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

A Synopsis Report

Submitted by

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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.

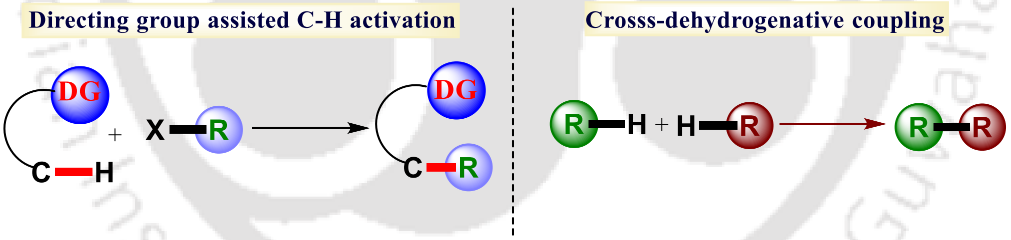
CHAPTER I. An Overview of *tert*-Butyl Nitrite Mediated C–H Functionalization Reactions

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.

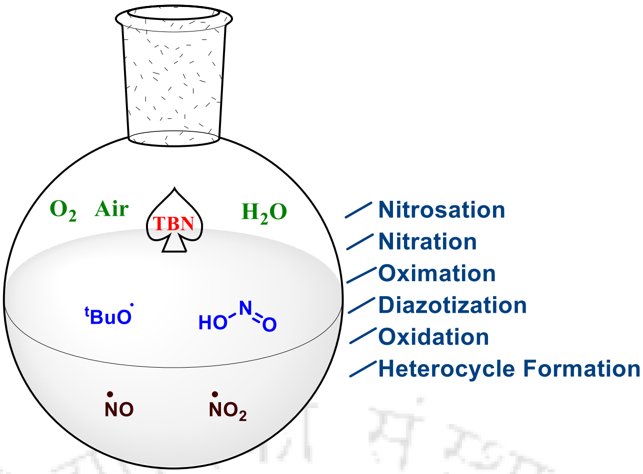
Though there are several advantages of direct C–H bond functionalization reactions but it also suffer from some limitations such as controlling the chemo–, regio– and stereoslectivity in a complex organic molecule is quite challenging. These challenges of selectivity in C–H bond functionalization can 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.



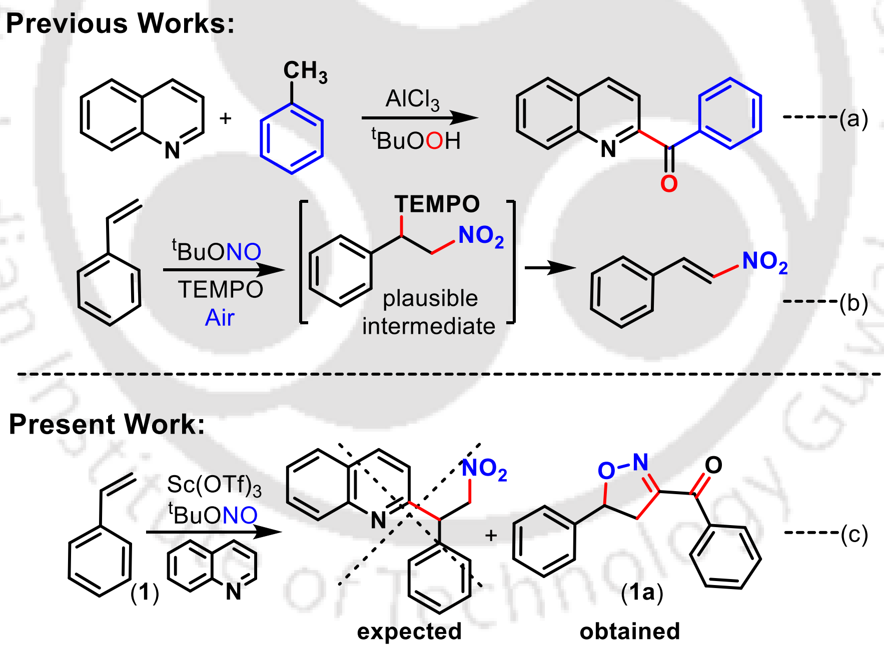
CHAPTER II. *tert*-Butyl Nitrite Mediated Domino Synthesis of Isoxazolines and Isoxazoles from Terminal Aryl Alkenes and Alkynes

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 °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% there by suggesting its possible involement as a base.

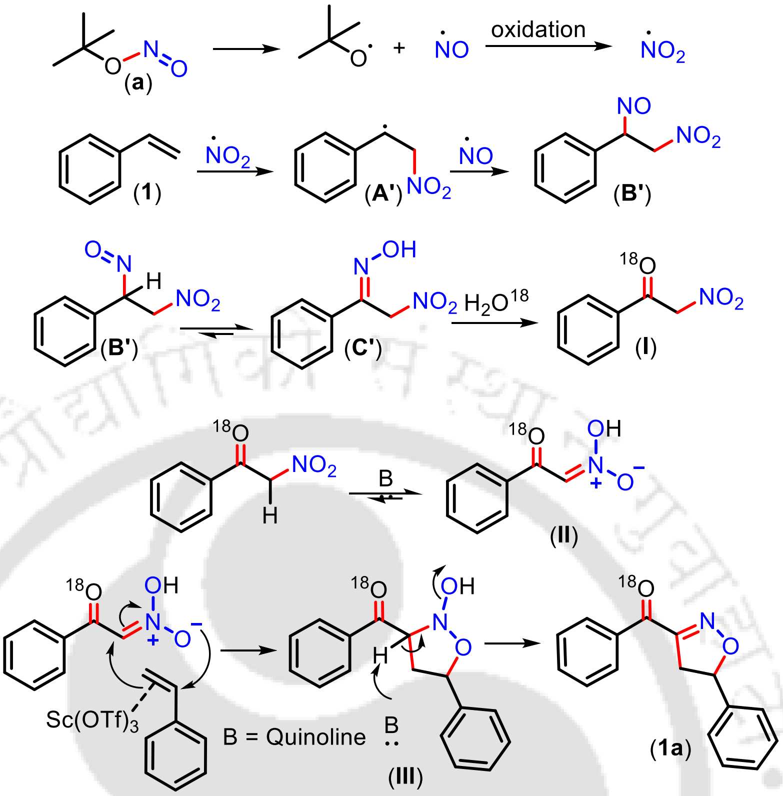
Isoxazolines, are an important class of heterocycle that have attracted considerable attention in the field of anticancer research. Some of the important isoxazoline scaffolds exhibiting potent anticancer properties are 3,5-diaryl-isoxazoline linked 2,3-dihydroquinazolinone hybrids, arylisoxazoline containing anthranilic diamides, 3,5-diaryl-isoxazoline linked pyrrolo[2,1-c][1,4]benzodiazepine (PBD) conjugates and dibenzo[b,f]azepinetethered 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

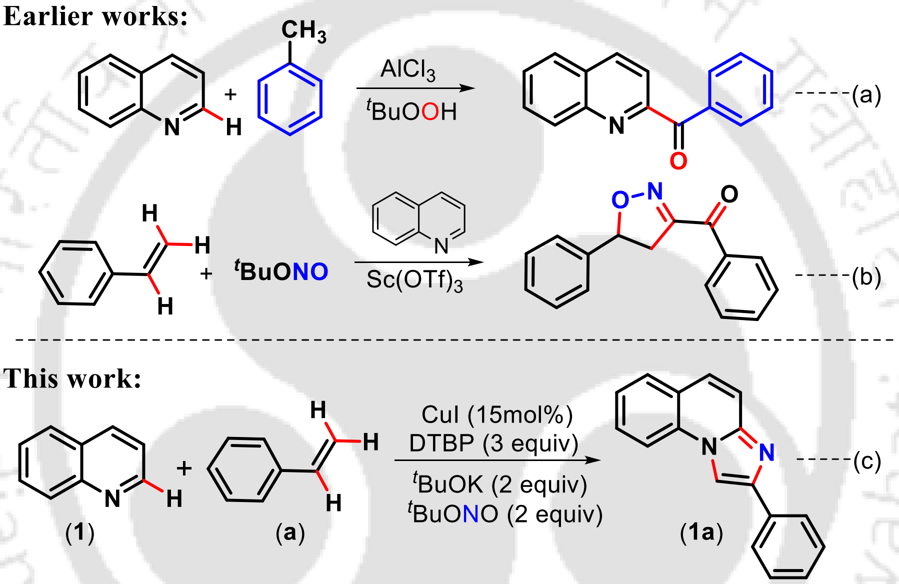
This chapter described *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[1,2-*a*]quinolines / imidazo[2,1-*a*]isoquinolines. *tert*-Butyl nitrite serves the dual role of an oxidant as well as a N1 synthon in a multi-component reaction involving quinolines/isoquinolines 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 *tert*-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*



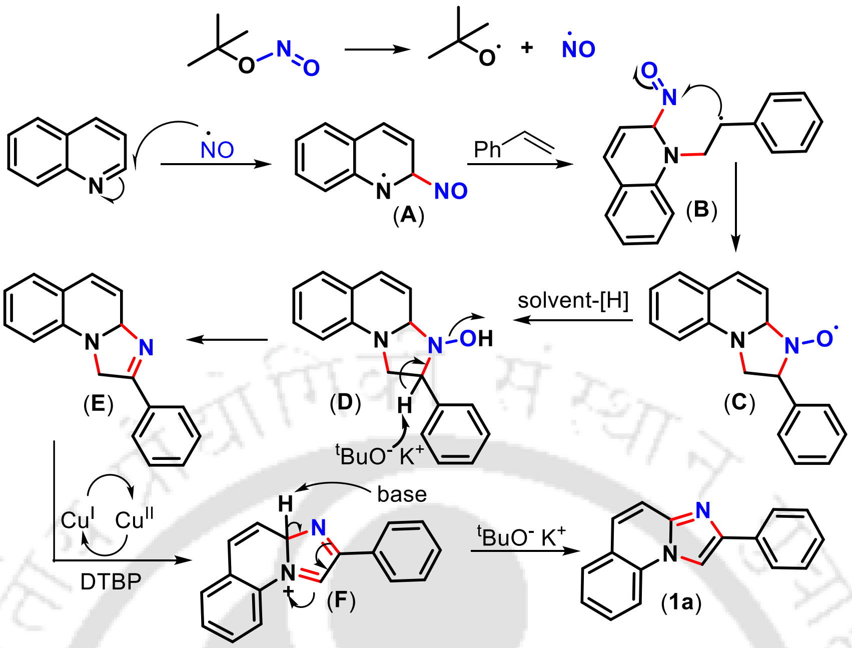
By judiciously choosing the catalyst and other reaction parameters it was possible to fuse styrene onto both quinoline and isoquinoline moieties in the presence of *tert*-butyl nitrite (TBN) (Scheme III.1). Our initial investigation started using quinoline (0.25 mmol), styrene (0.625 mmol), Cu(OTf)$_3$ (10 mol%), Cs$_2$CO$_3$ (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.

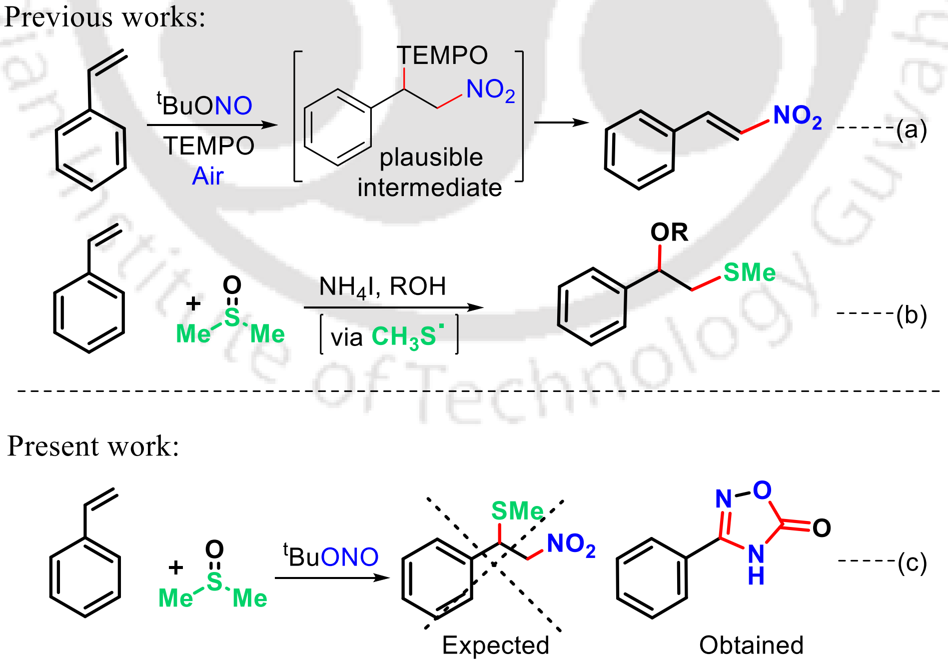
CHAPTER IV: *tert*-Butyl Nitrite Mediated Greener Synthesis of 1,2,4-Oxadiazol-5(4*H*)-ones from Terminal Aryl Alkenes

This chapter described *tert*-butyl nitrite mediated vinyl bond cleavage/cyclization's 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)]

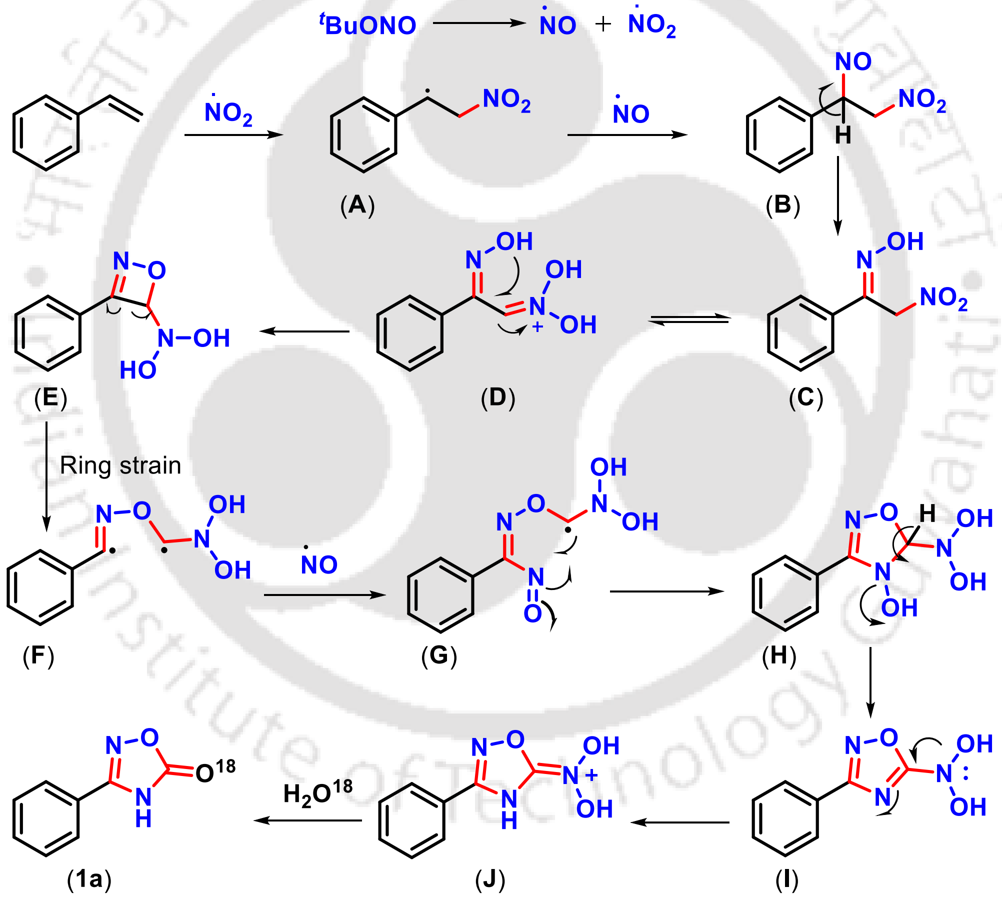
With this assumption, we commenced our preliminary studies by reacting styrene (**1**) with *tert*-butyl nitrite (^{t}BuONO) (**a**, 3.0 equiv) and Sc(OTf)$_3$ catalyst (10 mol%) in DMSO at 80 °C. Interestingly, the reaction resulted in the formation of a new product (47%), spectroscopic analysis of which confirmed the structure to be 3-phenyl-1, 2, 4-oxadiazol-5(4H)-one (**1a**) [Scheme IV.1 (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*-butyl nitrite (1 mmol) at 80 °C 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$^{\cdot}$ radical which is converts to a NO_2 radical under the aerobic reaction condition. The nitro radical ($NO_2^{\cdot}$) then attacks at the 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 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.

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*. (Accepted Manuscript).

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).