

**Synthesis of Imidazo[1,2-*a*]pyridines and their  
Functionalization *via* C–C and C–N Bond Formation  
using Transition Metal Catalysts**

**THESIS**

Submitted in partial fulfillment of the requirements for the degree

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# **Chapter IV**

## **Conclusion**

### 4.1. General conclusion

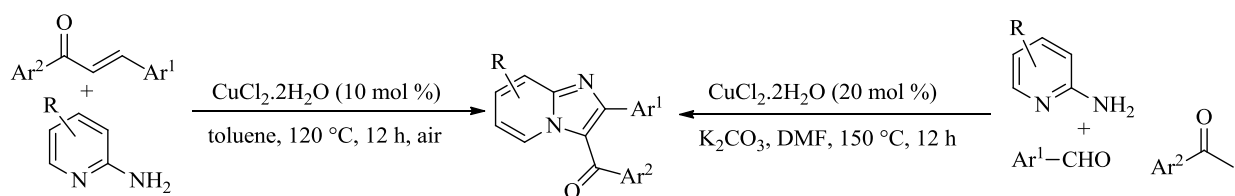
Organic chemical synthesis has reached at high degree of skilful. In recent years, the major concern in organic synthesis is to access the complex bioactive organic molecule in minimum number of synthetic steps from the simple and readily available precursors. In multi-step synthesis, preparation of complex molecule increases in proportion to chemical waste, labour work and time. In this context, development of multistep syntheses in single step utilizing the multi-bond forming protocols such as tandem or domino sequences, multi-component reactions and one-pot sequential reactions are given high priority in synthetic organic chemistry and transition metal-catalyzed consecutive multi-component reaction (MCR) and post MCR modification concept has become powerful approach for the diversity-oriented synthesis without the necessity of pre-activation of substrates. One of the major objectives of these reactions is the construction of C–C and C–heteroatom bonds by catalytic activation of the C–H bond with high efficiencies, high functional group tolerance and excellent regioselectivities.

The current thesis entitled “**Synthesis of Imidazo[1,2-*a*]pyridines and their Functionalization via C–C and C–N Bond Formation using Transition Metal Catalysts**” deals with the inexpensive and environment benign transition metal such as copper and vanadium for synthesis and functionalization of imidazo[1,2-*a*]pyridine by employing C–H functionalizations with multi-bond forming reactions like multi-component reactions, tandem sequences. Mainly, the thesis is focused on synthesis of 3-arylimidazo[1,2-*a*]pyridine and further functionalization of imidazo[1,2-*a*]pyridine with different azole by C–N coupling and with NMO by activating C(sp<sup>3</sup>)–H bond. The thesis is divided into four chapters.

### 4.2. Specific conclusion

The first chapter of this thesis describe the biological importance of imidazo[1,2-*a*]pyridine in different field. The chapter further deals with the brief history for the synthesis of imidazo[1,2-*a*]pyridine using different methodology. This chapter is mainly focused on synthesis of 3-arylimidazo[1,2-*a*]pyridine using copper-catalyzed tandem and multi-component reaction. This chapter is divided into two parts. **Part-A** demonstrates the direct synthesis of bioactive 3-arylimidazo[1,2-*a*]pyridines from chalcones and 2-aminopyridines. The reaction of chalcones and 2-aminopyridines in the presence of catalytic amount of CuCl<sub>2</sub>·2H<sub>2</sub>O was carried out in

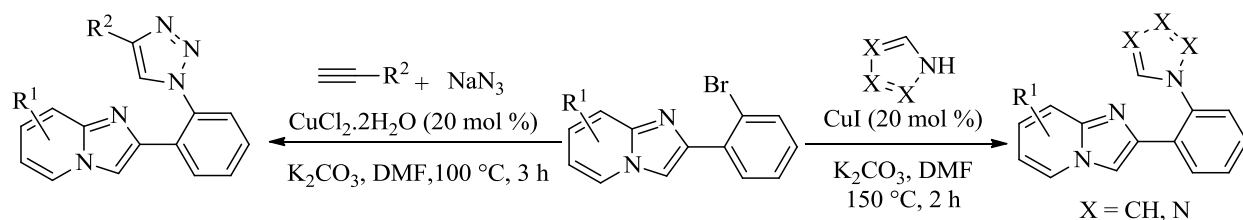
toluene at 120 °C for 12 h. A wide variety of chalcones and 2-aminopyridine with different functional group were well tolerated under the developed condition and resulted good to excellent yield of corresponding product. This protocol proved to be convenient as reaction proceeds smoothly without the necessity of any ligand in the presence of air as oxidant. Dual C–N bond formation in the presence of an economically attractive copper salt, ligand and additive-free conditions, and ubiquitous air as an oxidant are the salient features of this protocol. **Part-B** of the thesis employed the importance of multi-component reaction for the synthesis of 3-arylimidazo[1,2-*a*]pyridine. The reaction of aryketones, arylaldehydes and 2-aminopyridines in the presence of catalytic amount of copper(II) chloride and air as oxidant was performed in DMF along with K<sub>2</sub>CO<sub>3</sub> base. Different functional group such as methyl, methoxy, nitro, and halo as well as highly sensitive bromo substitution, heterocyclic ketones and aldehydes such as 2-acetylthiophene and thiophene-2-carbaldehyde resulted moderate to good yield of the product. Reaction mechanism includes chalcone synthesis by the reaction of aldehyde and ketone followed by CuCl<sub>2</sub> assists in the Michael addition followed by copper-catalyzed oxidative C–N bonding (**Scheme 4.1**).



**Scheme 4.1:** Synthesis of 3-arylimidazo[1,2-*a*]pyridine using copper-catalyzed C–N bonding

**The second chapter** of the thesis initiates with introduction of copper-catalyzed Ullmann C–N coupling and limitation of Ullmann coupling, followed by brief literature report on use of copper catalyst for C–N coupling reactions which could be applied for methods for synthesis of nitrogen containing heterocyclic compounds. Use of copper catalyst and ligand-free and additive-free conditions made the method more useful for synthesis of regioselective azole substituted imidazo[1,2-*a*]pyridine. This chapter is divided into two parts and **part A** reports the reaction of 2-(2-bromoaryl)imidazo[1,2-*a*]pyridines with different azoles in the presence of CuI without any use of external ligand. Series of azoles such as 2-methyl-1*H*-imidazole, 4-methyl-1*H*-imidazole, 1*H*-indole, and 1*H*-benzimidazole could be coupled with 2-(2-bromoaryl)imidazo[1,2-*a*]pyridines to give good to excellent (65–96%) yields of the product. Regioselectivity of the

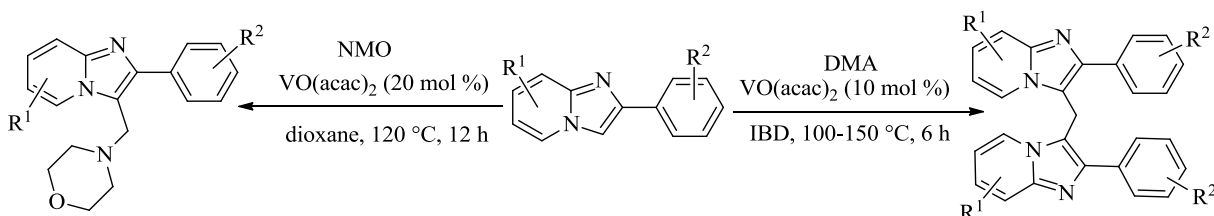
given reaction was proposed on the basis of two control experiments. Reaction of 6-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with imidazole resulted mono-coupled product while 6-bromo-2-phenylimidazo[1,2-*a*]pyridine was un-reactive. **Part B** describes the copper-catalyzed ligand and additive-free synthesis of 1,2,3-triazole-substituted imidazo[1,2-*a*]pyridines through *in situ* formation of 1,2,3-triazoles by the reaction between terminal alkynes and sodium azide followed by C–N bonding. Further functionalization of halo-substituted triazole-substituted imidazo[1,2-*a*]pyridines was achieved *via* Suzuki–Miyaura cross-coupling proving the importance in synthetic potential. The reaction mechanism was proposed based on literature which first occurs through the formation of 1,2,3-triazole *via* Click chemistry followed by C–N coupling in the presence of copper catalyst (**Scheme 4.2**).



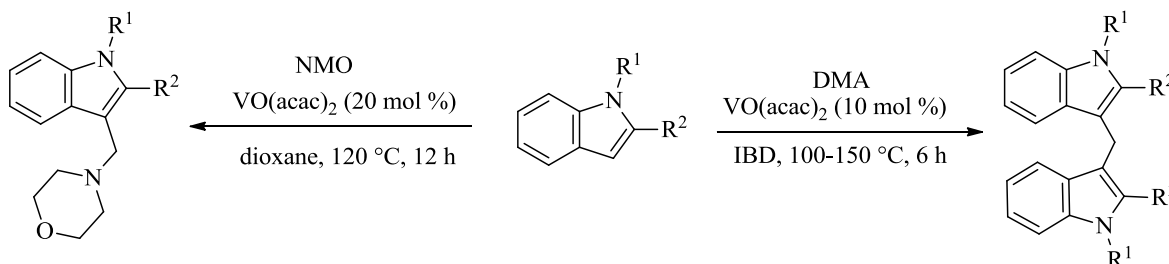
**Scheme 4.2:** Synthesis of azole and 1,2,3-triazole substituted imidazo[1,2-*a*]pyridine using Ullmann C–N coupling

**The third chapter** of the thesis shows the importance of the transition metal-catalyzed functionalization of C(sp<sup>3</sup>)–H bond *via* oxidative cross dehydrogenative coupling reactions and use of vanadium catalyzed reaction in industry as well as in organic synthesis. The chapter also discussed the comparison between copper catalyst and vanadium catalyst. Having variable positive oxidation state of 2 to 5, vanadium can be good alternate of expensive transition metal. Third chapter of thesis has two parts. **Part A** talks about vanadium-catalyzed aminomethylation of imidazo[1,2-*a*]pyridines through oxidative cross-coupling of sp<sup>3</sup>- and sp<sup>2</sup>- hybridized C–H bonds. The starting material 2-arylimidazo[1,2-*a*]pyridines were synthesized by the reaction of acetophenone and 2-aminopyridine in the presence of CuI. The reaction of electron withdrawing and electron donating group substituted 2-arylimidazo[1,2-*a*]pyridine was reacted with NMO in the presence of VO(acac)<sub>2</sub> in 1,4-dioxane to produce good to excellent yield of the product, however nitro substituent in the *para*-position of phenyl ring, could not be formed. In addition to 2-arylimidazo[1,2-*a*]pyridines, 2-substituted indoles could also be aminomethylated with the

standard reaction condition with moderate yield. Reaction mechanism proceed through vanadium-catalyzed formation of iminium ion followed by nucleophilic attack of 2-arylimidazo[1,2-*a*]pyridines. **Part B** of this chapter deals with vanadyl acetylacetonate catalyzed methylenation of imidazo[1,2-*a*]pyridines to give bis(imidazo[1,2-*a*]pyridin-3-yl)methanes using DMA as one carbon source. Reaction of 2-arylimidazo[1,2-*a*]pyridine with DMA in the presence of catalytic amount of VO(acac)<sub>2</sub> and IBD oxidant resulted bis(2-arylimidazo[1,2-*a*]pyridin-3-yl)methane in good to excellent yield. The synthesized compounds were characterized by NMR, HRMS analysis. Further the developed methodology was applied to 2-arylindole and bis(2-aryl-*1H*-indol-3-yl)methanes could be synthesized in moderate yield using DMA as one carbon source. The optimized method efficiently tolerated reactive functionalities such as methyl, methoxy, bromo, fluoro and chloro. Synthesis of unsymmetrical bis(imidazo[1,2-*a*]pyridin-3-yl)methane using two different imidazo[1,2-*a*]pyridine is an interesting application of the reaction. Gram-scale reaction demonstrated the potential for the scale-up processes. Catalytic amount of an earth-abundant and inexpensive vanadium catalyst, broad substrate scope, good to excellent yields, and simple isolation procedure are the salient features of the method. The reaction mechanism involves the vanadium-mediated formation of an iminium intermediate and electrophilic substitution. The reaction intermediate *N*-((2-(3-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)-*N*-methylacetamide was confirmed by analyzing mass of crude reaction mixture (**Scheme 4.3** and **4.4**).



**Scheme 4.3:** Vanadium-catalyzed aminomethylation and methylenation of imidazo[1,2-*a*]pyridine



**Scheme 4.4:** Vanadium-catalyzed aminomethylation and methylenation of indole

### 4.3. Future scope of the research work

In recent years, the major concern in organic synthesis is to access the potent heterocyclic organic structures involving fewer synthetic steps from simple and readily available precursors. In this direction, the use of transition metal-catalyzed multi-component reaction, C–H activation, C–C and C–heteroatom bond formation and C–N coupling reactions have become valuable tool for the construction of these heterocyclic compounds. As many natural products in addition to pharmacologically active molecules contains heterocyclic compounds as their central frameworks, synthesis of these molecules by means of combining transition metal-catalyzed reaction and tandem multi-component methodologies are an attractive alternative to traditional linear syntheses approaches.

In the thesis we have synthesized and functionalized imidazo[1,2-*a*]pyridine using transition metal copper and vanadium. As these molecules are referred as non-benzodiazepine due to pharmaceuticals properties which are similar to benzodiazepine. So the developed procedures can be tuned further to access the drugs in reduced number of steps or probably in single step. These procedures have wide scope and can be employed for the synthesis of diverse range of either bioactive heterocyclic molecules or to access new heterocyclic libraries for biological screenings. The synthetic methodologies and novel derivative of imidazo[1,2-*a*]pyridine heterocycles provided in the thesis will be fine and adoptable example for the systematic construction of heterocycles for biological screenings.