

## Abstract

The contents of this thesis have been divided into five chapters based on the results of experimental work performed during the complete course of the research period. The chapter 1 mainly discusses about synthetic strategy and utility of propargylamines. Chapter 2 describes regioselective one-pot, three-component synthesis of substituted 2*H*-indazoles from 2-nitroarylaldehyde, alkyne and amine catalyzed by CuBr/Zn(OTf)<sub>2</sub> system. Chapter 3 illustrates Ag(OTf) catalyzed synthesis of substituted pyrazole *N*-oxides and pyrazoles from propargylamines. Chapter 4 demonstrates synthesis of highly substituted 4-iodopyrazole *N*-oxides and pyrazoles from propargylamines. Chapter 5 explains that, a facile synthesis of benzo[1,4]oxazepine fused tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline analogues *via* Pictet-Spengler reaction of intramolecular cyclic iminium ion intermediates. Each chapter constitute four sections, describing introduction, present work, experimental work and spectral data, respectively.

### Chapter 1: Introduction on Synthetic Utility of A<sup>3</sup>-Coupling

Amines are aliphatic and aromatic derivatives of ammonia. Depending on the number of hydrocarbon groups replacing the hydrogen atoms in ammonia, amines can be categorized as primary, secondary and tertiary. One organic group attached to the nitrogen atom in ammonia is termed as primary, whereas those with two or three organic groups attached are secondary and tertiary amines, respectively. For example, one propargyl group attached to the nitrogen atom in ammonia is termed as propargylamine. Similarly, propargyl group with either one or two of organic groups like aliphatic/aromatic attached are named as secondary and tertiary propargylamines. Due to all-encompassing features of propargylamines, till date, numerous building blocks of nitrogen heterocycles as well as bioactive molecules have been developed in synthetic organic chemistry. In this thesis, our research interest mainly emphasizes on synthesis of complex nitrogen heterocycles using propargylamine intermediates.

Classically, propargylamines are prepared by the nucleophilic addition of metal alkynylides to imine electrophiles. This reaction sequence involves condensation of primary or secondary amines with aldehydes to form an imine or iminium ions followed by subsequent nucleophilic addition of *in situ* generated metal alkynylides. The existing method suffers from certain

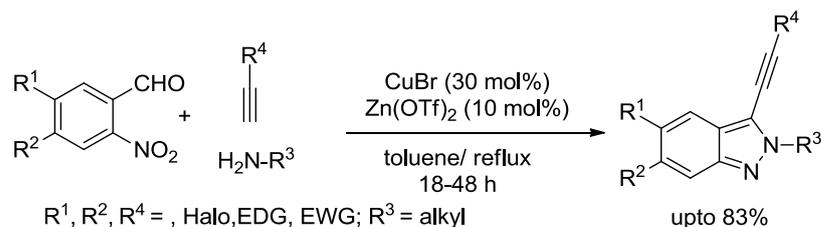
drawbacks like, it requires stoichiometric amount of strong bases like butyllithium, harsh reaction conditions and low functional groups tolerance.

To overcome these complications, in last few years an efficient transition-metal catalyzed one-pot, three-component reaction has been developed from commercially available aldehyde, alkyne and amines. This method commonly named as  $A^3$ -coupling. The term  $A^3$  was introduced by Li group and it has established a straightforward approach towards propargylamines. Interestingly,  $A^3$ -coupling reaction has been studied with different metal catalysts, especially coinage metals such as Cu, Ag and Au as well as Zn, Fe, In, and Ir. Out of these copper catalysts are highly effective for the synthesis of propargylamines.

Recently,  $A^3$ -coupling reactions play a key role for the construction of various building blocks of nitrogen-containing heterocycles as well as biologically active compounds, pharmaceuticals and natural products. Due to the flexibility of propargylamines, it can involve in different tandem cyclisation reactions and has become a powerful tool to build structurally diverse *N*-heterocyclic compound libraries. Moreover, complexity of propargylamine bearing additional functional groups could also be achieved easily.

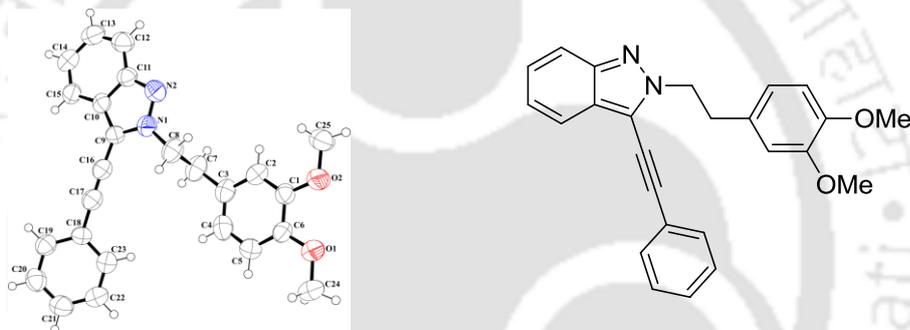
## **Chapter 2: Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from 2-Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)<sub>2</sub> System**

Indazoles are important class of nitrogen heterocycles, found rarely in nature and show significant biological importance in the medicinal chemistry. Recently, several methods have been employed for the synthesis of 2*H*-indazole. However, methods for synthesis of 2*N*,3*C*-substituted 2*H*-indazole are limited. Even though there are few strategies have developed for the synthesis of highly substituted 2*H*-indazole, these methods suffer from drawbacks such as multistep, low selectivity, and low yields. Multicomponent reactions are gaining importance in heterocyclic chemistry due to their ability to form a series of bonds in a single step. Here in we describe a regioselective synthesis of 3-(arylethynyl)-2*H*-indazoles derivatives *via* copper(I) bromide/zinc(II) triflate catalyzed one-pot, three component reaction using 2-nitroarylaldehydes, alkynes and amines as starting materials. (*Scheme 1*).



**Scheme 1:** Synthesis of 3-alkynyl-2H-indazole and the scope of the reaction

The reaction is highly regioselective and only 2*N*-substituted product could be obtained in high purity without any regioisomeric product. The compound 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2*H*-indazole was determined from  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectrometry experiments. Further, the structure of the compounds was confirmed by X-ray analysis (**Figure 1**).



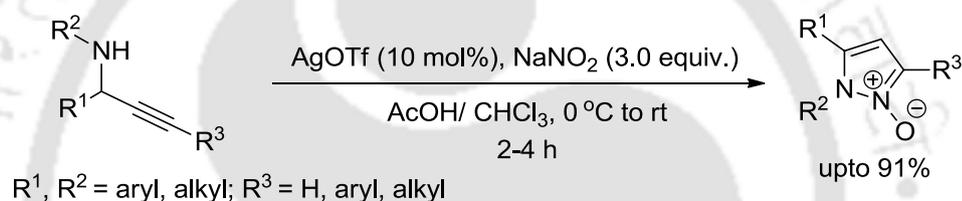
**Figure 1:** ORTEP diagram of compound 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2*H*-indazole

In conclusion, we have developed a practical and general one-pot procedure for the synthesis of 2*H*-indazoles from *ortho*-nitroarylaldehydes, primary amines and alkynes catalyzed by CuBr and Zn(OTf)<sub>2</sub>. This versatile one-pot, three-component procedure is a novel approach for the synthesis of highly substituted 2*H*-indazoles.

### Chapter 3: Synthesis of Substituted Pyrazole *N*-Oxides and Pyrazoles from Propargylamines

Pyrazoles are important class of nitrogen heterocyclic compounds due to their broad range of biological activities and also they are found in many pharmaceutical and agrochemical substances. Pyrazoles are generally synthesized by classical cyclocondensation of hydrazine derivatives with 1,3-diketones and  $\alpha,\beta$ -unsaturated aldehydes and ketones. In addition, they also synthesized by 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or

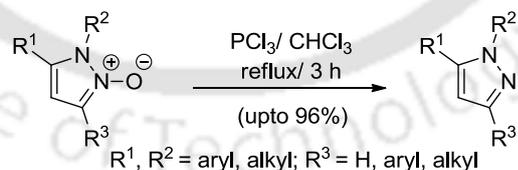
alkynes. Recently, halo cyclisation reactions also established for the synthesis of pyrazole. Similarly, Pyrazole *N*-oxides are gaining considerable interest as synthetic intermediates for the synthesis of highly substituted pyrazoles due to their regioselectivity and monoselectivity. Pyrazole *N*-oxides are susceptible to regioselective metalation and subsequent functionalization reactions. The functionalized pyrazole *N*-oxides could be easily reduced to pyrazole. Pyrazole *N*-oxides are prepared by the direct oxidation of pyrazoles with peracids, nitrosation of  $\alpha$ -bromo- $\alpha,\beta$ -unsaturated ketoximes, and cyclisation of alkynyl nitrosoamine. The major drawback of existing methods is low yields, multistep synthesis, and lack of regioselectivity. In continuation of previous chapter, we present in this chapter, a silver(I) catalyzed mild and efficient synthesis of substituted pyrazole *N*-oxides from propargylamines using  $\text{NaNO}_2/\text{AcOH}$  in one step process is described. (**Scheme 2**).



**Scheme 2:** Synthesis of substituted pyrazole *N*-oxides and the scope of the reaction

### Cleavage of *N*-oxide bond:

Deoxygenation of *N*-oxide was achieved by using  $\text{PCl}_3$  in chloroform under reflux for 3 h gave corresponding pyrazoles (**Scheme 5**).

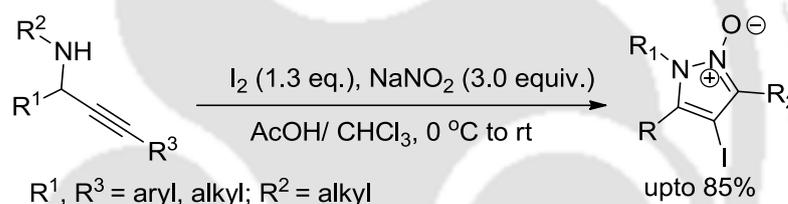


**Scheme 3:** Synthesis of pyrazoles from pyrazole *N*-oxides

In conclusion, a mild and efficient method has developed for the synthesis of substituted pyrazole *N*-oxide from propargylamine in excellent yields. The reaction is compatible with a wide range of functional groups such as ester, ether, nitrile,  $-\text{NO}_2$ , and halides. The pyrazole *N*-oxide can be converted to pyrazole and chlorinated pyrazole under different reaction conditions. Nitroaryl substituted pyrazole can be converted to pyrazolo-*N*-oxide-cinnoline, pyrazolo-quinoline and pyrazolo-cinnoline.

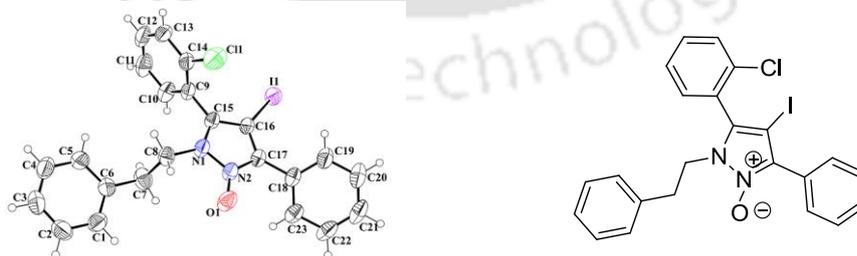
## Chapter 4: Synthesis of Highly Substituted 4-Iodopyrazoles *N*-Oxides and Pyrazoles from Propargylamines

In previous chapter we described a methodology for the synthesis of 1,5 and 1,3,5-substituted pyrazole *N*-oxides and pyrazoles from propargylamines using AgOTf and NaNO<sub>2</sub>/AcOH. Simultaneously, we also synthesised a few derivatives of highly substituted 4-chloropyrazole from 1,3,5-trisubstituted pyrazole *N*-oxides. These results encouraged us for further synthesis of highly substituted pyrazole *N*-oxides and pyrazoles *via* iodine mediated electrophilic cyclization reactions. This chapter demonstrates one-pot synthesis of highly substituted 4-iodopyrazole *N*-oxide and pyrazoles from propargylamines using NaNO<sub>2</sub> and iodine *via* 5-*endo-dig*-cyclisation process. To demonstrate further applicability of the iodopyrazole *N*-oxides, the iodo functionality was used for the Suzuki, Heck and Sonogashira cross-coupling reactions (**Scheme 4**).



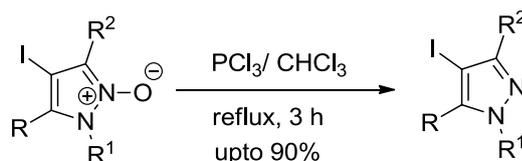
**Scheme 4:** Synthesis of 4-iodopyrazole *N*-oxides and scope of the reaction

The structure of the compounds is determined by NMR and mass spectrometry. It was further confirmed by X-ray crystallographic analysis of compound 5-(2-chlorophenyl)-4-iodo-1-phenethyl-3-phenyl-1*H*-pyrazole 2-oxide (**Figure 2**).



**Figure 2:** ORTEP diagram of compound 5-(2-chlorophenyl)-4-iodo-1-phenethyl-3-phenyl-1*H*-pyrazole 2-oxide

The reduction of pyrazole *N*-oxide to pyrazole can be achieved by treatment of phosphorous trichloride in refluxing chloroform for 3 h (**Scheme 5**).

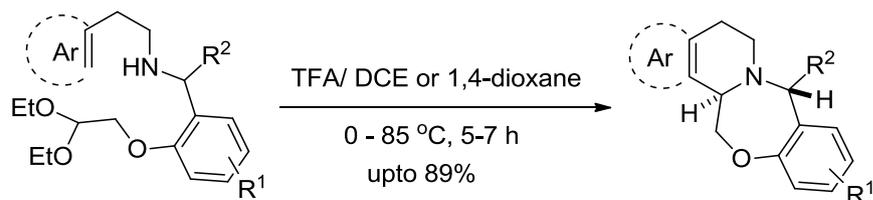


**Scheme 5:** 4-Iodopyrazole *N*-oxides to 4-iodopyrazoles

In conclusion, a mild and efficient method has been developed for the synthesis of iodo substituted pyrazole *N*-oxide from propargyl amine in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, -NO<sub>2</sub>, nitrile and halides. The iodo functionality was also successfully applied for Suzuki, Heck and Sonogashira cross-coupling reactions. Some of the pyrazole *N*-oxides were converted to pyrazoles by the treatment with phosphorous trichloride in refluxing chloroform.

### **Chapter 5: Intramolecular Pictet-Spengler Reaction of Cyclic Iminium Ions: A Novel Access to Benzo[1,4]oxazepine Fused Tetrahydroisoquinoline and Tetrahydro- $\beta$ -carboline Analogous**

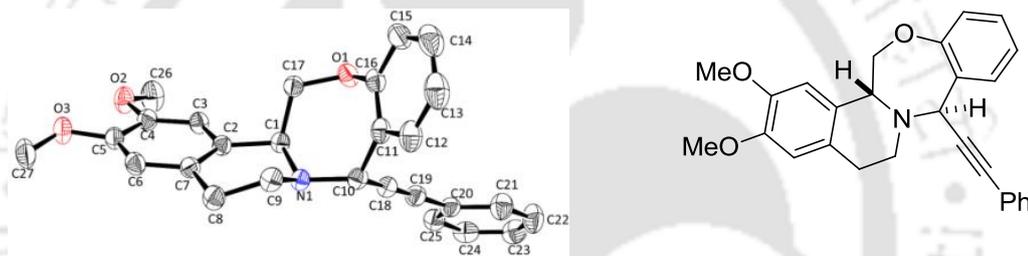
Synthesis of new class of heterocycles with diverse functionalities is always on forefront of attention in synthetic organic chemistry because of their high use in introducing new bioactive agents in medicinal chemistry. Particularly, synthesis of fused tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline scaffolds has a special interest to synthetic community. The Pictet-Spengler reaction is one of the leading techniques for construction of such valuable nitrogen heterocyclic compounds with wide range of biological activity and a diverse pharmacological profile. Recently, Ugi multicomponent reaction and subsequent acid promoted intramolecular Pictet-Spengler reaction is used for the synthesis of such privileged architectures. The reaction mechanism suggests that *in situ* generated *N*-acyliminium ion intermediates plays a key step for the development of novel library of heterocyclic compounds. Similarly, a few reports also describe the formation of such compounds *via* intramolecular Pictet-Spengler of cyclic iminium ion intermediates. This is due to less electrophilic character of cyclic iminium ions compared to cyclic *N*-acyliminium ions. In this chapter, describes a methodology for the facile synthesis of a new class of polyheterocyclic skeletons such as benzo[1,4]oxazepino-fused tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline scaffolds by reaction of 2-(2,2-diethoxyethoxy)benzaldehyde with 2-phenylethylamine and tryptamine, respectively *via* an *in situ* generated iminium ion and subsequent Pictet-Spengler reaction (**Scheme 6**).



Ar = Ph, Indole; R<sup>1</sup> = 3-OMe, 3-OEt, 5-Cl, 5-Br, 4-NEt<sub>2</sub>, 3,5-<sup>t</sup>Bu, 5-NO<sub>2</sub>; R<sup>2</sup> = H, Alkyne

**Scheme 6:** Synthesis of benzo[1,4]oxazepino-fused tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline analogues

The structure of the compounds was determined by NMR and mass spectrometry. The *trans* stereochemistry of the compound (8*R*\*,14*aR*\*)-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline was confirmed by X-ray crystallographic analysis (**Figure 3**).



**Figure 3:** Crystal structure of (8*R*\*,14*aR*\*)-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline

In conclusion, a straight forward synthesis of a new class of benzo[1,4]oxazepino fused tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline frameworks has been achieved in good yields. The synthetic strategy features an efficient generation of cyclic iminium ion to construct the benzo[1,4]oxazepino unit, and an intramolecular Pictet-Spengler reaction to install the tetrahydroisoquinoline or tetrahydro- $\beta$ -carboline rings as the key steps.