Chapter 6

Conclusions

6.1 GENERAL CONCLUSION

Among various onium salts, the pyridinium salt is an important heterocyclic motif which is widely present in a range of biological active compounds and alkaloids. These salts have extensively utilized in the diverse fields of synthetic and material chemistry as solvent, catalyst and reagent. On the other hand, imidazo[1,2-*a*]pyridine represent significant class of compounds with extensive biological, medicinal and optoelectronic applications. The synthesis and functionalization of imidazo[1,2-*a*]pyridine with novel methods is desirable both from economic and environmental point of view.

The current thesis entitled "**Synthesis of Functionalized Imidazo[1,2-*a*]pyridines and Amides using Pyridinium Salts**" deals with the use of innovative functionalized pyridinium salts as reactive synthon for the synthesis and functionalization of imidazo[1,2-*a*]pyridines by employing transition-metal (Pd and Cu) catalysis and transition metal-free synthetic approaches. The thesis also describes the design and synthetic application of imidazolium-supported 2-chloropyridinium salt as an efficient reagent for amide bond formation. Mainly, the thesis is focused on synthesis of functionalized imidazo[1,2-*a*]pyridine and amide derivatives by constructing C-C/C-X (X = N, O, S) bonds by utilizing pyridinium salts as reactive partner and reagent respectively. The thesis is divided into six chapters.

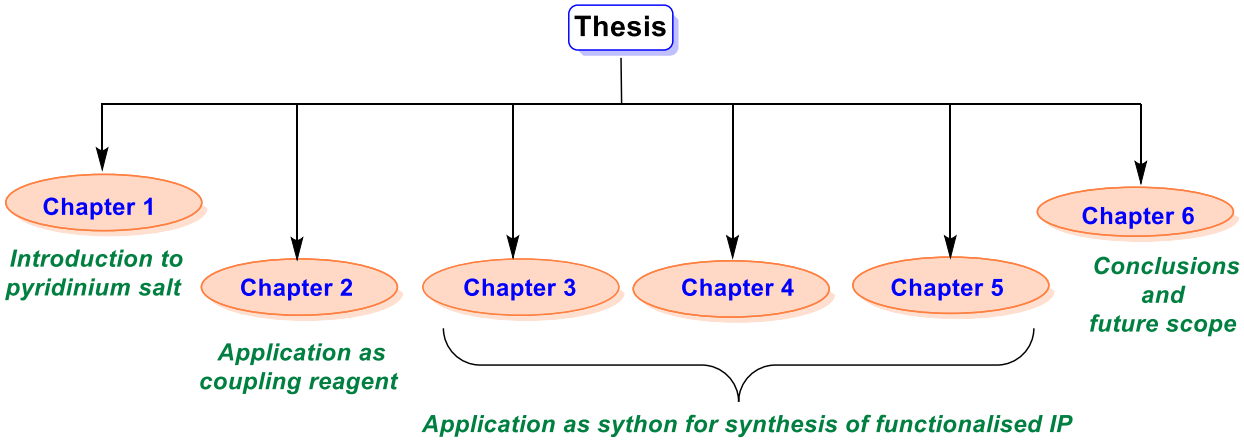


Figure 6.1 A Flow chart presentation of the current thesis

6.2 SPECIFIC CONCLUSIONS

In **chapter 1**, of the thesis, we have described the importance and chemical reactivity of pyridinium salts as an introductory chapter to provide a background on application of these salts as an active reactant and reagent. The utility of pyridinium salts for the synthesis of aza-fused heterocycles such as indolizine, pyrazolopyridine and imidazo[1,2-*a*]pyridines have been discussed based upon the research conducted by synthetic chemists in the past. The literature review for the utility of pyridinium salts as oxidizing, allylating, benzylating and thiocyanating reagent has also been covered (**Figure 6.2**).

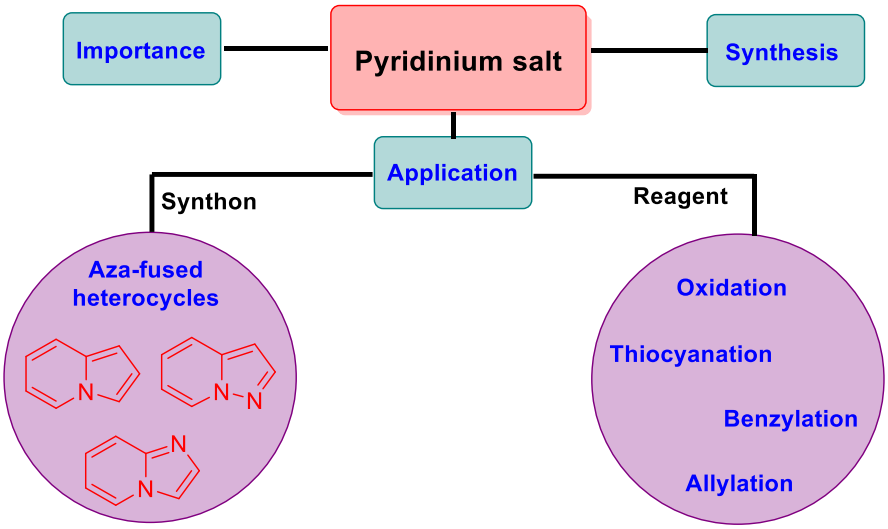
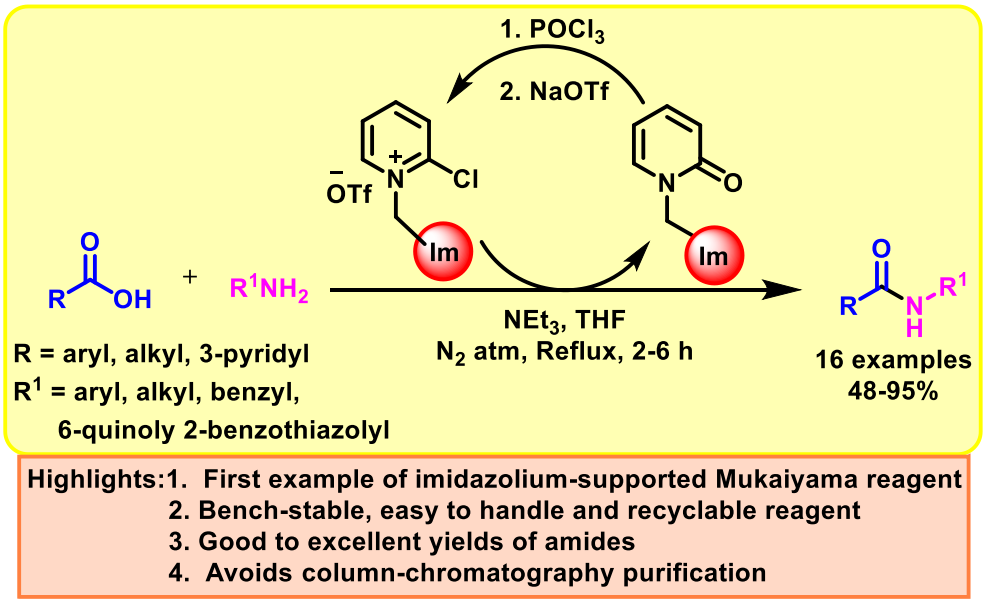


Figure 6.2 A diagrammatic representation of chapter 1

Chapter 2: Imidazolium-supported 2-Chloropyridinium Triflate: An Effective Coupling Reagent for Amide Bond Formation

The importance of amide bonds in naturally occurring molecules in inevitable. The construction of these bonds has appreciated by numerous research groups in form of a surplus research efforts and development of several coupling reagents. In these progressions, in **chapter 2**, we have presented a detailed synthetic protocol for the synthesis of imidazolium-supported 2-chloropyridinum trifluoromethanesulfonate reagent (Im-MR) as a novel coupling reagent for amide bond formation. The reagent was fully characterized using spectroscopic analysis like IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The applicability of the reagent was shown by performing amide coupling reaction of variously substituted aromatic, aliphatic and heterocyclic

carboxylic acids and amines to synthesize a library of amide derivatives in good to excellent yields. All the synthesized amide derivatives were fully characterized with the aid of IR, melting point, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The use of imidazolium-support on 2-chloropyridium salt offered better reactivity compared to earlier reported polymer and fluorous-supported reagents. Additionally, the byproduct imidazolium-supported pyridone was further utilized for the regeneration of Mukaiyama reagent and used up to 2 cycles. The significance of this protocol is evading column chromatography, shorter reaction time and good to excellent yields of amides.

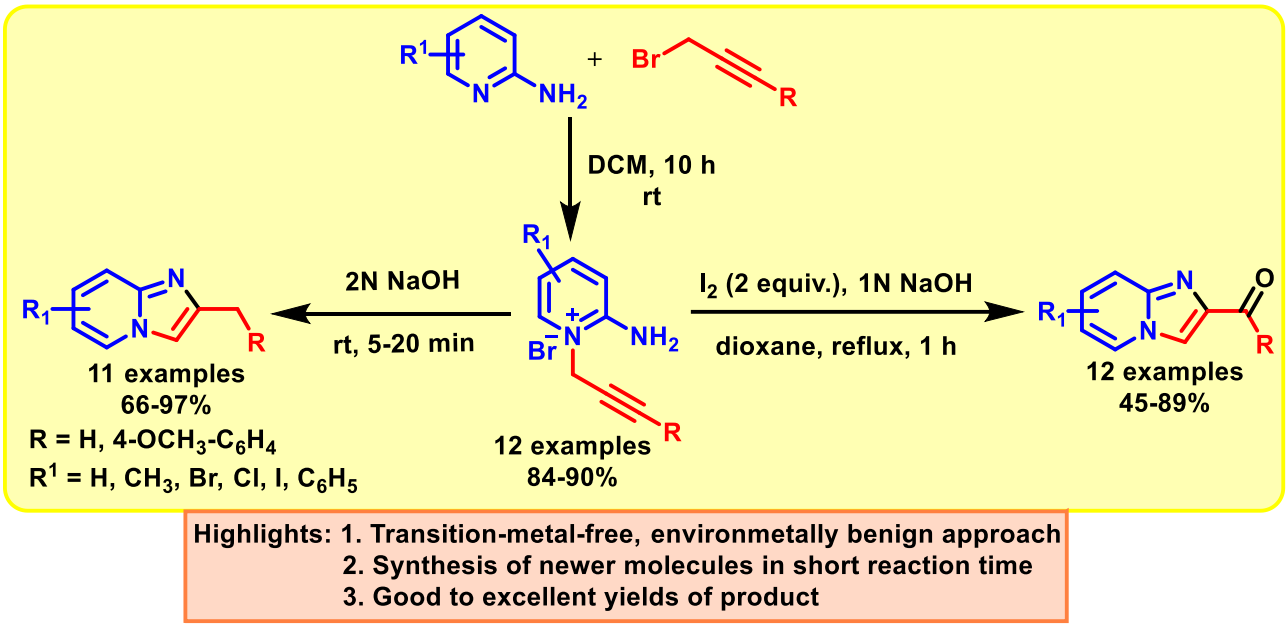


Scheme 6.1 Synthesis of amides using imidazolium-supported 2-chloropyridinium triflate

Chapter 3: Iodine-mediated Synthesis of 2-Carbonylimidazo[1,2-*a*]pyridines *via* Intramolecular Cyclization of *N*-Propargyl Pyridinium Salts

The introduction of functional groups in heterocyclic compounds is most sought after research activity over past few years. In this regard, formylation of imidazo[1,2-*a*]pyridines has gained meticulous interest due to their important application in construction of numerous drug related derivatives. The C-3 formylation of imidazo[1,2-*a*]pyridines is well explored in literature, however scarce reports are available for development of C-2 formylation of imidazo[1,2-*a*]pyridines. In **chapter 3**, we have explored the synthesis of 2-carbonylimidazo[1,2-*a*]pyridines from 2-amino-*N*-propargyl pyridinium bromide in the presence of molecular iodine and base through intramolecular iodocyclization reaction. Initially, the 12 examples of 2-amino-*N*-propargyl

pyridinium bromide derivatives were prepared from quaternization reaction of 2-aminopyridine derivatives with propargyl bromide. The synthesized pyridinium salts were subjected to iodocyclization reaction in presence of molecular iodine (2 equiv.) and base (1N NaOH) to afford 12 examples of 2-carbonylimidazo[1,2-*a*]pyridines in good to excellent (45-89%) yields. The mechanism of the reaction was believed to proceed *via 5-exo-dig* type iodocyclization of *N*-propargyl pyridinium bromides. Additionally, direct access to 2-methylimidazo[1,2-*a*]pyridines from *N*-propargyl pyridinium bromide was carried out in presence of base through intramolecular hydroamination reaction. All the synthesized compounds have been characterized by IR, NMR (^{1}H and ^{13}C) and mass analysis. This transition metal-free approach provides a facile and entirely novel route toward variously substituted 2-carbonylimidazo[1,2-*a*]pyridines and 2-methylimidazo[1,2-*a*]pyridines.

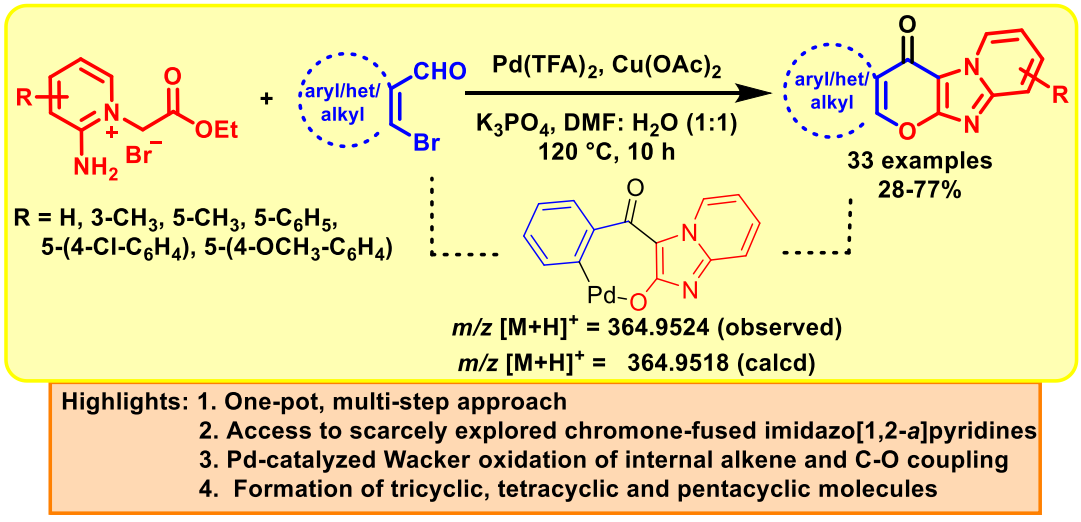


Scheme 6.2 Synthesis of 2-carbonyl/2-methyl/2-benzylimidazo[1,2-*a*]pyridines

Chapter 4: Tandem Reaction of 2-Aminopyridinium Salts and 2-Bromoaldehyde Derivatives: Access to Chromone-fused Imidazo[1,2-*a*]pyridines

The annulated aromatic systems containing two or more heterocyclic frameworks are frequently encountered in numerous natural and non-natural drug like products. The fourth chapter of the thesis initiates with the introduction of the importance of chromones and the synthesis of chromone-fused aza-heterocyclic molecules, followed by a brief literature report on the palladium-

catalyzed tandem reaction and Wacker oxidation. In **chapter 4**, we have reported the new synthetic route for the synthesis of 12*H*-chromeno[2',3':4,5]imidazo[1,2-*a*]pyridin-12-one *via* one-pot multi-step transformation of 2-aminopyridinium salts and 2-bromobenzaldehyde by using $Pd(CF_3CO_2)_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant. The versatility of the reaction was generalized with differently substituted aryl acetaldehydes and 2-aminopyridinium salts to obtain good yields of the 33 examples of product. Interestingly, heteroaromatic aldehydes such as 2-bromopyridine- 3-carbaldehyde and 2-bromothiophene-3-carbaldehyde also reacted to furnish the corresponding chromeno-fused imidazo[1,2-*a*]pyridines in 64% and 65% yields, respectively. Additionally, 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde was reacted with 2-aminopyridinium salts to give corresponding 5,6-dihydro-7*H*-benzo[7′,8′]-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridin-7-ones in 35% yield. The substituents on the pyridine ring of 2-aminopyridinium salts significantly influenced the reaction outcome such as in case of 5-phenyl substituted pyridinium salt, the formation of *N*-acetyl-2-aminopyridine derivatives was observed by cleavage of salts. A detailed mechanistic pathway study was carried out by performing a set of control experiments and mass-spectrometry (ESI-HRMS) study of the reaction mixture. The overall approach is believed to involve tandem base-mediated amidation and Knoevenagel condensation, followed by palladium-catalyzed Wacker type oxidation and intramolecular C−O coupling reaction. The developed tandem reaction was also successfully applied for the synthesis of pyrano-fused imidazo[1,2-*a*]pyridines by using 3-bromo-3-arylacrylaldehydes.

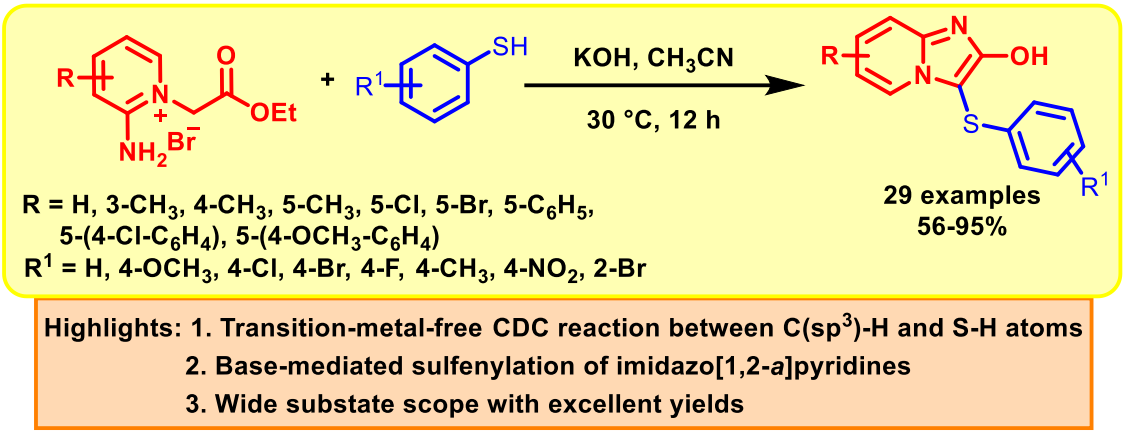


Scheme 6.3 Palladium-catalyzed synthesis of chromone-fused imidazo[1,2-*a*]pyridine

The synthesized chromone/pyrano-fused imidazo[1,2-*a*]pyridines were completely characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry analysis. In addition, the X-ray crystal structure of one of the synthesized derivative provides a transparent spectroscopic support. Compared with previously reported methods, this protocol is versatile, tolerates different functional groups, and gives moderate to good yields of chromeno-[2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-one derivatives.

Chapter 5: Base-mediated Tandem Intramolecular Amidation and Sulfenylation: Direct Access to 3-Sulfenylated Imidazo[1,2-*a*]pyridin-2-ols

In recent year, the C-S bond formation reaction has sparked significant research efforts among synthetic chemists because aryl sulfides and their derivatives are important auxiliary units in numerous naturally occurring and bioactive compounds. In **chapter 5**, we have reported a mild and transition metal-free cross-dehydrogenative C(sp^3)-H sulfenylation approach towards the synthesis of 3-sulfenylimidazo[1,2-*a*]pyridin-2-ol from readily available starting materials such as 2-aminopyridinum salts and thiols. The reaction of thiols substituted with electron-withdrawing and electron-donating group and pyridinium salts in the presence of KOH in acetonitrile at 30 °C was carried out to produce good to excellent yields of the product, however aliphatic and heterocyclic thiols could not react under optimized reaction condition. A wide variety of 2-aminopyridinum salts were tolerated under optimized reaction condition to yield good yields of desired products. The comparative study of different sulfenylating agents such as *p*-tosyl chloride, sulfonyl hydrazine, benzenesulfinic acid sodium salt and disulfide with thiol was carried out. To investigate a detailed reaction mechanism, several control experiments and mass-spectrometry (ESI-LC/MS HRMS) study of radical scavenging reaction were performed. The reaction was believed to proceed through base-mediated intramolecular amidation followed by intermolecular cross-dehydrogenative C(sp^3)-S bond formation *via* single electron transfer (SET) process. Furthermore, the hydroxyl functional group was utilized to synthesize of 2-aryl-3-sulfenylimidazo[1,2-*a*]pyridine derivatives through tosylation of hydroxyl group followed by palladium-catalyzed Suzuki coupling reaction.

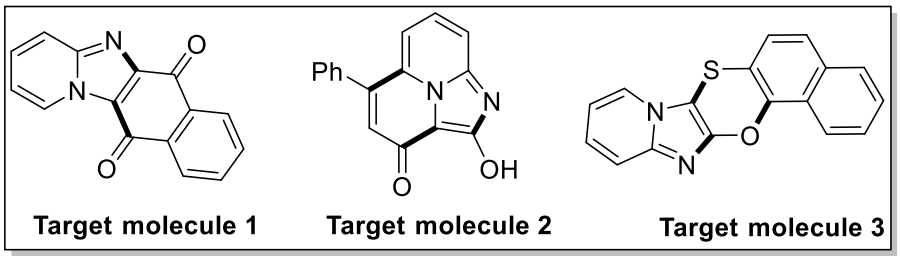


Scheme 6.4 KOH-mediated synthesis of 2-hydroxy-3-sulfenylimidazo[1,2-*a*]pyridine

The synthesized compounds were completely characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry analysis. The X-ray crystal structure of one of the synthesized derivative **29ad** in intermolecular hydrogen-bonding state was obtained. The introduction of important hydroxyl functional group and sulfenyl group in imidazo[1,2-*a*]pyridine molecules in single maneuver under transition metal-free approach, wide substrate scope and good to excellent yields (56-95%) of the products are the salient features of the protocol.

6.3 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. The current thesis reflects the development of new synthetic protocols for the construction of biologically active imidazo[1,2-*a*]pyridines and amides from pyridinium salts under transition metal-free as well as transition-metal catalysis conditions. The molecules appended with important functional groups like carbonyl, amide, sulfenyl and hydroxyl are synthesized. Thus, the developed procedures can be tuned further to access diverse range of either bioactive heterocyclic molecules or new heterocyclic libraries for biological screenings in reduced number of steps or probably in single step. The cross-dehydrogenative C−H activation for the formation of C−C and C−heteroatom bond have become valuable tool for the construction of these heterocyclic compounds. There exist an enormous scope for developing different imidazo[1,2-*a*]pyridine-fused heterocyclic frameworks by means of cross-dehydrogenative C-H activation of functionalized pyridinium salts.



On the other hand, the imidazolium-supported 2-chloropyridinium salts can be utilized for esters and thioester coupling reactions along with other organic transformation. Furthermore, the salt can be converted to other valuable alternate reagents such as thiocyanating and benzylating reagent which will persistently help to achieve various organic molecules in greener approaches.