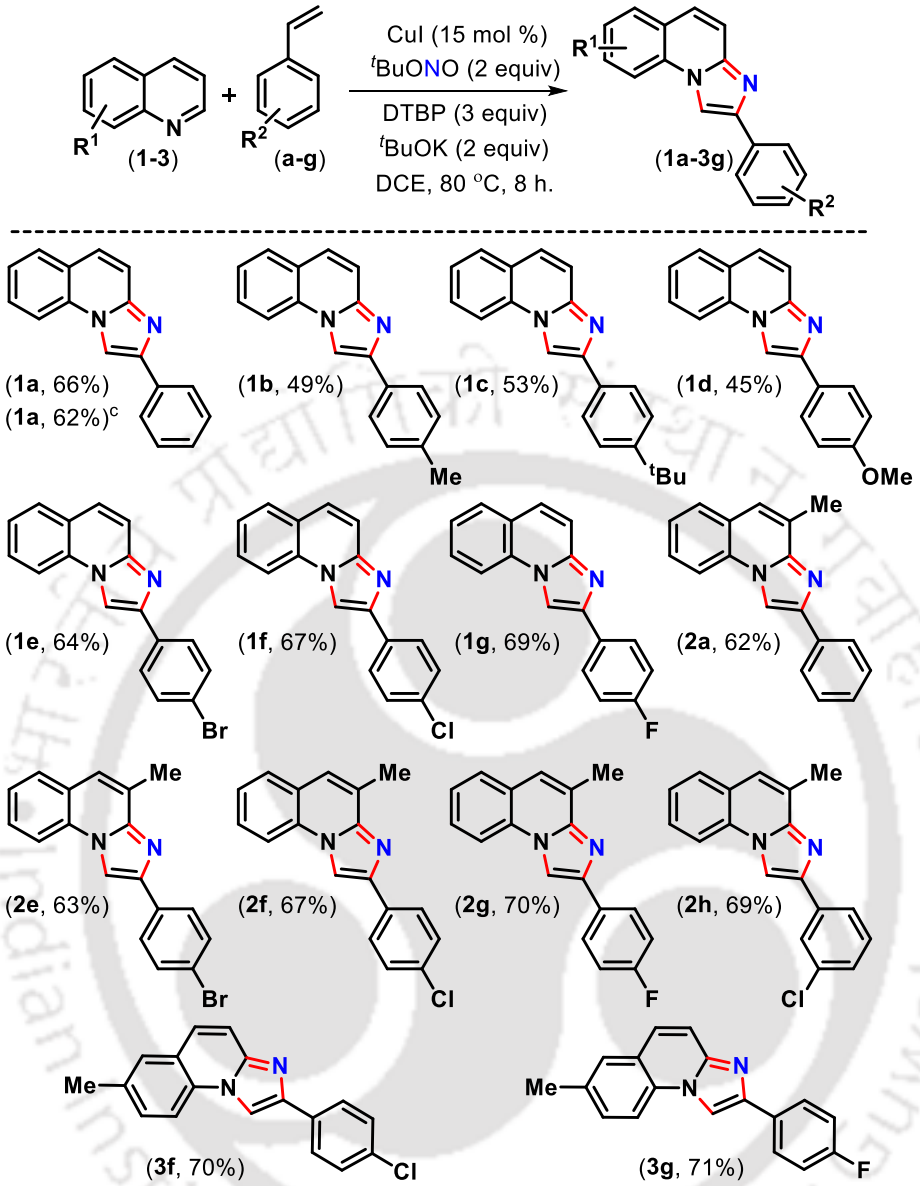


entry	catalyst (mol%)	base	solvent	additive	yield %[b]
1	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	DCE	-	43
2	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	*p*-xylene	-	31
3	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	toluene	-	29
4	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	PhCl	-	36
5	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	DMF	-	21
6	$Cu(OTf)_2$ (10.0)	Cs_2CO_3	DMSO	-	0
7	$Cu(OAc)_2$ (10.0)	Cs_2CO_3	DCE	-	33
8	$CuCl_2$ (10.0)	Cs_2CO_3	DCE	-	35
9	CuCl (10.0)	Cs_2CO_3	DCE	-	39
10	CuBr (10.0)	Cs_2CO_3	DCE	-	45
11	CuI (10.0)	Cs_2CO_3	DCE	-	49
12	CuI (10.0)	K_2CO_3	DCE	-	43
13	CuI (10.0)	KO^{t}Bu	DCE	-	53
14	CuI (10.0)	DMAP	DCE	-	31
15	CuI (10.0)	DBU	DCE	-	29
16	-	KO^{t}Bu	DCE	-	0
17	CuI(10.0)	-	DCE	-	27
18	CuI (10.0)	^{t}BuOK	DCE	DTBP	61
19	CuI (10.0)	^{t}BuOK	DCE	DDQ	56
20	CuI (10.0)	^{t}BuOK	DCE	$K_2S_2O_8$	55
21	CuI (10.0)	^{t}BuOK	DCE	TBPB	53
22	**CuI (15.0)**	**^{t}BuOK**	**DCE**	**DTBP**	**66**
23	CuI (20.0)	^{t}BuOK	DCE	DTBP	68
24	CuI (15.0)	^{t}BuOK	DCE	DTBP	66[c]
25	CuI (15.0)	^{t}BuOK	DCE	DTBP	62[d]
26	CuI (15.0)	^{t}BuOK	DCE	DTBP	53[e]
27	CuI (15.0)	^{t}BuOK	DCE	DTBP	40[f]

[a]Reaction conditions: Quinoline (**1**) (0.25 mmol), styrene (**a**) (0.625 mmol), catalyst (mol%), base (0.5 mmol), *tert*-butylnitrite (0.5 mmol) and additive (0.75 mmol) at 80 °C. [b]Yield after 8 h. [c]DTBP 4 equiv [d]DTBP 2 equiv [e]Temperature 100 °C. [f]Temperature 60 °C.

Substrate scope for synthesis of imidazo[1,2-*a*]quinolines: This multi-component synthesis of imidazo[1,2-*a*]quinolines was then explored with various quinolines and aromatic terminal alkenes (Scheme III.3.1) under optimized reaction condition. Styrenes having electron-donating substituents such as *p*-Me (**b**), *p*-^{t}Bu (**c**) and *p*-OMe (**d**) successfully coupled with quinoline (**1**), yielding their corresponding imidazo[1,2-*a*]quinolines (**1b**, 49%), (**1c**, 53%) and (**1d**, 45%) in moderate yields (Scheme III.3.1).

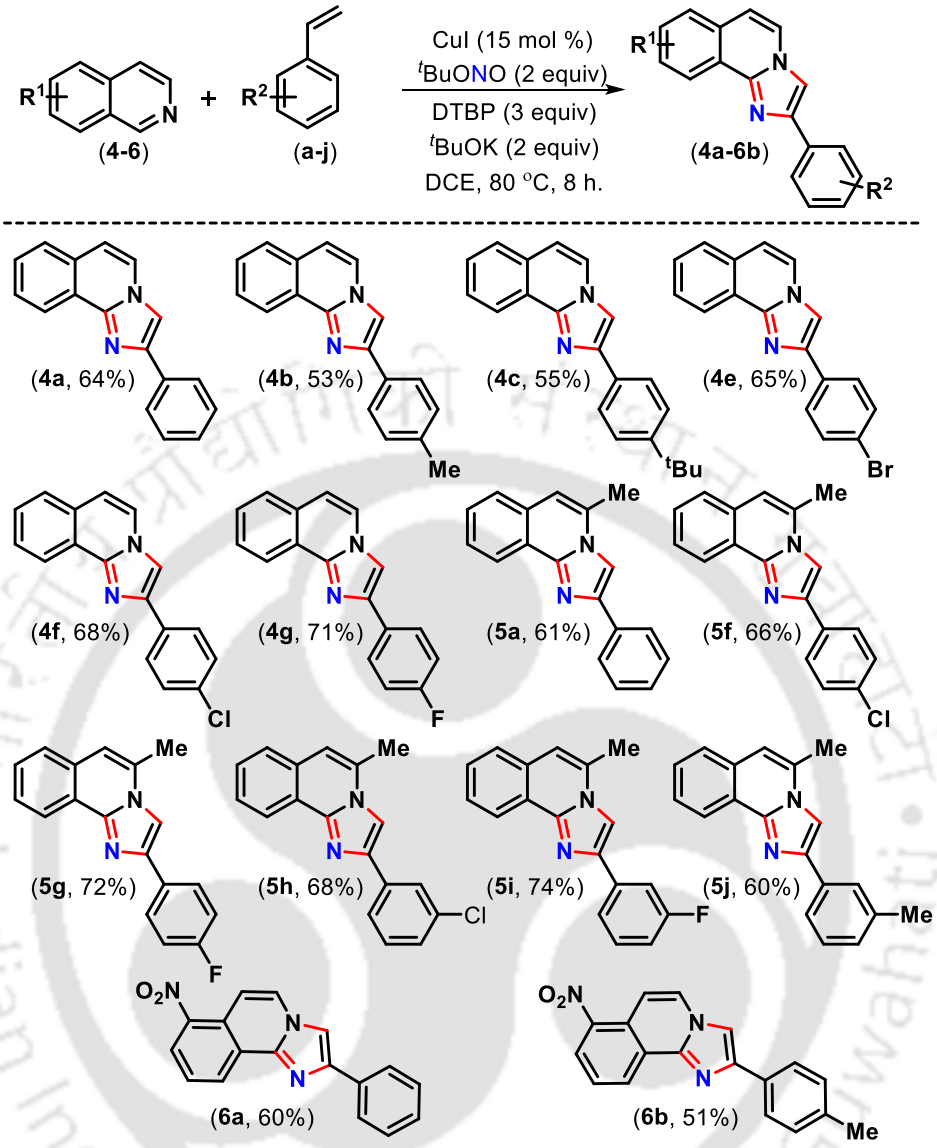
Scheme III.3.1. *Substrate scope for synthesis of imidazo[1,2-a]quinolines*[a,b]



[a]Reaction conditions: quinoline (**1**) (0.25 mmol), styrene (**a**) (0.625 mmol), CuI (0.038 mmol), ^{t}BuOK (0.5 mmol), *tert*-butyl nitrite (0.5 mmol) and DTBP (0.75 mmol) at 80 °C in DCE (1.5 mL). [b]Yields after 8 h. [c]Yield reported for 1 mmol scale.

Styrenes bearing electron-withdrawing substituents such as *p*-Br (**e**), *p*-Cl (**f**) and *p*-F (**g**), all provided their respective imidazo[1,2-*a*]quinolines (**1e**, 64%), (**1f**, 67%) and (**1g**, 69%) in moderate yields. In order to expand the scope of this methodology, substituted quinolines such as 3-methylquinoline (**2**) and 6-methylquinoline (**3**) were tested with various substituted styrenes (**a**), (**e**), (**f**), (**g**) and (**h**) and all afforded their respective fused products (**2a**, 62%), (**2e**, 63%), (**2f**, 67%), (**2g**, 70%), (**2h,** 69%), (**3f**, 70%) and (**3g**, 71%) in good yields (Scheme III.3.1).

Scheme III.3.2. *Substrate scope for synthesis of imidazo[2,1-a]isoquinolines* [a,b]



[a]Reaction conditions: isoquinoline (**1**) (0.25 mmol), styrene (**a**) (0.625 mmol), CuI (0.038 mmol), ^{t}BuOK (0.5 mmol), *tert*-butyl nitrite (0.5 mmol) and DTBP (0.75 mmol) at 80 °C in DCE (1.5 mL). [b]Yields after 8 h.

Substrate scope for synthesis of imidazo[2,1-*a*]isoquinolines: Owing to the importance of isoquinoline framework in many biological systems and with the positive outcome of the present coupling strategy with quinoline, we sought to test the similar fusion of isoquinoline with styrene. To our delight, the reaction of isoquinoline (**4**) with styrene (**a**) under the identical condition lead to the synthesis of analogues coupled product 2-phenylimidazo[2,1-*a*]isoquinoline (**4a**, 64%) (Scheme III.3.2). Encouraged by this positive result, we further executed this strategy to other styrenes and isoquinolines. Styrenes having electron-donating such as *p*-Me (**b**), *p*-^{t}Bu (**c**) or electron-withdrawing such as *p*-Br (**e**), *p*-Cl (**f**) and *p*-F (**g**) substituents, all underwent effective coupling with

isoquinoline (**4**) to produce their desired products [(**4b**, 53%), (**4c**, 55%), (**4e**, 65), (**4f**, 68%) and (**4g**, 71%)] as shown in Scheme III.3.2. The structure of the product (**4f**) has been further confirmed by single crystal X-ray diffraction study (Figure III.3.1).

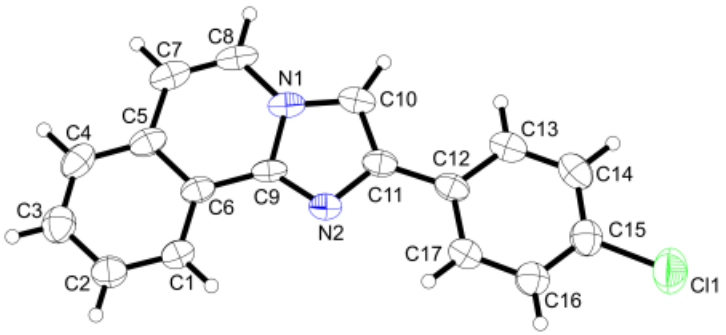
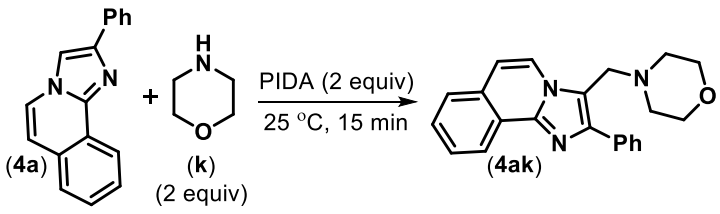


Figure III.3.1. *Ortep diagram of compound (4f)*

Furthermore, substituted isoquinolines such as 3-methylisoquinoline (**5**) and 5-nitroisoquinoline (**6**), both reacted smoothly with various substituted styrenes (**a**), (**b**), (**f**), (**g**), (**h**), (**i**) and (**j**) affording their corresponding imidazo[2,1-*a*]isoquinolines (**5a**, 61%), (**5f**, 66%), (**5g**, 72%), (**5h**, 68%), (**5i**, 74%), (**5j**, 60%), (**6a**, 60%) and (**6b**, 51%) in modest yields (Scheme III.3.2). In this protocol, both electron-donating and electron-withdrawing substituents on either of the substrate provided almost identical yields of their product. This may be due to the higher reactivity of reaction intermediates, in this multi-step strategy. However, in this process aliphatic alkenes failed to react completely which may be due to the instability of the radical generated during the reaction.

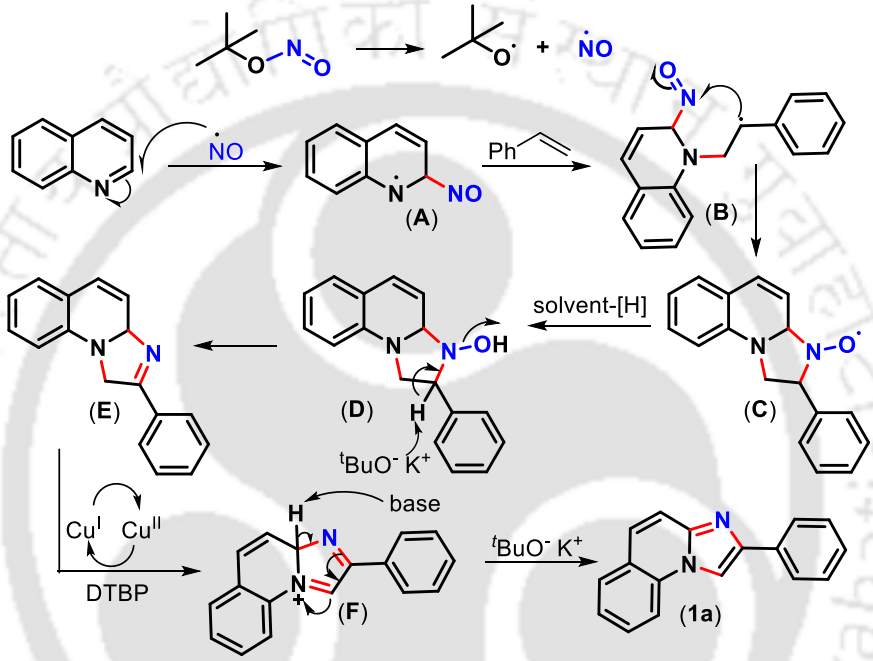
4-((2-Phenylimidazo[2,1-*a*]isoquinolin-3-yl)methyl)morpholine hydrochloride (**4ak**) is a very important compound possessing significant range of biological activities.[2d] It has been successfully applied in determining the functional activity of several living organisms.[2d] Compound (**4ak**) was successfully synthesized from (**4a**) by coupling it with morpholine (**k**). The later served the dual role of a one-carbon synthon as well as the morpholine unit following the protocol of Hajra *et.al* (Scheme III.3.3).[25]

Scheme III.3.3. *Synthesis of 4-((2-phenylimidazo[2,1-a]isoquinolin-3-yl)methyl)morpholine (**4ak**).*



In order to elucidate a plausible mechanism, an experiment was performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3 equiv) under otherwise identical condition. Retardation in the desired product (**1a**, <5%) formation suggests the radical nature of the reaction. Based on the intermediates detected by the HRMS analysis of the reaction mixture at various time intervals and from the literature reports, a plausible mechanism has been proposed for this transformation (Scheme III.3.4).

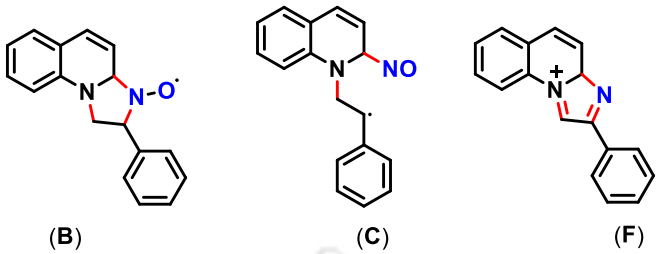
Scheme III.3.4. *Proposed mechanism for imidazo[1,2-a]quinolines synthesis*



The heterolytic cleavage of *tert*-butyl nitrite generates a NO· radical[26] which attacks at the more electrophilic C2 position of quinoline to generate a radical intermediate (**A**).[4,27] The nitrogen radical intermediate (**A**) then attacks at the terminal carbon of the styrene to form a benzylic radical species (**B**), which underwent an intramolecular radical coupling with the adjacent NO group to give a radical intermediate (**C**). The *N*-oxide radical intermediate (**C**) abstract a prtoton[28] from the solvent DCE to form a *N*-hydroxy intermediate (**D**). A base (^{t}BuOK) mediated dehydration of which resulted in the formation of intermediate (**E**). In the presence of CuI and DTBP, the intermediate (**E**) generates an iminium carbocation (**F**) *via* two sequential single electron transfer (SET) process.[24] Finally, loss of a proton from intermediate (**F**) leads to the formation of the desired product (**1a**). Intermediacy of (**B**), (**C**) and (**F**) have been detected by the HRMS analysis of reaction mixtures at various time intervals (Figure III.3.2). Formation of intermediates (**B**) and (**C**) are further confirmed by radical trapping experiments (Figure

III.3.2). A similar mechanism is expected to operate for isoquinoline (**4**) leading to 2-phenylimidazo[2,1-*a*]isoquinoline (**4a**).

Intermediates detected by the HRMS analysis of reaction mixture



(**B**) (**C**) (**F**)

Intermediates reconfirmed by TEMPO experiments

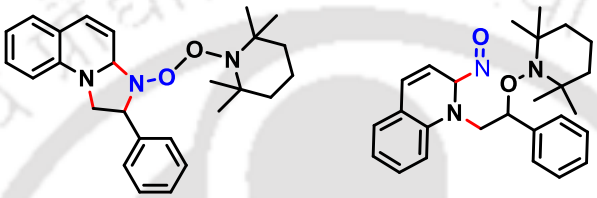


Figure III.3.2. *Intermediates detected by the HRMS analysis*

In conclusion, selective C1 or C2 functionalizations of isoquinolines or quinolines with concurrent *bis*-functionalization of styrenes in the presence of *tert*-butyl nitrite and Cu catalyst leads to the construction of imidazo[2,1-*a*]isoquinolines or imidazo[1,2-*a*]quinolines. In this radical mediated reaction *tert*-butyl nitrite serve as a *N*1 synthon and assist in the simultaneous installation of three new C–N bonds. This is an excellent illustration of novel reactivity of *tert*-butyl nitrite thereby, expending its utility towards the synthesis of complex molecules.

III.4. Experimental section

III.4.1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz) and in for ^{13}C NMR (100 and 150 MHz) $CDCl_3$ as the internal standard. MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

III.4.2. Crystallographic description:

Single crystal X-ray data were collected using a Rigaku Super Nova, single source at offset, Eos diffractometer.[1] The structures were solved by direct methods and refined by full-matrix least-squares calculations using SHELXTL software.[2,3] All the non-H atoms were refined in the anisotropic approximation against F^2 of all reflections. The H-atoms were placed at their calculated positions and refined in the isotropic approximation.

1. CrysAlisPro, Oxford Diffraction Ltd., Version 1, 171. 33.34d [release 27-02-2009 CrysAlis 171. NET].
2. SMART and SAINT, Siemens Analytical X-ray Instruments Inc., Madison, WI, **1996**.
3. G. M. Sheldrick, **2008**, *64*, 112-122.

Crystallographic description of 2-(4-chlorophenyl)imidazo[2,1-*a*]isoquinoline (4f):

$C_{17}H_{11}ClN_2$, crystal dimensions 0.21 x 0.12 x 0.10 mm, M_r = 278.73, Orthorhombic, space group P c a 21, a =12.3293(6), b = 3.9877(2), c = 26.5458(16) Å, α = 90 °, β = 90 °, γ = 90 °, V = 1305.14(12) Å^3, Z = 4, ρ_{calcd} = 1.419 mg/m^3, μ = 0.282 mm^{-1}, F(000) = 576.0, reflection collected / unique = 3304 / 1785, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0444, wR_2 = 0.0821, R indices (all data): R_1 = 0.0344, wR_2 = 0.0725, goodness of fit = 1.093. CCDC 1581324 for 2-(4-Chlorophenyl)imidazo[2,1-*a*]isoquinoline (4f) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

III.4.3. General procedure for the synthesis of 2-phenylimidazo[1,2-*a*]quinoline (1a) from quinoline (1) and styrene (a):

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added quinoline (**1**) (32 mg, 0.25 mmol), styrene (**a**) (65 mg, 0.625 mmol), CuI (7.2 mg, 0.038 mmol), ^{t}BuOK (56 mg, 0.5 mmol), *tert*-butyl nitrite (52 mg, 0.5 mmol), DTBP (110 mg, 0.75 mmol) and 1, 2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 °C for 8 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9.5:0.5) to give pure 2-phenylimidazo[1,2-*a*]quinoline (**1a**) (40 mg, yield 66%). The identity and purity of the product were confirmed by spectroscopic analysis.

III.4.4. General procedure for the synthesis of 4-((2-phenylimidazo[2,1-*a*]isoquinolin-3-yl)methyl)morpholine (4ak) from 2-phenylimidazo[2,1-*a*]isoquinoline (4a):

To a dried sealed tube was added 2-phenylimidazo[2,1-*a*]isoquinoline (**4a**) (49 mg, 0.2 mmol), morpholine (**b**) (35 mg, 0.4 mmol), PIDA [(diacetoxyiodo)benzene] (129 mg, 0.4 mmol) and stirred at room temperature for 15 min. After completion of the reaction the reaction mixture was quenched with water (2 mL) and ethyl acetate (5 mL). Then the reaction mixture was admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 7:3) to give pure 4-((2-phenylimidazo[2,1-*a*]isoquinolin-3-yl)methyl)morpholine (**4ak**) (55 mg, yield 80%). The identity and purity of the product were confirmed by spectroscopic analysis.

III.4.5. General procedure for free radical trapping experiments:

III.4.5.1. TEMPO experiment 1:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added quinoline (**1**) (32 mg, 0.25 mmol), styrene (**a**) (65 mg, 0.625 mmol), CuI (7.2 mg, 0.038 mmol), ^{t}BuOK (56 mg, 0.5 mmol), *tert*-butyl nitrite (52 mg, 0.5 mmol), DTBP (117 mg, 0.75 mmol), TEMPO (110 mg, 0.75 mmol) and 1, 2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C for 8 h. Then the reaction mixture was cooled and taken for HRMS analysis.

III.4.5.2. TEMPO experiment 2:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added quinoline (**1**) (32 mg, 0.25 mmol), styrene (**a**) (65 mg, 0.625 mmol), CuI (7.2 mg, 0.038 mmol), ^{t}BuOK (56 mg, 0.5 mmol), *tert*-butyl nitrite (52 mg, 0.5 mmol), DTBP (117 mg, 0.75 mmol) and 1, 2-dichloroethane (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 ^{o}C for 1 h. After 1 h, radical scavenger TEMPO (117 mg, 0.75 mmol) was added to the reaction mixture and the reaction mixture was allowed to reflux for another 1h. Then the reaction mixture was cooled and taken for HRMS analysis.

III.5. Mechanistic investigation:

III.5.1. ESI-MS study for the detection of reaction intermediates during the synthesis of 2-phenylimidazo[1,2-*a*]quinoline (1a) from quinoline (1), styrene (a) and *tert*-butyl nitrite at different time interval:

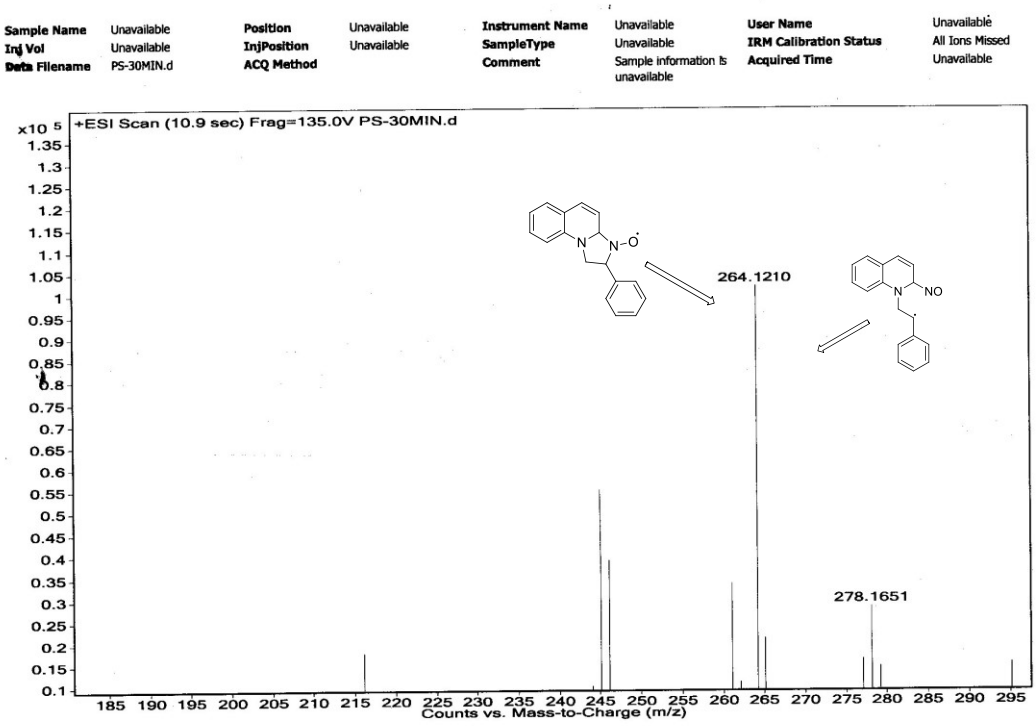


Figure III.5.1. *HRMS spectrum of reaction mixture after 30 minute*

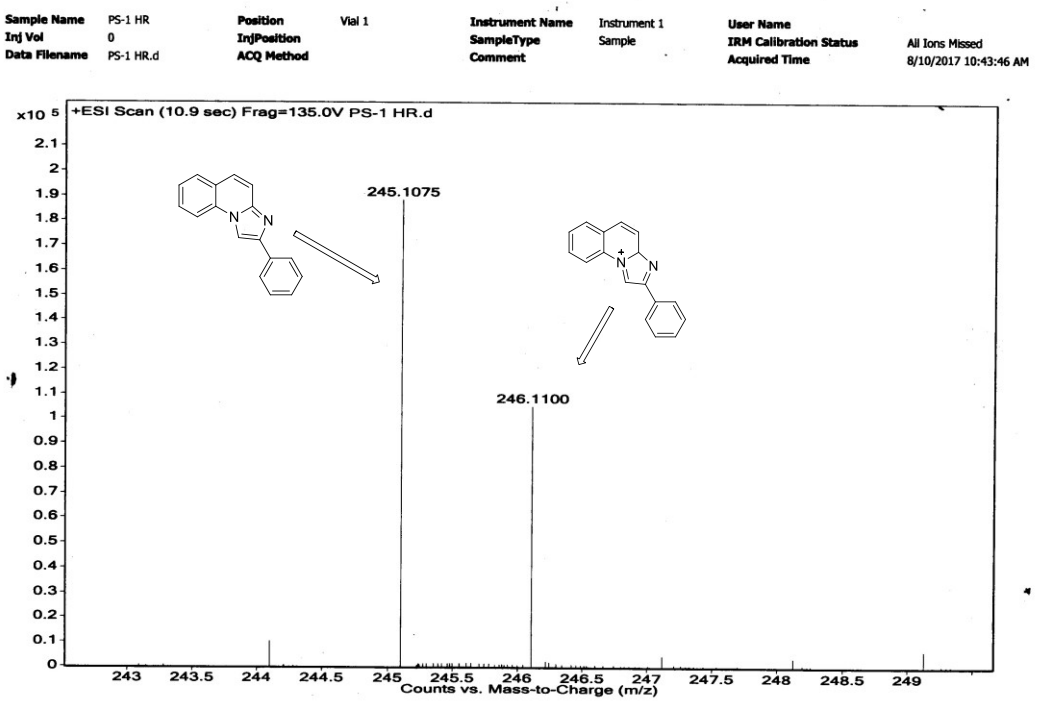


Figure III.5.2. *HRMS spectrum of reaction mixture after 1h.*

III.5.2. HRMS spectrum of TEMPO experiments:

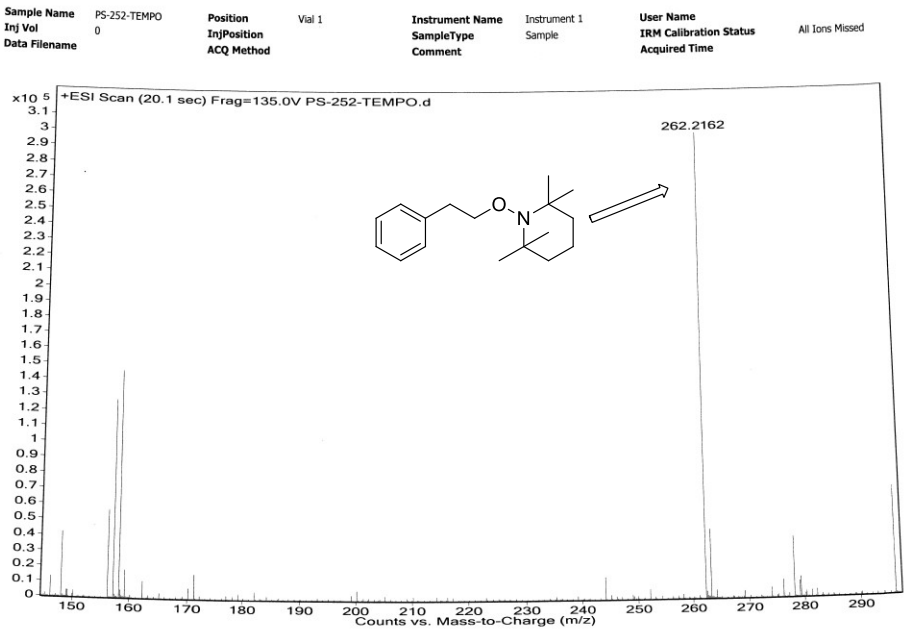


Figure III.5.3. *HRMS spectrum of TEMPO experiment 1*

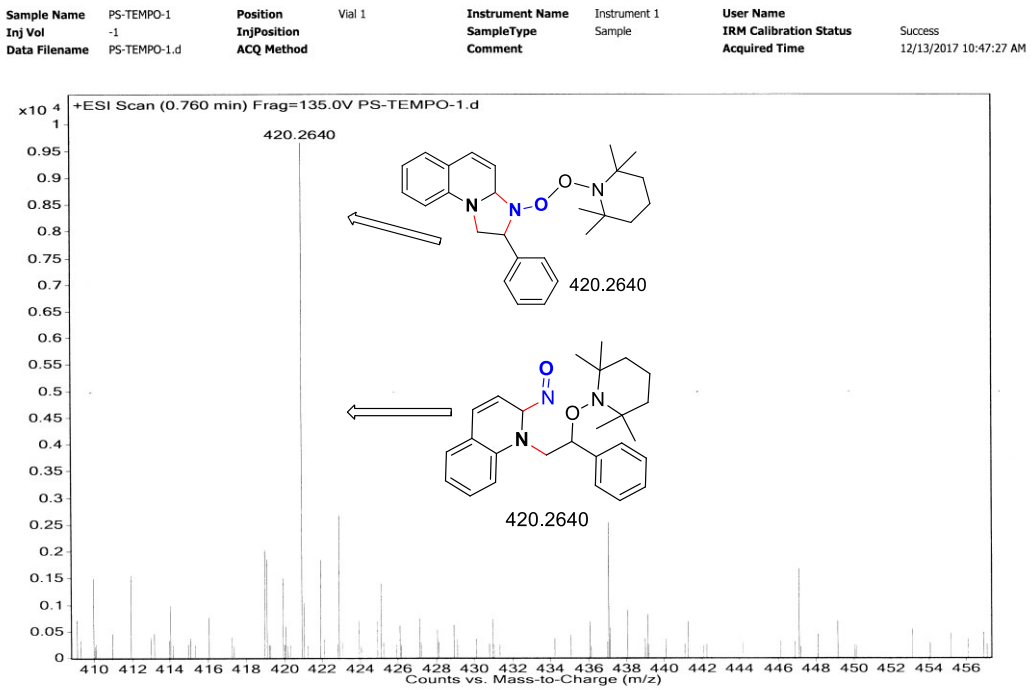


Figure III.5.4. *HRMS spectrum of TEMPO experiment 2*

III.6. References

(1) (a) Patel, R. V.; Park, S. W. *Eur. J. Med. Chem*. **2014**, *71*, 24. (b) Shang, X. F.; Natschke, S. L. M.; Liu, Y. Q.; Guo, X.; Xu, X. S.; Goto, M.; Li, J. C.; Yang, G. Z.; Lee, K. H. *Med. Res. Rev.* **2017**, 1. (c) Huang, C. Y.; Kavala, V.; Kuo, C. W.; Konala, A.; Yang, T. H.; Yao, C. F. *J. Org. Chem*. **2017**, *82*, 1961. (d) Iranshahy, M.; Quinn, R. J.; Iranshahi, M. *RSC Adv*. **2014**, *4*, 15900. (e) Kumar, S.; Bawa, S.; Gupta, H. *Mini. Rev. Med. Chem*. **2009**, *9*, 1648.

(2) (a) Ager, I. R.; Barnes, A. C.; Danswan, G. W.; Hairsine, P. W.; Kay, D. P.; Kennewell, P. D.; Matharu, S. S.; Miller, P.; Robson, P.; Rowlands, D. A.; Tully, W. R.; Westwood, R. *J. Med. Chem*. **1988**, *31*, 1098. (b) Kemnitzer, W.; Kuemmerle, J.; Jiang, S.; Zhang, H. Z.; Sirisoma, N.; Kasibhatla, S.; Grundy, C. C.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 6259. (c) Gueiffier, C. E.; Musiu, S.; Henry, N.; Véron, J. B.; Mavel, S.; Neyts, J.; Leyssen, P.; Paeshuyse, J.; Gueiffie, A. *Eur. J. Med. Chem*. **2013**, *64*, 448. (d) National Center for Biotechnology Information. PubChem Compound Database;

CID=16188015,
https://pubchem.ncbi.nlm.nih.gov/compound/16188015.(accessed july.13, 2017).

(3) (a) Chang, Y. M.; Park, Y. S.; Lee, S. H.; Yoon, C. M. *Tetrahedron. Lett*. **2004**, *45*, 9049. (b) Louërat, F.; Fort, Y.; Mamane, V. *Tetrahedron Lett*. **2009**, *50*, 5716. (c) Brown, W. D.; Gouliaev, A. H. *Synthesis* **2002**, *1*, 83. (d) Lai, J. Y. Q.; Ferguson, Y.; Jones, M. *synth. Commun.* **2003**, *33*, 3427. (e) Loska, R.; Majcher, M.; Makosza, M. *J. Org. Chem*. **2007**, *72*, 5574. (f) Loska, R.; Maükosza, M. *J. Org. Chem*. **2007**, *72*, 1354. (g) Nishida, T.; Ida, H.; Kuninobu, Y.; Kanai, M. *Nat. Commun*. **2014**, *5*, 3387.

(4) (a) Wan, M.; Lou, H.; Liu, L. *Chem. Commun*. **2015**, *51*, 13953. (b) Ali, W.; Behera, A.; Guin, S.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 5625.

(5) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471.

(6) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592.

(7) Xie, Y.; Hu, J.; Xie, P.; Qian, B.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 18327.

(8) (a) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150. (b) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419.

(9) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 6877.

(10) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856.

(11) Miyazaki, Y.; Ohta, N.; Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014**, *136*, 3732.

(12) (a) Maity, S.; Togati, N.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384. (b) Dutta, U.; Maity, S.; Kancherla, R.; Maiti, D. *Org. Lett.* **2014**, *16*, 6302.

(13) Kageyuki, I.; Osaka, I.; Takaki, K.; Yoshida, H. *Org. Lett*. **2017**, *19*, 830.

(14) Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *J. Org. Chem*. **2016**, *81*, 4020.

(15) Sau, P.; Santra, S. K.; Rakshit, A.; Patel, B. K. *J. Org. Chem*. **2017**, *82*, 6358.

(16) (a) Phelps, A. M.; Chan, V. S.; Napolitano, J. G.; Krabbe, S. W.; Schomaker, J. M.; Shekhar, S. *J. Org. Chem*. **2016**, *81*, 4158. (b) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Hana, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073. (c) Artyomov, V. A.; Shestopalov, A. M.; Litvinov, V. P. *Synthesis*. **1996**, 927. (d) Donthiri, R. R.; Pappula, V.; Reddy, N. N. K.; Bairagi, D.; Adimurthy, S. *J. Org. Chem*. **2014**, *79*, 11277. (e) Prasanna, P.; Kumar, S. V.; Gunasekaran, P.; Perumal, S. *Tetrahedron Lett.* **2013**, *4*, 126.

(17) (a) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed*. **2013**, *52*, 10573. (b) Dutta, U.; Lupton, D. W.; Maiti, D. *Org. Lett*. **2016**, *18*, 860. (c)

Pang, X.; Zhao, L.; Zhou, D.; He, P. Y.; An, Z.; Ni, J. X.; Yan, R. *Org. Biomol. Chem*. **2017**, *15*, 6318.

(18) Yu, J.; Jin, Y.; Zhang, H.; Yang, X.; Fu, H. *Chem. Eur. J*. **2013**, *19*, 16804.

(19) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073.

(20) Zhang, Y.; Chen, Z.; Wu, W.; Zhang, Y.; Su, W. *J. Org. Chem*. **2013**, *78*, 12494.

(21) Donthiri, R. R.; Pappula, V.; Reddy, N. N. K.; Bairagi, D.; Adimurthy, S. *J. Org. Chem*. **2014**, *79*, 11277.

(22) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. *Org. Lett*. **2013**, *15*, 6254.

(23) Upadhyay, S.; Chandra, A.; Singh, S.; Singh, R. M. *J. Heterocyclic. Chem*. **2011**, *48*, 1202.

(24) (a) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev*. **2011**, *111*, 1293. (b) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed*. **2014**, *53*, 74. (c) Gogoi, A.; Sau, P.; Ali, W.; Guin, S.; Patel, B. K. *Eur. J. Org. Chem*. **2016**, 1449. (d) Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc*. **2012**, *134*, 12334. (e) Gogoi, A.; Guin, S.; Rout, S. K.; Patel, B. K. *Org. Lett*. **2013**, *15*, 1802.

(25) Mondal, S.; Samanta, S.; Singsardar, M.; Hajra, A. *Org. Lett*. **2017**, *19*, 3751.

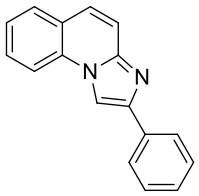
(26) (a) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun*. **2013**, *49*, 514. (b) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal*. **2011**, *353*, 2643. (c) Galliker, B.; Kissner, R.; Nauser, T.; Koppenol, W. H. *Chem. Eur. J*. **2009**, *15*, 6161. (d) Taniguchi, T.; Sugiura, Y.; Hatta, T.; Yajima, A.; Ishibashi, H. *Chem. Commun.* **2013**, *49*, 2198. (e) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun*. **2011**, *47*, 12462.

(27) Siddaraju, Y.; Lamani, M.; Prabhu, K. R. *J. Org. Chem*. **2014**, *79*, 3856.

(28) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal*. **2011**, *353*, 2643.

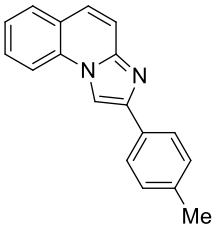
III.7. Spectral data

*2-Phenylimidazo[1,2-a]quinoline (**1a**):*



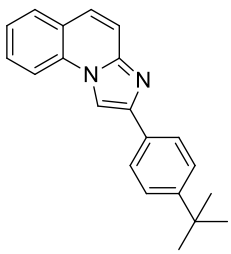
Yield: 66% (40mg) as a brownish solid; mp = 103.4–105.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (s, 1H), 8.01 (d, 2H, J = 7.8 Hz), 7.97 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 7.8 Hz), 7.67 (t, 1H, J = 7.8 Hz), 7.61 (d, 1H, J = 9.6 Hz), 7.54 (d, 1H, J = 9.0 Hz), 7.49–7.45 (m, 3H), 7.35 (t, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.7, 144.2, 133.6, 132.6, 129.4, 129.1, 128.9, 128.1, 126.9, 126.1, 125.1, 123.6, 116.9, 115.3, 107.0; IR (KBr, cm^{-1}): 2958, 2923, 2852, 1637, 1603, 1557, 1538, 1505, 1463, 1447; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{13}N_2$, $[M+H]^+$: 245.1073, found 245.1072.

*2-(p-Tolyl)imidazo[1,2-a]quinoline (**1b**):*



Yield: 49% (32 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.29 (s, 1H), 7.96 (d, 1H, J = 8.4 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.82 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.62 (d, 1H, J = 9.6 Hz), 7.53 (d, 1H, J = 9.0 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.28–7.26 (m, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 144.1, 137.9, 132.6, 130.7, 129.7, 129.4, 129.1, 126.8, 125.9, 125.0, 123.6, 116.9, 115.4, 106.6, 21.5; IR (KBr, cm^{-1}): 2958, 2921, 2851, 1635, 1601, 1551, 1531, 1461, 1421; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{15}N_2$, $[M+H]^+$: 259.1230, found 259.1233.

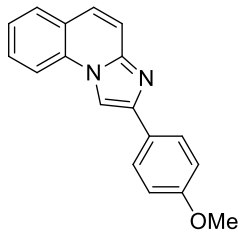
*2-(4-(tert-Butyl)phenyl)imidazo[1,2-a]quinoline (**1c**):*



Yield: 53% (40 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.30 (s, 1H), 7.97 (d, 1H, J = 8.4 Hz), 7.94 (d, 2H, J = 8.4 Hz), 7.82 (d, 1H, J = 7.2 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.62 (d, 1H, J = 9.6 Hz), 7.53 (d, 1H, J = 9.6 Hz), 7.50–7.46 (m, 3H), 1.37 (s, 9H); ^{13}C

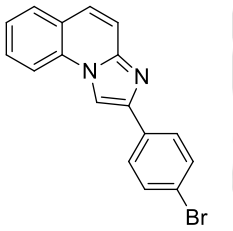
NMR ($CDCl_3$, 100 MHz): δ 151.2, 144.9, 144.2, 132.7, 130.9, 129.5, 129.1, 126.6, 125.9, 125.8, 124.9, 123.6, 117.1, 115.4, 106.6, 34.9, 31.6; IR (KBr, cm^{-1}): 2959, 2924, 2853, 1638, 1614, 1556, 1493, 1462, 1447, 1418; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{21}H_{21}N_2$, $[M+H]^+$: 301.1699, found 301.1691.

*2-(4-Methoxyphenyl)imidazo[1,2-a]quinoline (**1d**):*



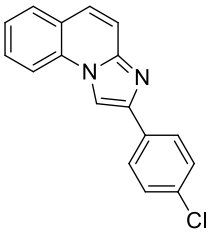
Yield: 45% (32 mg) as a brownish gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.25 (s, 1H), 7.96 (d, 1H, J = 8.4 Hz), 7.94 (d, 2H, J = 9.0 Hz), 7.83 (d, 1H, J = 7.8 Hz), 7.67 (t, 1H, J = 7.8 Hz), 7.63 (d, 1H, J = 9.0 Hz), 7.55 (d, 1H, J = 9.6 Hz), 7.48 (t, 1H, J = 7.5 Hz), 7.00 (d, 2H, J = 8.4 Hz), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.9, 143.9, 143.7, 134.1, 132.4, 129.6, 129.4, 127.5, 125.3, 123.7, 116.3, 115.4, 114.5, 114.1, 106.1, 55.6; IR (KBr, cm^{-1}): 2953, 2927, 2850, 1638, 1612, 1559, 1511, 1495, 1461; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{15}N_2O$, $[M+H]^+$: 275.1179, found 275.1169.

*2-(4-Bromophenyl)imidazo[1,2-a]quinoline (**1e**):*[16c]



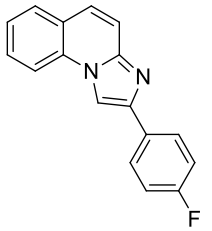
Yield: 64% (51 mg) as a deep brownish solid; mp = 149.5–153.1 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.30 (s, 1H), 7.93 (d, 1H, J = 8.4 Hz), 7.86 (d, 2H, J = 8.4 Hz), 7.81 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.2 Hz), 7.58–7.56 (m, 3H), 7.53 (d, 1H, J = 9.6 Hz), 7.48 (t, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.4, 143.9, 132.8, 132.6, 132.1, 129.5, 129.2, 127.5, 126.9, 125.1, 123.6, 121.9, 117.0, 115.3, 107.1; IR (KBr, cm^{-1}): 2957, 2922, 2848, 1633, 1559, 1535, 1473, 1446, 1416; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2Br$, $[M+H]^+$: 323.0178, found 323.0172.

*2-(4-Chlorophenyl)imidazo[1,2-a]quinoline (**1f**):*



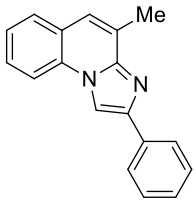
Yield: 67% (46 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.30 (s, 1H), 7.95 (d, 1H, J = 8.4 Hz), 7.91 (d, 2H, J = 8.4 Hz), 7.83 (d, 1H, J = 7.8 Hz), 7.67 (t, 1H, J = 7.6 Hz), 7.60–7.54 (m, 2H), 7.49 (t, 1H, J = 7.9 Hz), 7.42 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.4, 143.9, 133.9, 132.7, 132.3, 129.6, 129.3, 129.2, 127.3, 127.1, 125.2, 123.7, 116.9, 115.3, 107.1; IR (KBr, cm^{-1}): 2955, 2923, 2852, 1633, 1557, 1479, 1467, 1448, 1416; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2Cl$, $[M+H]^+$: 279.0684, found 279.0680.

*2-(4-Fluorophenyl)imidazo[1,2-a]quinoline (**1g**):*



Yield: 69% (45 mg) as a brownish solid; mp = 90.4–95.1 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.26 (s, 1H), 7.97–7.94 (m, 3H), 7.82 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 9.0 Hz), 7.54 (d, 1H, J = 9.6 Hz), 7.48 (t, 1H, J = 7.5 Hz), 7.14 (t, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 161.7, 159.6, 144.4, 144.1, 132.7, 129.5, 129.2, 127.8 (d, J = 8.1 Hz), 126.9, 125.1, 123.6, 116.9, 115.9 (d, J = 21.6 Hz), 115.3, 106.7, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.3 (s); IR (KBr, cm^{-1}): 2955, 2922, 2851, 1635, 1555, 1538, 1510, 1493, 1463, 1448, 1407; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2F$, $[M+H]^+$: 263.0979, found 263.0975.

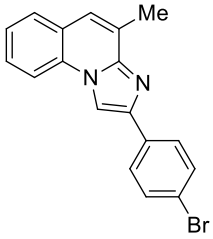
*4-Methyl-2-phenylimidazo[1,2-a]quinoline (**2a**):*



Yield: 62% (40 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.32 (s, 1H), 8.03 (d, 2H, J = 7.2 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.8 Hz), 7.47–7.43 (m, 3H), 7.35–7.33 (m, 2H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 144.7, 134.2, 131.9, 128.9, 128.6, 127.90, 127.87, 126.9,

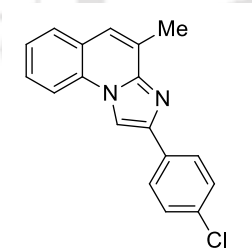
126.2, 124.9, 124.5, 124.1, 115.2, 107.3, 17.6; IR (KBr, cm^{-1}): 2958, 2923, 2853, 1637, 1556, 1532, 1461, 1411; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{15}N_2$, $[M+H]^+$: 259.1230, found 259.1233.

*2-(4-Bromophenyl)-4-methylimidazo[1,2-a]quinoline (**2e**):*



Yield: 63% (53 mg) as a brownish gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.30 (s, 1H), 7.91–7.89 (m, 3H), 7.74 (d, 1H, J = 7.8 Hz), 7.60–7.55 (m, 3H), 7.44 (t, 1H, J = 7.5 Hz), 7.33 (s, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 143.5, 133.2, 131.9, 131.8, 128.6, 127.9, 127.7, 126.8, 124.9, 124.7, 124.1, 121.7, 115.1, 107.4, 17.5; IR (KBr, cm^{-1}): 2955, 2923, 2853, 1637, 1615, 1531, 1458, 1415; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Br$, $[M+H]^+$: 337.0335, found 337.0330.

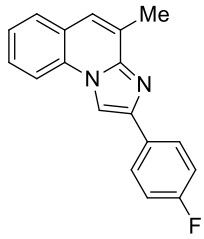
*2-(4-Chlorophenyl)-4-methylimidazo[1,2-a]quinoline (**2f**):*



Yield: 67% (49 mg) as a brownish solid; mp = 141.3–144.5 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.28 (s, 1H), 7.95 (d, 2H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 7.8 Hz), 7.58 (t, 1H, J = 7.2 Hz), 7.45–7.39 (m, 3H), 7.32 (s, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 143.5, 133.5, 131.8, 129.1, 128.6, 127.9, 127.4, 126.8, 124.9, 124.7, 124.1, 115.1, 107.4, 17.5; IR (KBr, cm^{-1}): 2955, 2926, 2850, 1631, 1604, 1530, 1463, 1435, 1405; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Cl$, $[M+H]^+$: 293.0840, found 293.0837.

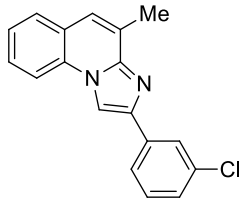
*2-(4-Fluorophenyl)-4-methylimidazo[1,2-a]quinoline (**2g**):*

Yield: 70% (48 mg) as a brownish gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.25 (s, 1H), 7.99–7.98 (m, 2H), 7.89 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.58 (t, 1H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.32 (s, 1H), 7.14



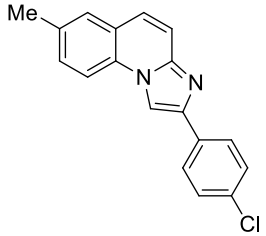
(t, 2H, J = 8.7 Hz), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 161.6, 145.2, 143.8, 131.8, 130.4, 128.6, 127.9 (d, J = 3.6 Hz), 127.8, 126.8, 124.9, 124.7, 124.1, 115.8 (d, J = 21.5 Hz), 115.1, 106.9, 17.6, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.8 (s); IR (KBr, cm^{-1}): 2956, 2923, 2848, 1633, 1605, 1552, 1533, 1493, 1460, 1420, 1407; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2F$, $[M+H]^+$: 277.1136, found 277.1135.

*2-(3-Chlorophenyl)-4-methylimidazo[1,2-a]quinoline (**2h**):*



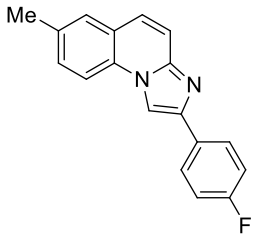
Yield: 69% (50 mg) as a light brownish solid; mp = 95.3–99.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (s, 1H), 8.03 (s, 1H), 7.89 (d, 2H, J = 7.8 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.38 (t, 1H, J = 7.8 Hz), 7.32 (s, 1H), 7.29 (d, 1H, J = 8.4 Hz), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 143.3, 136.1, 134.9, 131.8, 130.2, 128.6, 127.9, 127.8, 126.9, 126.2, 125.0, 124.8, 124.2, 124.1, 115.1, 107.7, 17.5; IR (KBr, cm^{-1}): 2960, 2923, 2852, 1637, 1601, 1569, 1532, 1459, 1427, 1410; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Cl$, $[M+H]^+$: 293.0840, found 293.0841.

*2-(4-Chlorophenyl)-7-methylimidazo[1,2-a]quinoline (**3f**):*



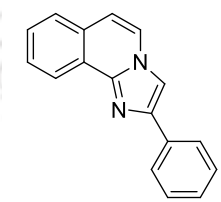
Yield: 70% (51 mg) as a deep brownish solid; mp = 145.1–147.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.22 (s, 1H), 7.89 (d, 2H, J = 8.4 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.57 (s, 1H), 7.54 (d, 1H, J = 9.6 Hz), 7.45 (d, 2H, J = 9.0 Hz), 7.39 (d, 2H, J = 8.4 Hz), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 143.5, 134.9, 133.6, 132.4, 130.7, 130.5, 129.1, 127.2, 126.8, 123.5, 116.8, 115.1, 106.9, 21.3; IR (KBr, cm^{-1}): 2950, 2922, 2853, 1628, 1616, 1567, 1529, 1482, 1465, 1423, 1403; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Cl$, $[M+H]^+$: 293.0840, found 293.0831.

*2-(4-fluorophenyl)-7-methylimidazo[1,2-a]quinoline (**3g**):*



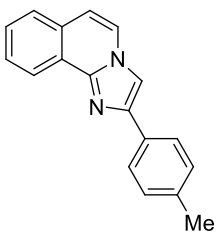
Yield: 71% (49 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.21 (s, 1H), 7.96–7.94 (m, 2H), 7.81 (d, 1H, J = 8.4 Hz), 7.58 (s, 1H), 7.55 (d, 1H, J = 9.6 Hz), 7.46 (d, 2H, J = 9.6 Hz), 7.13 (t, 2H, J = 8.7 Hz), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 161.6, 144.2, 143.9, 134.8, 130.8, 130.5, 130.2, 130.1, 129.1, 127.7 (d, J = 8.1 Hz), 126.7, 123.6, 116.9, 115.9 (d, J = 21.6 Hz), 115.1, 106.5, 21.3, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.6 (s); IR (KBr, cm^{-1}): 2958, 2923, 2848, 1634, 1604, 1508, 1492, 1458, 1421; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2F$, $[M+H]^+$: 277.1136, found 277.1126.

*2-Phenylimidazo[2,1-a]isoquinoline (**4a**):*



Yield: 64% (39 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.76 (d, 1H, J = 7.8 Hz), 8.01 (d, 2H, J = 7.8 Hz), 7.91 (d, 1H, J = 7.2 Hz), 7.83 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.3 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.46 (t, 2H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.2 Hz), 7.05 (d, 1H, J = 7.2 Hz); 13C NMR ($CDCl_3$, 150 MHz): δ 144.0, 143.4, 133.9, 129.7, 128.9, 128.5, 128.4, 127.9, 127.1, 126.1, 123.84, 123.78, 123.1, 113.5, 110.1; IR (KBr, cm^{-1}): 2955, 2922, 2851, 1631, 1605, 1541, 1490, 1455; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{13}N_2$, $[M+H]^+$: 245.1073, found 245.1083.

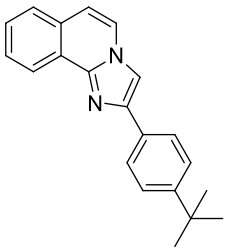
*2-(p-Tolyl)imidazo[2,1-a]isoquinoline (**4b**):*



Yield: 53% (34 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.77 (d, 1H, J = 7.8 Hz), 7.92–7.89 (m, 3H), 7.80 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.64 (t, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.26–7.24 (m, 2H), 7.05 (d, 1H, J = 7.2 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$,

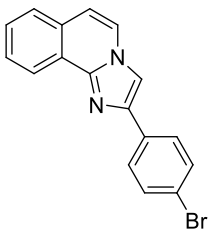
150 MHz): δ 144.1, 143.3, 137.7, 129.7, 129.6, 128.43, 128.38, 127.1, 126.0, 123.8, 123.1, 113.4, 109.7, 21.5; IR (KBr, cm^{-1}): 2958, 2930, 2849, 1635, 1603, 1553, 1545, 1480, 1453; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{15}N_2$, $[M+H]^+$: 259.1230, found 259.1239.

*2-(4-(tert-Butyl)phenyl)imidazo[2,1-a]isoquinoline (**4c**):*



Yield: 55% (41 mg) as a brownish gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.74 (d, 1H, J = 7.8 Hz), 7.94–7.90 (m, 3H), 7.80 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.64 (t, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.48 (d, 2H, J = 8.4 Hz), 7.04 (d, 1H, J = 7.2 Hz), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 150.9, 144.2, 143.3, 131.2, 129.7, 128.4, 127.1, 125.88, 125.85, 123.9, 123.8, 123.1, 113.3, 109.8, 34.9, 31.6; IR (KBr, cm^{-1}): 2958, 2923, 2850, 1635, 1551, 1461, 1454; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{21}H_{21}N_2$, $[M+H]^+$: 301.1699, found 301.1689.

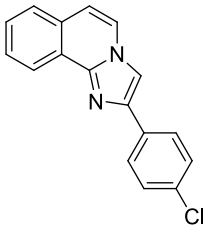
*2-(4-Bromophenyl)imidazo[2,1-a]isoquinoline (**4e**):*



Yield: 65% (52 mg) as a brownish solid; mp = 132.1–134.6 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.70 (d, 1H, J = 7.8 Hz), 7.88 (t, 3H, J = 7.2 Hz), 7.81 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.59–7.56 (m, 3H), 7.05 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 143.1, 133.1, 132.0, 129.7, 128.6, 128.5, 127.6, 127.2, 123.9, 123.7, 123.1, 121.7, 113.6, 110.2; IR (KBr, cm^{-1}): 2955, 2922, 2845, 1637, 1556, 1539, 1513, 1455, 1474, 1400; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2Br$, $[M+H]^+$: 323.0178, found 323.0174.

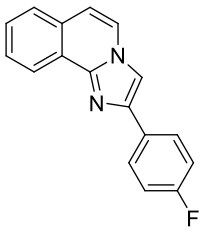
*2-(4-Chlorophenyl)imidazo[2,1-a]isoquinoline (**4f**):*

Yield: 68% (47 mg) as a brownish solid; mp = 160.6–165.3 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.71 (d, 1H, J = 7.8 Hz), 7.94 (d, 2H, J = 8.4 Hz), 7.89 (d, 1H, J = 7.2 Hz),



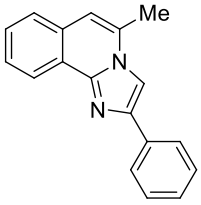
7.79 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.41 (d, 2H, J = 8.4 Hz), 7.04 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 143.1, 133.5, 132.7, 129.7, 129.1, 128.5, 128.4, 127.3, 127.2, 123.9, 123.7, 123.1, 113.6, 110.1; IR (KBr, cm^{-1}): 2960, 2923, 2850, 1633, 1554, 1543, 1475, 1456, 1404; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2Cl$, $[M+H]^+$: 279.0684, found 279.0689.

*2-(4-Fluorophenyl)imidazo[2,1-a]isoquinoline (**4g**):*



Yield: 71% (46 mg) as a brownish solid; mp = 135.2–137.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.71 (d, 1H, J = 8.4 Hz), 7.98–7.96 (m, 2H), 7.90 (d, 1H, J = 7.2 Hz), 7.77 (s, 1H), 7.70 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.14 (t, 2H, J = 8.7 Hz), 7.05 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 161.5, 143.5, 143.3, 130.39, 130.36, 129.7, 128.4 (d, J = 5.2 Hz), 127.7 (d, J = 8.1 Hz), 127.2, 123.9, 123.7, 123.1, 115.8 (d, J = 21.5 Hz), 113.4, 109.7, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.9 (s); IR (KBr, cm^{-1}): 2958, 2923, 2853, 1642, 1555, 1515, 1494, 1480, 1454; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_2F$, $[M+H]^+$: 263.0979, found 263.0986.

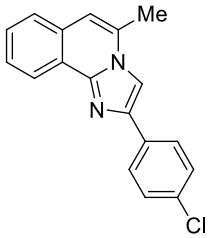
*5-Methyl-2-phenylimidazo[2,1-a]isoquinoline (**5a**):*



Yield: 61% (39 mg) as a brownish solid; mp = 109.3–113.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.73 (d, 1H, J = 7.8 Hz), 8.05 (d, 2H, J = 7.2 Hz), 7.80 (s, 1H), 7.65 (d, 1H, J = 7.8 Hz), 7.60 (t, 1H, J = 6.9 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.46 (t, 2H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.2 Hz), 6.88 (s, 1H), 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.9, 134.3, 131.6, 130.2, 128.9, 128.3, 127.8, 127.4, 126.4, 126.1, 123.7, 122.6, 111.8, 107.4, 18.9; IR (KBr, cm^{-1}): 2955, 2921, 2845, 1648, 1605, 1557, 1520,

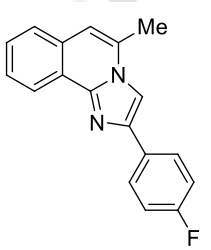
1474, 1456, 1445, 1404; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{15}N_2$, $[M+H]^+$: 259.1230, found 259.1232.

*2-(4-Chlorophenyl)-5-methylimidazo[2,1-a]isoquinoline (**5f**):*



Yield: 66% (48 mg) as a light brownish solid; mp = 128.9–134.1 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.69 (d, 1H, J = 7.8 Hz), 7.97 (d, 2H, J = 8.4 Hz), 7.75 (s, 1H), 7.64 (d, 1H, J = 7.2 Hz), 7.60 (t, 1H, J = 6.9 Hz), 7.55 (t, 1H, J = 6.9 Hz), 7.41 (d, 2H, J = 8.4 Hz), 6.87 (s, 1H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 142.8, 133.4, 132.7, 131.6, 130.2, 129.0, 128.5, 127.5, 127.3, 126.4, 123.7, 122.4, 112.0, 107.5, 18.8; IR (KBr, cm^{-1}): 2955, 2923, 2853, 1639, 1554, 1473, 1458, 1405; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Cl$, $[M+H]^+$: 293.0840, found 293.0842.

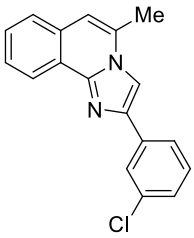
*2-(4-Fluorophenyl)-5-methylimidazo[2,1-a]isoquinoline (**5g**):*



Yield: 72% (50 mg) as a light brownish solid; mp = 129.5–132.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.70 (d, 1H, J = 7.8 Hz), 8.01–7.99 (m, 2H), 7.72 (s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.14 (t, 2H, J = 8.7 Hz), 6.87 (s, 1H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 161.5, 143.9, 143.2, 131.6, 130.52, 130.48, 130.2, 128.4, 127.7 (d, J = 7.9 Hz), 127.4, 126.4, 123.6, 122.5, 115.8 (d, J = 21.4 Hz), 111.8, 107.1, 18.8, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.9 (s); IR (KBr, cm^{-1}): 2958, 2923, 2853, 1631, 1559, 1492, 1458, 1408; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2F$, $[M+H]^+$: 277.1136, found 277.1134.

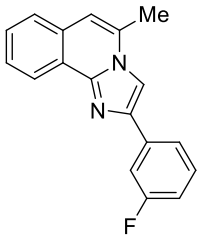
*2-(3-Chlorophenyl)-5-methylimidazo[2,1-a]isoquinoline (**5h**):*

Yield: 68% (49 mg) as a light brownish solid; mp = 120.4–123.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.70 (d, 1H, J = 7.8 Hz), 8.04 (s, 1H), 7.91 (d, 1H, J = 7.8 Hz), 7.78 (s,



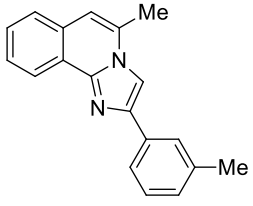
1H), 7.64 (d, 1H, J = 7.8 Hz), 7.60 (t, 1H, J = 7.2 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 7.8 Hz), 6.88 (s, 1H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 142.6, 136.2, 134.9, 131.6, 130.2, 130.1, 128.5, 127.6, 127.4, 126.4, 126.1, 124.1, 123.7, 122.5, 112.0, 107.8, 18.8; IR (KBr, cm^{-1}): 2955, 2852, 1633, 1604, 1555, 1530, 1460, 1447, 1420; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2Cl$, $[M+H]^+$: 293.0840, found 293.0845.

*2-(3-Fluorophenyl)-5-methylimidazo[2,1-a]isoquinoline (**5i**):*



Yield: 74% (51 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.71 (d, 1H, J = 7.8 Hz), 7.80–7.76 (m, 3H), 7.63 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.41–7.38 (m, 1H), 7.02–6.99 (m, 1H), 6.86 (s, 1H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 162.3, 143.9, 142.9, 136.6 (d, J = 8.5 Hz), 131.6, 130.3 (t, J = 9.8 Hz), 128.5, 127.4, 126.4, 123.7, 122.5, 121.59, 121.56, 114.5 (d, J = 21.2 Hz), 112.9 (d, J = 22.6 Hz), 112.0, 107.8, 18.8, ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -116.5 (s); IR (KBr, cm^{-1}): 2959, 2921, 2851, 1629, 1601, 1555, 1521, 1460; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_2F$, $[M+H]^+$: 277.1136, found 277.1135.

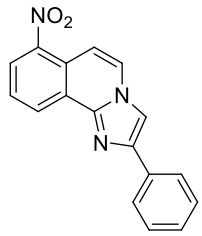
*5-Methyl-2-(m-tolyl)imidazo[2,1-a]isoquinoline (**5j**):*



Yield: 60% (41 mg) as a brownish solid; mp = 110.4–113.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.74 (d, 1H, J = 8.4 Hz), 7.91 (s, 1H), 7.82 (d, 1H, J = 7.8 Hz), 7.78 (s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.60 (t, 1H, J = 7.2 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.34 (t, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 7.2 Hz), 6.87 (s, 1H), 2.65 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.7, 138.5, 134.0, 131.6, 130.2, 128.8, 128.6, 128.3, 127.3, 126.8, 126.3,

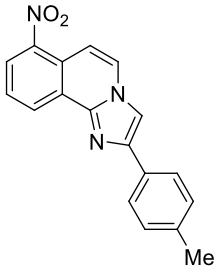
123.8, 123.2, 122.5, 111.8, 107.4, 21.7, 18.9; IR (KBr, cm^{-1}): 2958, 2921, 2854, 1637, 1605, 1557, 1531, 1465, 1410; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{19}H_{17}N_2$, $[M+H]^+$: 273.1386, found 273.1376.

*7-Nitro-2-phenylimidazo[2,1-a]isoquinoline (**6a**):*



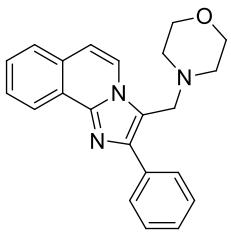
Yield: 60% (43 mg) as a deep brownish solid; mp = 139.3–141.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.08 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, J = 7.2 Hz), 8.09 (d, 1H, J = 7.8 Hz), 8.01 (d, 2H, J = 7.2 Hz), 7.90 (s, 1H), 7.85 (d, 1H, J = 7.8 Hz), 7.72 (t, 1H, J = 7.8 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.36 (t, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.3, 142.1, 133.5, 129.7, 129.1, 128.36, 128.35, 127.4, 126.19, 126.16, 125.6, 125.3, 122.5, 110.4, 107.5; IR (KBr, cm^{-1}): 2960, 2923, 2852, 1632, 1550, 1515, 1468, 1446; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{17}H_{12}N_3O_2$, $[M+H]^+$: 290.0924, found 290.0927.

*7-Nitro-2-(p-tolyl)imidazo[2,1-a]isoquinoline (**6b**):*



Yield: 51% (39 mg) as a brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.08 (d, 1H, J = 7.8 Hz), 8.29 (d, 1H, J = 7.8 Hz), 8.10 (d, 1H, J = 7.8 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.88 (s, 1H), 7.85 (d, 1H, J = 7.8 Hz), 7.72 (t, 1H, J = 8.1 Hz), 7.28 (d, 2H, J = 7.8 Hz), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.5, 142.0, 138.2, 130.7, 129.76, 129.71, 127.3, 126.2, 126.09, 126.06, 125.5, 125.3, 122.5, 110.1, 107.4, 21.5; IR (KBr, cm^{-1}): 2957, 2923, 2853, 1630, 1555, 1523, 1462; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{18}H_{14}N_3O_2$, $[M+H]^+$: 304.1081, found 304.1079.

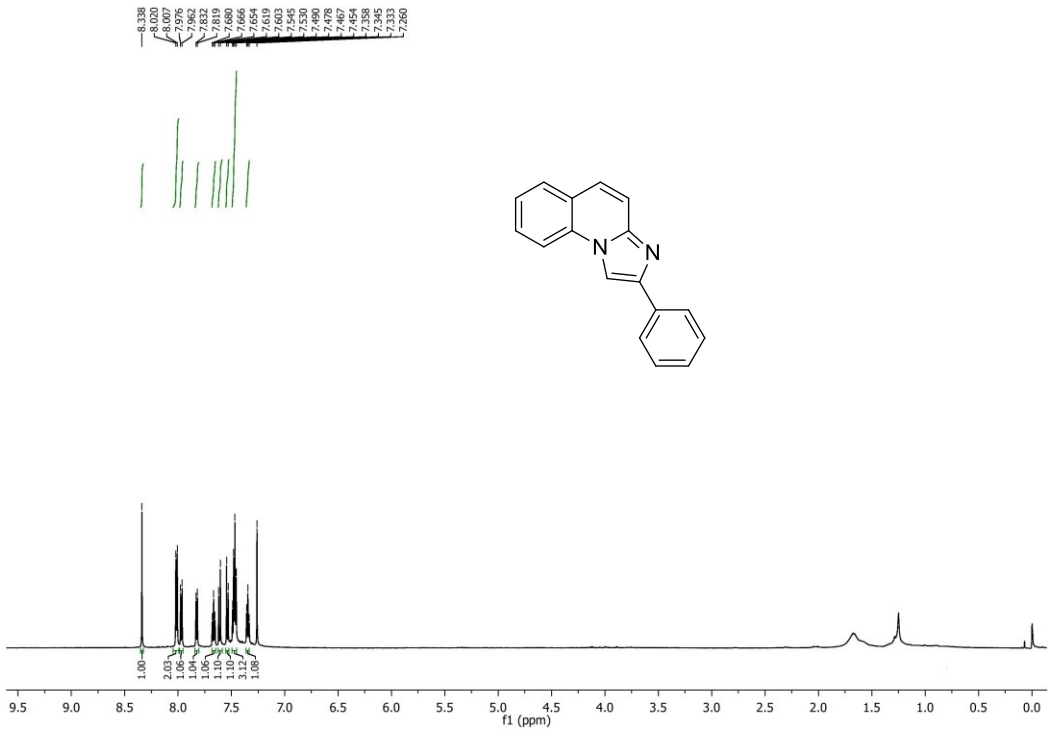
*4-((2-Phenylimidazo[2,1-a]isoquinolin-3-yl)methyl)morpholine (**4ak**):*



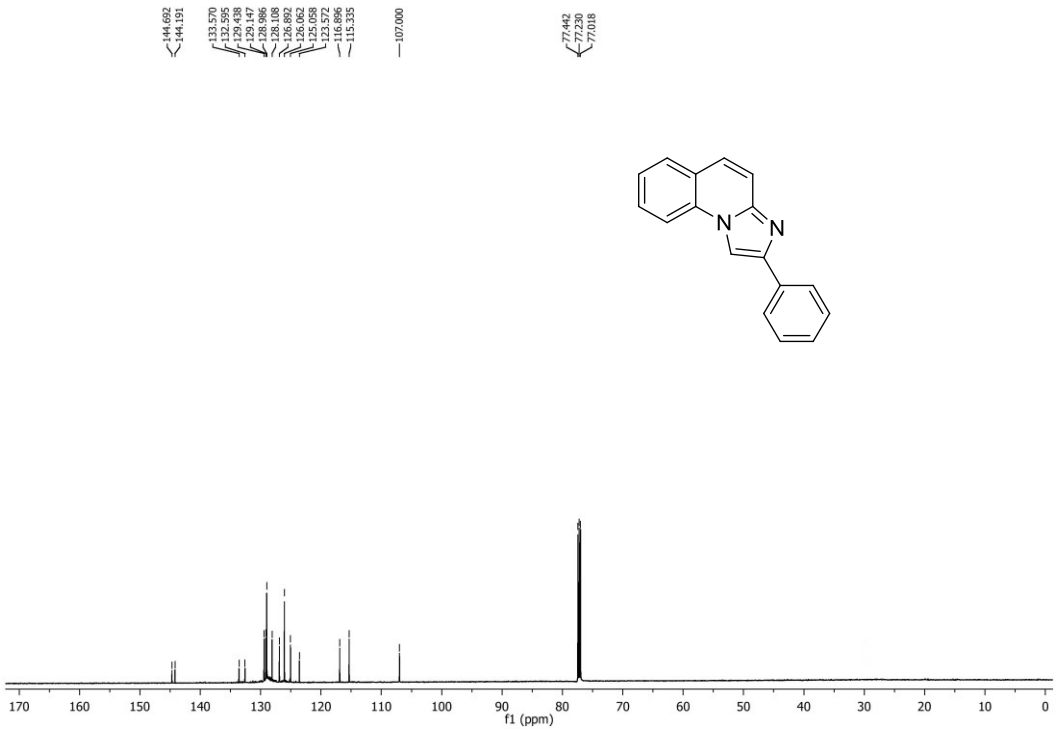
Yield: 80% (55 mg) as a light brownish solid; mp = 140.7–144.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.74 (d, 1H, J = 7.8 Hz), 8.27 (d, 1H, J = 7.2 Hz), 7.83 (d, 2H, J = 7.2 Hz), 7.73 (d, 1H, J = 7.8 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.09 (d, 1H, J = 7.2 Hz), 3.98 (s, 2H), 3.68 (t, 4H, J = 3.9 Hz), 2.50 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 143.0, 134.8, 129.7, 129.1, 128.7, 128.4, 128.1, 127.7, 126.9, 123.8, 123.7, 122.8, 117.9, 112.6, 67.2, 53.4, 52.2; IR (KBr, cm^{-1}): 2948, 2917, 2850, 1638, 1521, 1454; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{22}H_{22}N_3O$, $[M+H]^+$: 344.1757, found 344.1752.

III.8. Spectra

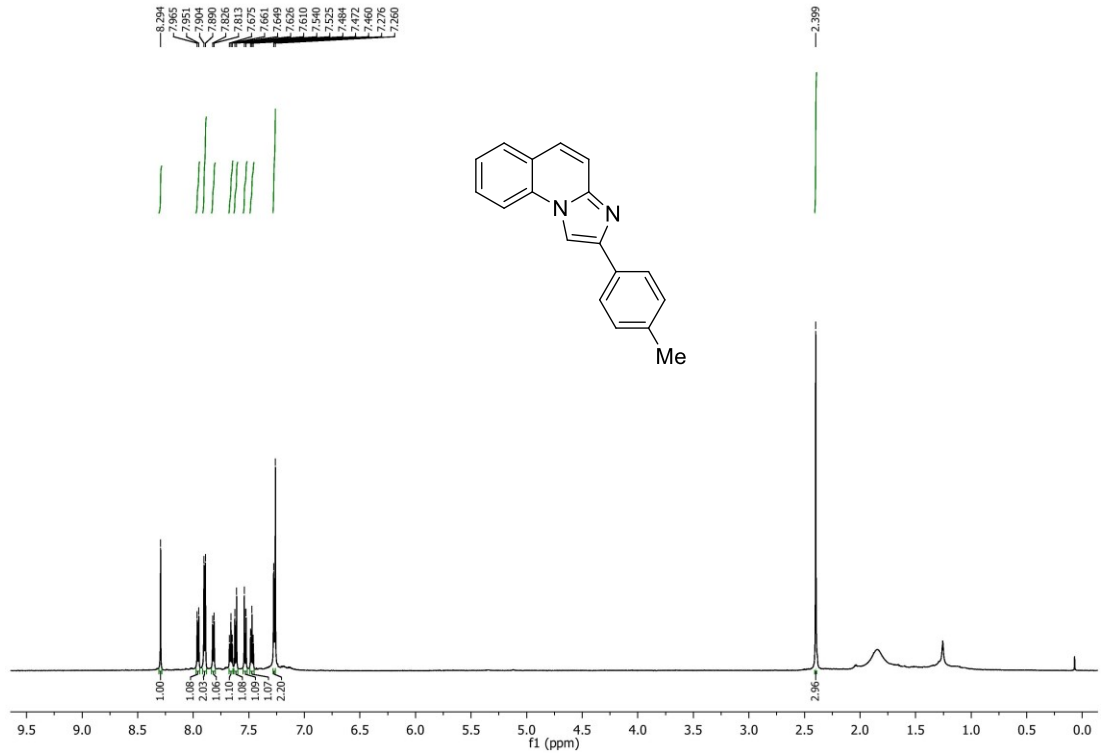
2-Phenylimidazo[1,2-*a*]quinoline (1a): ^{1}H NMR ($CDCl_3$, 600 MHz)



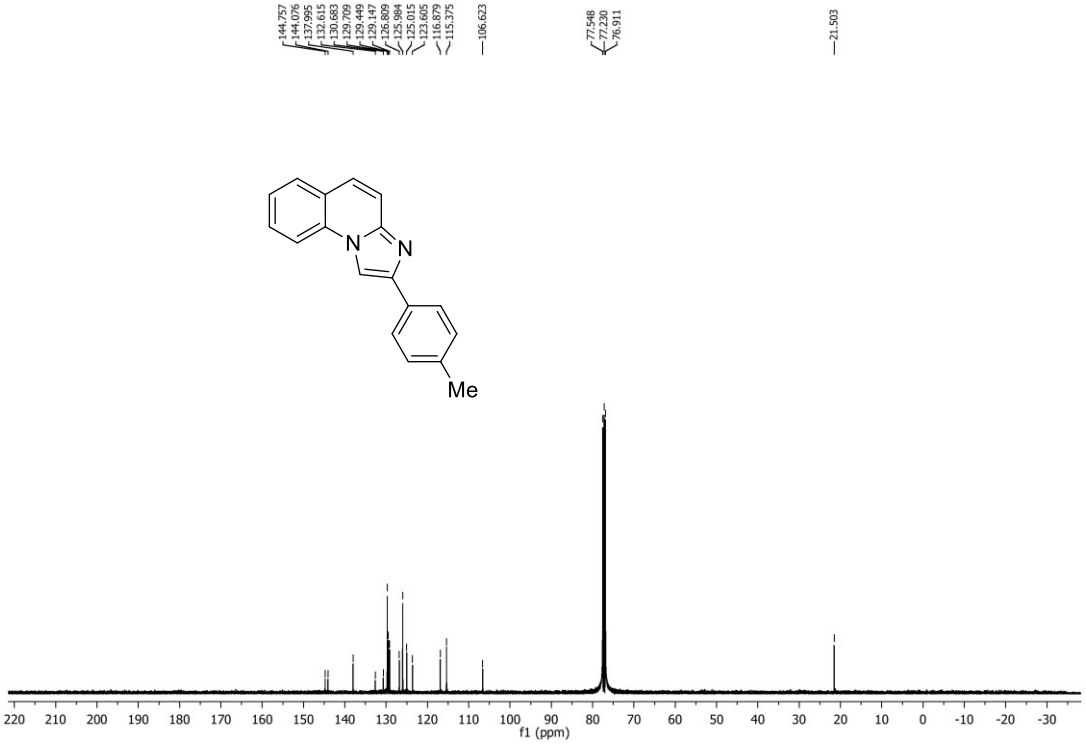
2-Phenylimidazo[1,2-*a*]quinoline (1a): ^{13}C NMR ($CDCl_3$, 150 MHz)



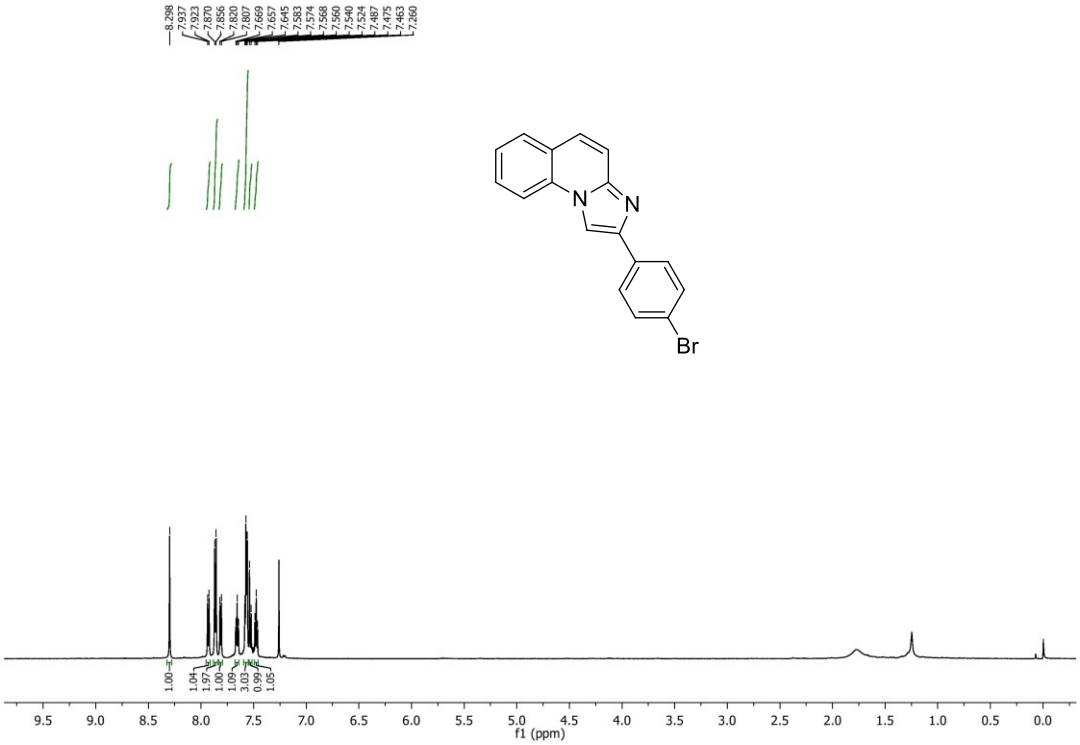
2-(*p*-Tolyl)imidazo[1,2-*a*]quinoline (1b): ^{1}H NMR ($CDCl_3$, 600 MHz)



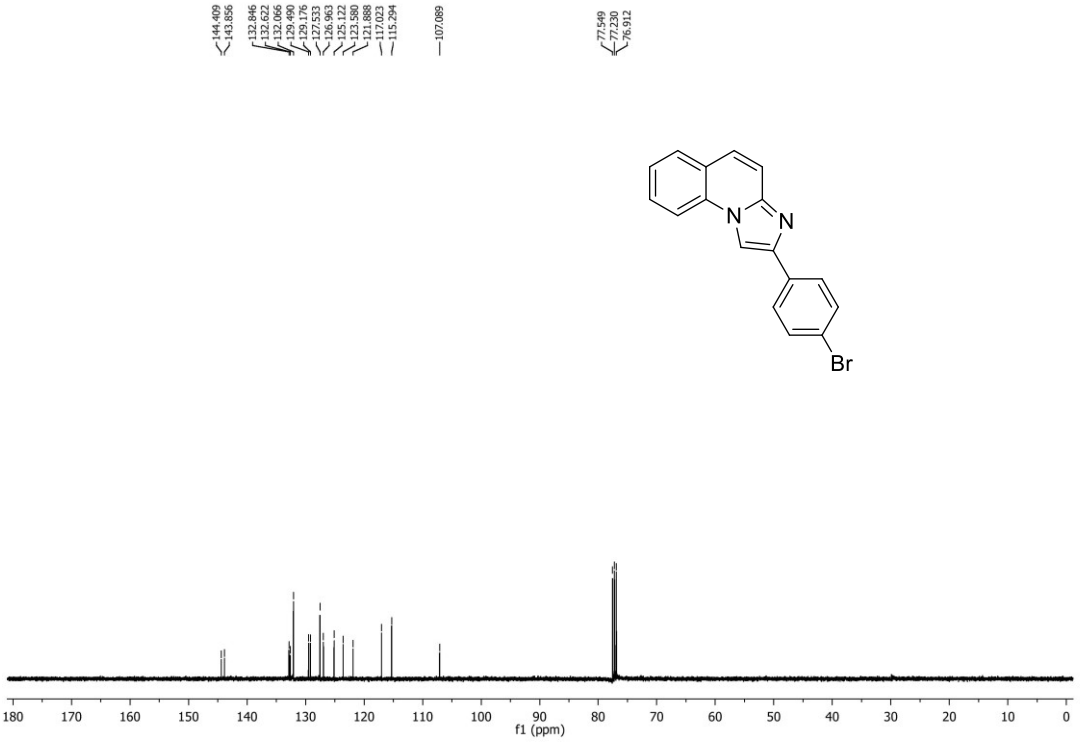
2-(*p*-Tolyl)imidazo[1,2-*a*]quinoline (1b): ^{13}C NMR ($CDCl_3$, 100 MHz)



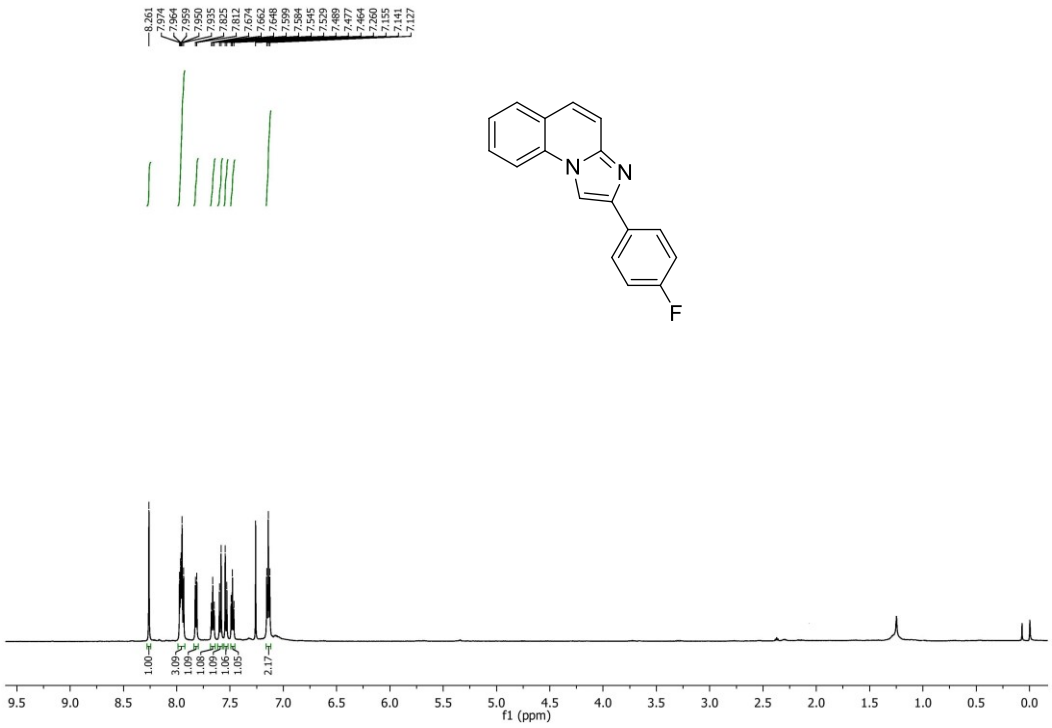
2-(4-Bromophenyl)imidazo[1,2-*a*]quinoline (1e): ^{1}H NMR ($CDCl_3$, 600 MHz)



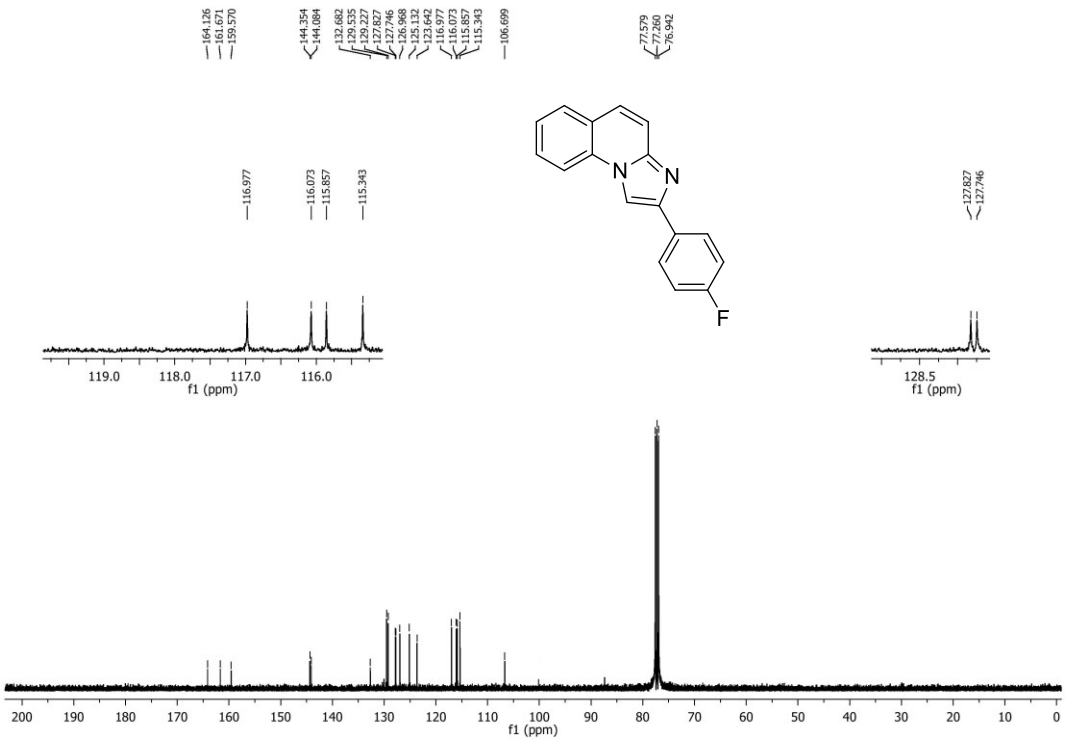
2-(4-Bromophenyl)imidazo[1,2-*a*]quinoline (1e): ^{13}C NMR ($CDCl_3$, 100 MHz)



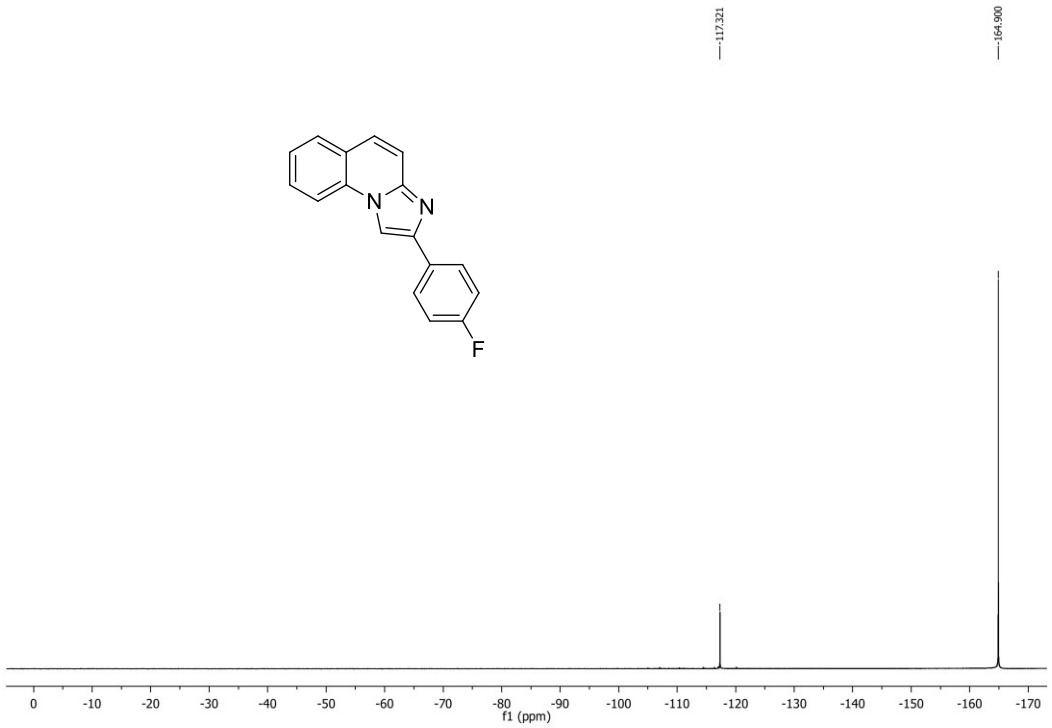
2-(4-Fluorophenyl)imidazo[1,2-*a*]quinoline (1g): ^{1}H NMR ($CDCl_3$, 600 MHz)



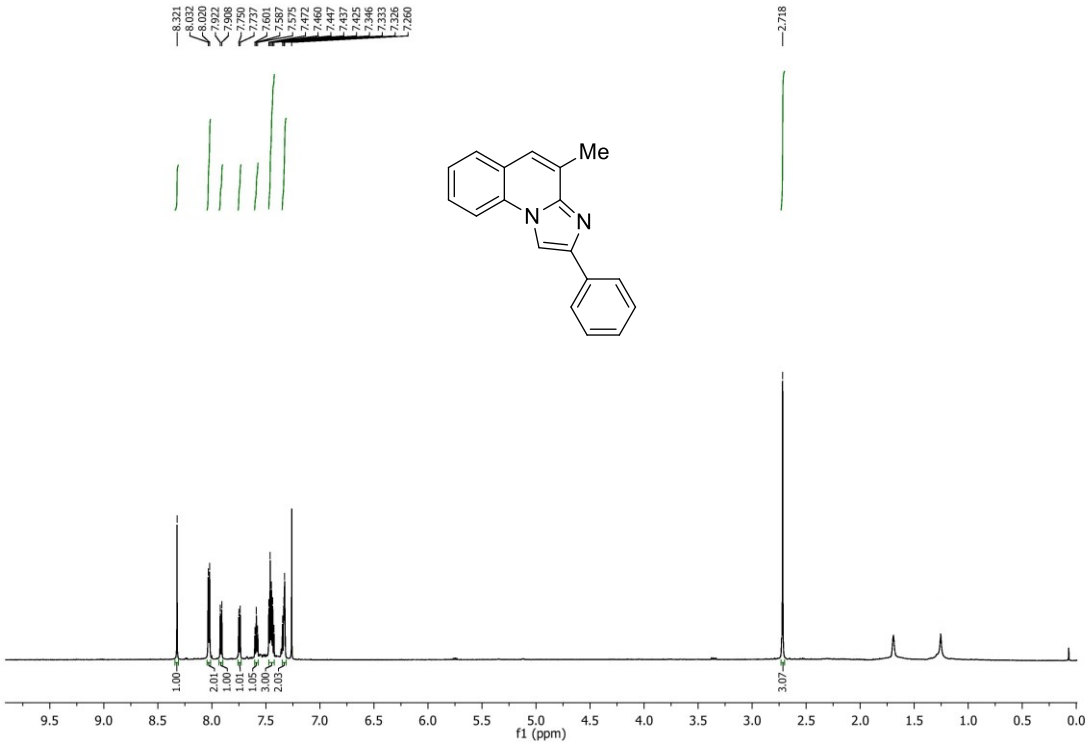
2-(4-Fluorophenyl)imidazo[1,2-*a*]quinoline (1g): ^{13}C NMR ($CDCl_3$, 100 MHz)



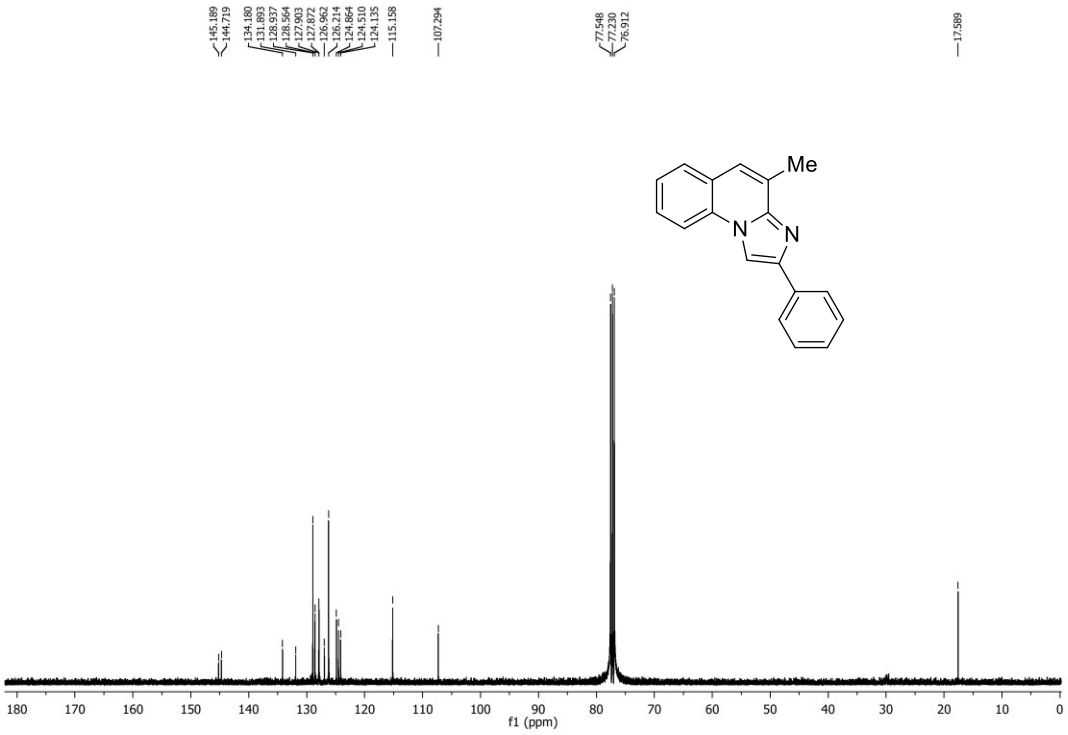
2-(4-Fluorophenyl)imidazo[1,2-*a*]quinoline (1g): ^{19}F NMR ($CDCl_3$ + C_6F_6)



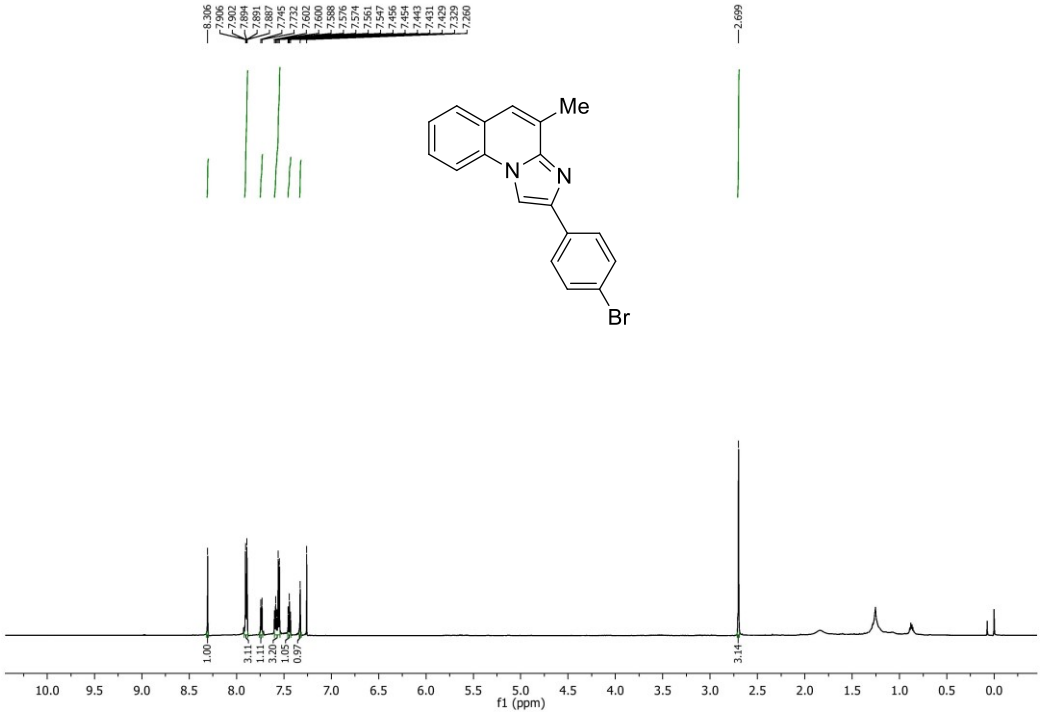
4-Methyl-2-phenylimidazo[1,2-*a*]quinoline (2a): ^{1}H NMR ($CDCl_3$, 600 MHz)



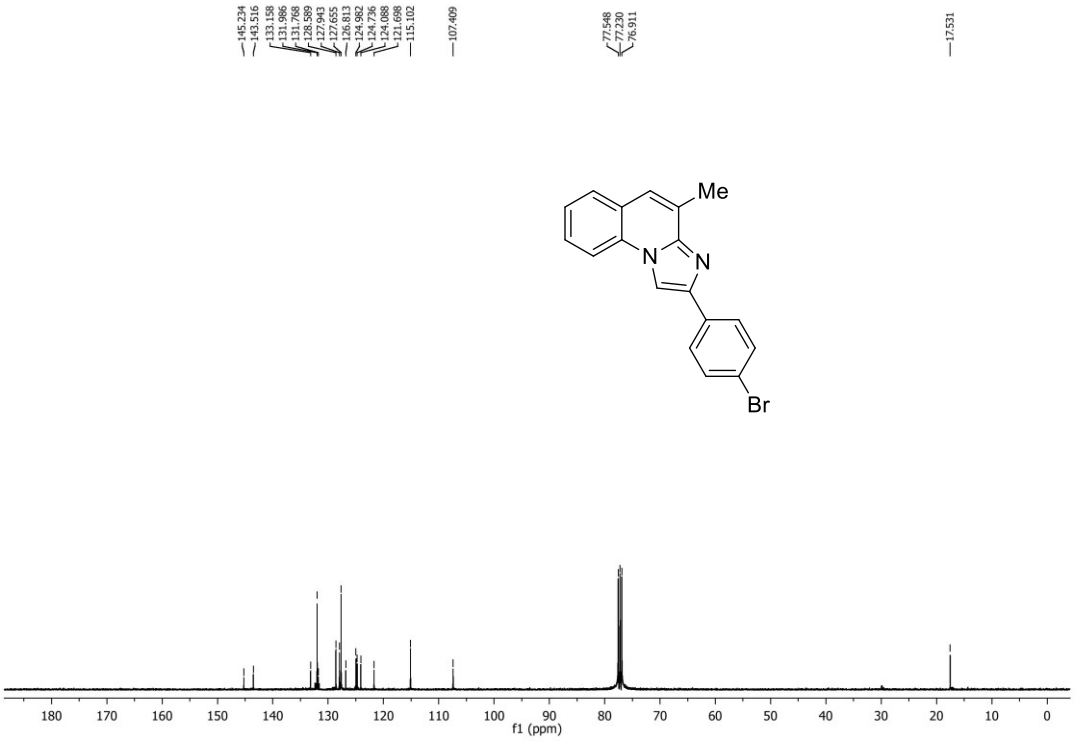
4-Methyl-2-phenylimidazo[1,2-*a*]quinoline (2a): ^{13}C NMR ($CDCl_3$, 100 MHz)



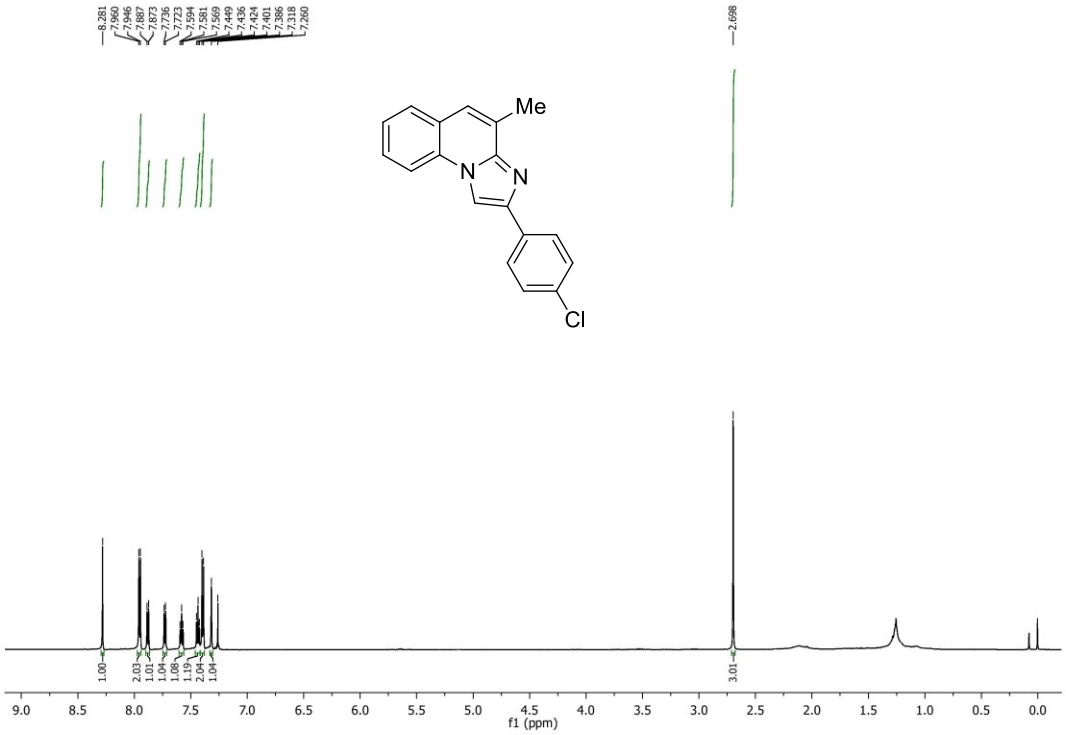
2-(4-Bromophenyl)-4-methylimidazo[1,2-*a*]quinoline (2e): ^{1}H NMR ($CDCl_3$, 600 MHz)



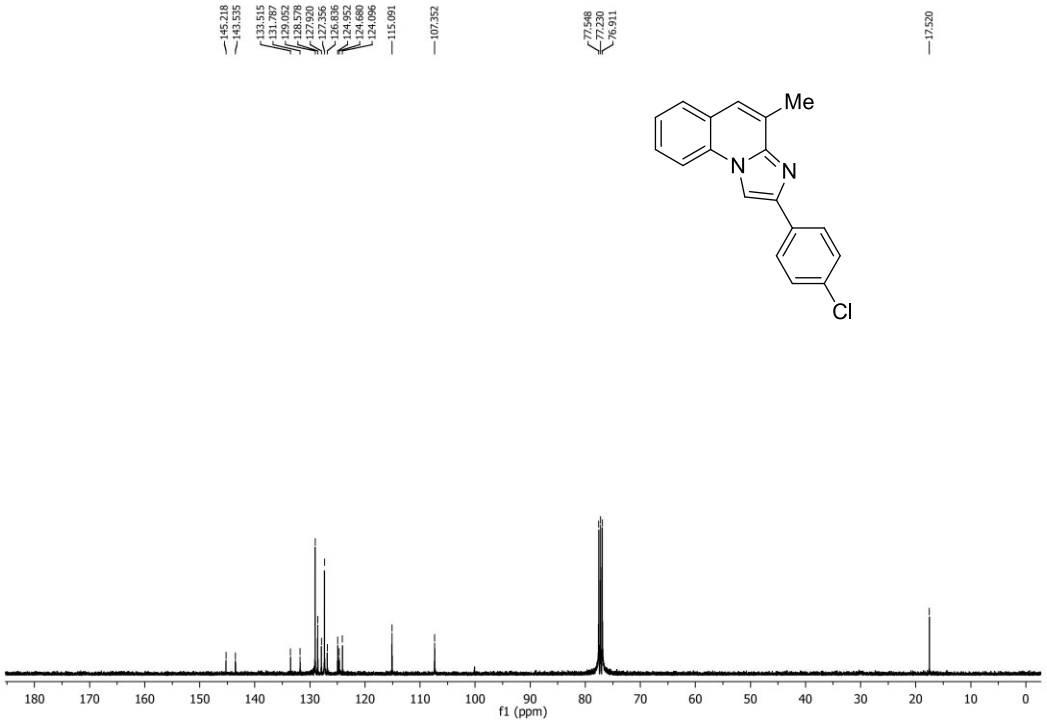
2-(4-Bromophenyl)-4-methylimidazo[1,2-*a*]quinoline (2e): ^{13}C NMR ($CDCl_3$, 100 MHz)



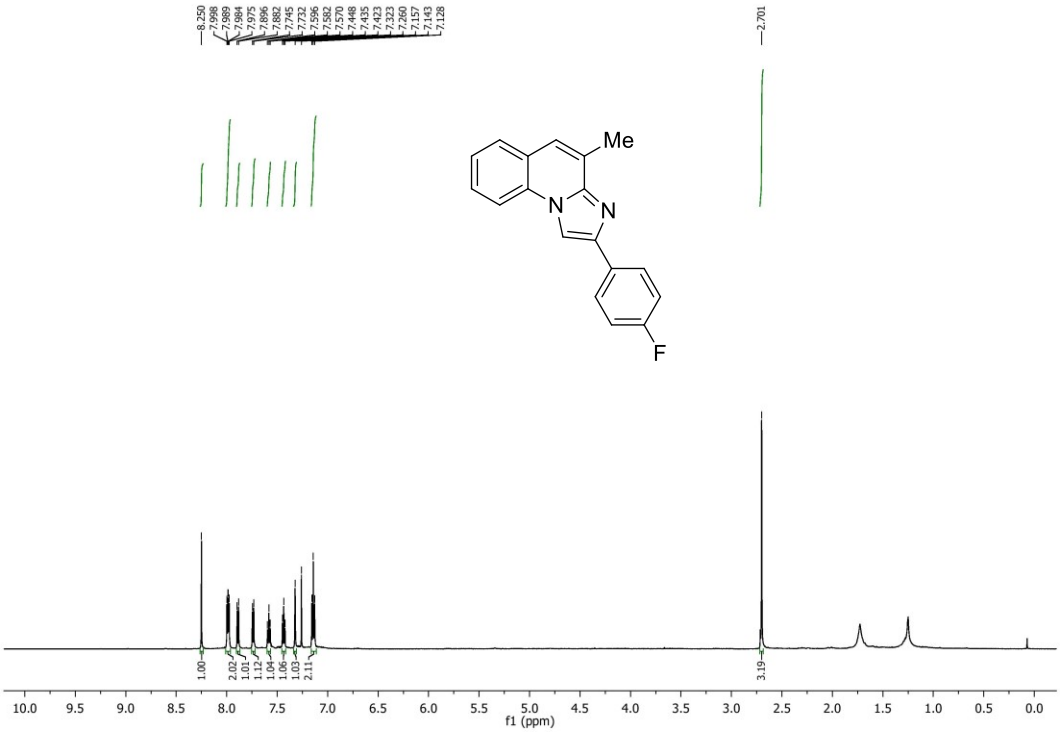
2-(4-Chlorophenyl)-4-methylimidazo[1,2-*a*]quinoline (2f): ^{1}H NMR ($CDCl_3$, 600 MHz)



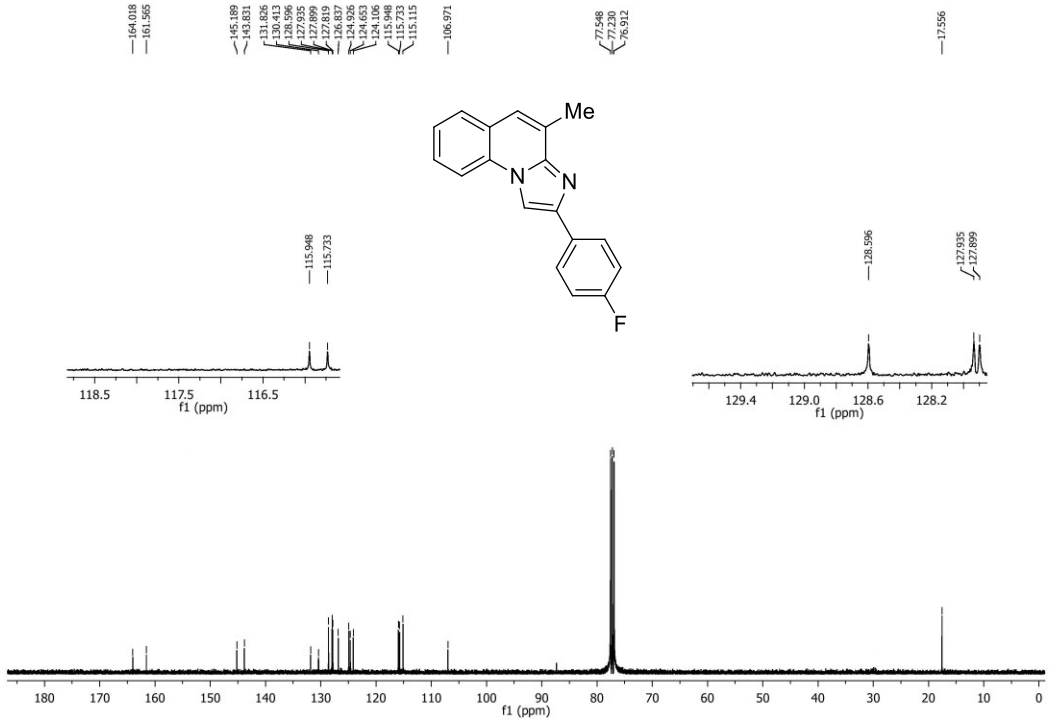
2-(4-Chlorophenyl)-4-methylimidazo[1,2-*a*]quinoline (2f): ^{13}C NMR ($CDCl_3$, 100 MHz)



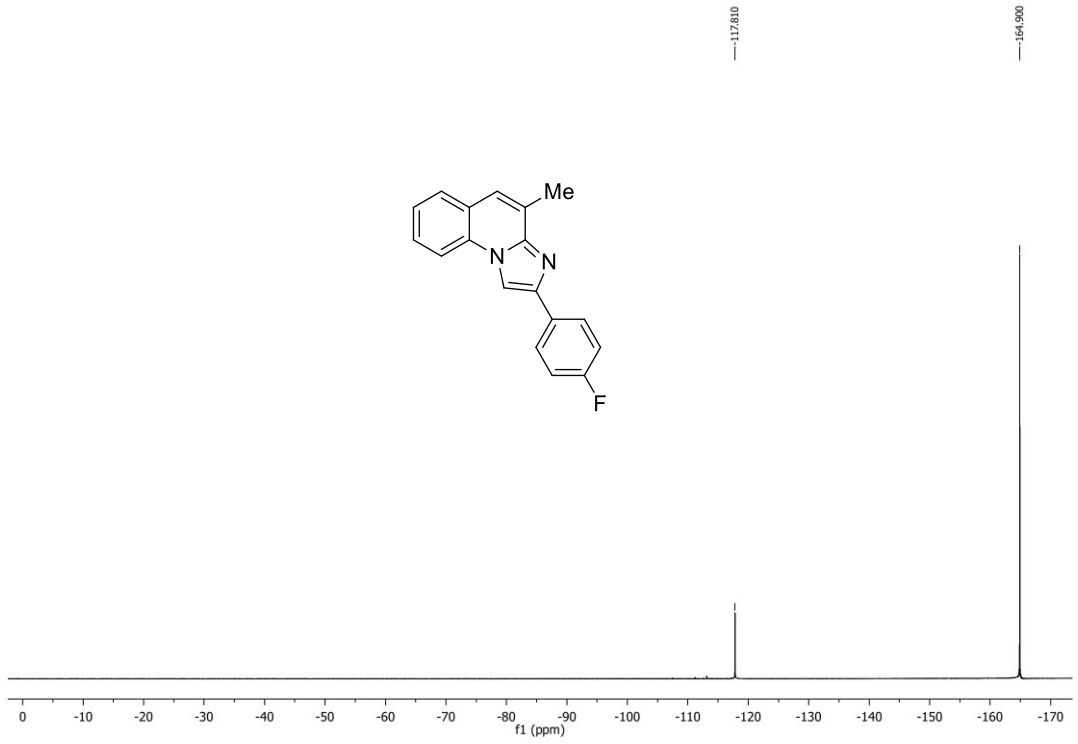
2-(4-Fluorophenyl)-4-methylimidazo[1,2-*a*]quinoline (2g): ^{1}H NMR ($CDCl_3$, 600 MHz)



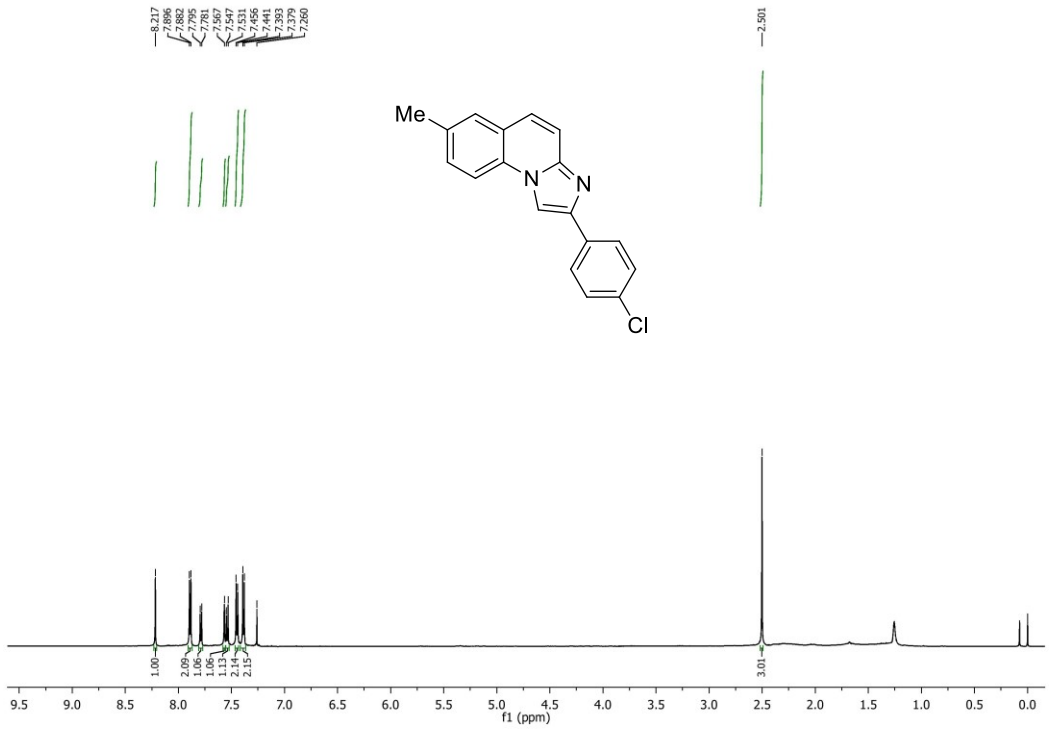
2-(4-Fluorophenyl)-4-methylimidazo[1,2-*a*]quinoline (2g): ^{13}C NMR ($CDCl_3$, 100 MHz)



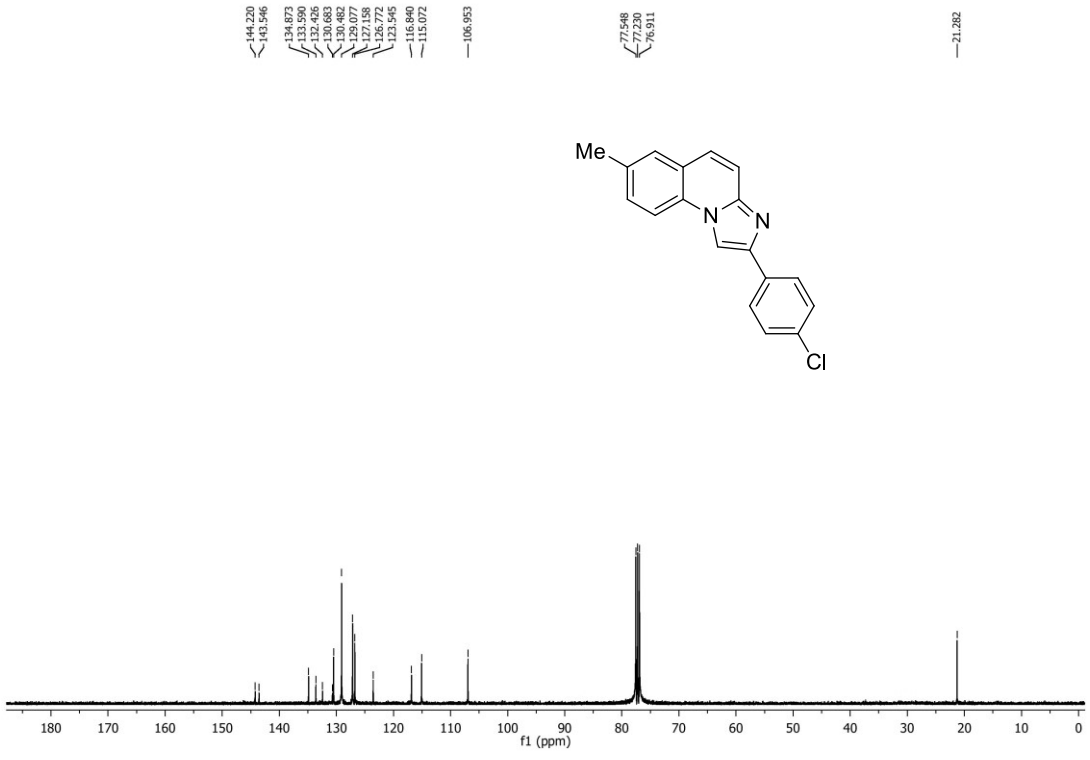
2-(4-Fluorophenyl)-4-methylimidazo[1,2-*a*]quinoline (2g): ^{19}F NMR ($CDCl_3$ + C_6F_6)



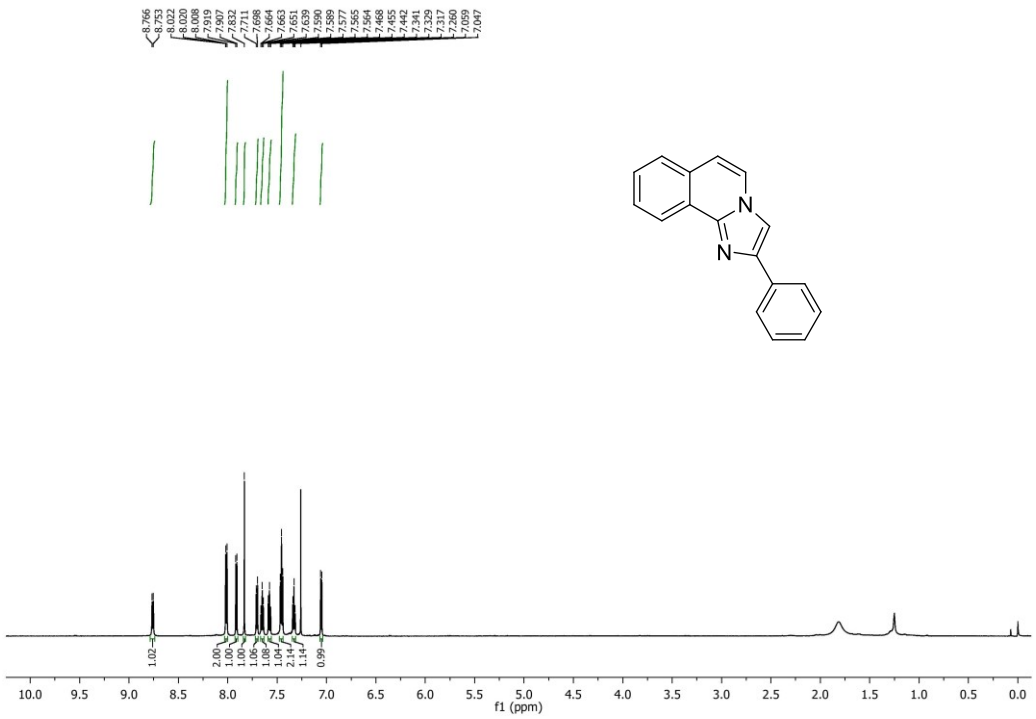
2-(4-Chlorophenyl)-7-methylimidazo[1,2-*a*]quinoline (3f): ^{1}H NMR ($CDCl_3$, 600 MHz)



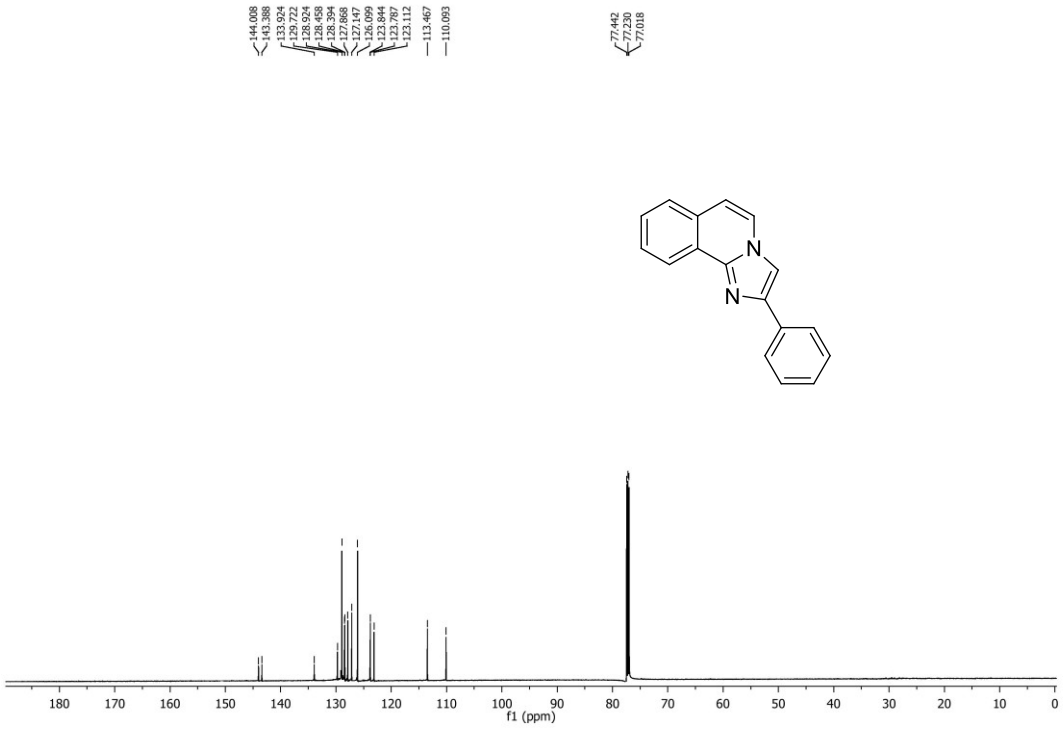
2-(4-Chlorophenyl)-7-methylimidazo[1,2-*a*]quinoline (3f): ^{13}C NMR ($CDCl_3$, 100 MHz)



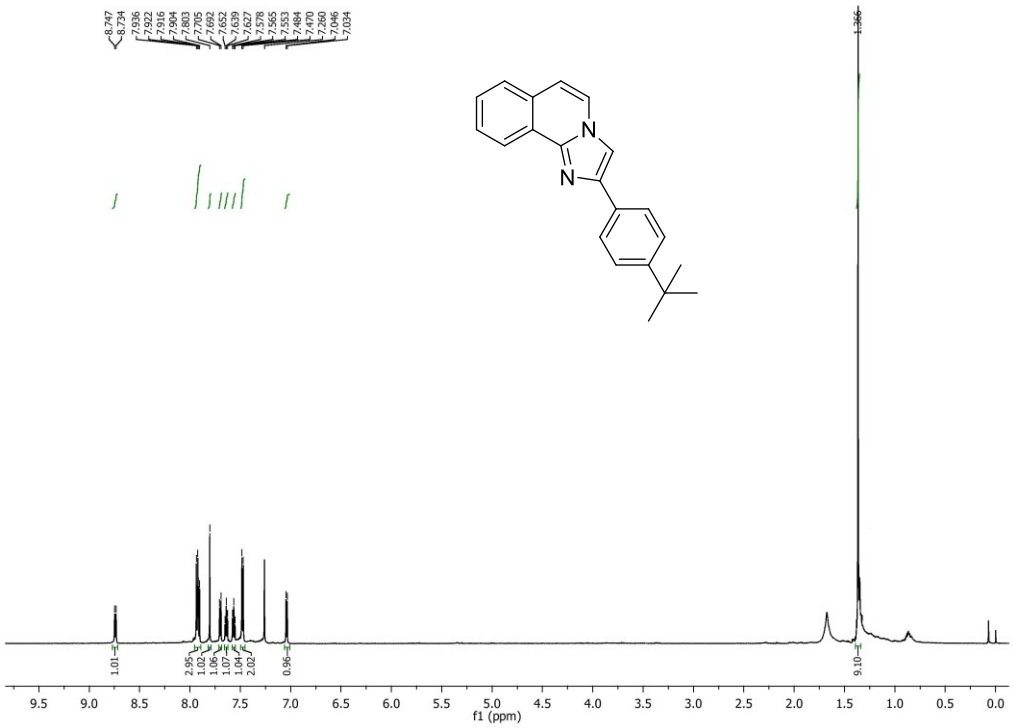
2-Phenylimidazo[2,1-*a*]isoquinoline (4a): ^{1}H NMR ($CDCl_3$, 600 MHz)



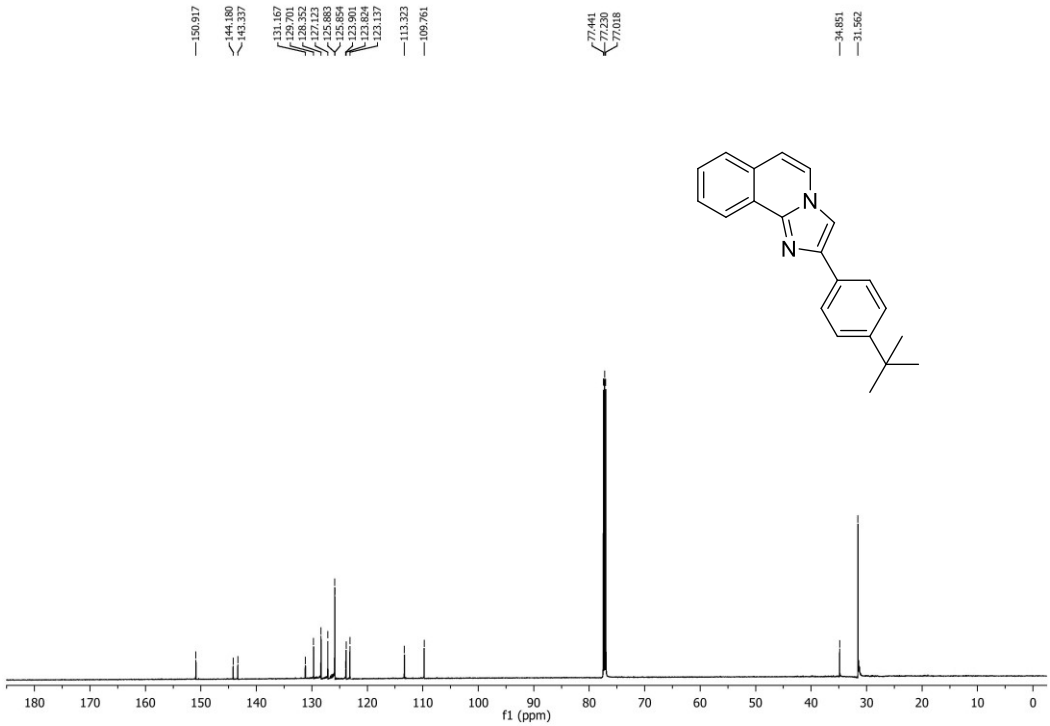
2-Phenylimidazo[2,1-*a*]isoquinoline (4a): ^{13}C NMR ($CDCl_3$, 150 MHz)



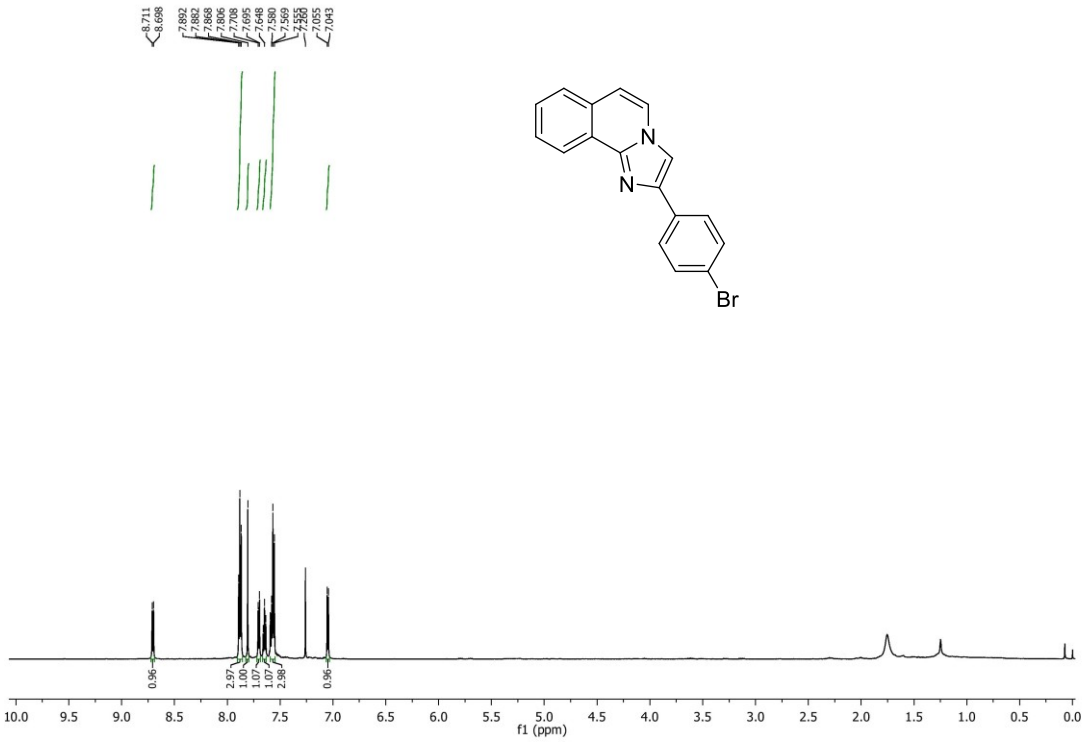
2-(4-(*tert*-Butyl)phenyl)imidazo[2,1-*a*]isoquinoline (4c): ^{1}H NMR ($CDCl_3$, 600 MHz)



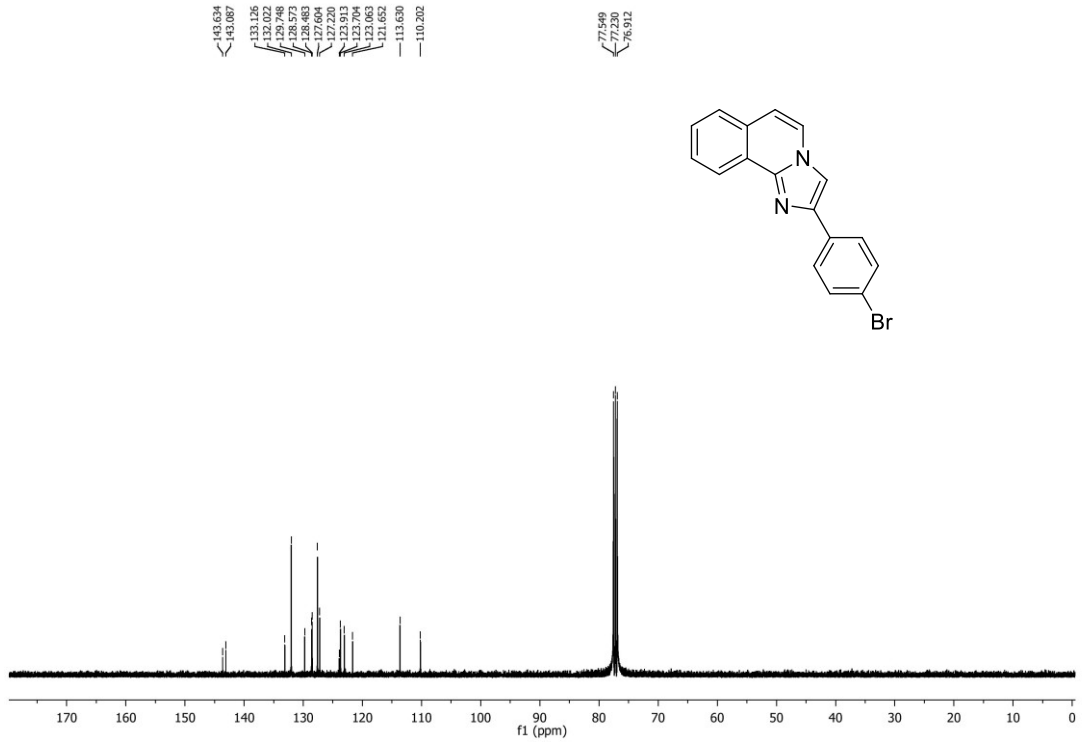
2-(4-(*tert*-Butyl)phenyl)imidazo[2,1-*a*]isoquinoline (4c): ^{13}C NMR ($CDCl_3$, 150 MHz)



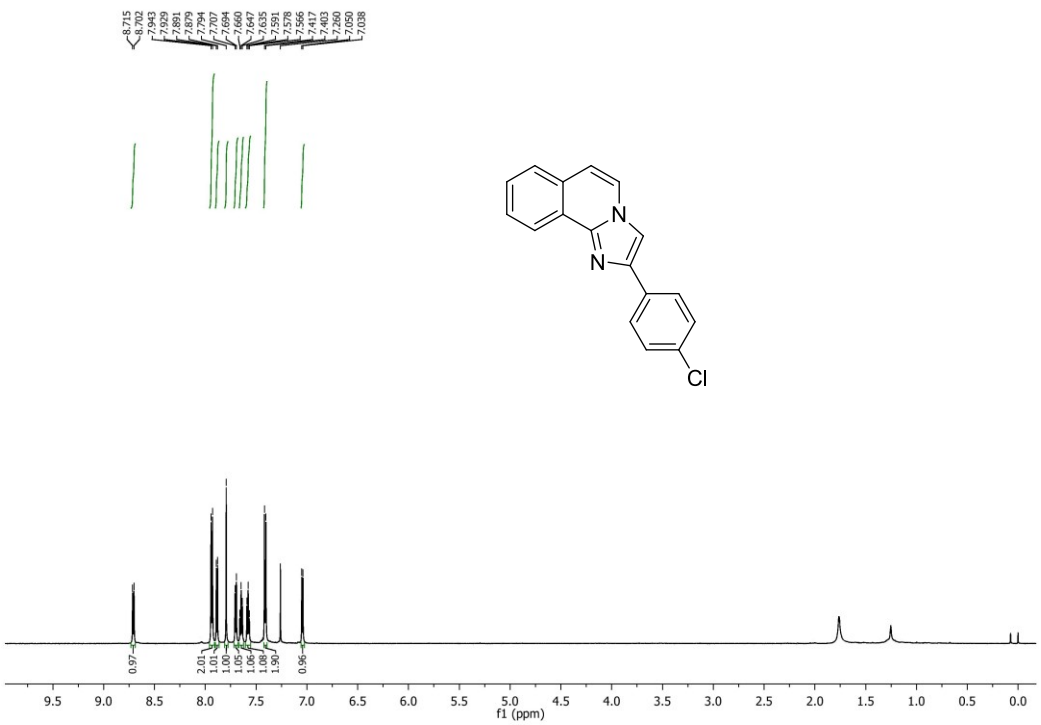
2-(4-Bromophenyl)imidazo[2,1-*a*]isoquinoline (4e): ^{1}H NMR ($CDCl_3$, 600 MHz)



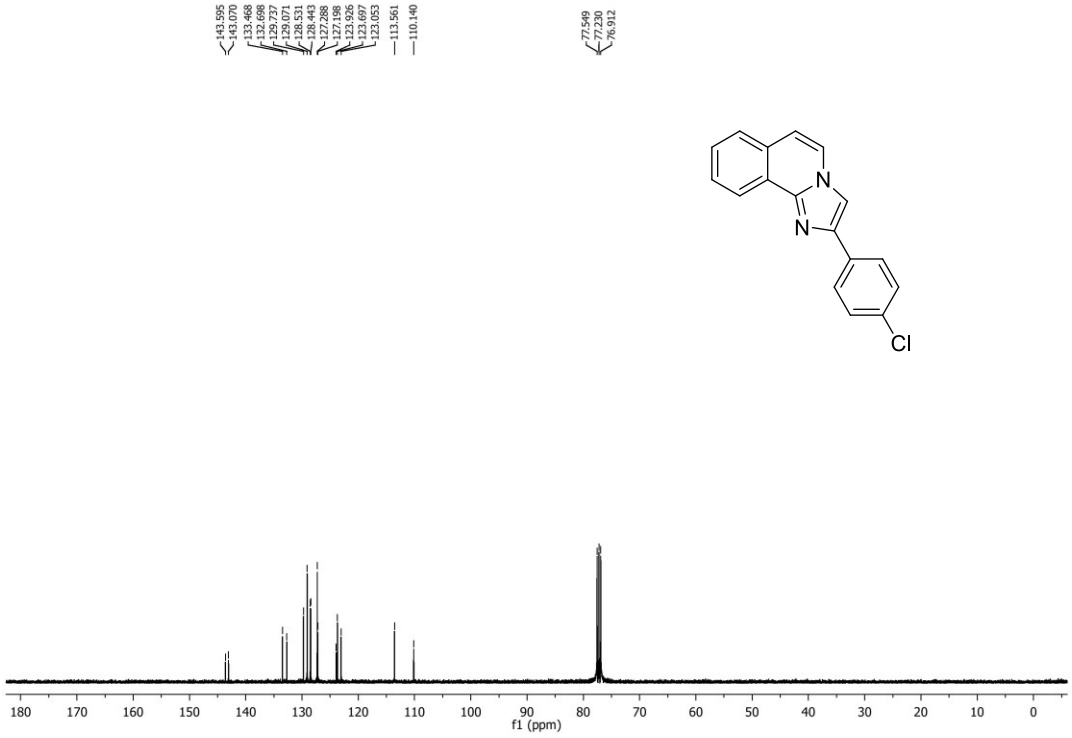
2-(4-Bromophenyl)imidazo[2,1-*a*]isoquinoline (4e): ^{13}C NMR ($CDCl_3$, 100 MHz)



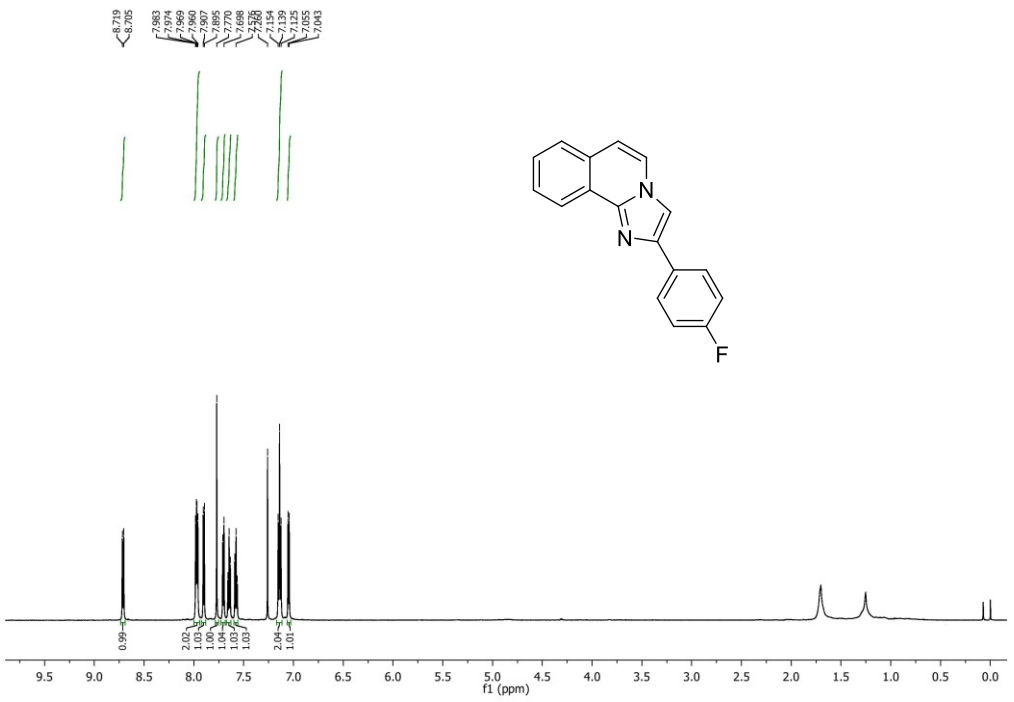
2-(4-Chlorophenyl)imidazo[2,1-*a*]isoquinoline (4f): ^{1}H NMR ($CDCl_3$, 600 MHz)



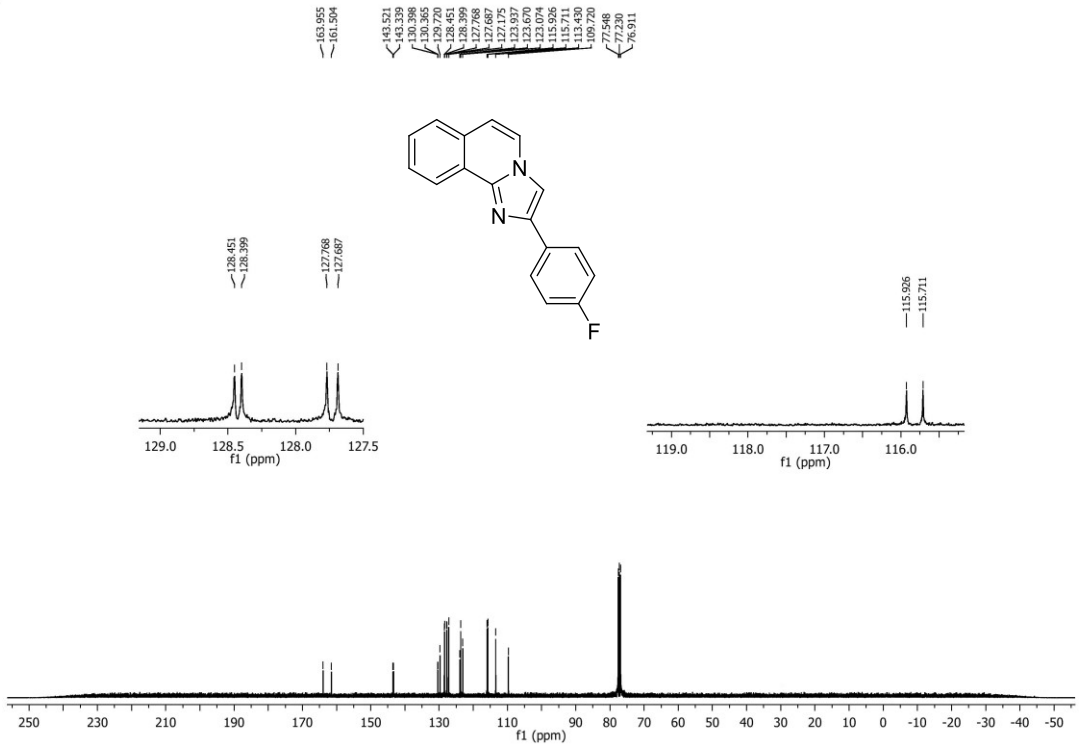
2-(4-Chlorophenyl)imidazo[2,1-*a*]isoquinoline (4f): ^{13}C NMR ($CDCl_3$, 100 MHz)



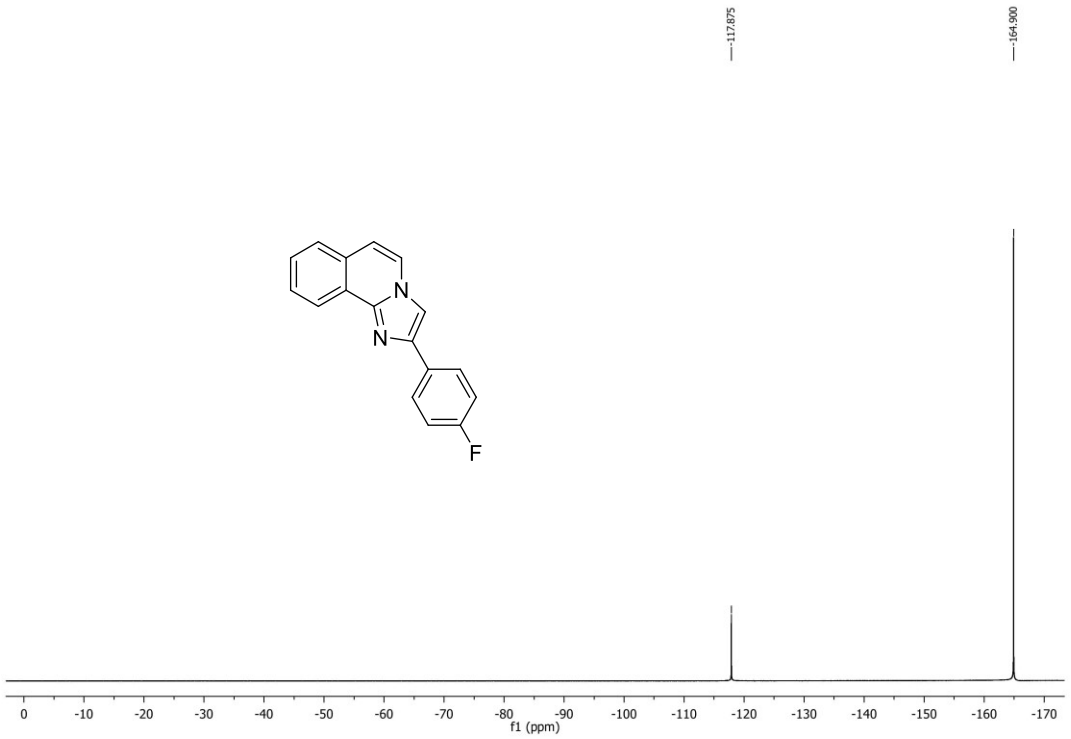
2-(4-Fluorophenyl)imidazo[2,1-*a*]isoquinoline (4g): ^{1}H NMR ($CDCl_3$, 600 MHz)



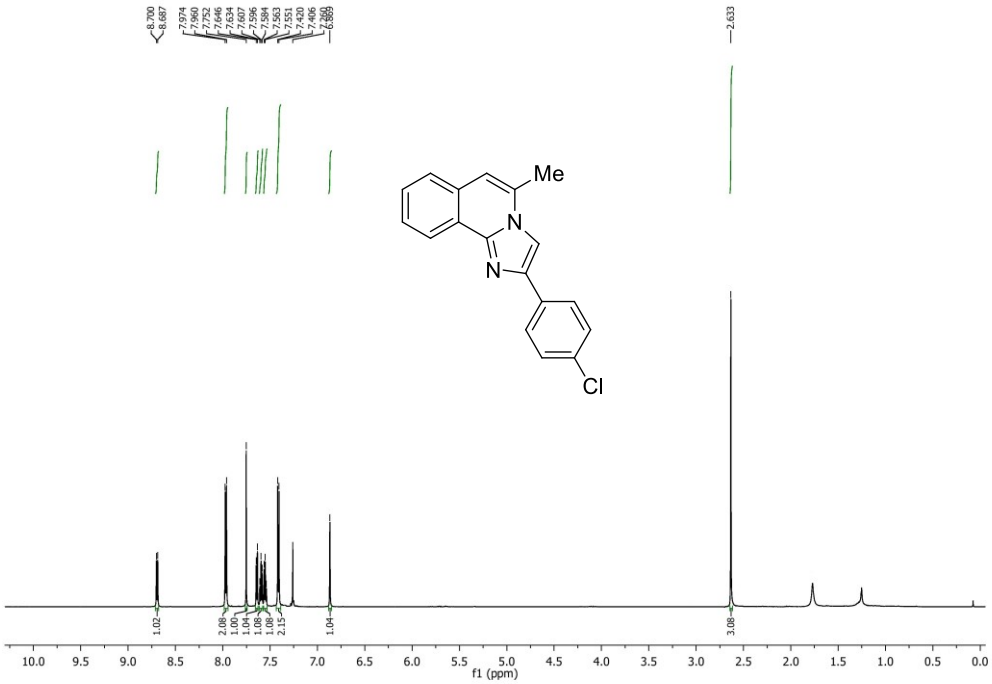
2-(4-Fluorophenyl)imidazo[2,1-*a*]isoquinoline (4g): ^{13}C NMR ($CDCl_3$, 100 MHz)



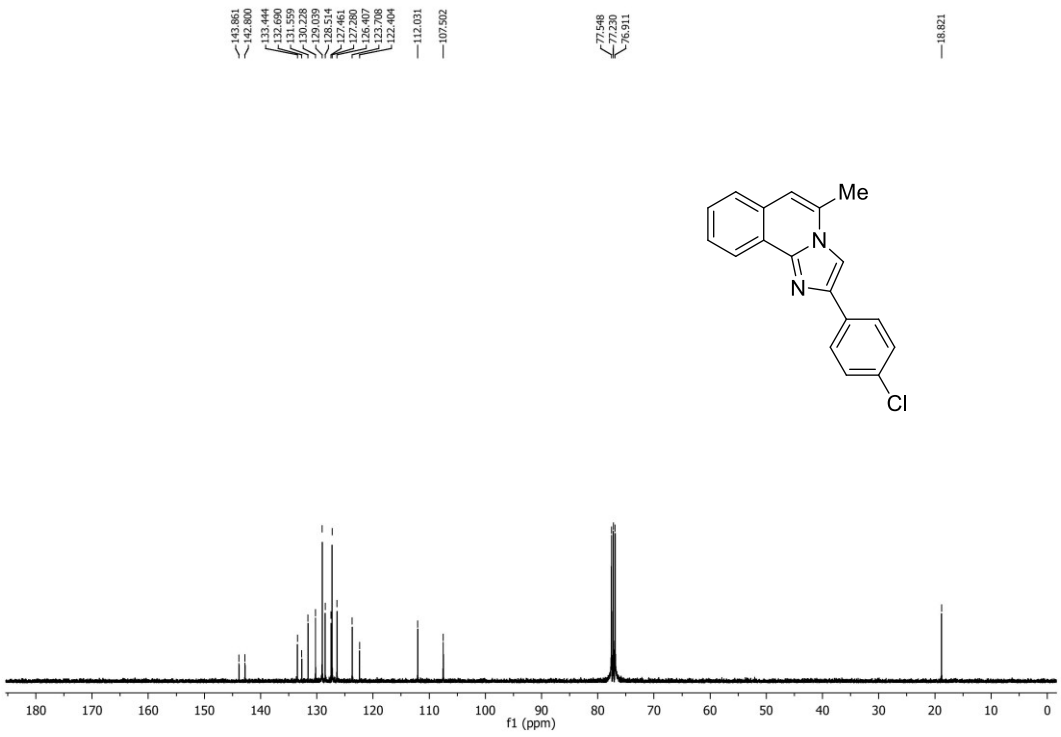
2-(4-Fluorophenyl)imidazo[2,1-*a*]isoquinoline (4g): ^{19}F NMR ($CDCl_3$ + C_6F_6)



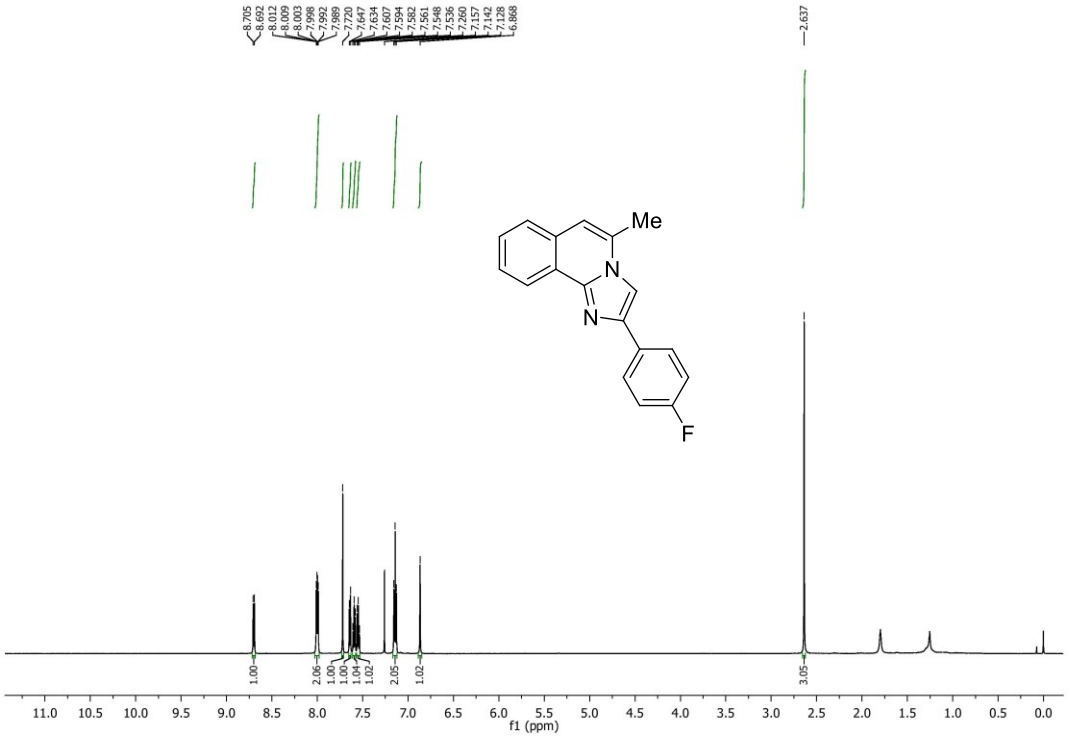
2-(4-Chlorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5f): ^{1}H NMR ($CDCl_3$, 600 MHz)



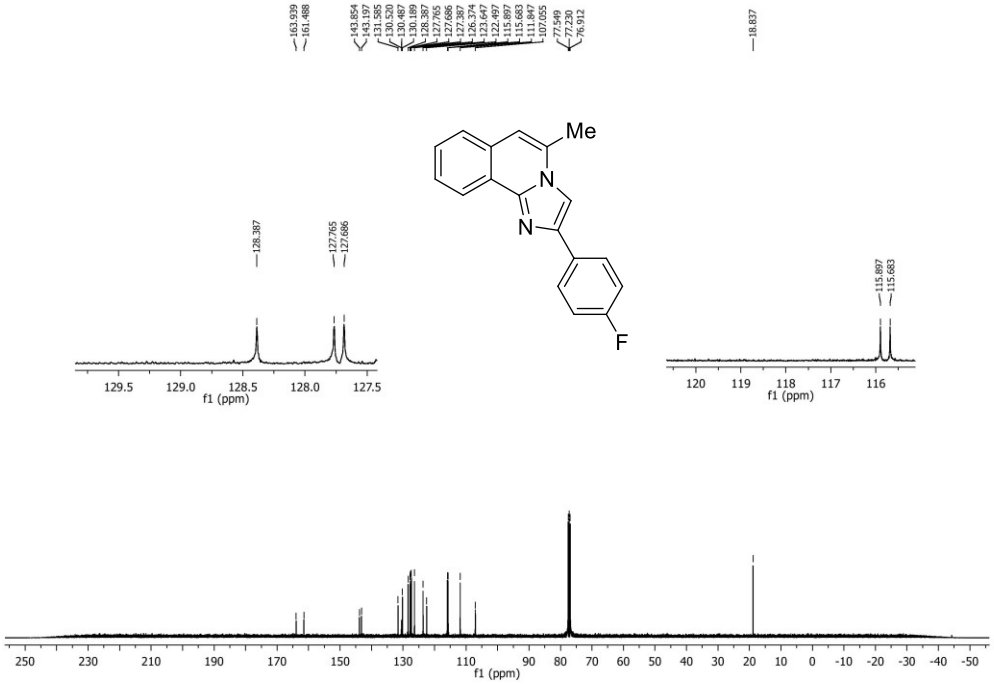
2-(4-Chlorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5f): ^{13}C NMR ($CDCl_3$, 100 MHz)



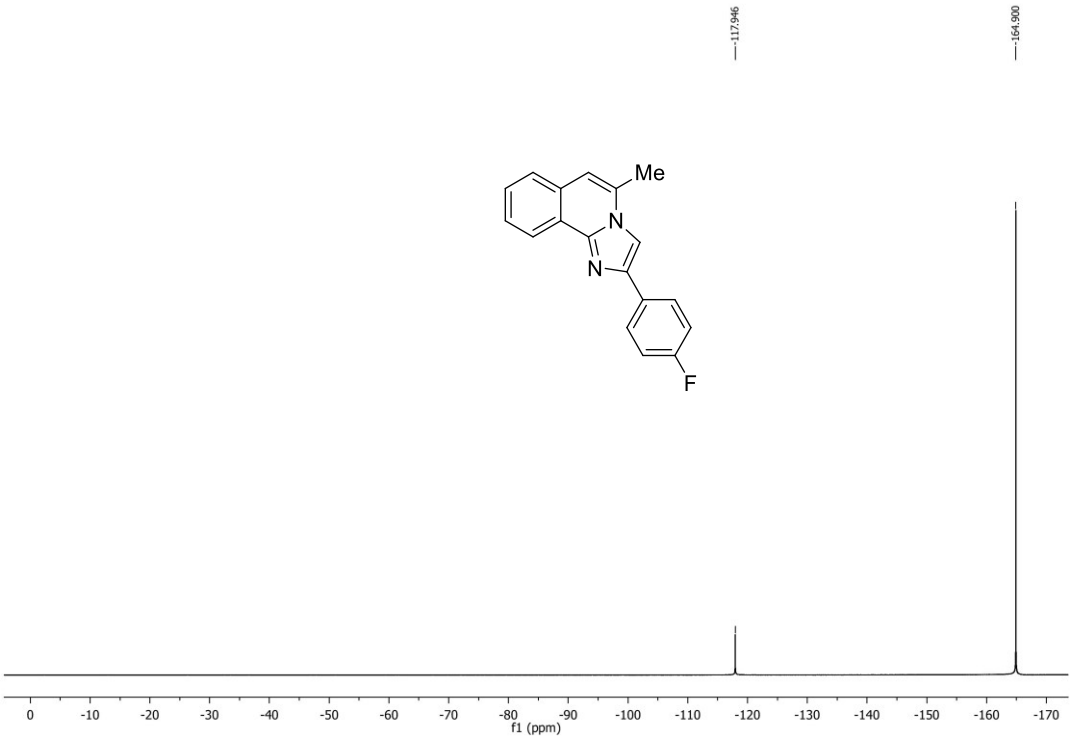
2-(4-Fluorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5g): ^{1}H NMR ($CDCl_3$, 600 MHz)



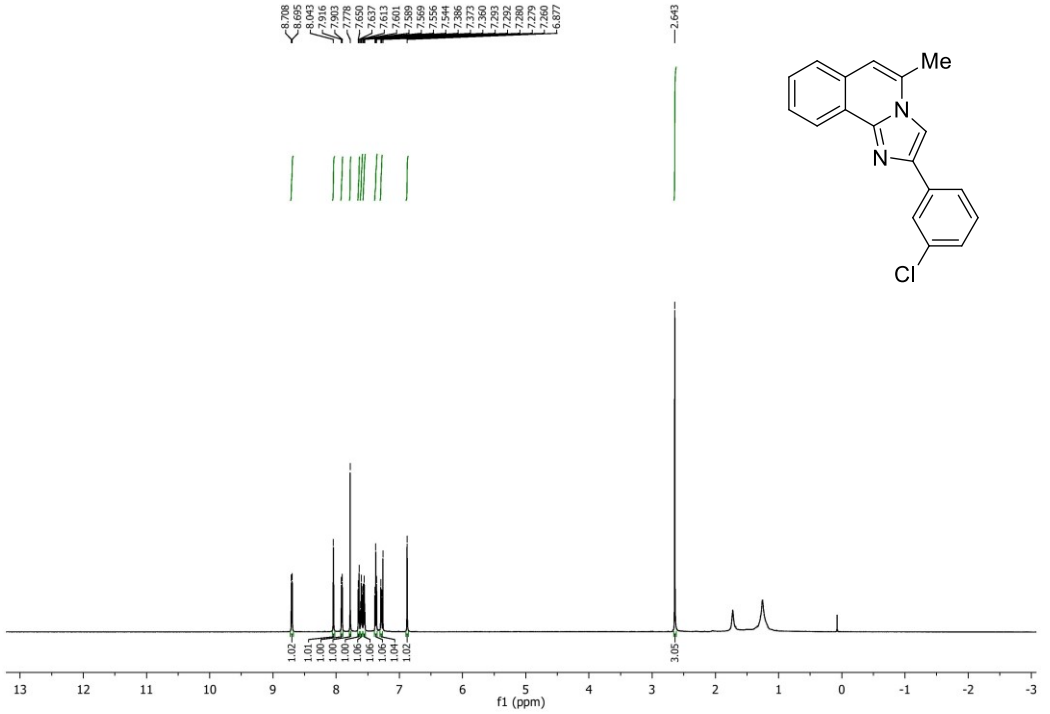
2-(4-Fluorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5g): ^{13}C NMR ($CDCl_3$, 100 MHz)



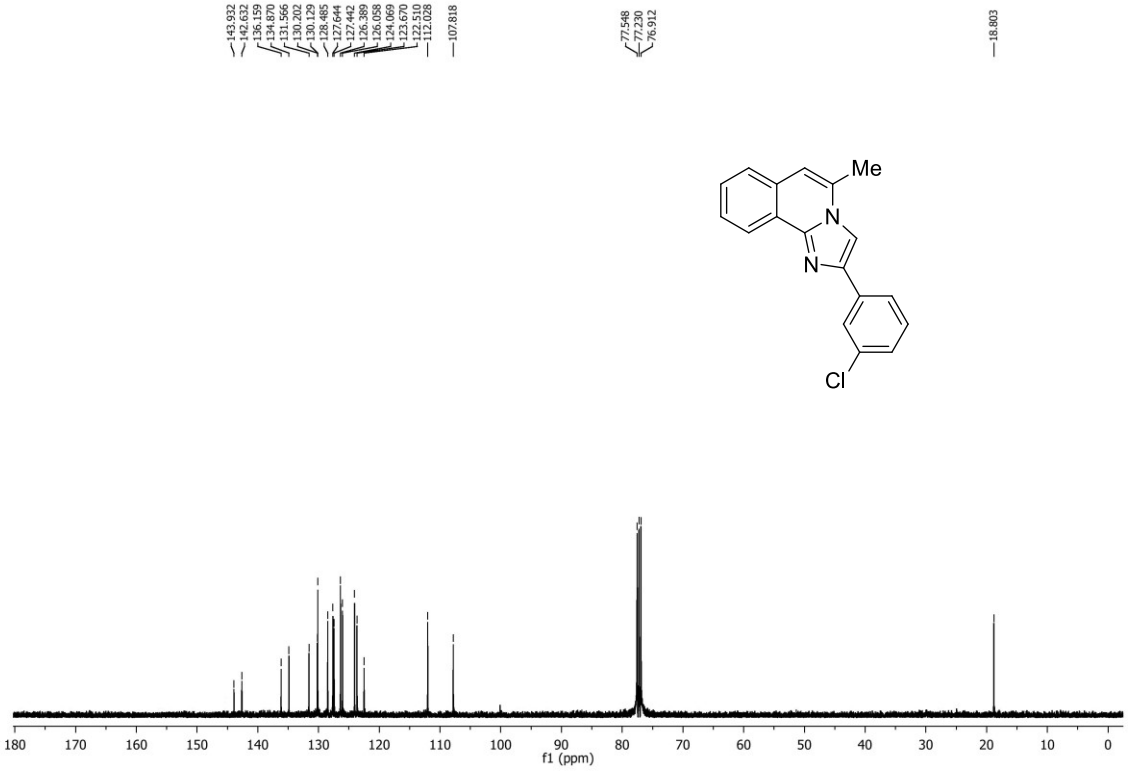
2-(4-Fluorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5g): ^{19}F NMR ($CDCl_3$ + C_6F_6)



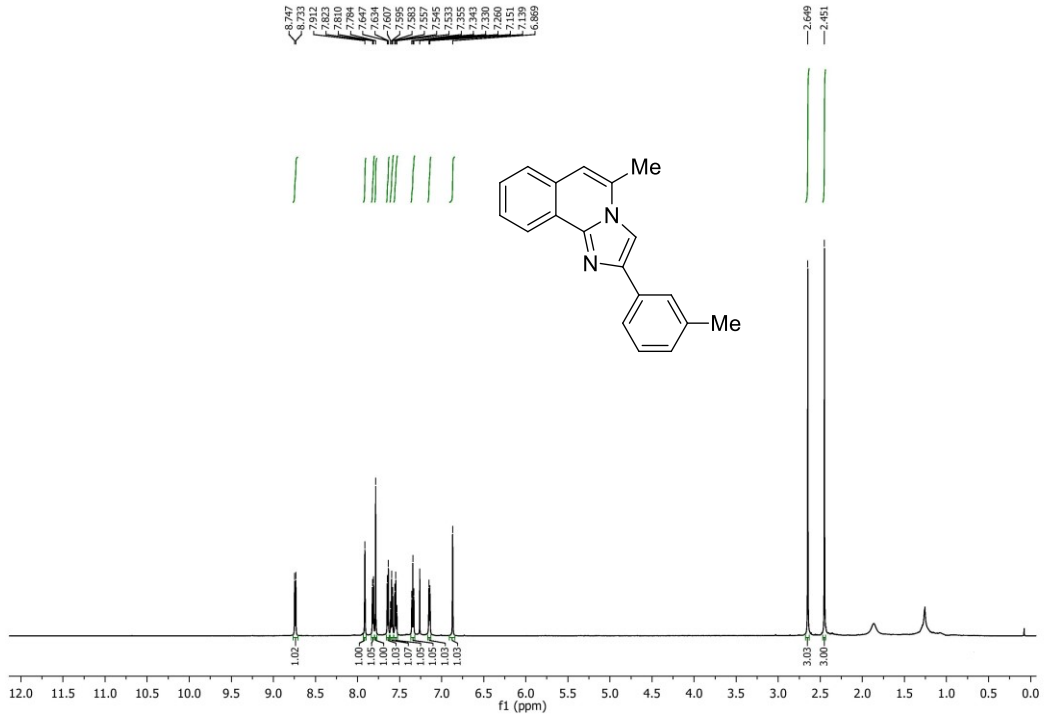
2-(3-Chlorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5h): ^{1}H NMR ($CDCl_3$, 600 MHz)



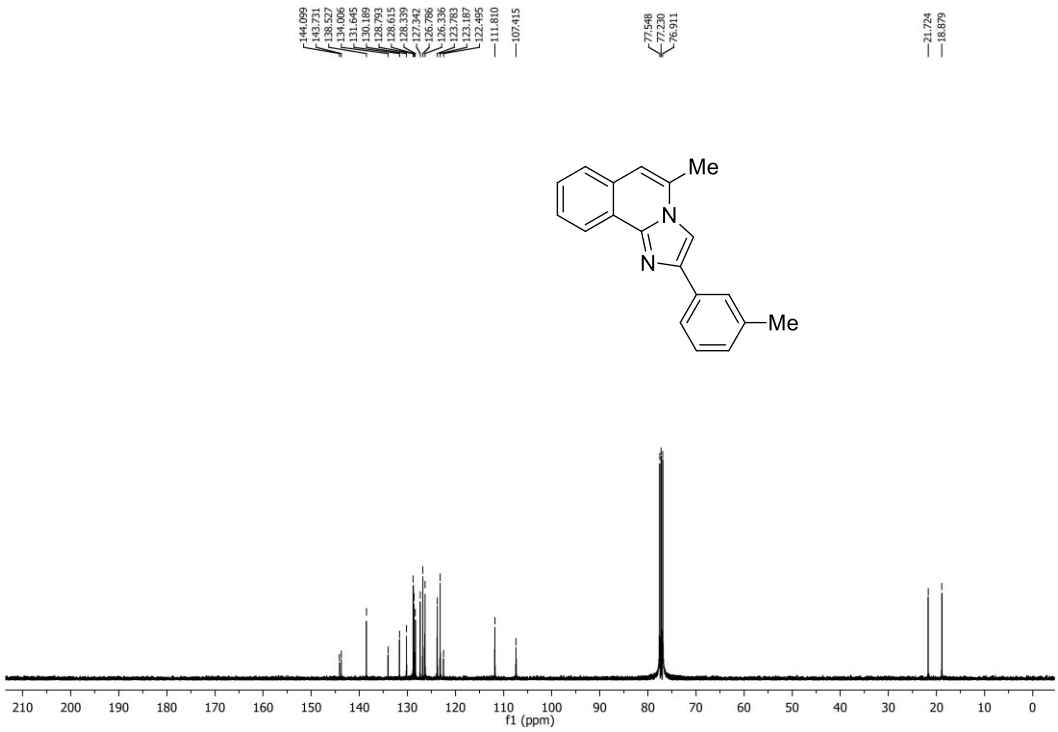
2-(3-Chlorophenyl)-5-methylimidazo[2,1-*a*]isoquinoline (5h): ^{13}C NMR ($CDCl_3$, 100 MHz)



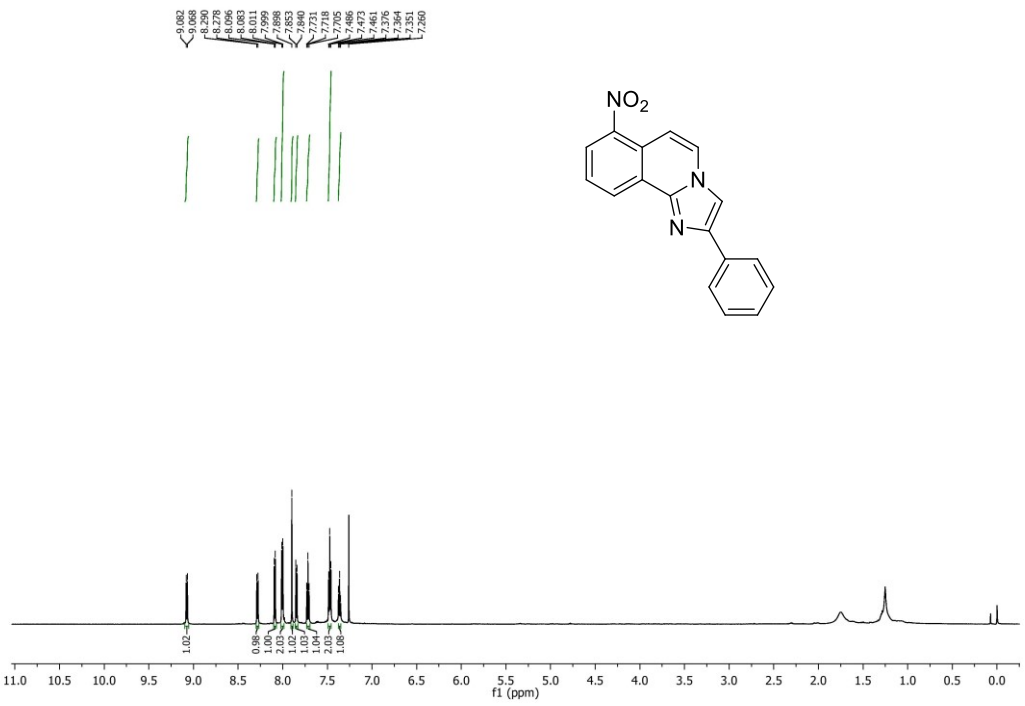
5-Methyl-2-(*m*-tolyl)imidazo[2,1-*a*]isoquinoline (5j): ^{1}H NMR ($CDCl_3$, 600 MHz)



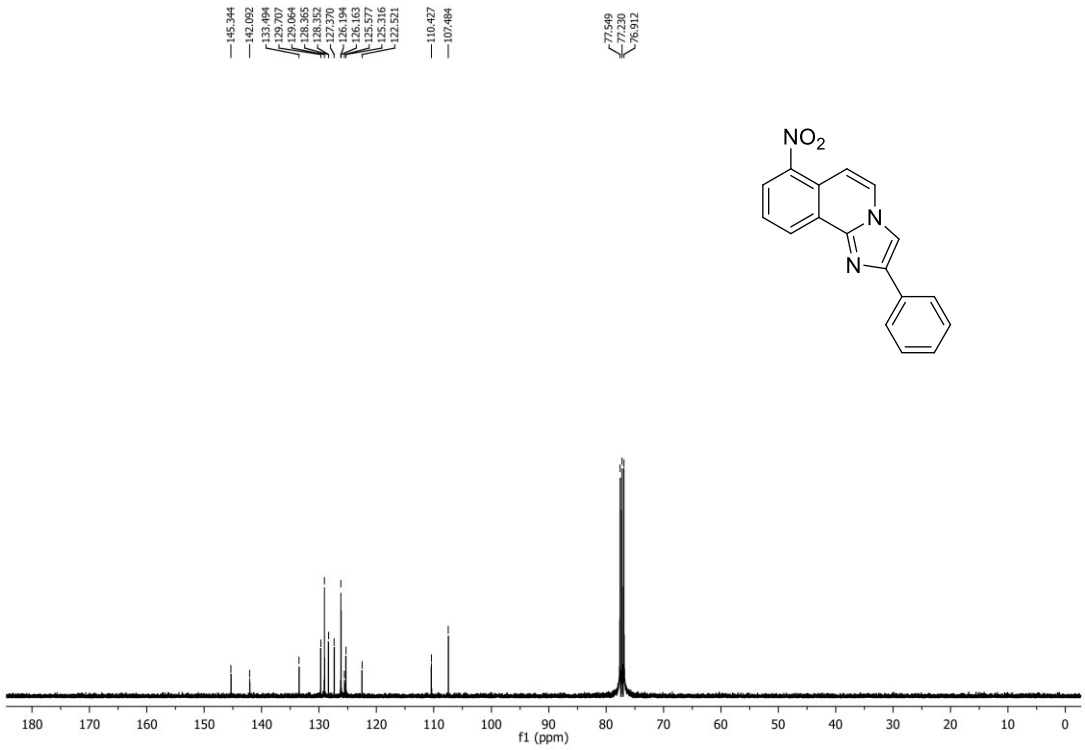
5-Methyl-2-(*m*-tolyl)imidazo[2,1-*a*]isoquinoline (5j): ^{13}C NMR ($CDCl_3$, 100 MHz)



7-Nitro-2-phenylimidazo[2,1-*a*]isoquinoline (6a): ^{1}H NMR ($CDCl_3$, 600 MHz)

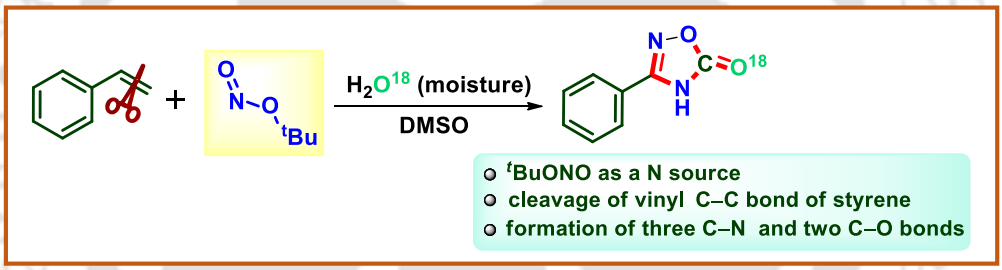


7-Nitro-2-phenylimidazo[2,1-*a*]isoquinoline (6a): ^{13}C NMR ($CDCl_3$, 100 MHz)



CHAPTER IV

tert-Butyl Nitrite Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(4H)-ones from Terminal Aryl Alkenes



ABSTRACT: tert-Butyl nitrite mediated vinyl bond cleavage/cyclization of aromatic alkenes leads to the formation of 3-phenyl-1,2,4-oxadiazol-5(4H)-ones. An unprecedented consecutive three C–H functionalization of styrene and formation of new three C–N and two C–O bonds are involved during this 1,2,4-oxadiazol-5(4H)-ones synthesis.

Manuscript under communication

CHAPTER IV

tert-Butyl Nitrite Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(*4H*)-ones from Terminal Aryl Alkenes

IV.1. Introduction

Nitrogen-containing heterocyclic frameworks are ubiquitous found in many naturally occurring and synthetic compounds exhibiting remarkable biological and medicinal properties. These heterocycles have engrossed the synthetic chemists to develop newer methodologies for their synthesis. Among the *N*-containing heterocycles, 1,2,4-oxadiazol-5(*4H*)-one form the integral part of many natural products and pharmaceutically and biologically active molecules. Their derivatives serve as inhibitors of S-nitrosoglutathione reductase (GSNOR) (compound **I**, Figure IV.1.1)[1a], in vitro and in vivo angiotensin II (AII) receptor antagonistic activities (compound **II**, Figure IV.1.1)[1b], selective noncompetitive antagonists for the homomeric kainate receptor subtype GluR5 (compound **III**, Figure IV.1.1)[1c] and inhibition of secretory phospholipase A_2 (compound **IV**, Figure IV.1.1).[1d] Thus, considerable attention has been devoted to exploit newer routes and especially one-pot synthetic strategies for these *N*- heterocycle and their derivatives.

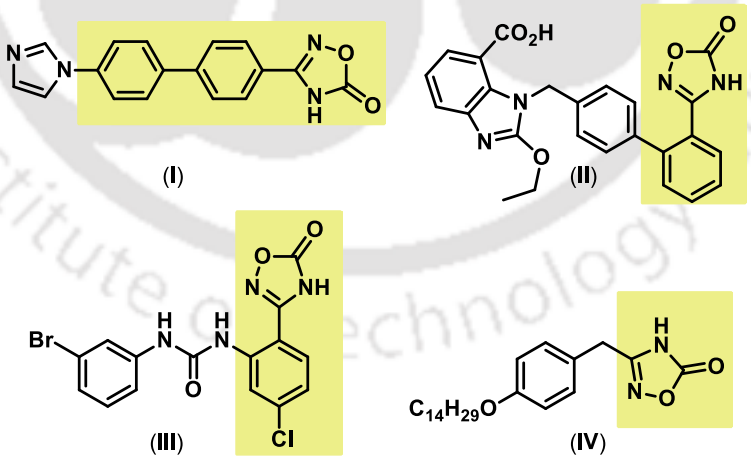
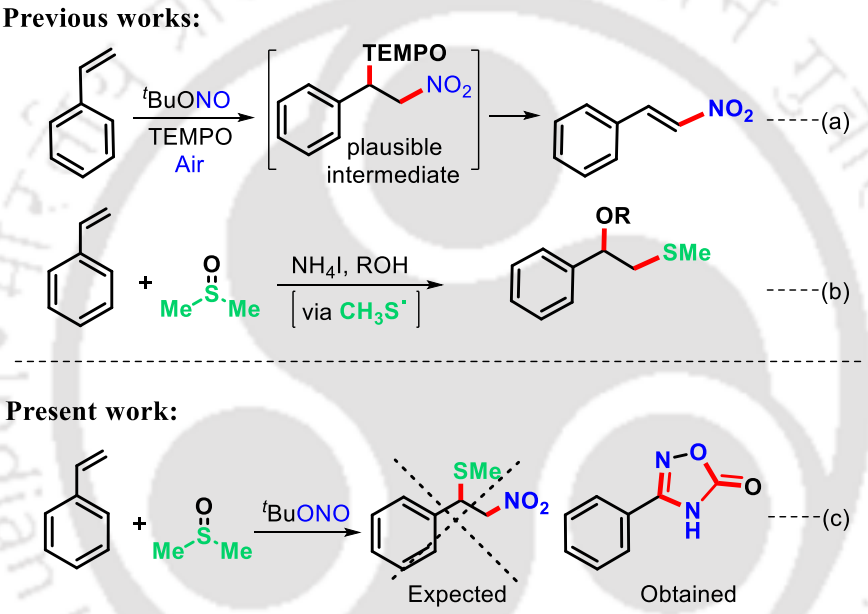


Figure IV.1.1. *Representative examples of clinically important 1,2,4-oxadiazol*

In this regard, only few methods are available for the construction of 3-phenyl-1,2,4-oxadiazol-5(*4H*)-one.[2] However, all the existing strategies involves condensation of amidoximes with carboxylic acid esters or carbonyldiimidazole. These strategies often

requires amidoximes as the reacting partners, which often needs additional reaction steps for its synthesis, thus affecting the overall efficiency. Therefore, it is highly desirable to develop an efficient and simple method for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(*4H*)-one and its derivatives.

Of late direct C–H bond functionalization process has emerged as a valuable tool in organic synthesis, providing more sustainable synthetic methodologies with minimum steps and waste.[3] Among the various C–H bond functionalization reactions, the functionalization of alkenes using *tert*-butyl nitrite, are powerful shortcut for the construction of a diverse array of complex molecules in a single operation.[4]



Scheme IV.1.1. *C–H Functionalization of alkene to 1,2,4-oxadiazol*

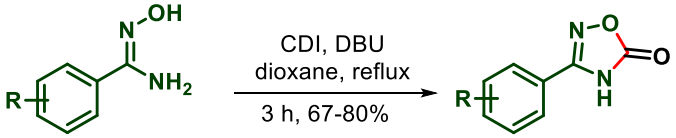
Recently, Maiti *et al.* reported the nitration of alkenes using *tert*-butyl nitrite as a nitrating agent. The reaction proceeds via a radical pathway where the *in situ* generated nitroalkane radical intermediate is trapped by the radical scavenger TEMPO [Scheme IV.1.1 (a)].[5] During the oxysulfenylation of alkenes utilizing ammonium iodide, DMSO and alcohols, a radical pathway is associated with the generation of methylthiyl radical (MeS•) from DMSO [Scheme IV.1.1 (b)].[6] Taking cues from these we were inquisitive to see the reaction of an alkene with *tert*-butyl nitrite in the presence of DMSO in lieu of TEMPO. Will it offer similar difunctionalized product or a completely differential reactivity may be observed that may drive the formation of some other product? [Scheme IV.1.1 (c)].

With this assumption, we commenced our preliminary investigation by reacting styrene (**1**) with *tert*-butyl nitrite (^{t}BuONO) (**a**, 3.0 equiv) and Sc(OTf)$_3$ catalyst (10 mol%) in DMSO at 80 ^{o}C. Interestingly, the reaction resulted in the formation of a new product (47%), spectroscopic analysis of which confirmed the structure to be 3-phenyl-1, 2, 4-oxadiazol-5(*4H*)-one (**1a**) [Scheme IV.1.1 (c)]. The product structure reveals that synthesis of 1, 2, 4-oxadiazol is realized via the cleavage of a vinylic C–C bond and with concurrent construction of three C–N and two C–O bonds. Here in this oxadiazol moiety, the incorporation of two N atoms are possibly from TBN through the oxidative functionalization of C(sp2)–H bonds. Herein, we disclose a *tert*-butyl nitrite mediated simple and straightforward synthesis of oxadiazol architecture from terminal alkenes under a metal and additive free conditions. The importance and scope of the present chemistry is threefold: (1) To the best of our knowledge, such one-pot green synthesis of 1, 2, 4-oxadiazol using only terminal alkene and *tert*-butyl nitrite is unprecedented in the literature. (2) Construction of oxadiazol from commercially available terminal alkenes generate potential opportunity for easy access to many biologically active compounds. (3) The mechanistic study indicates that the initial NO and NO_2 radical addition and followed by alkene bond cleavage/cyclization of aromatic alkenes lead to the formation of 1,2,4-oxadiazol-5(*4H*)-ones.

IV.2. Strategies for the synthesis of 1,2,4-oxadiazoles

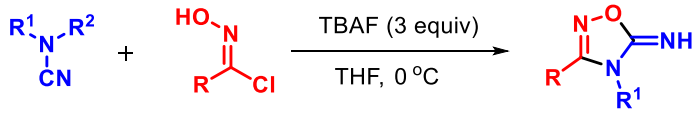
Heterocycles are ubiquitous units found in many natural products. Among the nitrogen-fused heterocycles, 1,2,4-oxadiazols exhibit several biological and pharmacological activities. A number of novel, and efficient methods are now available for their synthesis.

Deprez and co-worker established an efficient protocol to synthesize 1,2,4-oxadiazol-5-one via the condensation of amidoximes with carbonyldiimidazole (CDI) (Scheme IV.2.1).[2b] Subsequent diversification of 1,2,4-oxadiazol was accomplished using a Sonogashira coupling.



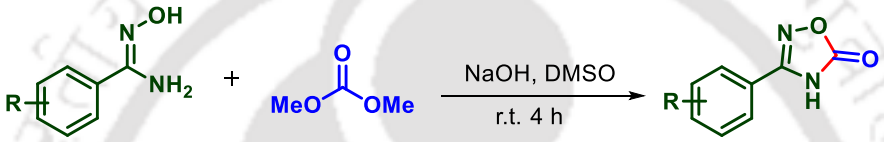
Scheme IV.2.1. *Synthesis of 1,2,4-oxadiazol-5-one*

Moses, Sharma and co-workers reported an intermolecular cyclizative capture of *in situ* generated cyanamide anion and nitrile oxides enables the synthesis of oxadiazol-5-imines (Scheme IV.2.2).[2a]



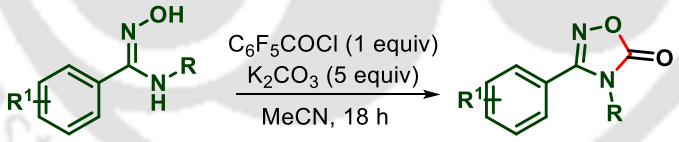
Scheme IV.2.2. *TBAF-Mediated cyclizative capture reaction*

Shetnev *et al.* described a novel strategy for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles via the condensation between amidoximes and carboxylic acid esters in super base medium NaOH/DMSO (Scheme IV.2.3).[7] This protocol provides convenient access to several biologically important 1,2,4-oxadiazoles.



Scheme IV.2.3. *One-pot synthesis of 1,2,4-oxadiazoles*

Zhu group developed a new method to synthesize 1,2,4-oxadiazol-5-one by reaction of amidoximes with pentafluorobenzoylchloride (Scheme IV.2.4).[8] The reaction proceeds *via* the cleavage of C–C bond with the release of pentafluorobenzene under very mild conditions.



Scheme IV.2.4. *Synthesis of 1,2,4-oxadiazol-5-ones from amidoximes*

IV.3. Present work

In the light of the aforementioned protocols, the present method for the construction of 1,2,4-oxadiazol-5-ones using only styrene, and *tert*-butyl nitrite is unprecedented in literature.

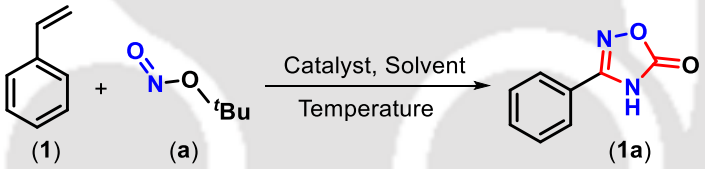
Optimization of reaction conditions:

As has been mentioned earlier, an initial trial reaction was performed using styrene (**1**) with *tert*-butyl nitrite (^{t}BuONO) (**a**, 3.0 equiv) and $Sc(OTf)_3$ catalyst (10 mol%) in DMSO at 80 °C. Interestingly, the reaction resulted in the formation of a new product (47%),

spectroscopic analysis of which explicitly confirmed the structure to be 3-phenyl-1, 2, 4-oxadiazol-5(*4H*)-one (**1a**).

Encouraged by the above *tert*-butyl nitrite mediated C–H functionalization of aromatic alkenes, further optimizations were carried out by varying various reaction parameters. Initially, a variety of solvents such as DMSO (47%), DMF (31%), DMA (29%), CH_3CN (0%), and DCE (0%) were tested (Table IV.3.1, entries 1–5). Among various solvents examined, DMSO (47%) was found to be more effective. When $Cu(OTf)_2$ (10 mol%) was employed in lieu of $Sc(OTf)_3$ (10 mol%) under otherwise identical conditions resulted in a suppressed yield (41%) of (**1a**) (Table IV.3.1, entry 6). Interestingly significant improvement of the product (**1a**) yield (59%) was observed in the absence of catalyst (Table IV.3.1, entries 7). This result suggests that catalyst has no role for this transformations. Next, increasing the *tert*-butyl nitrite loading up to 4 equivalent was beneficial for the reaction (Table IV.3.1, entry 8). No noticeable enhancement in the yield (69%) was observed when the TBN loading was further increased up to 5 equivalent (Table IV.3.1, entry 9).

Table IV.3.1. *Optimization of the reaction conditions*[a]



entry	catalyst (mol %)	solvent	TBN (equiv)	yield %[b]
1	$Sc(OTf)_3$ (10)	DMSO	^{t}BuONO (3)	47
2	$Sc(OTf)_3$ (10)	DMF	^{t}BuONO (3)	31
3	$Sc(OTf)_3$ (10)	DMA	^{t}BuONO (3)	29
4	$Sc(OTf)_3$ (10)	CH_3CN	^{t}BuONO (3)	0
5	$Sc(OTf)_3$ (10)	DCE	^{t}BuONO (3)	0
6	$Cu(OTf)_2$ (10)	DMSO	^{t}BuONO (3)	41
7	-	DMSO	^{t}BuONO (3)	59
8	**-**	**DMSO**	**^{t}BuONO (4)**	**67**
9	-	DMSO	^{t}BuONO (5)	69
10	-	DMSO	^{t}BuONO (4)	51[c]
11	-	DMSO	^{t}BuONO (4)	57[d]

[a]Reaction conditions: Styrene (**1**) (0.25 mmol) and *tert*-butyl nitrite (**a**) (equiv) and solvent (2 mL) at 80 °C. [b]Yield after 6 h. [c]Temperature100 °C. [d]Temperature 60 °C.

Reaction carried out both at higher 100 °C (51%) or lower 60 °C (57%) temperature were detrimental to the product formation. (Table IV.3.1, entries 10 and 11). After screening of various reaction parameters, the optimized condition for this transformation

is the use of styrene (0.25 mmol), *tert*-butyl nitrite (1 mmol) at 80 °C in DMSO solvent (Table IV.3.1, Entry 8).

Scope of the synthesis of 3-phenyl-1,2,4-oxadiazol-5(*4H*)-one was then explored with various aromatic terminal alkenes (Scheme IV.3.1) under the optimized reaction condition. Styrenes having moderately electron-donating substituents such as *m*-Me (**2**), *p*- Me (**3**), *p*-^{t}Bu (**4**), yielded their corresponding 1,2,4-oxadiazols (**2a**), (**3a**), and (**4a**) in the range of 64–69% (Scheme IV.3.1). The structure of the product (**3a)** has been further confirmed by single crystal X-ray diffraction study (Figure IV.3.1).

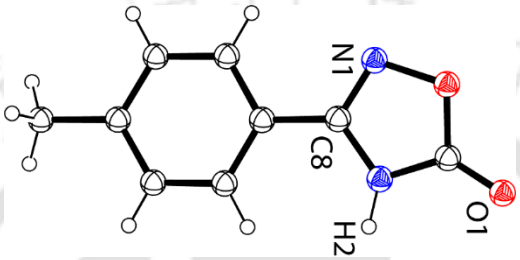
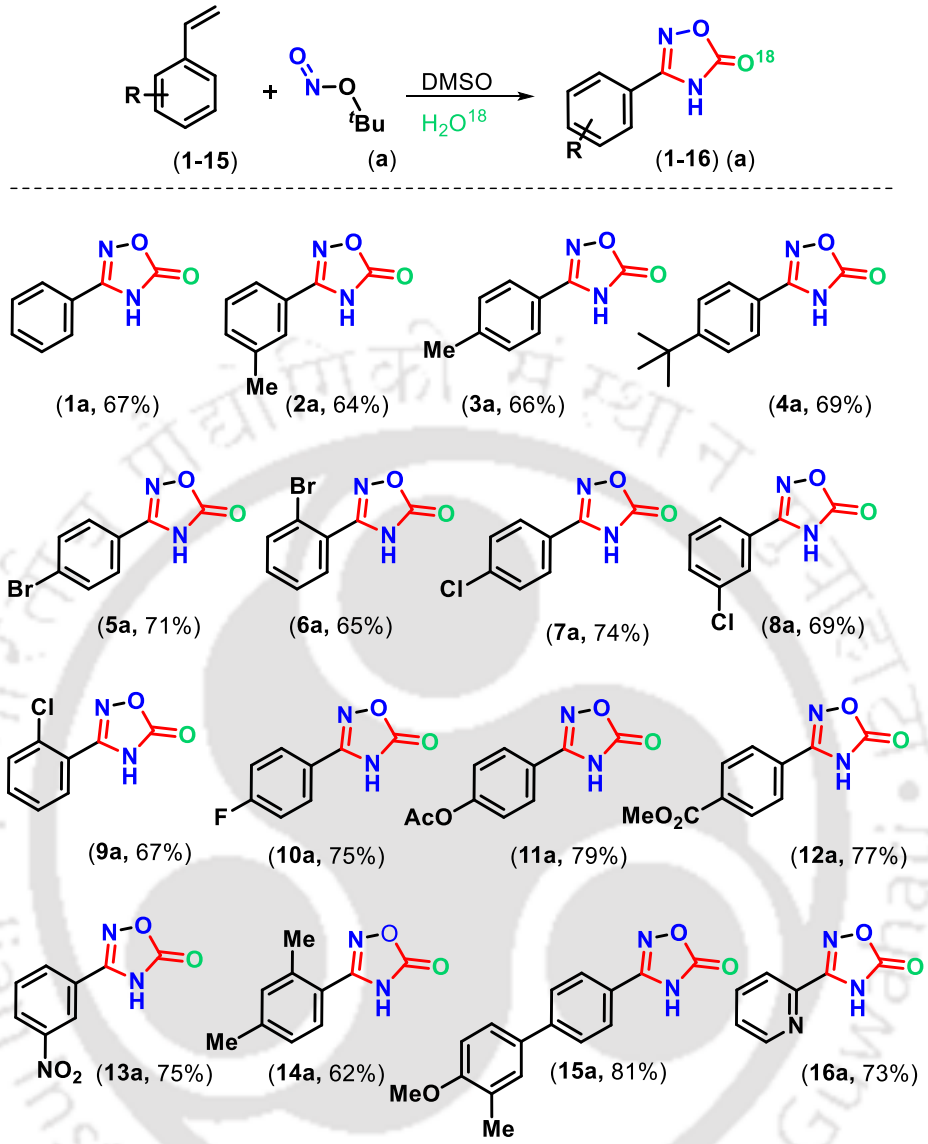


Figure IV.3.1. *ORTEP diagram of compound (**3a**)*

Styrenes containing moderately electron-withdrawing groups such as *p*-Br (**5**), *o*-Br (**6**), *p*-Cl (**7**), *m*-Cl (**8**), *o*-Cl (**9**), and *p*-F (**10**) all provided their corresponding 1, 2, 4-oxadiazols (**5a**, 71%), (**6a**, 65%), (**7a**, 74%), (**8a**, 69%), (**9a**, 67%) and (**10a**, 75%) in moderate yields (Scheme IV.3.1). However, styrene possessing strongly electron-withdrawing substituents such as *p*-OAc (**11**), *p*-CO_2Me (**12**), and *m*-nitro (**13**), all reacted smoothly with *tert*-butyl nitrite affording their corresponding 1,2,4-oxadiazols (**11a**, 79%), (**12a**, 77%), and (**13a**, 75%) in modest yields (Scheme IV.3.1). Other aromatic alkenes such as 2,4-dimethylstyrene (**14**), 4-phenylstyrene (**15**), and 2-vinylpyridine (**16**) all underwent reactions successfully to produce their desired products [(**14a**, 62%), (**15a**, 81%), and (**16a**, 73%)] as shown in Scheme IV.3.1. In this domino process, both electron-donating and electron-withdrawing substituents provided almost identical yields of their products. This may be due to the higher reactivity of reaction intermediates in this transformation. However, in this protocol aliphatic alkenes failed to react with *tert*-butyl nitrite which may be due to the instability of the radical produced during the reaction.

Scheme IV.3.1. *Substrate scope for synthesis of 1, 2, 4-oxadiazols* [a,b]

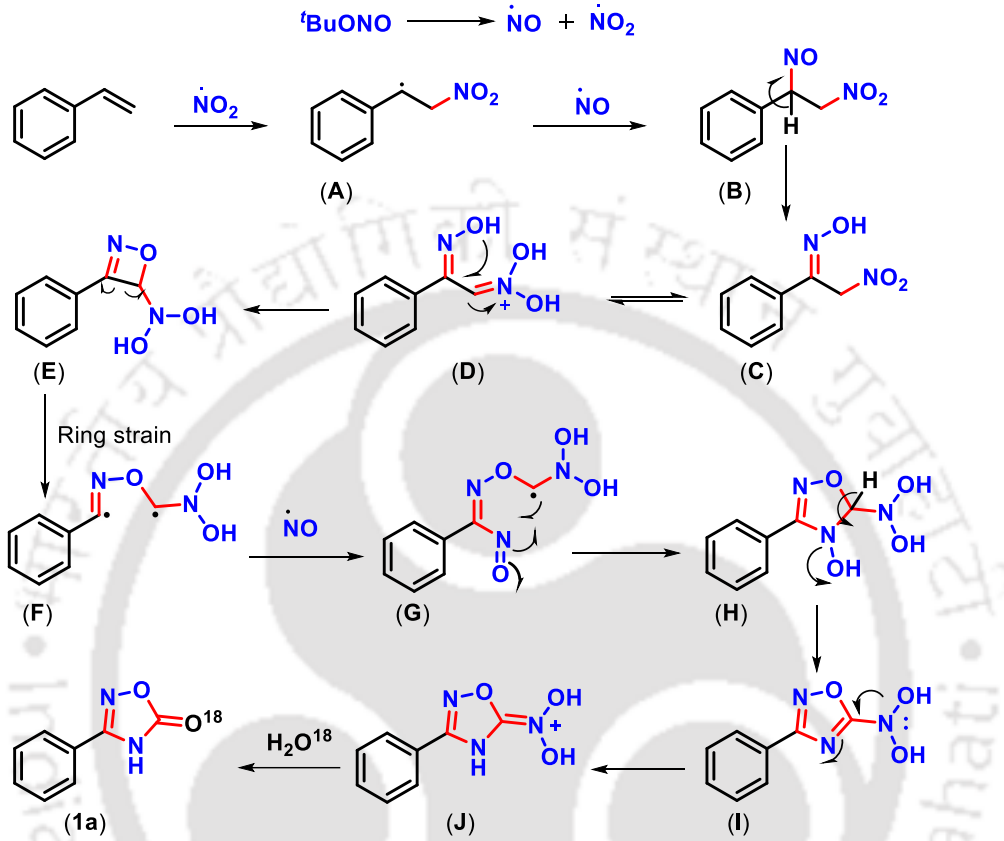


[a]Reaction conditions: alkene (**1-16**) (0.25 mmol), *tert*-butyl nitrite (**a**) (1 mmol) at 80 °C in DMSO. [b] Yield after 6 h.

To illuminate the probable mechanism of this one pot synthesis of 1,2,4-oxadiazols, some control experiments were carried out. At first, to find out the source of keto oxygen in product (**1a**), the reaction between styrene (**1**) and *tert*-butyl nitrite (**a**) was performed in the presence of H_2O^{18} under otherwise identical condition. Incorporation of an ^{18}O labeled product suggests that oxygen from the water is the possible source of oxygen of keto group. In order to elucidate a plausible mechanism, a reaction was carried out in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv) under otherwise identical condition. Obstruction in the desired product (**1a**, <3%) formation suggest the radical nature of the reaction. Based on literature reports and the

intermediates detected by the HRMS analysis of the reaction mixture at various time intervals, a plausible mechanism has been proposed for this transformation (Scheme IV.3.2).

Scheme IV.3.2. *Proposed mechanism for 3-phenyl-1,2,4-oxadiazol-5(4H)-one synthesis*



Heterolytic cleavage of *tert*-butyl nitrite generates a NO· radical which is converts to a NO_2 radical under the aerobic reaction condition.[9] The nitro radical (NO_2·) then attacks at the more reactive terminal carbon of the styrene to generate a nitroalkane radical intermediate (**A**). The in situ generated radical intermediate (**A**) couples with another NO radical to give a C-nitroso intermediate (**B**). Then C-nitroso intermediate (**B**) rearranges to produce α-nitrooxime (**C**), which is tautomerized to give another intermediate (**D**). The intermediate (**D**) undergoes an intramolecular cyclization reactions which leads to the formation of an unstable four membered ring (**E**).[10] Because of the ring strain, the four membered ring undergoes ring opening to generate intermediate (**F**). This reactive radical intermediate (**F**), then couple with NO radicals, followed by a radical cyclization resulted in the formation of intermediate (**H**). Dehydration of intermediate (**H**) generates an intermediate (**I**). Finally the intermediate (**I**) tautomerize to another intermediate (**J**) which is hydrolyzed with the moisture present in the solvent/open atmosphere to give the desired

product (**1a**). Almost all intermediates have been detected by the HRMS analysis of reaction mixtures at various time intervals there by supporting our mechanism.

In conclusion, we have developed an efficient metal free protocol for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(*4H*)-ones from aromatic terminal alkenes using *tert*-butyl nitrite only. Herein three sp^2 C–H functionalizations of styrene and formation of new three C–N and two C–O bonds are involved during this 1,2,4-oxadiazol-5(*4H*)-ones synthesis. These synthetic strategy generate potential opportunity for easy access of many biologically active compounds.

IV.4. Experimental section

IV.4.1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz) and in for ^{13}C NMR (100 and 150 MHz) DMSO-d_6 as the internal standard. MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

IV.4.2. Crystallographic description:

Diffraction data were collected at 292 K with MoKα radiation (λ = 0.71073 Å) using a Bruker Nonius SMART APEX CCD diffractometer equipped with graphite monochromator and Apex CD camera. The SMART software was used for data collection and for indexing the reflections and determining the unit cell parameters. Data reduction and cell refinement were performed using SAINT[1,2] software and the space groups of these crystals were determined from systematic absences by XPREP and further justified by the refinement results. The structures were solved by direct methods and refined by full-matrix least-squares calculations using SHELXTL-97[3] software. All the non-H atoms were refined in the anisotropic approximation against F^2 of all reflections.

1. G. M. Sheldrick, SADABS, 1996, based on the method described in: R. H. Blessing, *Acta Crystallogr.* 1995, **A51**, 33–38.
2. SMART and SAINT, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1996.
3. G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112–122.

Crystallographic description of 3-(*p*-tolyl)-1,2,4-oxadiazol-5(4H)-one (3a):

$C_{17}H_{11}ClN_2$, crystal dimensions 0.26 x 0.22 x 0.14 mm, M_r = 176.17, Orthorhombic, space group P 21/c, a = 9.8201(13), b = 11.2635(14), c = 7.6733(10) Å, α = 90 °, β = 103.464 °(8), γ = 90 °, V = 825.41(19) Å^3, Z = 4, ρ_{calcd} = 1.418 mg/m^3, μ = 0.103 mm^{-1}, F(000) = 368.0, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0362, wR_2 = 0.0735(1463), goodness of fit = 1.000.

IV.4.3. General procedure for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(4H)-one (1a) from styrene (1) and *tert*-butyl nitrite (a):

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added styrene (**1**) (26 mg, 0.25 mmol), *tert*-butyl nitrite (**a**) (103 mg, 1 mmol), and DMSO (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 °C for 6 h. The reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9:1) to give pure 3-phenyl-1,2,4-oxadiazol-5(4H)-one (**1a**) (27 mg, yield 67%). The identity and purity of the product were confirmed by spectroscopic analysis.

H_2O^{18} Labelling experiment for the formation of 3-phenyl-1,2,4-oxadiazol-5(4H)-one (1a) from styrene:

To an oven-dried 10 mL round bottom flask fitted with a reflux condenser was added sequentially styrene (**1**) (26 mg, 0.25 mmol), *tert*-butyl nitrite (**a**) (103 mg, 1 mmol), H_2O^{18} (9 mg, 0.5 mmol), and DMSO (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 80 °C. After completion of the reaction (6 h) the crude product was admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure. The identity of the ^{18}O labeled product was confirmed by HRMS (Figure IV.5.4) and $^{13}C\{^1H\}$ NMR (Figure IV.5.5).

IV.5. Mechanistic Investigation:

IV.5.1. ESI-MS study for the detection of reaction intermediates during the synthesis of 3-phenyl-1,2,4-oxadiazol-5(*4H*)-one (1a) from styrene (1) and *tert*-butyl nitrite (a) at different time interval:

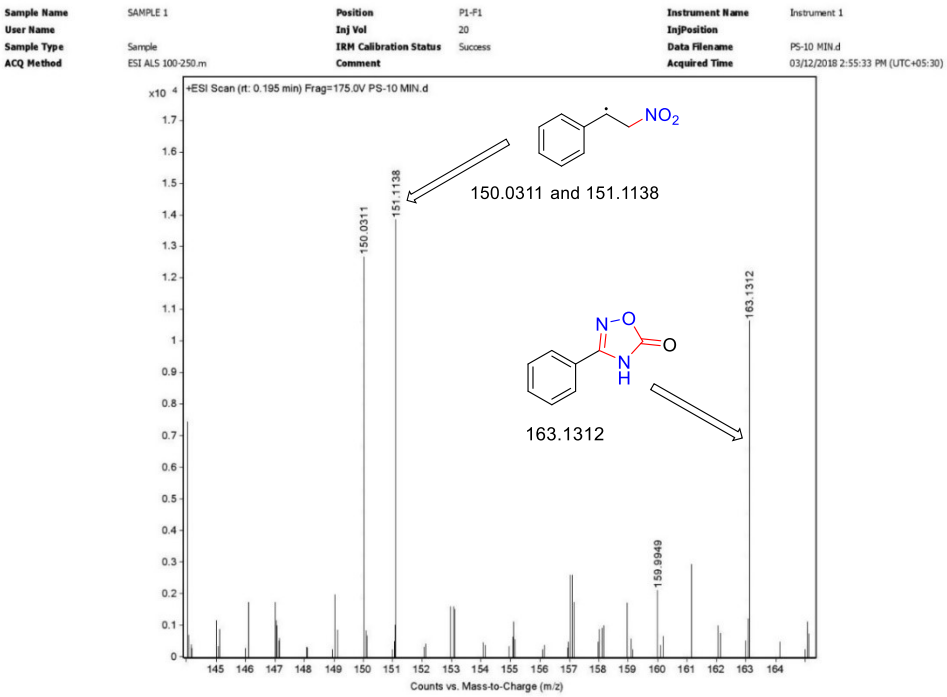


Figure IV.5.1. *HRMS spectrum of reaction mixture after 10 minute*

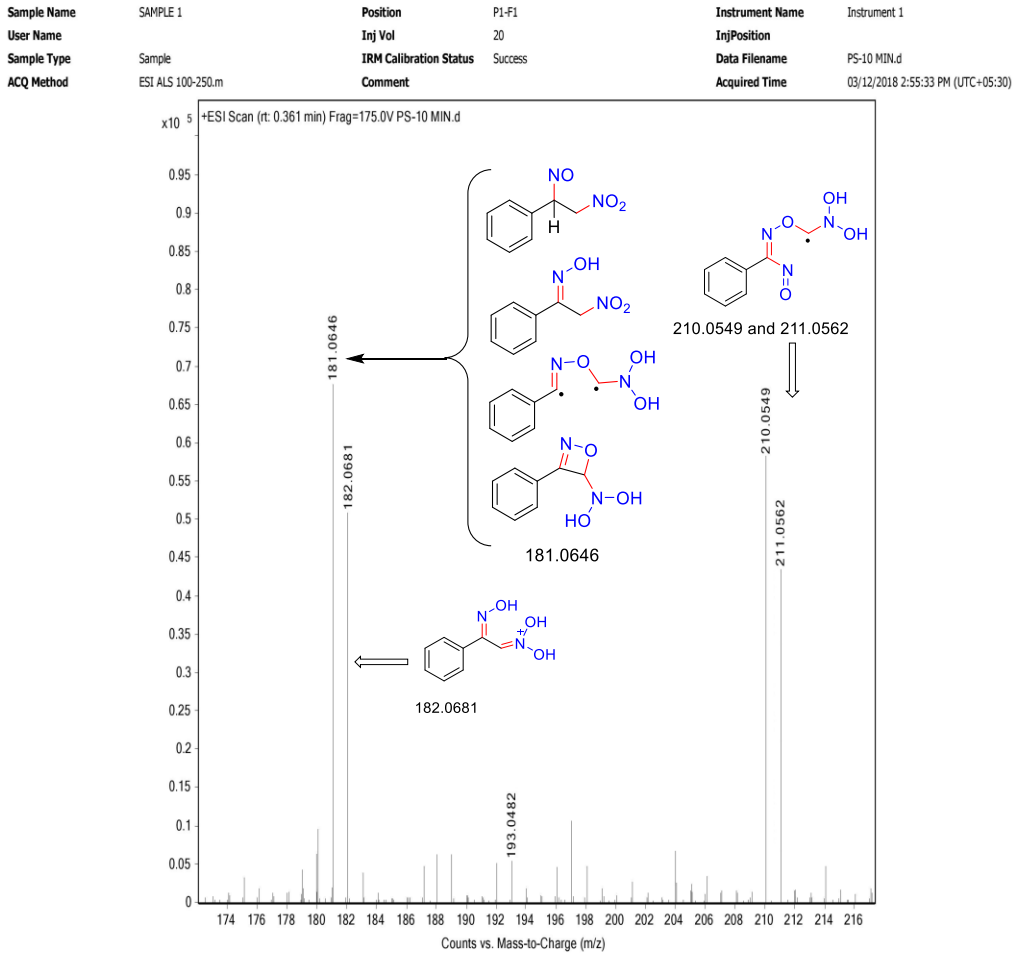


Figure IV.5.2. *HRMS spectrum of the reaction mixture after 10 minute*

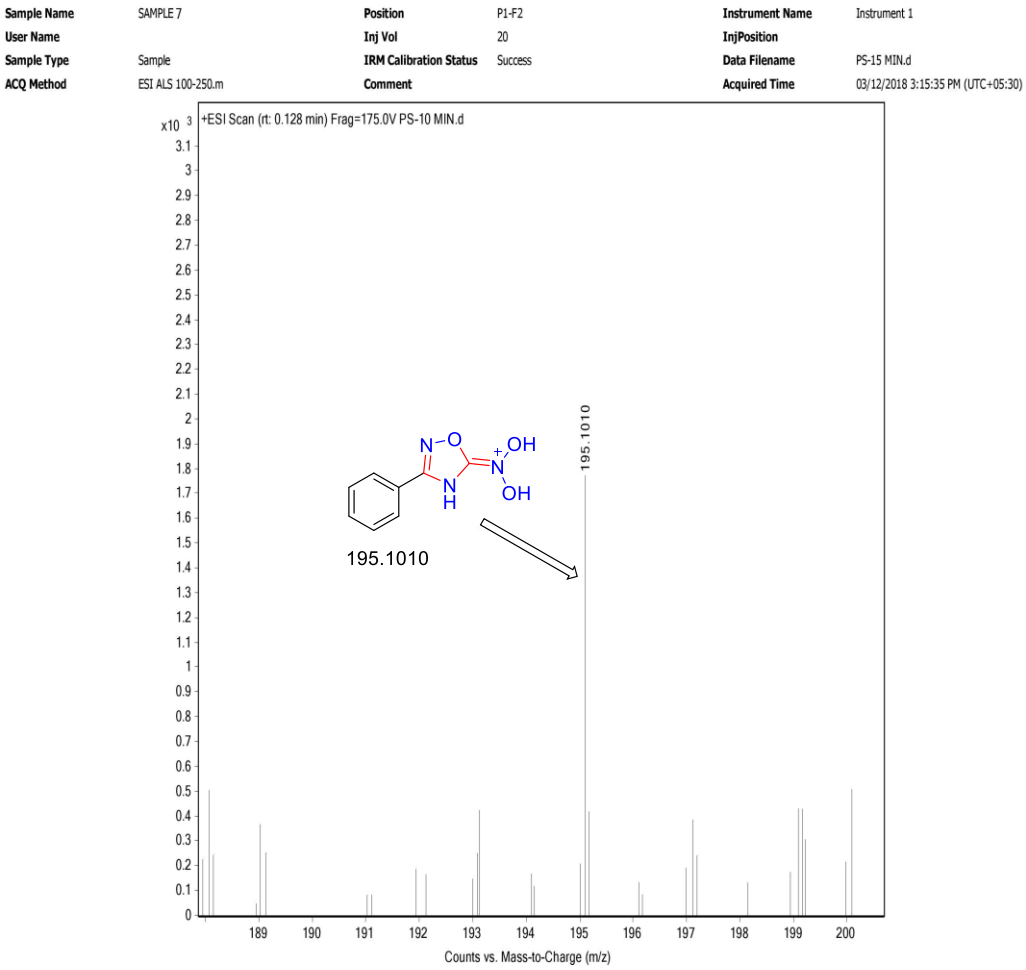


Figure IV.5.3. *HRMS spectrum of the reaction mixture after 15 minute*

IV.5.2. ESI-MS and $^{13}C\{^{1}H\}$ NMR for the H_2O^{18} labelled experiment for the formation of 3-phenyl-1,2,4-oxadiazol-5(4H)-one (1a) from styrene

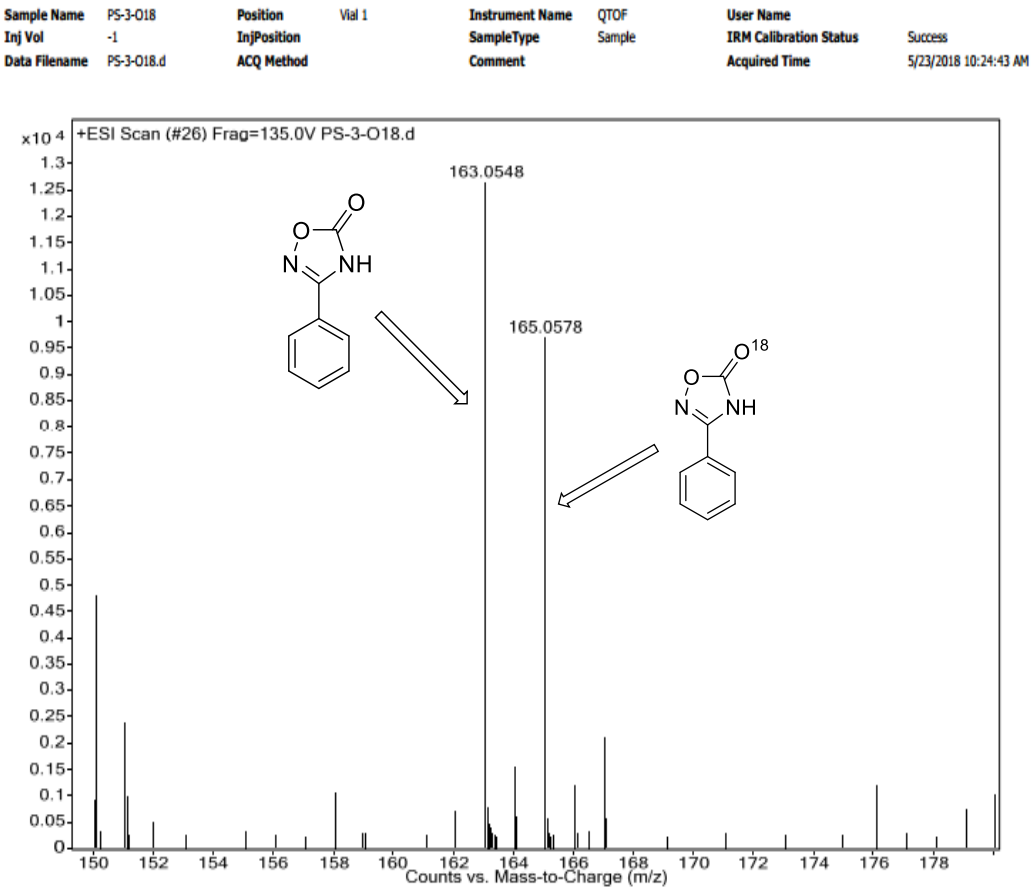


Figure IV.5.4. *HRMS spectrum of ^{18}O labelled* ***(1a)***

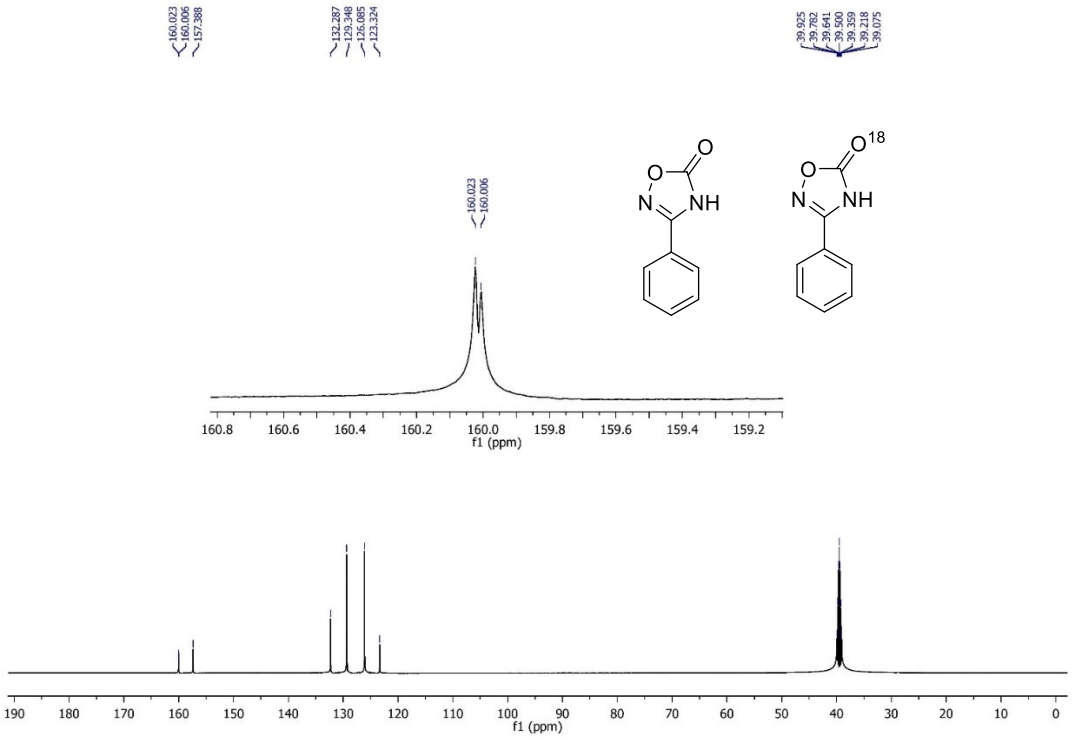


Figure IV.5.5. *$^{13}C\{^{1}H\}$ NMR spectrum of ^{18}O labelled (**1a**)*

IV.6. Reference

(1) (a) Gharat, L. A.; Muthukaman, N.; Tondlekar, S.; Khairatkar, J. N.; Shah, D. M.; Kadam, S. R. PCT Int. Appl., 2016046782, 217pp. Patent **2016** CODEN: PIXXD2. (b) Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem*. **1996**, 39, 5228. (c) Valgeirsson, J.; Nielsen, E. Ø.; Peters, D.; Mathiesen, C.; Kristensen, A. S.; Madsen, U. *J. Med. Chem*. **2004**, *47*, 6948. (d) Dong, C. Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Meddad-Bel Habich, N.; Huet, J.; Redeuilh, C.; Ombetta, J.-E.; Godfroid, J.-J.; Massicot, F.; Heymans, F. *Bioorg. Med. Chem*. **2005**, *13*, 1989.

(2) (a) Bhat, S. V.; Robinson, D.; Moses, J. E.; Sharma, P. *Org. Lett*. **2016**, *18*, 1100. (b) Charton, J.; Cousaert, N.; Bochu, C.; Willand, N.; Deprez, B.; Deprez-Poulain, R.´ *Tetrahedron Lett*. **2007**, *48*, 1479.

(3) (a) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev*. **2011**, *111*, 1293. (c) Colby, D.; Bergman, A. R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev*. **2010**, *39*, 712. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science*, **2010**, *327*, 315. (f) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev*. **2007**, *36*, 1173. (g) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev*. **2007**, *36*, 1058.

(4) (a) Sau, P.; Santra, S. K.; Rakshit, A.; Patel, B. K. *J. Org. Chem*. **2017**, *82*, 6358. (b) Sau, P.; Rakshit, A.; Modi, A.; Behera, A.; Patel, B. K. *J. Org. Chem*. **2018**, *83*, 1056. (c) Mir, B. A.; Singh, S. J.; Kumar, R.; Patel, B. K. *Adv. Synth. Catal*. **2018**, *360*, 3801. (d) Qi, Z.; Jiang, Y.; Wang, Y.; Yan, R. *J. Org. Chem*. **2018**, *83*, 8636. (e) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495–10499.

(5) Maity, S.; Togati, N.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384.

(6) Gao, X.; Pan, X.; Gao, J.; Jiang, H.; Yuan, G.; Li, Y. *Org. Lett*. **2015**, *17*, 1038.

(7) Baykov, S.; Sharonova, T.; Shetnev, A.; Rozhkov, S.; Kalinin, S.; Smirnov, A. V. *Tetrahedron* **2017**, *73*, 945.

(8) Gerfaud, T.; Wei, H. L.; Neuville, L.; Zhu, J. P. *Org. Lett*. **2011**, *13*, 6172.

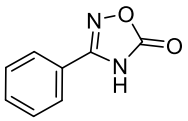
(9) (a) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal*. **2011**, *353*, 2643. (b) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun*. **2013**, *49*, 514. (c) Taniguchi, T.; Sugiura, Y.; Hatta, T.; Yajima, A.; Ishibashi, H. *Chem. Commun.* **2013**, *49*, 2198. (d) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun*. **2011**,

47, 12462. (e) Galliker, B.; Kissner, R.; Nauser, T.; Koppenol, W. H. *Chem. Eur. J.* **2009**, *15*, 6161.

(10) Dutta, U.; Lupton, D. W.; Maiti, D. *Org. Lett.* **2016**, *18*, 860.

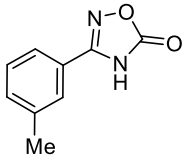
IV.7. Spectral data

*3-Phenyl-1,2,4-oxadiazol-5(4H)-one (**1a**):*



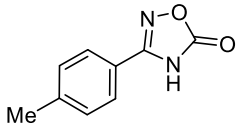
Yield: 67% (27mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 13.01 (s, 1H), 7.81 (d, 2H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.2 Hz), 7.58 (t, 2H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 159.9, 157.4, 132.3, 129.3, 126.1, 123.3; IR (KBr, cm^{-1}): 3128, 3049, 1762, 1741, 1608, 1551, 1462, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_7N_2O_2$, $[M+H]^+$: 163.0502, found 163.0506.

*3-(m-Tolyl)-1,2,4-oxadiazol-5(4H)-one (**2a**):*



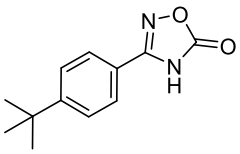
Yield: 64% (28 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 12.91 (s, 1H), 7.64 (s, 1H), 7.59 (d, 1H, J = 7.2 Hz), 7.47–7.43 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 159.9, 157.4, 138.8, 132.8, 129.2, 126.4, 123.3, 123.2, 20.9; IR (KBr, cm^{-1}): 3120, 3041, 1760, 1741, 1609, 1550, 1461, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_9H_9N_2O_2$, $[M+H]^+$: 177.0659, found 177.0654.

*3-(p-Tolyl)-1,2,4-oxadiazol-5(4H)-one (**3a**):*



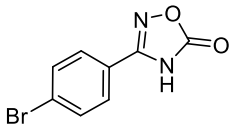
Yield: 66% (29 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 12.89 (s, 1H), 7.69 (d, 2H, J = 7.8 Hz), 7.39 (d, 2H, J = 8.4 Hz), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 159.9, 157.3, 142.4, 129.8, 125.9, 120.5, 21.1; IR (KBr, cm^{-1}): 3127, 3049, 1761, 1745, 1609, 1552, 1461, 1254; HRMS (ESI/Q-TOF) (m/z): calcd for $C_9H_9N_2O_2$, $[M+H]^+$: 177.0659, found 177.0649.

*3-(4-(tert-Butyl)phenyl)-1,2,4-oxadiazol-5(4H)-one (**4a**):*



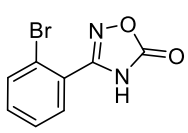
Yield: 69% (38 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 12.95 (s, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 8.4 Hz), 1.29 (s, 9H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 160.1, 157.3, 155.3, 126.2, 125.9,120.5, 34.9, 30.8; IR (KBr, cm^{-1}): 3126, 3041, 1761, 1745, 1607, 1550, 1461, 1255; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{12}H_{15}N_2O_2$, $[M+H]^+$: 219.1128, found 219.1120.

*3-(4-Bromophenyl)-1,2,4-oxadiazol-5(4H)-one (**5a**):*



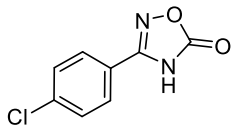
Yield: 71% (42 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.81 (d, 2H, J = 8.8 Hz), 7.74 (d, 2H, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.9, 156.8, 132.4, 127.9, 125.9, 122.6; IR (KBr, cm^{-1}): 3127, 3045, 1761, 1745, 1607, 1555, 1461, 1261; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6BrN_2O_2$, $[M+H]^+$: 240.9607, found 240.9611.

*3-(2-Bromophenyl)-1,2,4-oxadiazol-5(4H)-one (**6a**):*



Yield: 65% (38 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.92 (s, 1H), 7.87–7.85 (m, 1H), 7.70–7.68 (m, 1H), 7.59–7.57 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.5, 157.5, 133.61, 133.57, 131.8, 128.2, 125.2, 121.5; IR (KBr, cm^{-1}): 3130, 3050, 1760, 1745, 1609, 1553, 1460, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6BrN_2O_2$, $[M+H]^+$: 240.9607, found 240.9601.

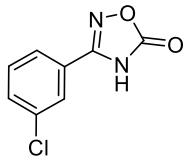
*3-(4-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (**7a**):*



Yield: 74% (36 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 13.06 (s, 1H), 7.82 (d, 2H, J = 8.4 Hz), 7.67 (d, 2H, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.8, 156.6, 136.9, 129.5, 127.8, 122.2; IR (KBr, cm^{-1}): 3129, 3049, 1761, 1741, 1608, 1551, 1462, 1259; HRMS

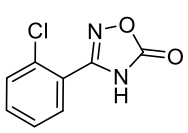
(ESI/Q-TOF) (m/z): calcd for $C_8H_6ClN_2O_2$, $[M+H]^+$: 197.0112, found 197.0110.

*3-(3-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (**8a**):*



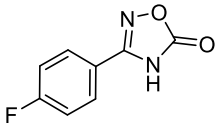
Yield: 69% (34 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.85–7.84 (m, 1H), 7.79–7.76 (m, 1H), 7.72–7.69 (m, 1H), 7.63–7.59 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.8, 156.4, 133.9, 132.0, 131.3, 125.9, 125.3, 124.7; IR (KBr, cm^{-1}): 3128, 3049, 1762, 1741, 1608, 1551, 1462, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6ClN_2O_2$, $[M+H]^+$: 197.0112, found 197.0119.

*3-(2-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (**9a**):*



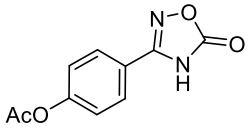
Yield: 67% (32 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.85 (s, 1H), 7.73–7.69 (m, 2H), 7.68–7.64 (m, 1H), 7.57–7.53 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.6, 156.4, 133.5, 132.0, 131.4, 130.5, 127.8, 122.9; IR (KBr, cm^{-1}): 3130, 3046, 1762, 1745, 1608, 1552, 1462, 1259; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6ClN_2O_2$, $[M+H]^+$: 197.0112, found 197.0122.

*3-(4-Fluorophenyl)-1,2,4-oxadiazol-5(4H)-one (**10a**):*



Yield: 75% (34 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.89–7.85 (m, 2H), 7.44 (t, 2H, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.4, 162.9, 159.9, 156.6, 128.8 (d, J = 9.1 Hz), 119.9 (d, J = 3.2 Hz), 116.6 (d, J = 22.2 Hz); IR (KBr, cm^{-1}): 3128, 3049, 1761, 1741, 1611, 1551, 1462, 1255; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6FN_2O_2$, $[M+H]^+$: 181.0408, found 181.0405.

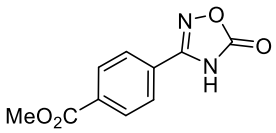
*4-(5-Oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenyl acetate (**11a**):*



Yield: 79% (43 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.99 (s, 1H), 7.85 (d, 2H, J = 8.4 Hz), 7.37

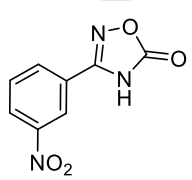
(d, 2H, J = 8.8 Hz), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.9, 159.9, 156.9, 153.2, 130.9, 127.6, 122.9, 120.9, 20.9; IR (KBr, cm^{-1}): 3128, 3048, 1762, 1741, 1609, 1551, 1461, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{10}H_9N_2O_4$, $[M+H]^+$: 221.0557, found 221.0553.

*Methyl 4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzoate (**12a**):*



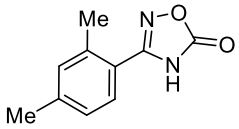
Yield: 77% (42 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.15 (s, 1H), 8.13 (d, 2H, J = 8.0 Hz), 7.95 (d, 2H, J = 8.0 Hz), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.4, 159.9, 156.8, 132.6, 129.9, 127.5, 126.5, 52.5; IR (KBr, cm^{-1}): 3125, 3049, 1765, 1741, 1611, 1551, 1462, 1255; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{10}H_9N_2O_4$, $[M+H]^+$: 221.0557, found 221.0550.

*3-(3-Nitrophenyl)-1,2,4-oxadiazol-5(4H)-one (**13a**):*



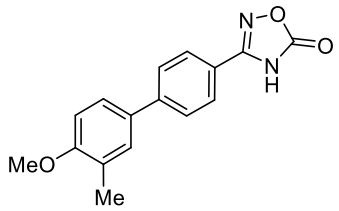
Yield: 75% (39 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.62 (s, 1H), 8.46–8.44 (m, 1H), 8.23–8.22 (m, 1H), 7.87 (t, 1H, J = 8.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.9, 156.3, 148.2, 132.2, 131.2, 126.7, 125.0, 121.1; IR (KBr, cm^{-1}): 3128, 3049, 1766, 1748, 1608, 1551, 1468, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_8H_6N_3O_4$, $[M+H]^+$: 208.0353, found 208.0357.

*3-(2,4-Dimethylphenyl)-1,2,4-oxadiazol-5(4H)-one (**14a**):*



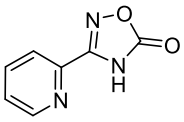
Yield: 62% (29 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.70 (s, 1H), 7.46 (d, 1H, J = 7.6 Hz), 7.23 (s, 1H), 7.19 (d, 1H, J = 7.6 Hz), 2.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.7, 157.9, 141.4, 137.1, 132.1, 128.8, 126.8, 119.9, 20.8, 20.6; IR (KBr, cm^{-1}): 3131, 3051, 1768, 1745, 1609, 1551, 1467, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{10}H_{11}N_2O_2$, $[M+H]^+$: 191.0815, found 191.0810.

*3-(4'-Methoxy-3'-methyl-[1,1'-biphenyl]-4-yl)-1,2,4-oxadiazol-5(4H)-one (**15a**):*



Yield: 81% (57 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.92 (s, 1H), 7.97 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz), 7.57–7.55 (m, 2H), 7.04 (d, 1H, J = 9.2 Hz), 3.83 (s, 3H), 2.22 (s, 3H); 13C NMR (DMSO-d_6, 150 MHz): δ 167.3, 157.7, 144.2, 130.8, 129.9, 128.9, 128.7, 126.3, 126.1, 125.6, 110.8, 55.4, 16.2; IR (KBr, cm^{-1}): 3128, 3051, 1762, 1748, 1633, 1608, 1551, 1526, 1462, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_{16}H_{15}N_2O_3$, $[M+H]^+$: 283.1077, found 283.1075.

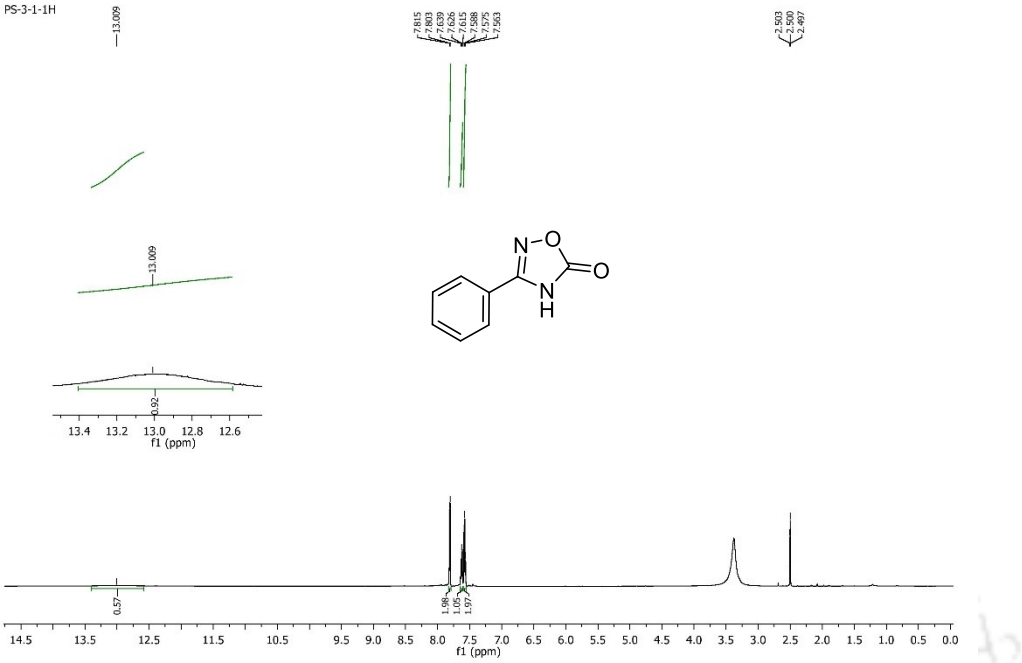
*3-(Pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (**16a**):*



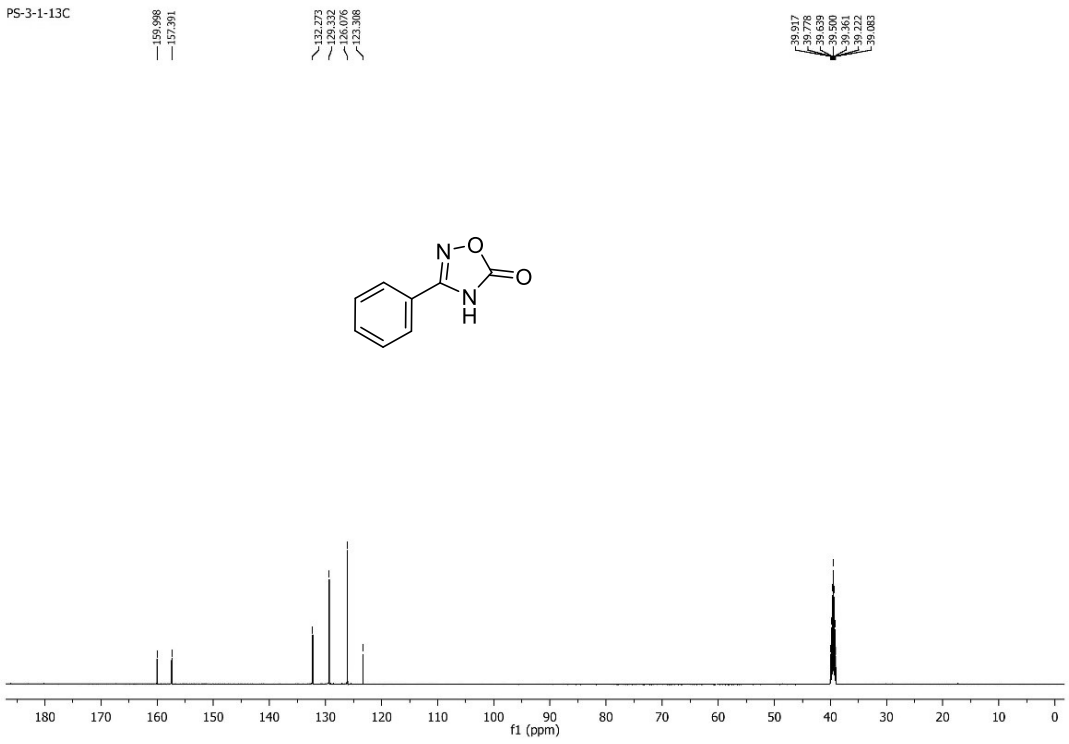
Yield: 73% (30 mg) as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.17 (s, 1H), 8.77–8.76 (m, 1H), 8.07–7.98 (m, 2H), 7.67–7.64 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.7, 157.7, 149.9, 142.7, 137.9, 126.8, 121.5; IR (KBr, cm^{-1}): 3128, 3051, 1768, 1741, 1611, 1551, 1462, 1257; HRMS (ESI/Q-TOF) (m/z): calcd for $C_7H_6N_3O_2$, $[M+H]^+$: 164.0455, found 164.0455.

IV.8. Spectra

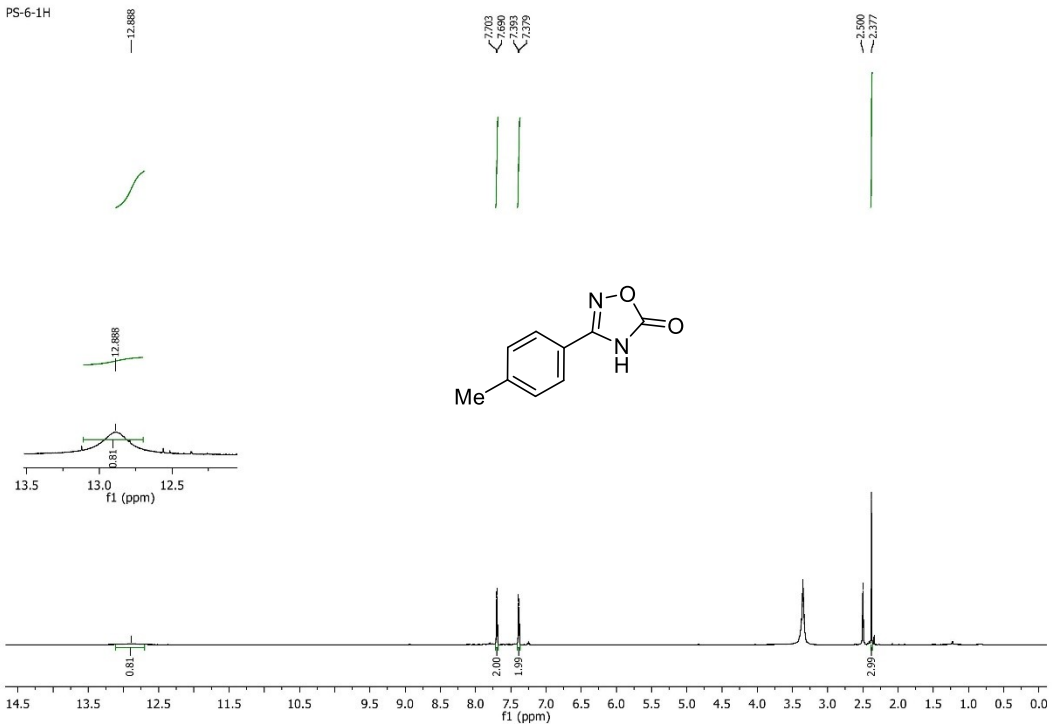
3-Phenyl-1,2,4-oxadiazol-5(4H)-one (1a): ^{1}H NMR (DMSO-*d*$_6$, 600 MHz)



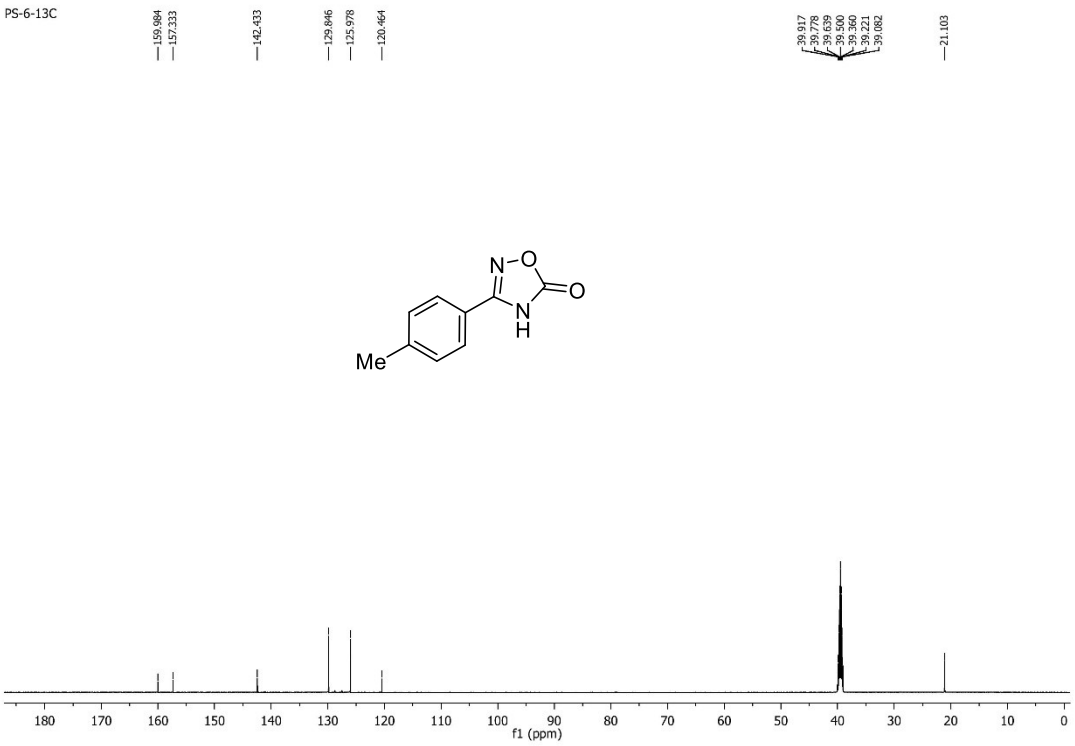
3-Phenyl-1,2,4-oxadiazol-5(4H)-one (1a): ^{13}C NMR (DMSO-*d*$_6$, 150 MHz)



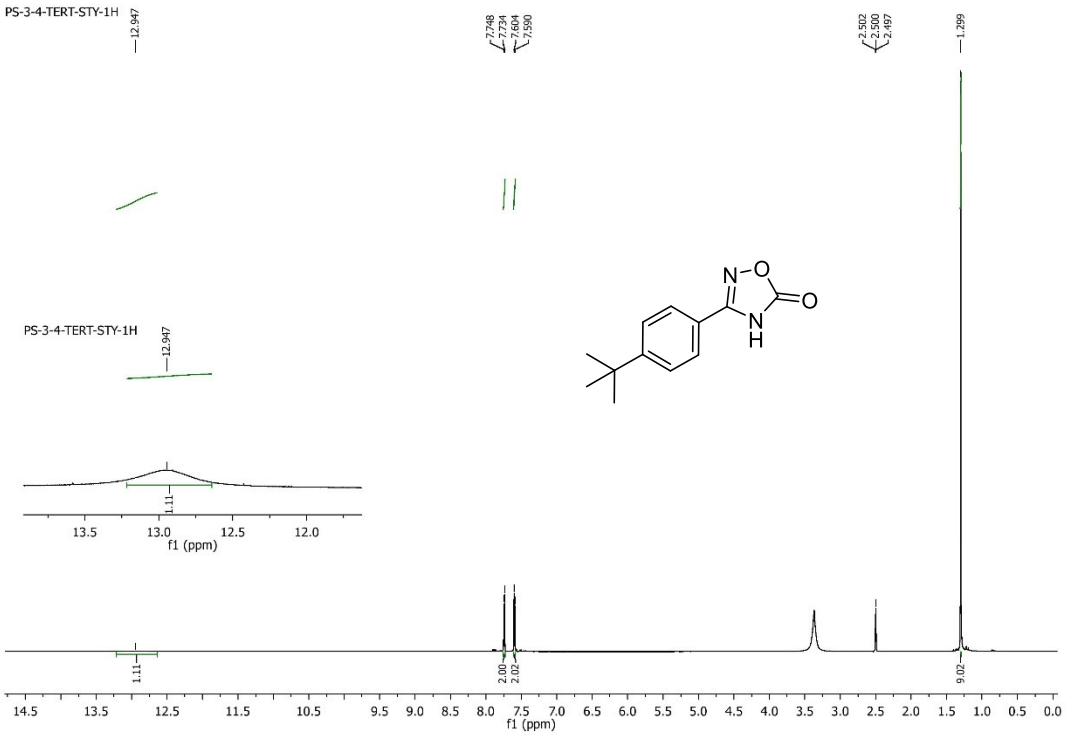
3-(p-Tolyl)-1,2,4-oxadiazol-5(4H)-one (3a): ^{1}H NMR (DMSO-*d*$_6$, 600 MHz)



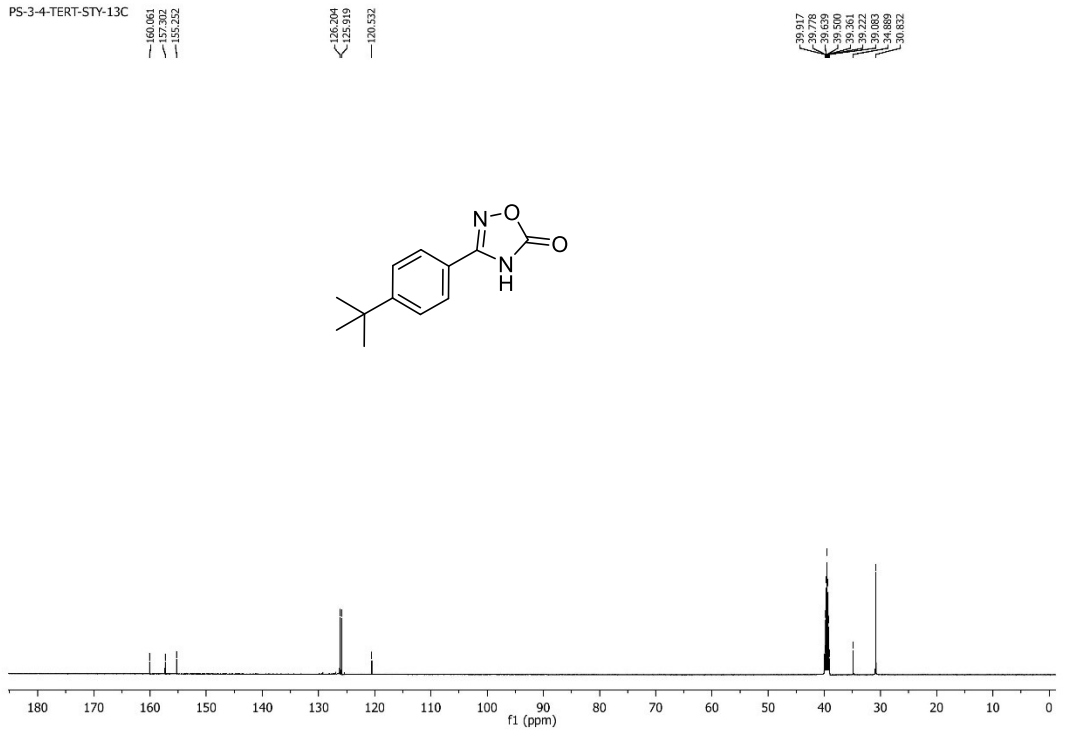
3-(p-Tolyl)-1,2,4-oxadiazol-5(4H)-one (3a): ^{13}C NMR (DMSO-*d*$_6$, 150 MHz)



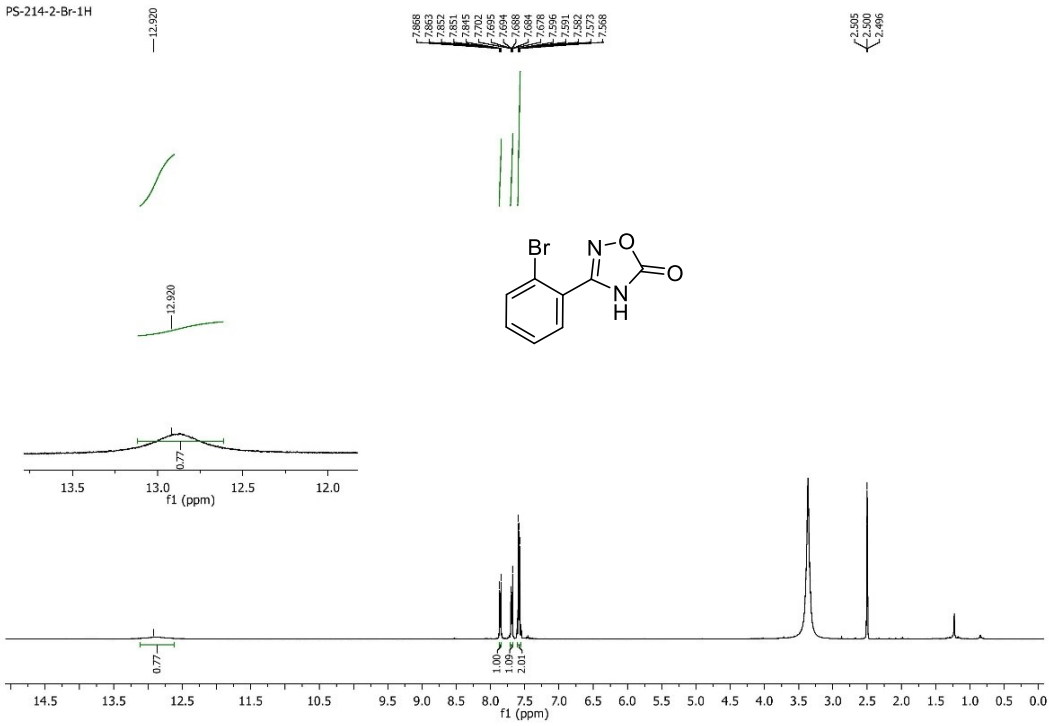
3-(4-(tert-Butyl)phenyl)-1,2,4-oxadiazol-5(4H)-one (4a): ^{1}H NMR (DMSO-*d*$_6$, 600 MHz)



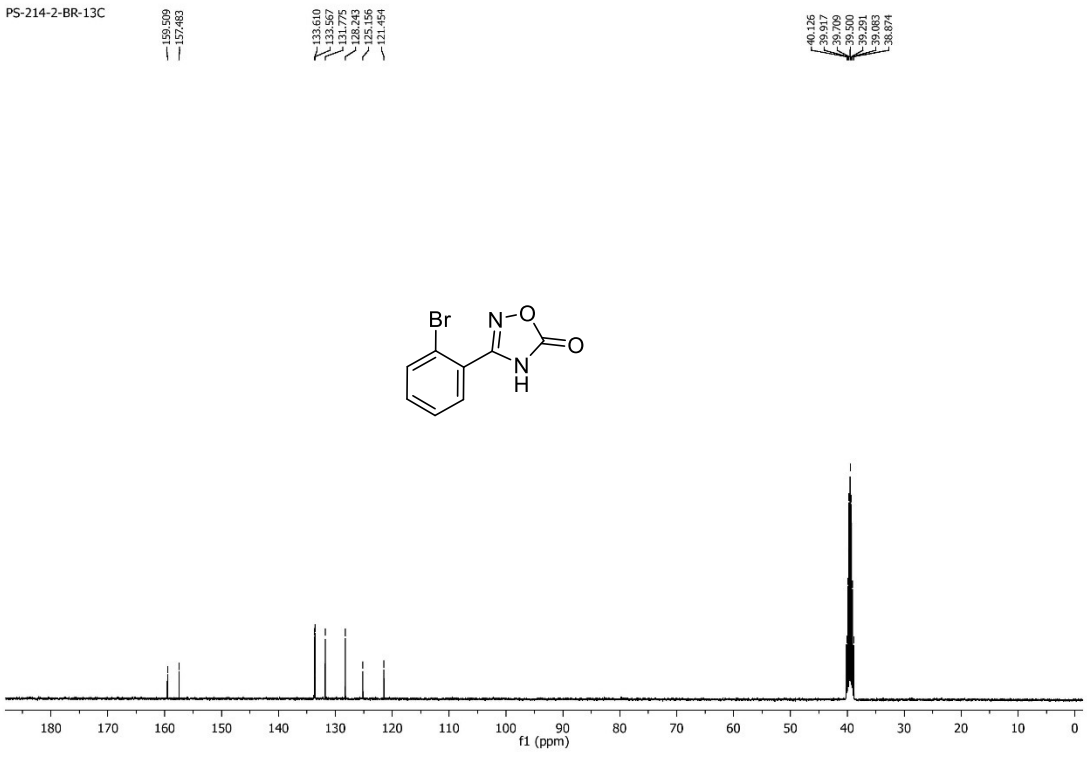
3-(4-(tert-Butyl)phenyl)-1,2,4-oxadiazol-5(4H)-one (4a): ^{13}C NMR (DMSO-*d*$_6$, 150 MHz)



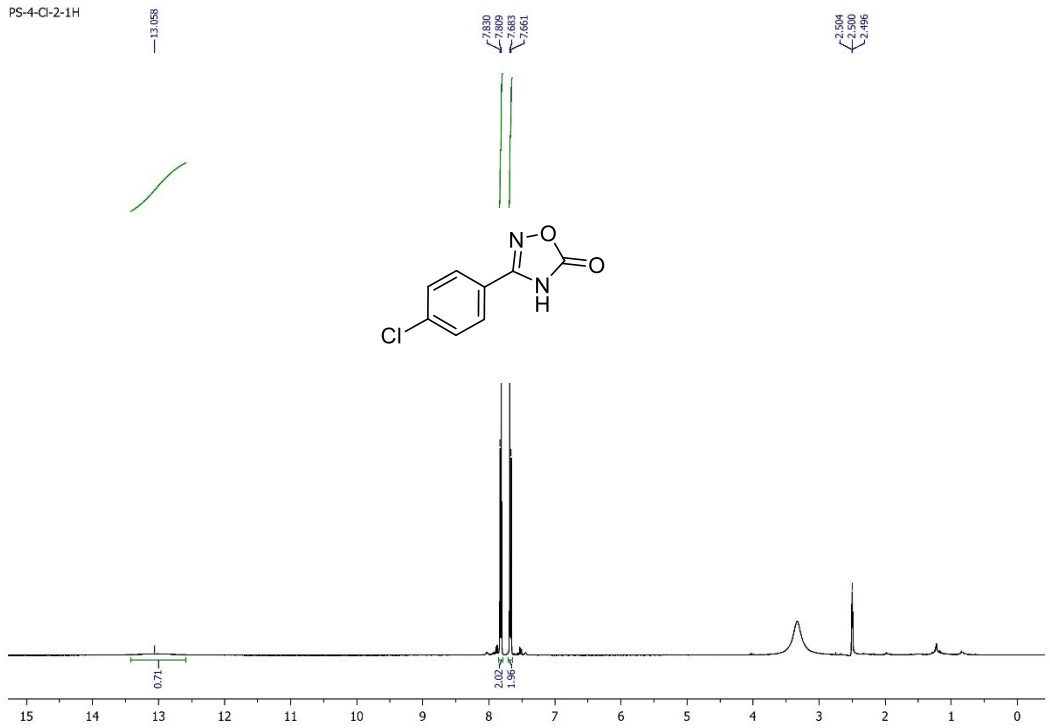
3-(2-Bromophenyl)-1,2,4-oxadiazol-5(4H)-one (6a): ^{1}H NMR (DMSO-*d*$_6$, 400 MHz)



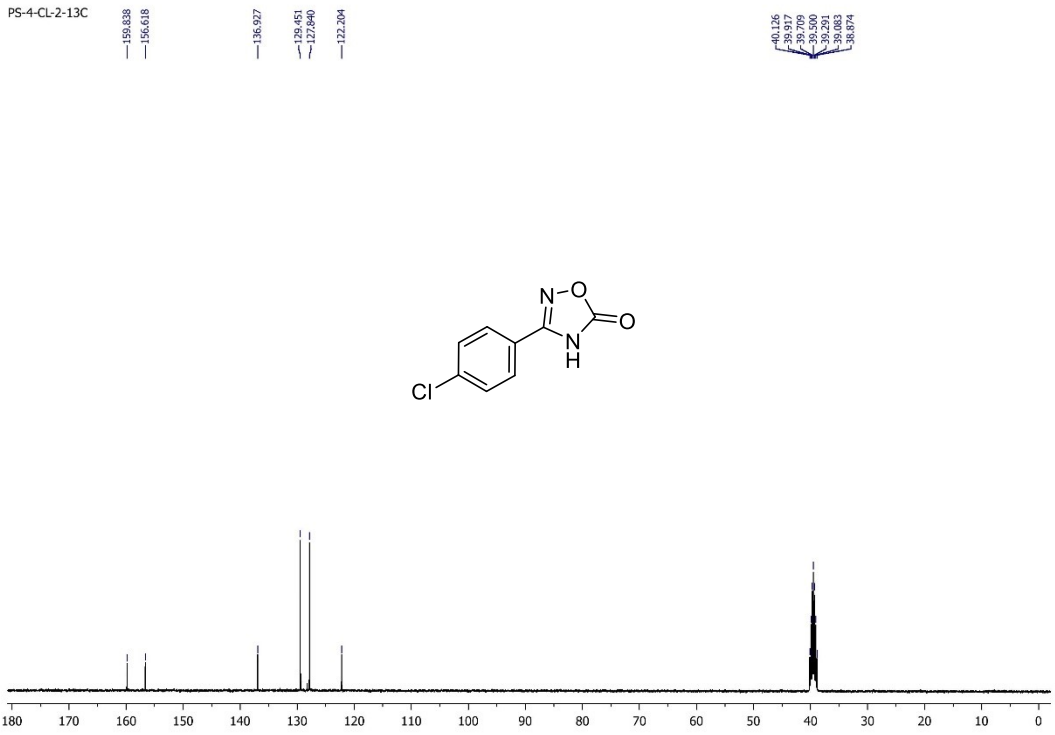
3-(2-Bromophenyl)-1,2,4-oxadiazol-5(4H)-one (6a): ^{13}C NMR (DMSO-*d*$_6$, 100 MHz)



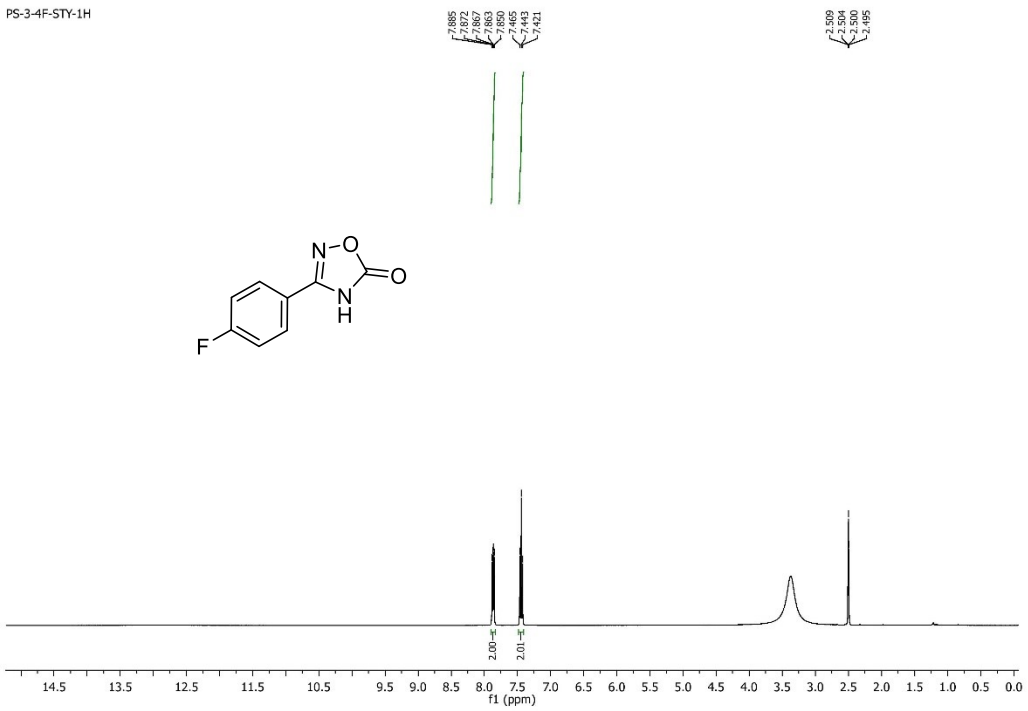
3-(4-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (7a): ^{1}H NMR (DMSO-d_6, 400 MHz)



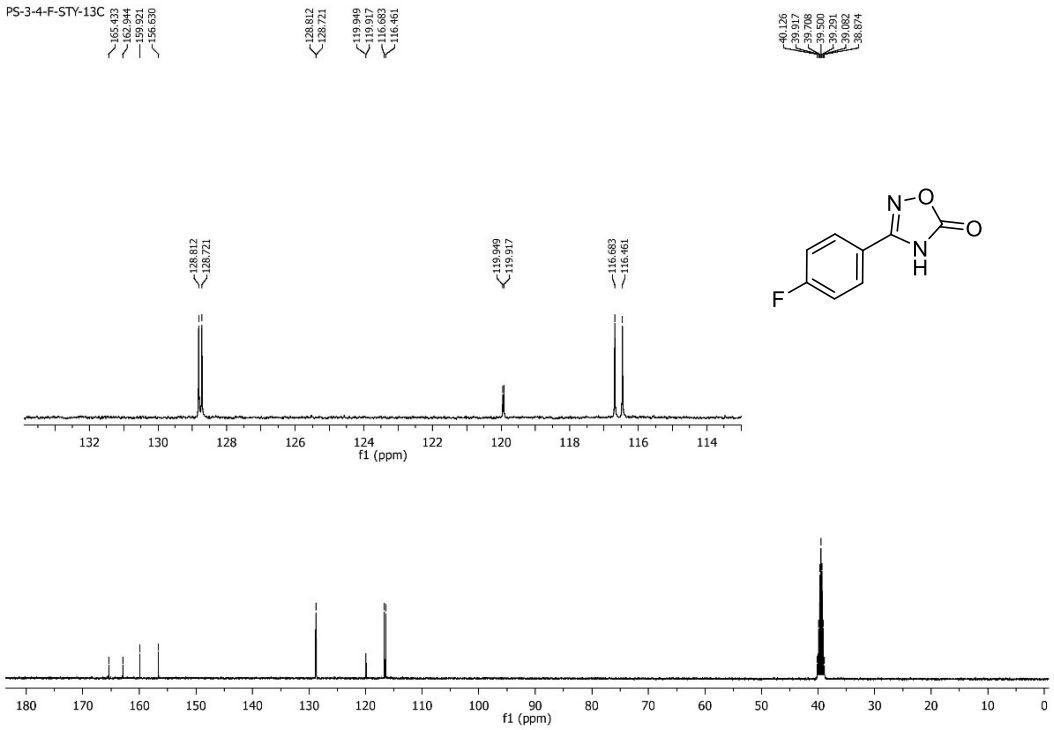
3-(4-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (7a): ^{13}C NMR (DMSO-d_6, 100 MHz)



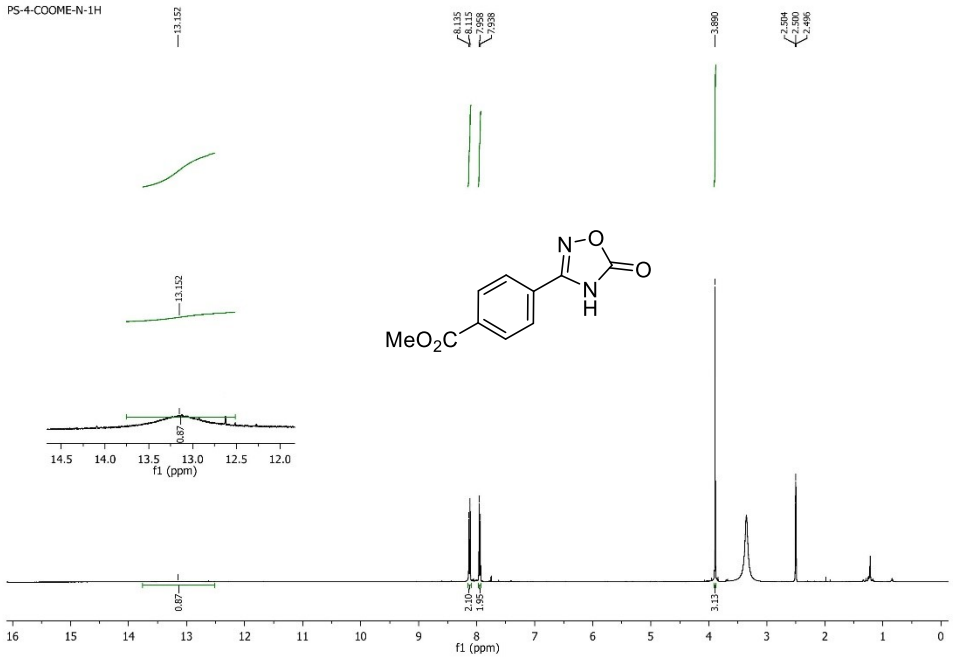
3-(4-Fluorophenyl)-1,2,4-oxadiazol-5(4H)-one (10a): ^{1}H NMR (DMSO-*d*$_6$, 400 MHz)



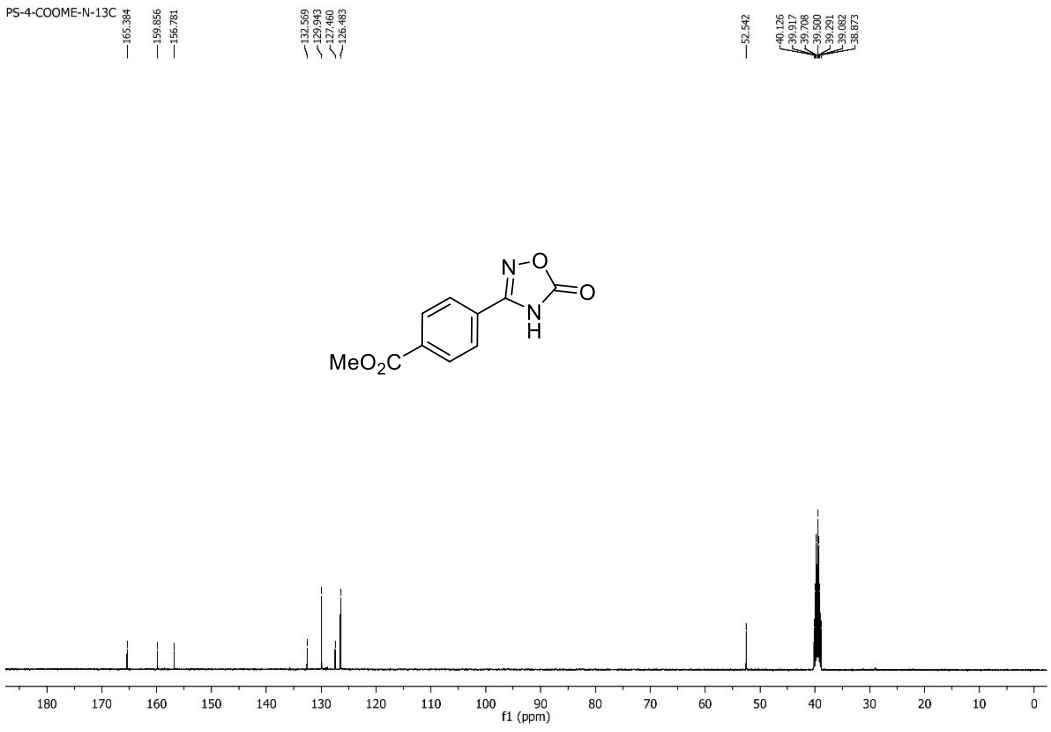
3-(4-Fluorophenyl)-1,2,4-oxadiazol-5(4H)-one (10a): ^{13}C NMR (DMSO-*d*$_6$, 100 MHz)



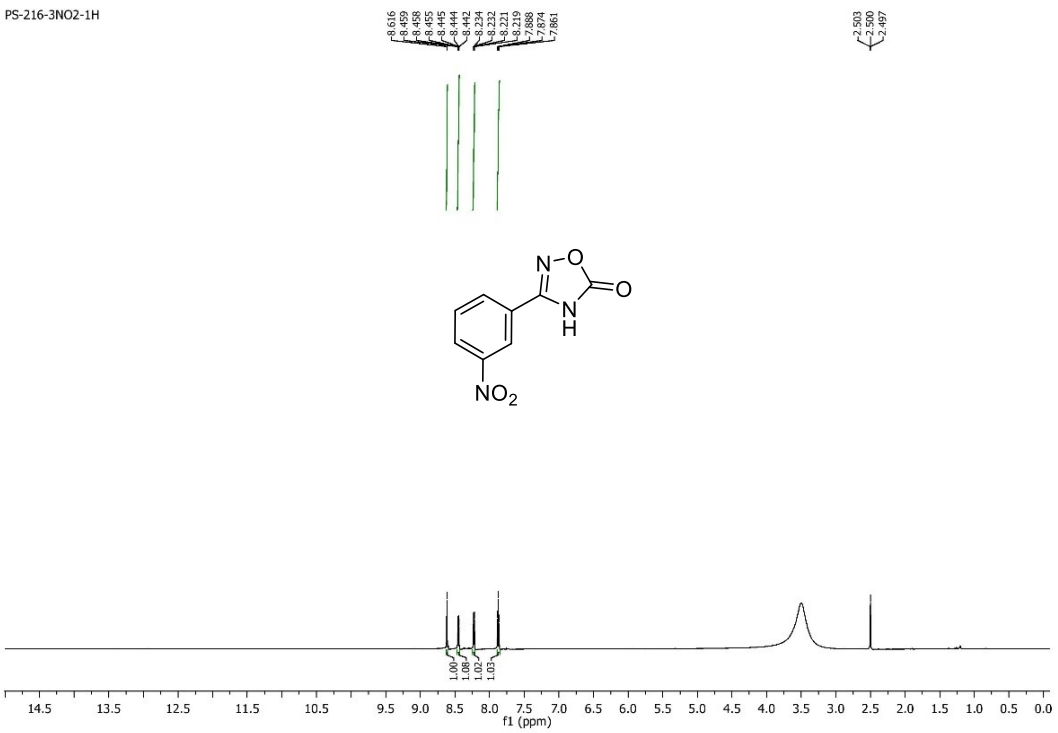
Methyl 4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzoate (12a): ^{1}H NMR (DMSO-*d*$_6$, 400 MHz)



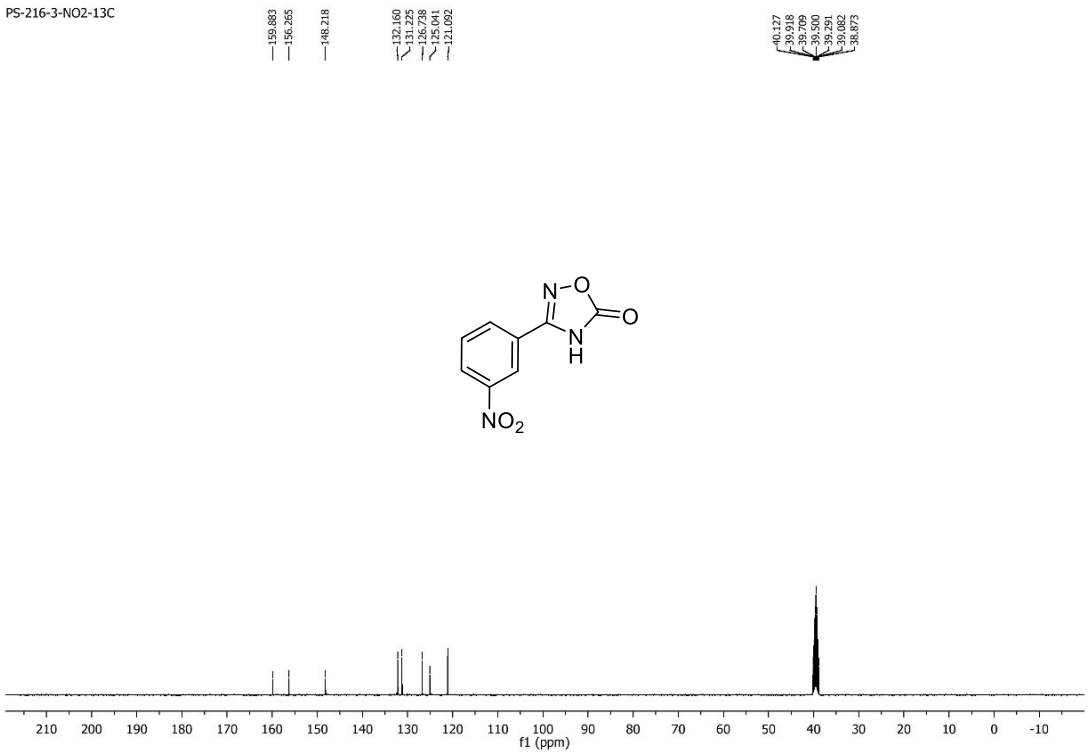
Methyl 4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzoate (12a): ^{13}C NMR (DMSO-*d*$_6$, 100 MHz)



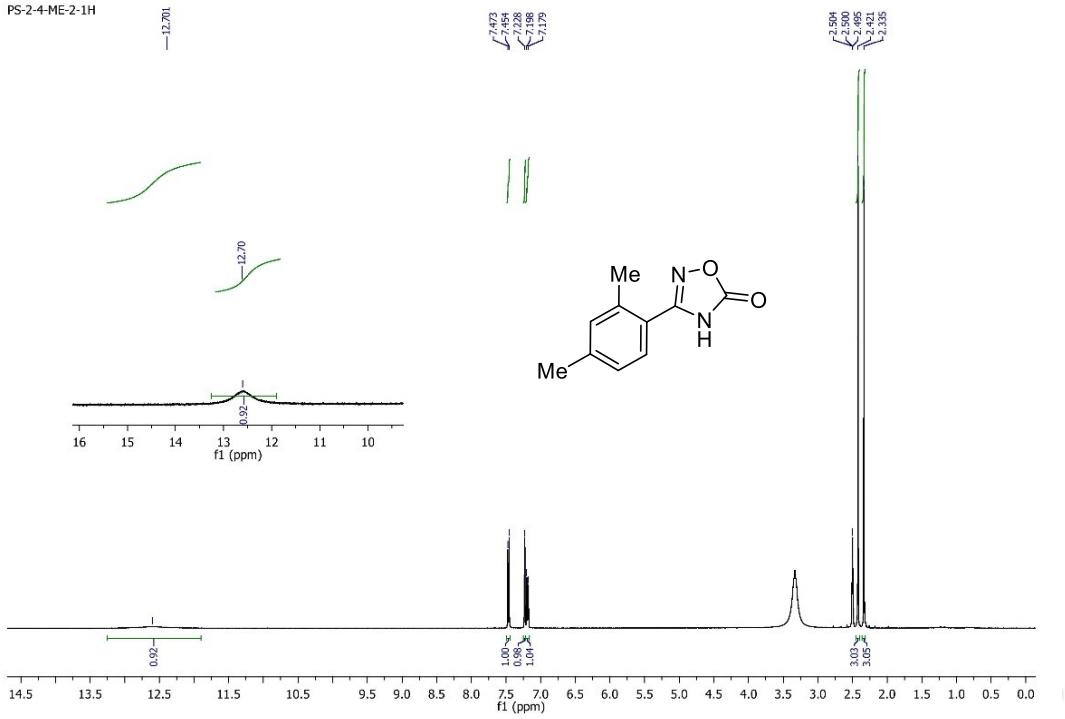
3-(3-Nitrophenyl)-1,2,4-oxadiazol-5(4H)-one (13a): ^{1}H NMR (DMSO-*d*$_6$, 600 MHz)



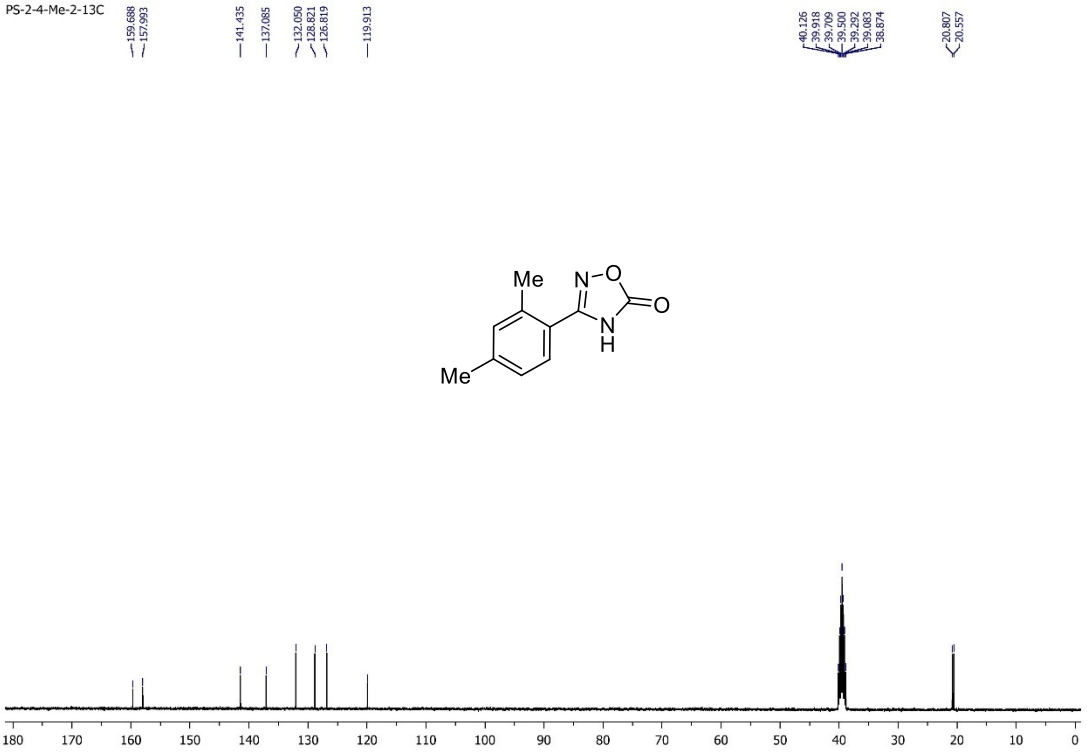
3-(3-Nitrophenyl)-1,2,4-oxadiazol-5(4H)-one (13a): ^{13}C NMR (DMSO-*d*$_6$, 100 MHz)



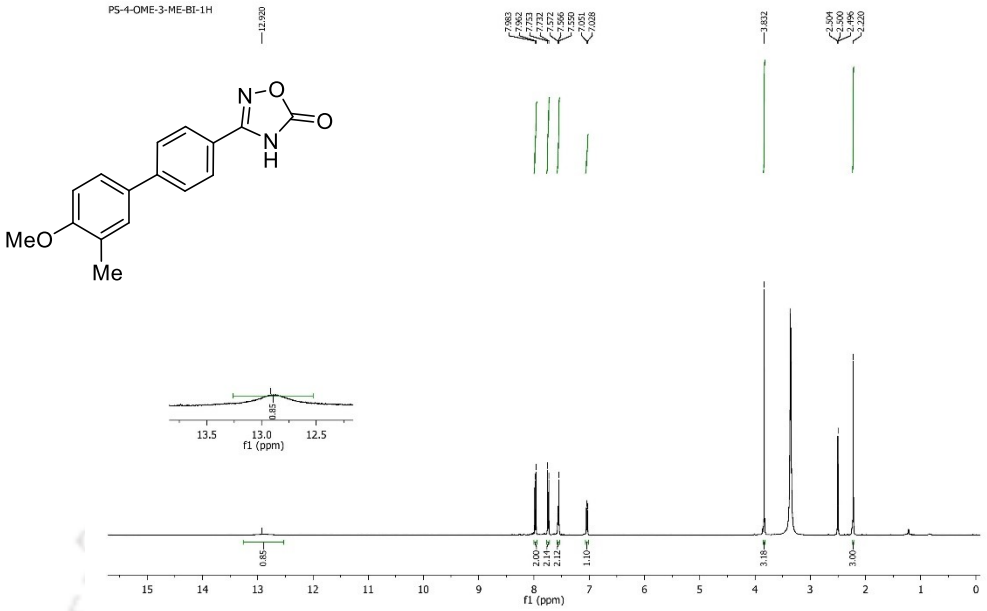
3-(2,4-Dimethylphenyl)-1,2,4-oxadiazol-5(4H)-one (14a): ^{1}H NMR (DMSO-d_6, 400 MHz)



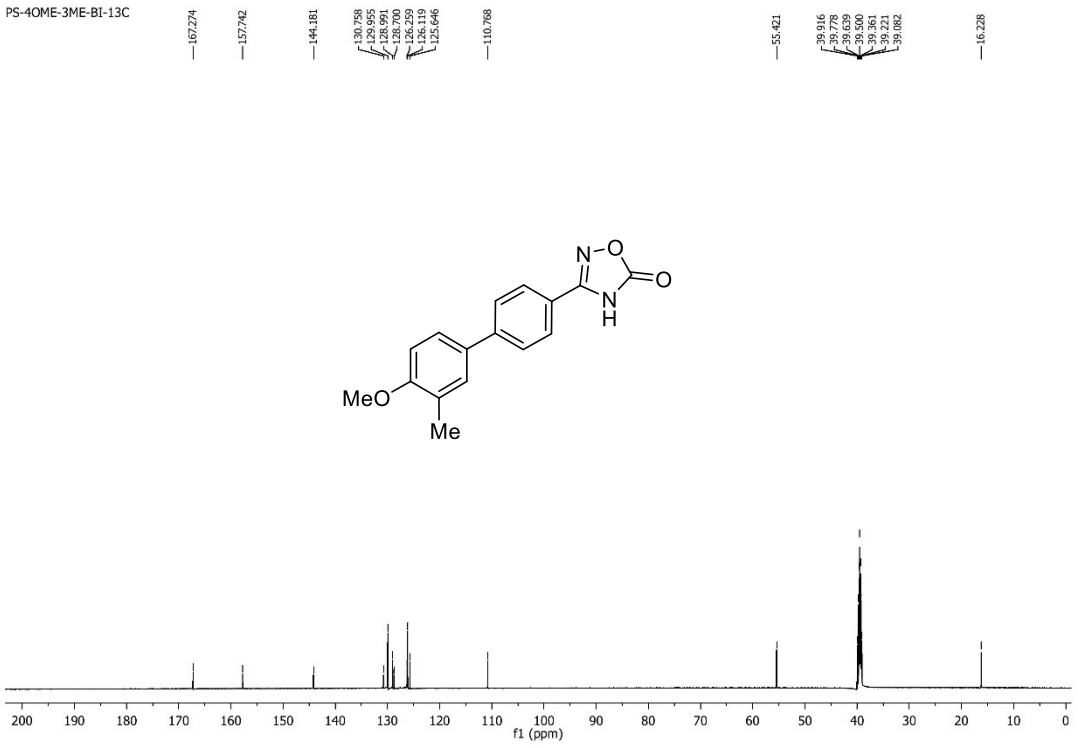
3-(2,4-Dimethylphenyl)-1,2,4-oxadiazol-5(4H)-one (14a): ^{13}C NMR (DMSO-d_6, 100 MHz)



3-(4'-Methoxy-3'-methyl-[1,1'-biphenyl]-4-yl)-1,2,4-oxadiazol-5(4H)-one (15a): ^{1}H NMR (DMSO-d_6, 400 MHz)



3-(4'-Methoxy-3'-methyl-[1,1'-biphenyl]-4-yl)-1,2,4-oxadiazol-5(4H)-one (15a): ^{13}C NMR (DMSO-d_6, 150 MHz)



List of Publications

1. Copper(II)-Catalyzed Synthesis of -Indoloquinoxalin-6-ones through Oxidative Mannich Reaction

   Gogoi, A.; **Sau, P**.; Ali, W.; Guin, S.; Patel, B. K. *Eur. J. Org. Chem*. **2016**, 1449.
2. *tert*-Butyl Nitrite-Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes

   Sau, P.; Santra, S. K.; Rakshit, A.; Patel, B. K. *J. Org. Chem*. **2017**, *82*, 6358.
3. Base-Promoted Synthesis of Quinoline-4(1H)-thiones from o-Alkynylanilines and Aroyl Isothiocyanates

   Modi, A.; **Sau, P**.; Patel, B. K. *Org. Lett*. **2017**, *19*, 6128.
4. Three sequential C−N bond formations: *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[1,2-*a*]quinolines and imidazo[2,1-*a*]isoquinolines

   Sau, P.; Rakshit, A.; Modi, A.; Behera, A.; Patel, B. K. *J. Org. Chem*. **2018**, *83*, 1056.
5. Cyano-Sacrificial (Arylthio)arylamination of Quinoline and Isoquinoline *N*-Oxides Using N-(2-(Arylthio)aryl)cyanamides

   Behera, A.; **Sau, P**.; Sahoo, A. K.; Patel, B. K. *J. Org. Chem*. **2018**, *83*, 11218.
6. A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1H)-thiones with Alkynes

   Modi, A.; Sau, P.; Chakraborty, N.; Patel, B. K. *Adv. Synth. Catal*. **2019**, *6*, 1368.
7. *tert*-Butyl Nitrite-Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(4H)-ones from Terminal Aryl Alkenes

   Sau, P.; Rakshit, A.; Patel, B. K. (Manuscript under communication)