
Abstract

Selective transformation of ubiquitous but inert C-H bonds into C-C, C-N, C-O, C-X is the central interest to modern organic chemistry. Direct transformation of C-H bond into C-N bond has been emerged as a high impact area of research, because it allows the preparation of nitrogen-containing cyclic and acyclic compounds which are biologically active or which can act as synthetic scaffolds for pharmaceuticals. The contents of this thesis entitled “*C-H Aminations and Syntheses of Heterocycles Using Nitrosoarene*” have been divided into six chapters. The first chapter of the thesis provides a review on different aspects of C-H amination with various aminating agents. All the other chapters describe the C-N bond forming reactions of nitrosoarenes. Chapter 2 describes C(sp²)-H arylation of 2-hydroxyarene to provide 2-hydroxy-di(het)aryl amines. Chapter 3 illustrates C(sp³)-H functionalization enabled annulation of nitrosoarenes and N-heterocycles to ring-fused imidazoles. Selective N-terminal proline modification of peptides via amino-oxazole synthesis and application of modified peptides in cell imaging have been described in chapter 4. Chapter 5 demonstrates indole synthesis via C(sp²)-H functionalization of nitrosoarene and β-C(sp³)-H functionalization of secondary amines. Finally, chapter 6 contains copies of ¹H and ¹³C NMR spectra.

Chapter 1: Introduction on C-H Aminations:

This chapter describes the brief history of C-H amination reactions. Various strategies for C-H amination, different aminating agents, challenges for direct C-H amination, development of new methodologies to address those challenges and advantages of direct C-H amination over classical approaches in organic synthesis have been discussed. Different aminating agents utilized for C-H amination has been shown in **Figure 1**.

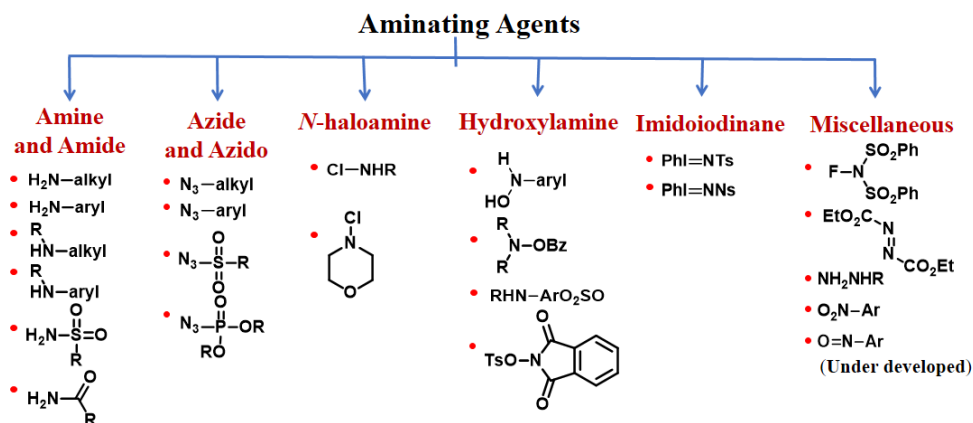


Figure 1: Various aminating agents.

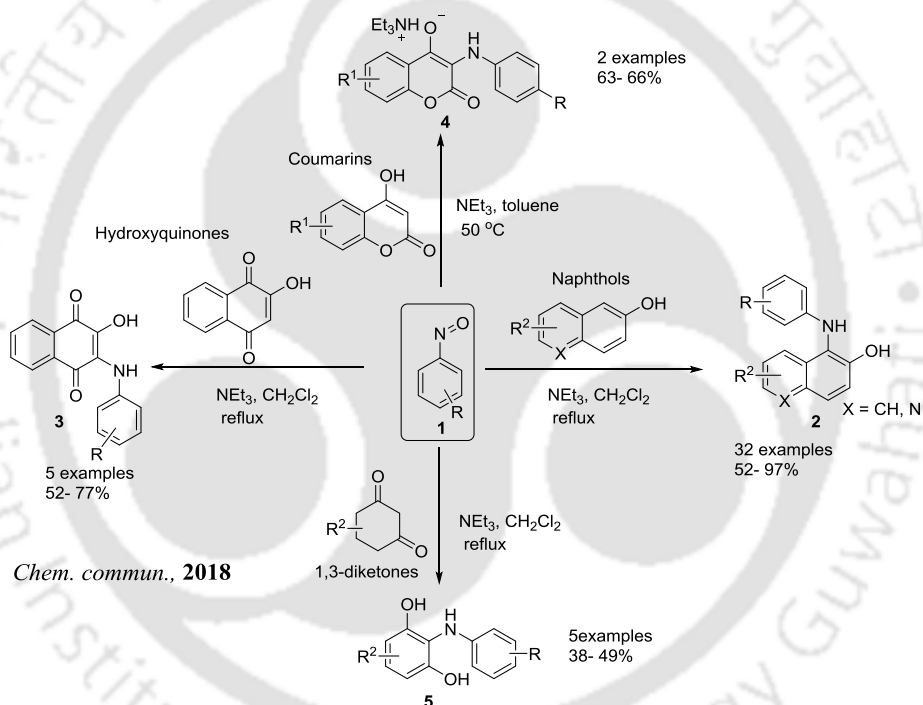
Classical arylamination via Copper catalyzed Ullmann-Goldberg coupling, Chan-Lam coupling and palladium catalyzed Migita-Kosugi reaction and the Buchwald-Hartwig amination have been widely used. Apart from the classical approaches of amination, such as reductive carbonyl amination, nucleophilic displacement of a leaving group and imine alkylation, the development of novel transition metal catalyzed C-H amination and C-H arylamination have been tremendously progressed over the years. On the other hand, photo-redox catalyzed C-H amination indubitably was an important discover Amination using aminating agents like azide, *N*-haloamines, hydroxyl amine and nitroarene have also been made remarkable progress in this field. However, in spite of the advancement in the field of amination reactions, the previous strategies have some limitations. For example, the Buchwald-Hartwig amination involved preactivated electrophiles (aryl halides) and amines in the presence of Pd catalyst. Thus the scope of these reactions are somewhat limited because aryl halides which sometimes are not readily available. The main drawbacks of metal catalyzed arylamination reactions are the use of expensive metal, synthesis of aryl halides or pseudohalides, undesired byproducts. Moreover, amination using other aminating agents like azide, *N*-haloamines, hydroxyl amine, nitroarene and nitrosoarene suffer from limitations related to the use of harsh reaction condition, functional group incompatible and general applicability. Nitrosoarenes are readily available. Due to high polarizability of N=O bond it can react easily with nucleophiles and proved to be an important synthetic building block in synthetic organic chemistry to install amine functionality in molecules. However, very few reports on C-H amination using nitrosoarene are known. Therefore, the aim of this thesis is to develop novel synthetic methodologies for C-N bond formation using nitrosoarene under operationally simple conditions without using metallic reagents/ catalyst.

Chapter 2: Metal Free Direct C(sp²)-H Arylaminations Using Nitrosoarenes to 2-hydroxy-di(het)aryl Amines as Potent Multifunctional A β -aggregation Modulators:

Diarylamines and their derivatives are ubiquitous structural motifs of natural products, active pharmaceuticals, antioxidants, dyes, and agrochemical agents. Direct amination of inert carbon-hydrogen (C-H) bonds is one of the most versatile approaches for the construction C-N bond. Transition metal catalyzed cross-coupling reaction, metal and photoredox catalyzed direct amination of C-H bonds, amination reactions involving varieties of electrophilic amine sources are the main approaches

for diarylamine synthesis. However, the involvement of metallic reagents and stoichiometric metal-based or organic reductants, functional group incompatibility are the major drawbacks of these previous reports.

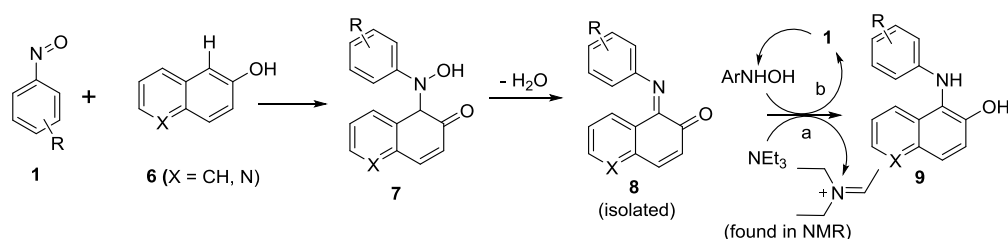
This chapter reports a metal free direct C(sp²)-H arylation reaction using nitrosoarenes as amine source to provide 2-hydroxy-di(het)aryl amines. The direct arylation of a broad range of substrates, such as naphthols, hydroxyquinolines, hydroxyquinones, coumarins and 1,3-cyclohexadiones were achieved under operationally simple and mild conditions without the aid of additional reagents/steps for the N-O bond reduction. The optimized reaction conditions were employed to obtain structurally diverse 2-hydroxy-di(het)aryl amines with good to excellent yields.



Scheme 1: Scope of arylation reactions using nitrosoarenes.

Based on the experimental results, a plausible reaction mechanism for this metal-free reductive arylation reaction has been depicted in Scheme 2. Naphthol derivatives reacted with nitrosoarene to provide corresponding iminoquinone **8** probably through the corresponding hydroxylamine derivative **7**. The reduction of the iminoquinone **8** occurred via two possible pathways. In the major pathway, NEt₃ reduced iminoquinone **8** either via electron transfer mechanism or via ionic mechanism to produce desired aminated product **9**. Consequently, triethylamine was oxidized to the corresponding iminium ion which was detected by ¹H-NMR. Additionally, arylhydroxylamine formed from the nitrosoarene during the auto-

oxidation-reduction process could also be involved for the reduction of **8** to the desired product in the minor pathway.



Scheme 2: Proposed mechanism.

Interestingly, the novel 2-hydroxydiaryl amines were found to be highly potential $A\beta$ - aggregation inhibitors. The potential of **2a** and **2b** in inhibiting the $A\beta$ -

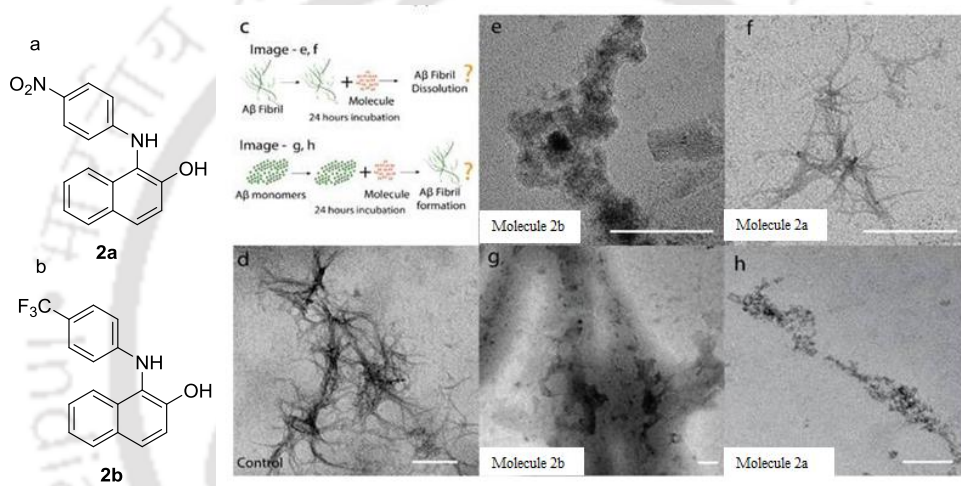


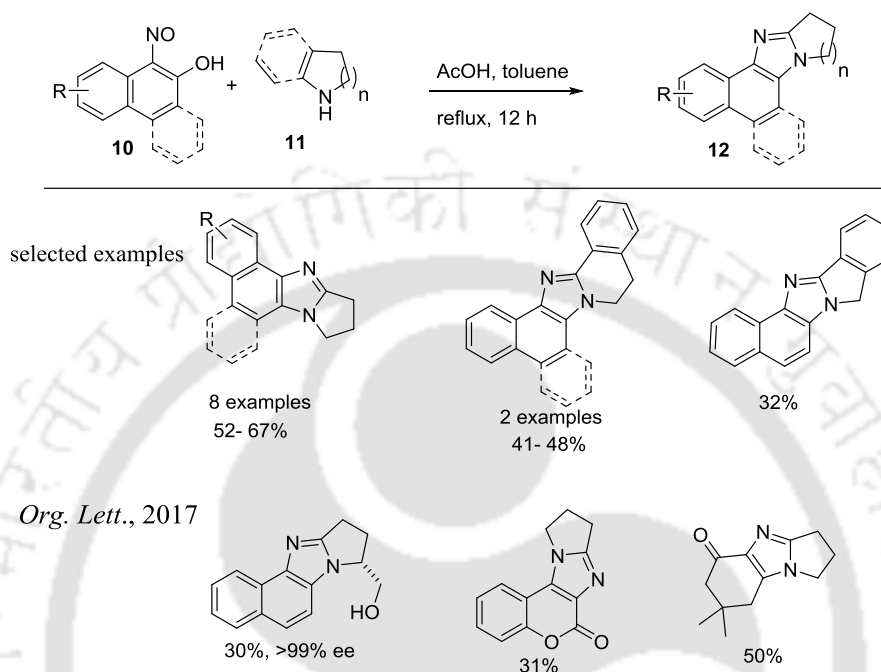
Figure 2: (a) & (b) molecular structure of **2a** & **2b** respectively. (c) Illustration of the experimental design. (d) Control image of untreated $A\beta$ -40. (e) & (f) TEM micrographs of pre-formed $A\beta$ -40 fibril incubated with molecule **2b** and **2a** for 24 hours, respectively. (g) & (h) TEM micrograph of molecule **2b** & **2a**, respectively, incubated with $A\beta$ -40 monomers for 24 hours. (Scale bars, 100 nm)

aggregation was confirmed by the changes in the fibrillary morphology observed by transmission electron microscopy (**Figure 2**). Furthermore, the dissolution of the pre-formed $A\beta$ -40 fibril was observed with the treatment with **2b** (**Figure 2e**).

Chapter 3: Metal Free $C(sp^3)$ -H Functionalization Enabled Annulation of Nitrosoarenes and N -heterocycles to Ring-fused Imidazoles

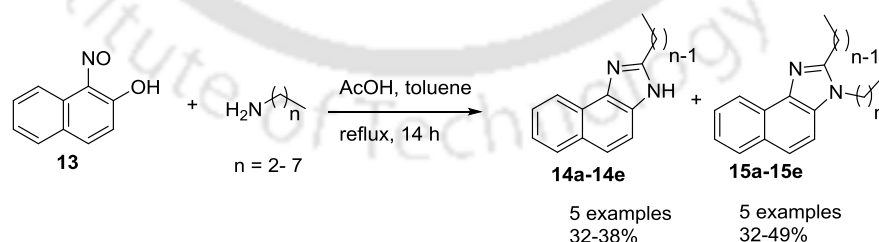
Imidazoles are privileged moiety which are present in many bioactive molecules including natural products. Particularly, ring-fused benzimidazole derivatives were identified as the important pharmacophore for anticancer activity. Syntheses of this valuable scaffolds

mainly relied on the multistep reaction sequences. A metal-free C(sp³)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles for the synthesis of ring-fused imidazoles has been developed. Structurally diverse novel polycyclic imidazoles were prepared readily from the reaction of 2-hydroxy-C-nitroso compounds and secondary cyclic amines in the presence of acetic acid in refluxing toluene.



Scheme 3: Scope of metal free C(sp³)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles.

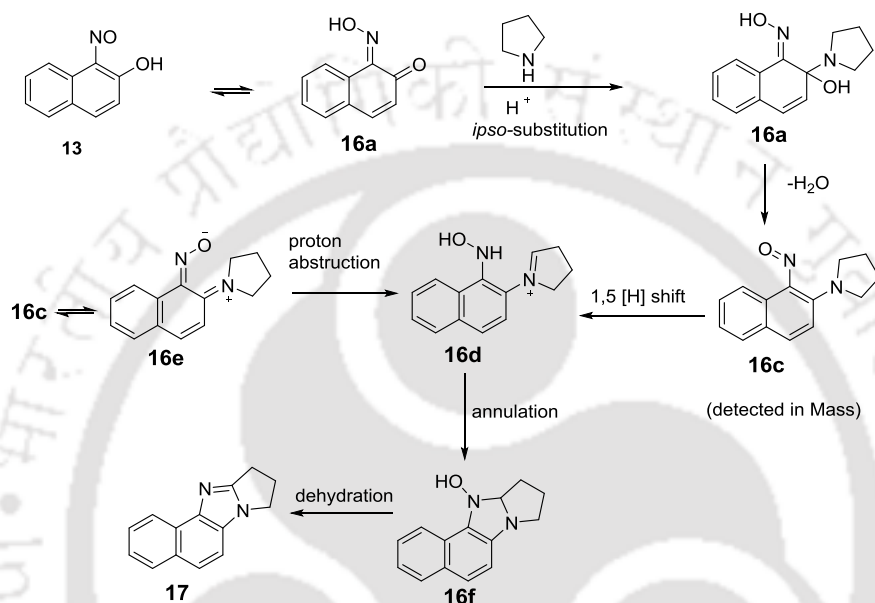
Moreover, aliphatic primary amines with varied chain length also participated in annulation reaction with the 2-nitrosonaphthol under the standard reaction conditions. The desired naphtho-imidazoles along with corresponding *N*-alkylated derivatives were isolated with very good to excellent combined yields.



Scheme 4: Scope of metal free C(sp³)-H functionalization enabled annulation of nitrosoarenes with acyclic amines.

Based on the experimental evidence, a plausible mechanism for the annulations reaction has been depicted in **Scheme 5**. Nitrosonaphthalene derivative **16c** could be formed from the nucleophilic *ipso*-substitution reaction of nitrosonaphthol **13** or its keto-oxime tautomer **16a** with pyrrolidine through intermediate **16b**. Amino nitroso derivative **16c** then readily

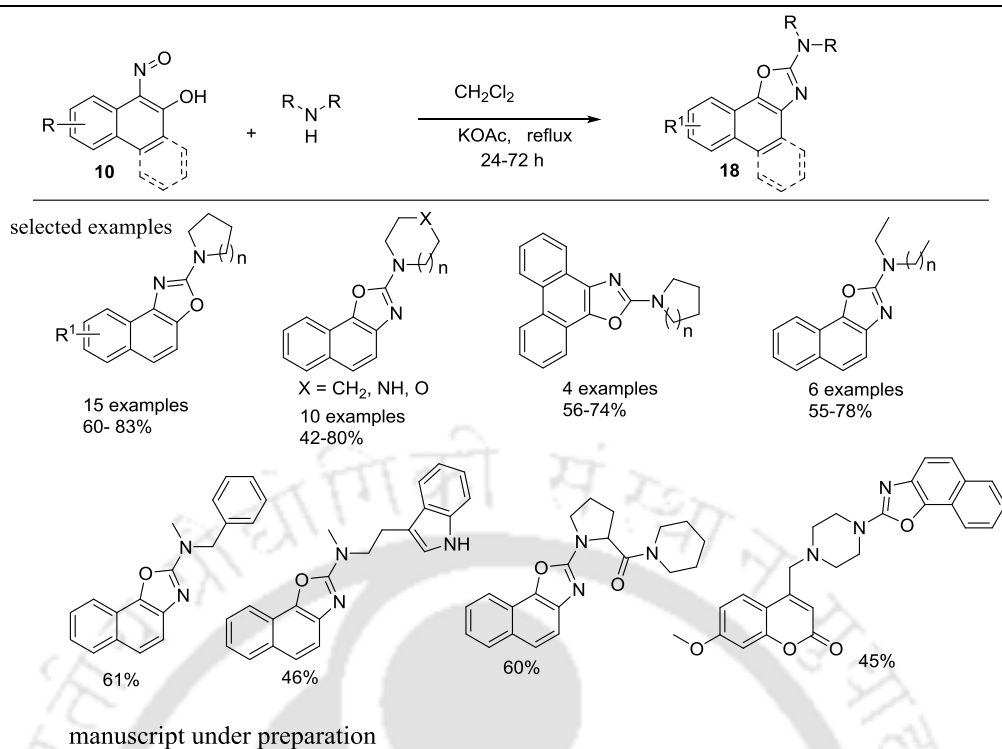
undertook a 1, 5-hydride shift to provide the iminium ion **16d**. Alternatively, the iminium ion **16d** could also be produced through deprotonation of iminium ion **16e** which was produced from isomerisation/ mesomerization of **16c**. Annulation of **16d** followed by acid mediated dehydration of resulting *N*-hydroxy derivative **16f** provided the desired imidazole **17**. **16c** was detected in mass the spectrometry, this supports the intermediacy of **16.3** in the reaction.



Scheme 5: Proposed mechanism for metal free annulation of nitrosoarene and *N*-heterocycles.

Chapter 4: Selective *N*-terminal proline modification of peptides via aminooxazole synthesis and application in cell imaging

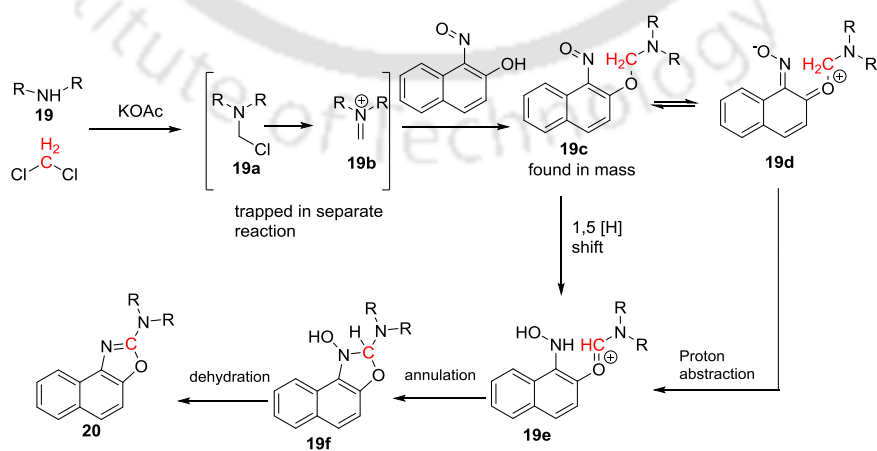
2-aminoxazoles is one of the most promising pharmacologically interesting class of heterocycles. However, the known methods for the synthesis of aminooxazole have their own limitations due to the involvement of vigorous reaction conditions, multiple numbers of reaction steps and production of adverse by-products. Thus the previously reported synthetic methods to obtain 2-aminoxazoles mostly suffer from the requirement of multiple reaction steps, metals, strong oxidants, harsh reaction conditions, and undesirable by-products. In this chapter, a novel method for the synthesis of 2-amino-oxazole derivatives has been developed under simple and mild reaction condition where dichloromethane was used as the C2 source of 2-aminoxazole. 2-hydroxy-C-nitroso compounds on reaction with amines and dichloromethane in presence of base afforded corresponding 2-aminoxazoles derivative. The reaction is operationally simple, very



Scheme 6: Scope of 2-aminoxazole synthesis.

general and highly efficient in *N*-functionalizing both cyclic and acyclic amines. The generality of this method has been proven by the use of a wide range of saturated amine based substrates.

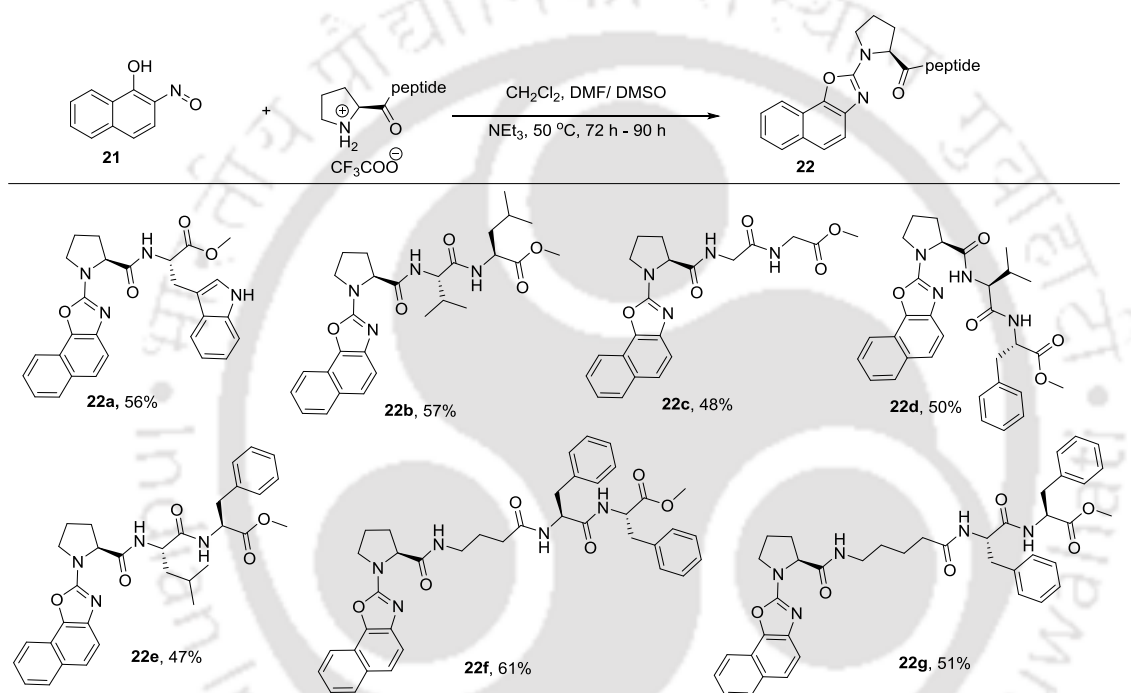
Based on the results of controlled experiments a plausible mechanism for this oxidative cyclization reaction is presented in **Scheme 7**. Amine **19** reacted with dichloromethane in presence of the base to generate the iminium ion **19b** which on reaction with 1-nitroso-2-naphthol afforded **19c**. Then **19c** readily undertook a 1,5-hydride shift to provide the.



Scheme 7: Proposed mechanism for the synthesis of 2-aminonaphthoxazole.

iminium ion **19e** which also could be obtained by the isomerisation of **19d**. Annulation of **19e** followed by dehydration of resulting *N*-hydroxy derivative **19f** provided the desired 2-aminoxazole **20**.

Utilizing this developed method for synthesis of aminooxazole derivatives, spacer free *N*-terminal modification of peptides has been achieved to afford fluorescent peptides. 2-hydroxy-*C*-nitroso on reaction with various peptides afforded corresponding 2-aminoxazoles derivative



Scheme 8: *N*-terminal peptide modification.

The modified peptides have been successfully used for imaging of HeLa cells and found to be used as excellent luminescent probes for rapid staining of cell cytoplasm.

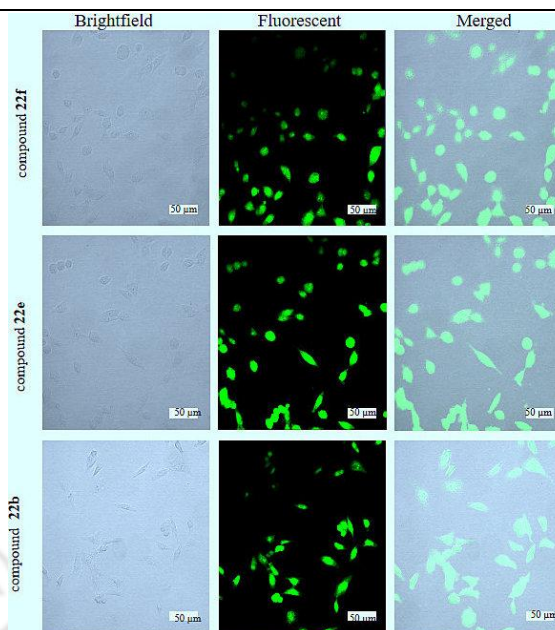
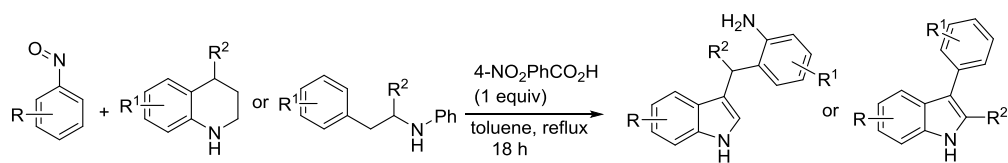


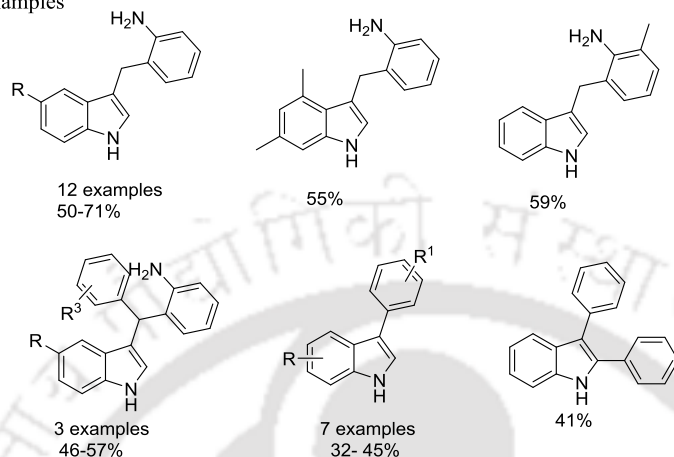
Figure 3: Confocal laser scanning microscopy images of HeLa cells stained with **22f**, **22e** and **22b** respectively. Cells were incubated with 40 μM of the compounds for 20 min. Excitation: 458 nm Emission range: 480-605 nm. Scale bar: 50 μm .

Chapter 5: Direct $\text{C}(\text{sp}^2)\text{-H}$ functionalization of nitrosoarene and $\beta\text{-C}(\text{sp}^3)\text{-H}$ functionalization of secondary amines to Indoles

Functionalized indoles are ubiquitous in biologically active natural products, pharmaceuticals, and agro-chemicals. The indole alkaloids are the structural analog of endogenous amines and neurotransmitters. Over the past decades, several pioneering methods have been developed for the synthesis of indole derivatives. Most of the previous methods require prefunctionalized precursors thereby lengthening the synthetic path. Therefore, the availability and synthesis of the suitably substituted precursors limit the scope of these reactions. A metal-free unprecedented method for the synthesis of indole derivatives via $\text{C}(\text{sp}^2)\text{-H}$ functionalization of nitrosoarene and $\alpha, \beta\text{-C}(\text{sp}^3)\text{-H}$ functionalization of aliphatic amines has been developed. Diversely substituted indoles were prepared by the reaction of various nitrosoarenes and various amines in the presence of 4- NO_2 -benzoic acid in refluxing toluene.

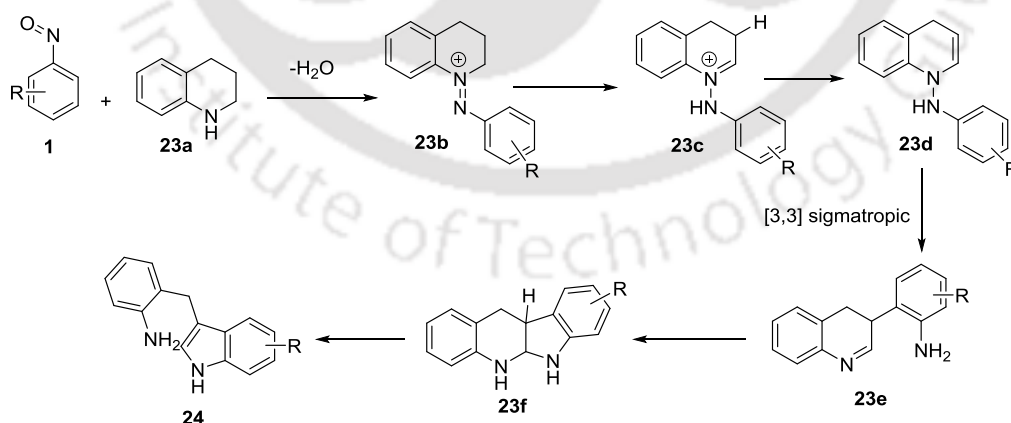


selected examples



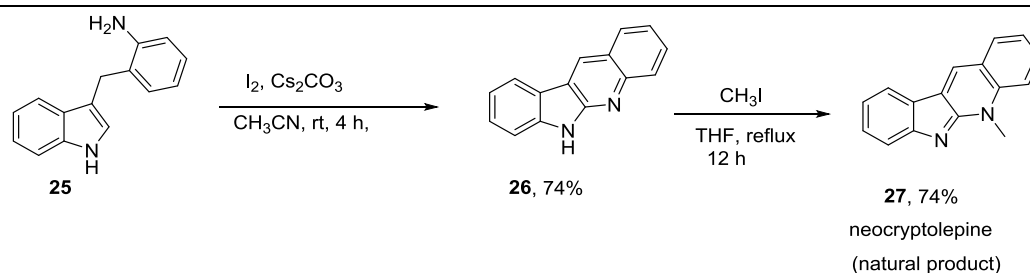
Scheme 9: Selected examples of 3-benzyl- and 3-aryl indoles.

Based on the experimental results a plausible mechanism has been depicted in **Scheme 10**. Tetrahydroquinoline reacted with nitrosoarene to afford imminium ion **23b** which isomerizes to **23c**. Further isomerization of **23c** gave rise to ene-hydrazine **23d** which underwent [3, 3] sigmatropic rearrangement to provide **23e**. Annulation to **23e** followed by ring opening of **23f** afforded indole **24**.



Scheme 10: Plausible mechanism for the synthesis of 3-benzylindoles.

Cyclization reaction of indole **25** was successfully achieved by using molecular iodine and Cs_2CO_3 to provide biologically important norneocryptolepine. Further *N*-methylation of **26** with CH_3I provided natural product neocryptolepine **27** (**Scheme 11**).



Scheme 11: Synthesis of neocryptolepine.

Summary:

In summary, the thesis describes the C-N bond forming reaction of nitrosoarenes and heterocycles syntheses. Synthesis of 2-hydroxy-di(het)aryl amines was achieved by C(sp²)-H arylation of using nitrosoarene. Synthesis of biologically privileged moiety ring-fused imidazole was achieved via C(sp³)-H functionalization of nitrosoarenes and *N*-heterocycles. The selective *N*-terminal proline modification of peptides via aminooxazole synthesis was developed and application of these modified peptides in cell imaging has been studied. Indole synthesis via C(sp²)-H functionalization of nitrosoarenes and β -C(sp³)-H functionalization of secondary amines were also established. In future, the focus will be to investigate and explore the functionalization of acyclic amines with nitrosoarenes. Also, the possibility of functionalization of other aliphatic cyclic amines with nitrosoarenes to afford heterocycles such as indole, quinoxaline, quinoline will be studied in the near future.