Chapter I

Synthesis of 3-Aroylimidazo[1,2-*a*]pyridines *via* Copper-Catalyzed C–N Bonding

1.1. Introduction

Modern synthetic chemistry require high efficiency in terms of minimization of synthetic steps accompanied by maximization of complexity,[1-2] and the demand continues to rise for solutions and strategies that exceed continuously in terms of creativity.[3] Excellent examples in this respect are tandem reactions and multi-component reactions which are the most powerful tools for organic synthesis.[3-7] These reactions provide atom-economical, high yielding one-pot and environmentally benign methods as compared to conventional methods by obviating the steps of separation and purification of the reaction intermediates as well as reducing the number of synthetic steps of reaction. The "ideal synthesis" should lead to synthesis of desired product in minimum steps, good overall yield and should be environment friendly which minimize the cost and improve the overall performance of the reaction.[8]

1.1.1. Tandem reaction

The term tandem is described as chemical process that comprises at least two consecutive reactions such that each subsequent reaction occurs only in virtue of the chemical functionality formed in the previous step. These types of reactions are also known as cascade or domino reactions.

The term domino reactions was first coined by Tietze[6] as "a process involving two or more bond-forming transformations (usually C–C bonds and C–N bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as consequence of the functionality formed in the previous step". Cascade reactions mainly include multiple component domino sequences. In other words, these are classes of reactions where sequential transformation of substrate occurs *via* two or more mechanically distinct processes. A simple representation of tandem process is shown in **figure 1.1.** The targeted product **D** could be obtained in two steps *via* intermediate **C** in the conventional methods while tandem reaction offers the same product in single step starting from the precursors **A** and **B**.

The major advantages of tandem reactions are that they

- avoid isolation of intermediates and reduces the labor and time
- reduce the waste generation
- build large number of complexity in single step

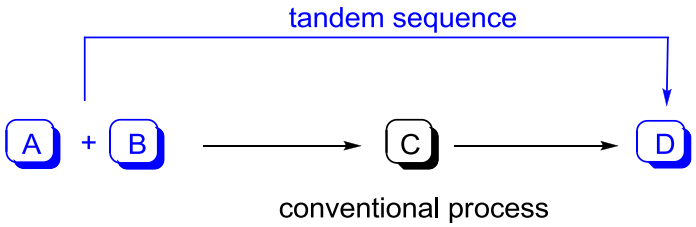
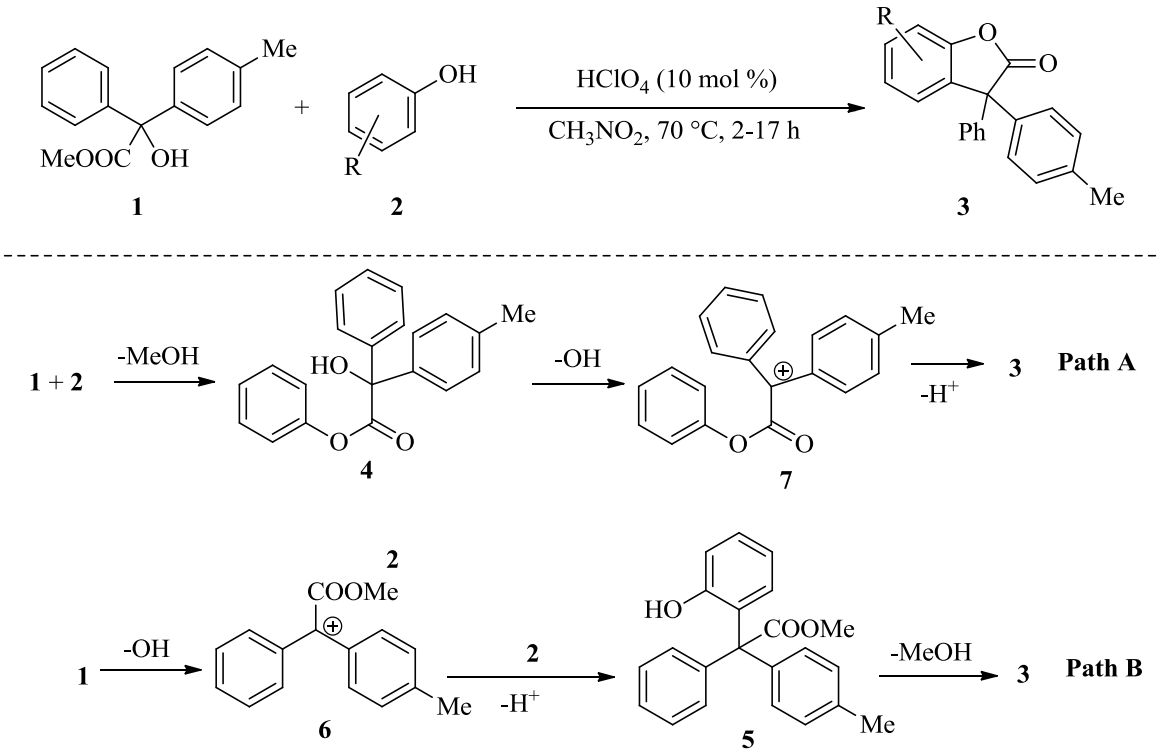


Figure 1.1: Design of tandem reaction

Some selected examples have been described from the recent literature on application of tandem reaction towards the synthesis of bioactive heterocyclic compounds.

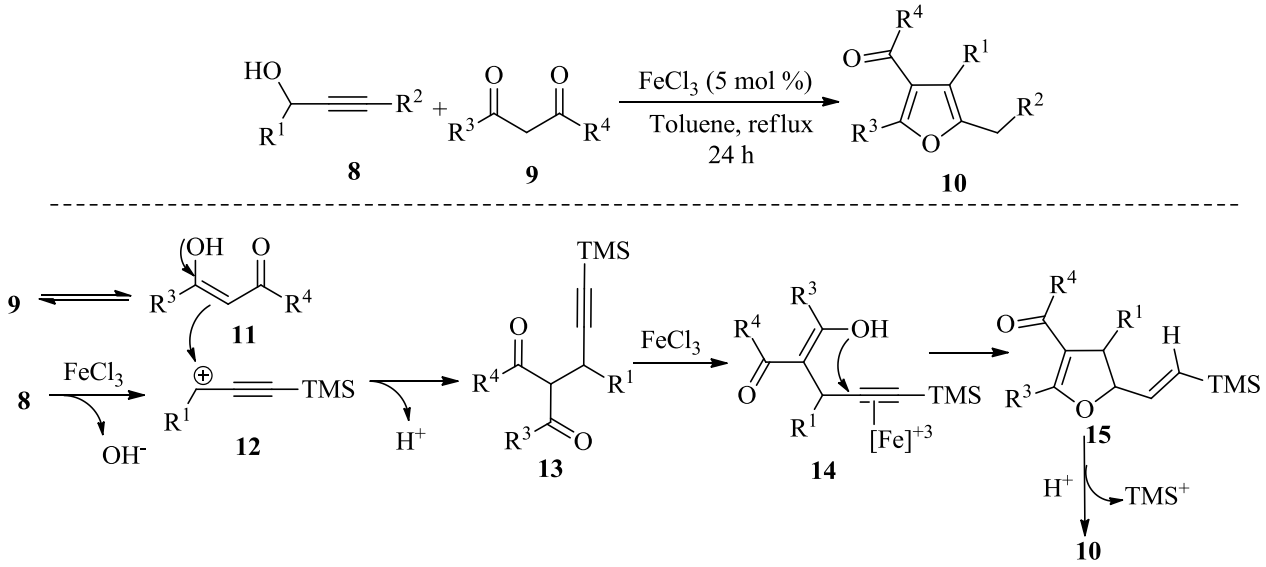
Synthesis of furan derivatives *via* tandem reaction

Zhou and co-workers described metal-free tandem Friedel−Crafts/lactonization reaction for the synthesis of medicinally important benzofuranones (**3**) using range of different tertiary *α*-hydroxy acid esters (**1**) and substituted phenols (**2**) (**Scheme 1.1**).[9] The reaction mechanism was studied through NMR and concluded that the reaction proceeds *via* the sequential Friedel−Crafts/lactonization reaction. Reaction mechanism was proposed to happen through two possible pathways (**Path A** and **Path B**).



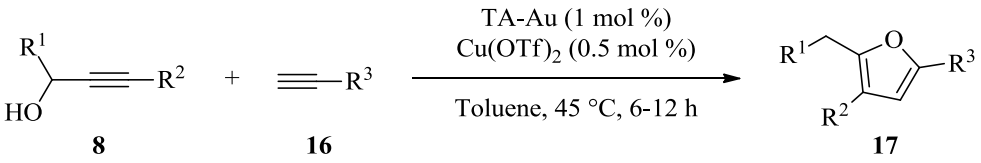
Scheme 1.1: Synthesis of 3,3-disubstituted benzofuranones

Zhan *et al.* reported the reaction of propargylic alcohols or acetates (**8**) with 1,3-dicarbonyl compounds (**9**) in the presence of $FeCl_3$-catalyst to synthesize furan derivatives (**10**) *via* tandem propargylation–cycloisomerization process in one-pot (**Scheme 1.2**).[10] Reaction commenced with ionization of propargylic alcohol to process propargylic cation (**12**), followed by nucleophilic attack of the enol (**11**) to give an alkynyl ketone (**13**). On the other side, alkyne binds with iron to give π-alkyne iron complex (**14**) and 5-*exo*-*dig* nucleophilic attack of the hydroxyl group on complex generate the alkenyl-iron derivative which on further protonolysis, isomerization and desilylation furnishes the final product (**10**).



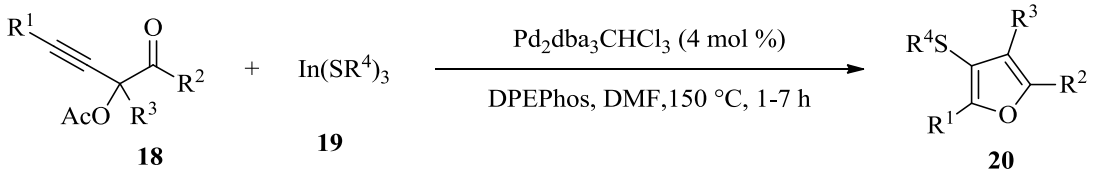
Scheme 1.4: Synthesis of furans and mechanism for the propargylation–cycloisomerization tandem reaction

Recently, Shi *et al.* reported synthesis of substituted furan (**17**) using combination of triazole-gold (TA-Au) and copper catalysts in one-pot through three-step tandem reaction of propargyl alcohol (**8**) and alkynes (**16**) (**Scheme 1.3**).[11] The product was achieved *via* alcohol addition to alkyne followed by Saucy−Marbet rearrangement, and cyclization of allene-ketone providing the better overall efficiency. The developed procedure facilitated the synthesis of various furans with large substrate scope including aromatic, aliphatic and heteroaromatic alkynes to give good to excellent yield of multi-substituted furan, however, tertiary propargyl alcohols failed to produce furans.



Scheme 1.3: Synthesis of furans *via* tandem reaction

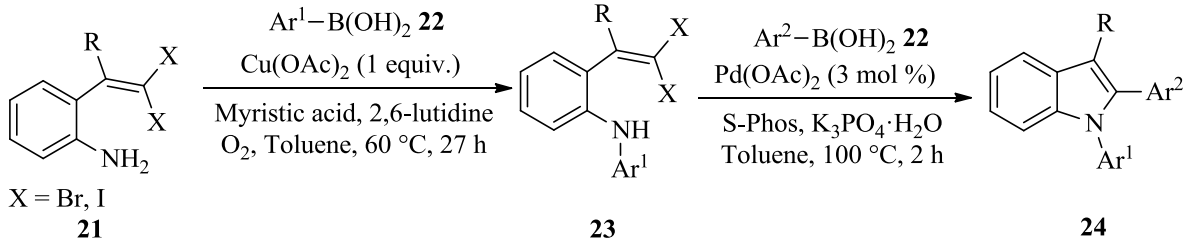
Lee and co-workers developed an efficient method for the synthesis of multi-substituted furans (**20**) and pyrroles *via* tandem palladium-catalyzed reaction of propargyl acetates (**18**) with indium organothiolates (**19**) (**Scheme 1.4**).[12] Propargyl acetates bearing acyl groups underwent propargyl substitution reaction with indium organothiolates to produce allenyl ketones and the sequential cycloisomerization reaction led to the formation of multi-substituted furans in one-pot. Reaction was well explored with the scope of both propargyl acetates bearing different acyl groups and indium reagents.



Scheme 1.4: Synthesis of multi-substituted furans *via* tandem palladium-catalyzed reaction

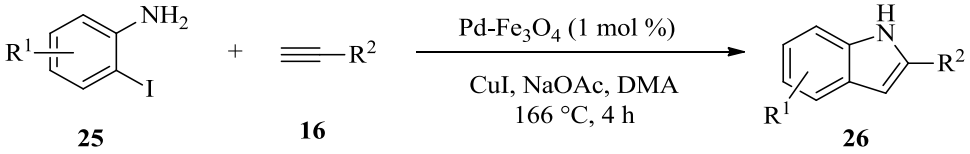
Synthesis of indole and benzimidazoles derivatives *via* tandem reaction

Lautens *et al.* synthesized 2-substituted and 2,3-disubstituted indoles (**24**) with palladium catalyst using tandem C–N/Suzuki-Miyaura coupling from readily prepared *ortho-gem*-dihalovinylanilines (**21**) (**Scheme 1.5**).[13] Various commercially available aryl and heteroaryl boronic acids (**22**) and different substituted *ortho-gem*-dibromovinylanilines (**21**) were evaluated to produce range of 2-substituted and 2,3-disubstituted indoles (**24**) in good to excellent yield. The developed methodology was further explored for an orthogonal combinatorial approach to synthesize 1,2-disubstituted or 1,2,3-trisubstituted indoles (**24**).



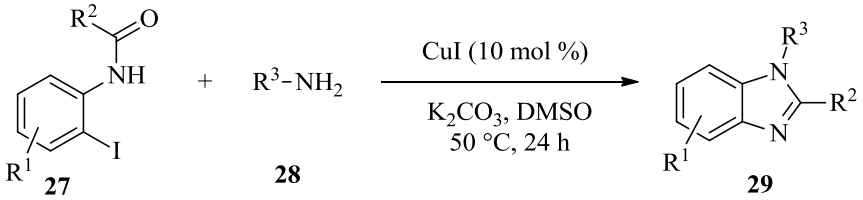
Scheme 1.5: Synthesis of 1,2,3-trisubstituted indoles using C–N/Suzuki-Miyaura reaction

Kim *et al*. described an efficient and greener method for the synthesis of indole derivatives (**26**) *via* tandem cyclization of 2-iodoaniline (**25**) and phenylacetylene (**16**) using recyclable Pd-Fe_3O_4 nanocrystal catalysts (**Scheme 1.6**).[14] The developed methodology can be used for variety of terminal alkynes and 2-haloanilines to produce 2-substituted indole in good to excellent yield. The used catalyst could be conveniently recovered with an external magnet and recycled up to ten times without any loss of their catalytic activity. The reaction sequence includes Pd-Fe_3O_4 nanocrystal-catalyzed Sonogashira coupling followed by tandem cyclization.



Scheme 1.6: Synthesis of 2-substituted indole using tandem reaction

Ma *et al.* described one-pot synthetic approach for benzimidazoles (**29**) using *ortho*-halide (I or Br) functionalized *N*-acyl aromatic amines (**27**) (**Scheme 1.7**).[15] The substitution variation in both the R^1 and R^2 of the substrates **27** was allowed in the synthesis of product in good to excellent yield. The *ortho*-subtituent effect of the NHCOR group turned out to be an important factor for the transformation.



Scheme 1.7: Synthesis of 1,2-disubstituted benzimidazoles from 2-iodoacetanilides

1.1.2. Multi-component reaction

The rapid synthesis of diverse set of complex molecules can be achieved using diversity-oriented synthesis. Multi-component reactions play vital role for the synthesis of complex molecules. Multi-component reactions (MCRs) or multi-component assembly process are the reactions where three or more easily accessible compounds react together in single step to form product displaying features of all inputs without isolating the intermediate.[16] These reactions have become an important tool for generating organic compounds with high degree of molecular diversity in organic synthesis.[17-20] MCRs play an important role in modern synthetic chemistry and offer significant advantages over conventional multi-step syntheses.[21-24] Multi-component

reactions are efficient and effective methods in the sustainable and diversity-oriented synthesis of heterocycles. Furthermore, the combination of established multi-component reactions with post reaction transformations such as Ullmann reaction, Suzuki reaction and C–N coupling reaction opens the way for the synthesis of vast number of diverse and complex products.[25] In particular, transition metal-catalyzed multi-component sequences have recently gained considerable interest.[26] These reactions have broad substrate scope and capability to tolerate diverse functionalities. These reactions allow the construction of novel libraries of drug-like molecules with structural diversity, that are of pharmaceutical interest.[27] In addition, reducing the number of synthetic steps and overall reaction time, low cost and operational simplicity are the features of MCRs that contribute to the requirements of an environmentally friendly process (**Figure 1.2**).

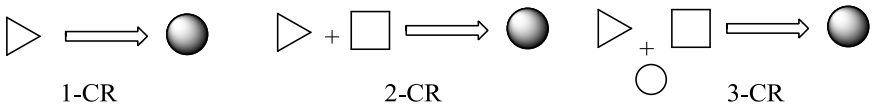
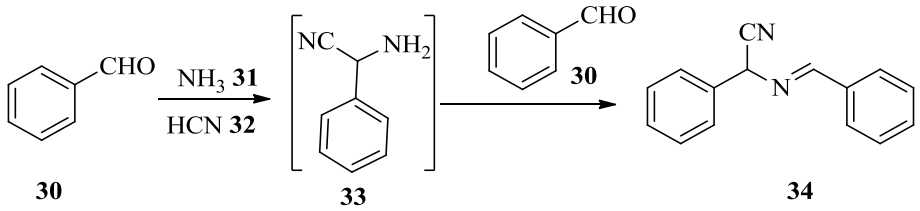


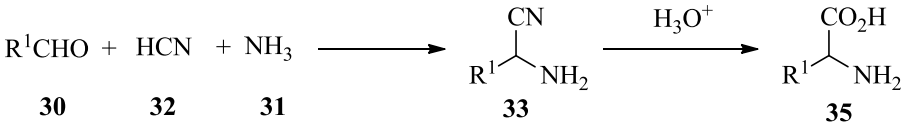
Figure 1.2: General representation of multi-component reaction

The first MCR was developed by Laurent and Gerhardt to synthesize benzoyl azotide (**34**). In this reaction benzaldehyde (**30**) reacted with ammonia (**31**) and hydrogen cyanide (**32**) to give aminobenzyl cynide (**33**) which on further reaction with another molecule of benzaldehyde (**30**) yielded Schiff base, known as benzoyl azotide (**34**) (**Scheme 1.8**).[18]



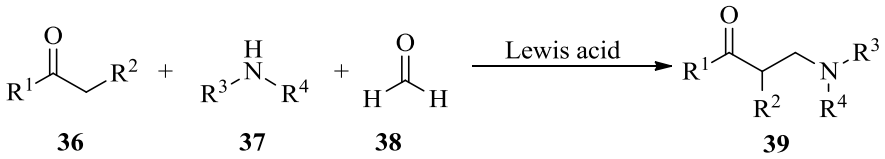
Scheme 1.8: Synthesis of benzoyl azotide using MCR

First true MCR was developed by Strecker for the synthesis of α-aminonitriles in 1850, he developed three component reactions (3CR) of aldehydes (**30**), hydrogen cynide (**32**) and ammonia (**31**) for the synthesis of *α*-aminonitriles (**33**). Hydrolysis of *α*-aminonitriles (**33**) led to the formation of valuable *α*-amino acids (**35**) (**Scheme 1.9**).[28] The reaction proceeds through formation of iminium ion by the reaction of aldehyde and ammonia *via* H_2O elimination. Nucleophilic attack of cyanide ion on iminium carbon yields the product *α*-aminonitriles which can be further hydrolyzed to corresponding amino acids.



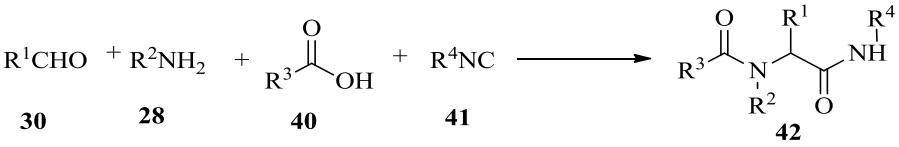
Scheme 1.9: Strecker synthesis of α-amino acids

In 1912, Mannich disclosed three component reaction of carbonyl compounds (**36**), primary or secondary amines (**37**) and formaldehyde (**38**) for the synthesis of β-amino carbonyl compounds (**39**) which are commonly known as Mannich bases (**Scheme 1.10**).[29]



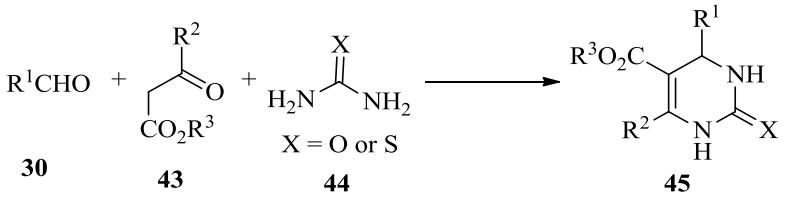
Scheme 1.10: Mannich reaction for the synthesis of β-amino carbonyl compounds

In 1959, Ugi reported four component reaction for the synthesis of α-acylamino amides (**42**). This reaction made significant breakthrough in the field of MCRs. Ugi reaction is one of the widely employed methods for the synthesis of diamides by the reaction of aldehydes (**30**), primary amines (**28**), carboxylic acid (**40**) and isonitriles (**41**) (**Scheme 1.11**).[30] In this reaction prior formation of imine by reaction between aldehyde and amine that follows addition of carboxylate ion across isocyanide carbon. The resulted acylated isoamide undergoes acyl transfer to deliver the desired α-acylamino amides.



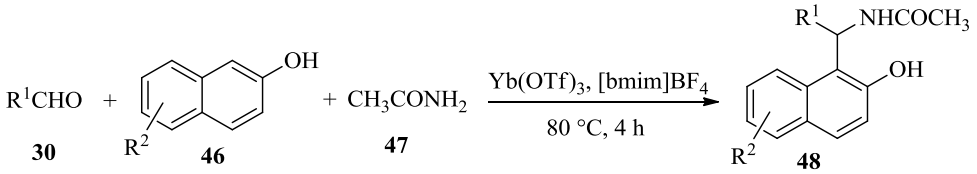
Scheme 1.11: Ugi reaction for the synthesis of α-acylamino amides

Another important contribution in area of multi-component reaction is by Biginelli for the synthesis of dihydropyrimidine (**45**) through the acid catalyzed condensation of arylaldehyde (**30**), β-ketoesters (**43**) and urea or thiourea (**44**) (**Scheme 1.12**).[31] Due to great medicinal aspect of pyrimidine, this method has gained wide interest. Reaction proceeds through the formation of an aldol intermediate by the condensation of aldehyde (**30**) with active methylene compound ester or 1,3-diketone (**43**). Nucleophilic addition of urea or thiourea (**44**) on aldol adduct with the subsequent elimination of H_2O affords the corresponding product.



Scheme 1.12: Synthesis of dihydropyrimidines *via* Biginelli reaction

The amidoalkyl naphthols are important scaffolds for the synthesis of 1,3-amino oxygenated compounds.[32-33] In addition, they are potent building blocks in medicinal chemistry.[34] The most recognized method to achieve these motifs is acid catalyzed three component reaction (3CR) of aldehydes (**30**), *β*-naphthol (**46**) and acetamide (**47**). A wide range of reports are available in the literature with diverse Lewis acid as well as Brönsted acid as catalysts under variable reaction conditions.[35-36] Recently, our group has synthesized these motifs by employing environmental benign lanthanide triflate $Yb(OTf)_3$ as catalyst in eco-friendly ionic liquid, $[bmim]BF_4$ media (**Scheme 1.13**).[37]

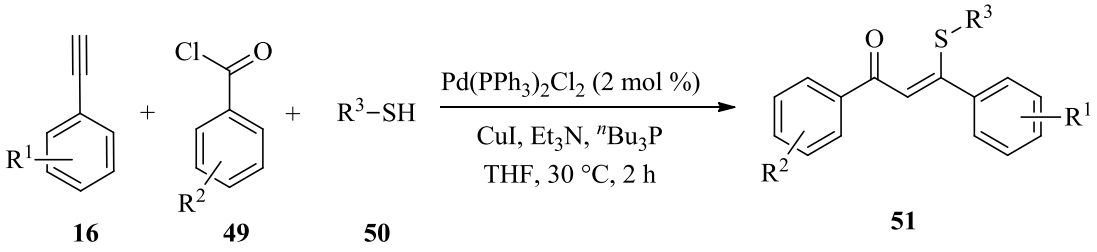


Scheme 1.13: $Yb(OTf)_3$-catalyzed synthesis of amidoalkyl naphthols

In last decade, a plethora of reports have appeared on MCRs either to improve the reaction conditions or to synthesize potential bioactive compounds in reduced number of steps.[38-40] In addition, there are several articles where these multi-component reactions are amalgamated with other valuable C−C as well as C−heteroatom bond forming reactions in domino sequence to access complex structures in single step.[41-43] Transition metal-catalyzed MCRs have been designed for various reaction sequences achieving impressive diversity in the resulting molecular assembly. The efforts to perform and develop suitable reaction condition for the sequential reactions as one-pot procedures brought attention to an emerging challenge for an organic chemist. This combination of two strategies (multi-component and tandem approach) would avoid undesired interactions between the components of the multi-catalytic systems reducing the ultimate waste production.[44]

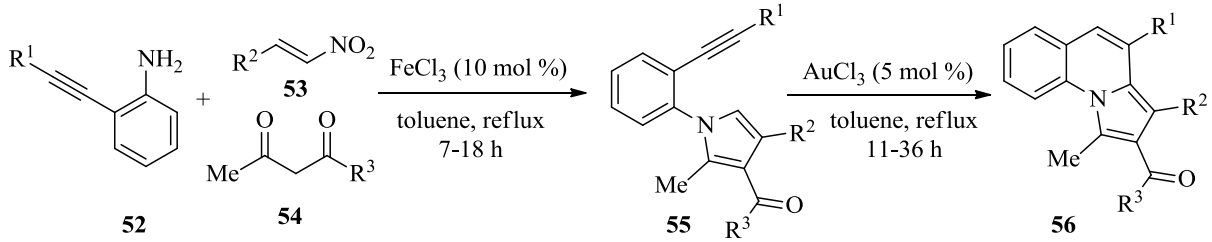
Tang group reported metal-catalyzed multi-component tandem reaction which formulated multiple bonds in highly concise fashion in one-pot. A combination of the Sonogashira coupling

reaction and the hydrothiolation reaction of electron deficient alkynone intermediates has been achieved in one-pot using alkynes (**16**), benzoyl chlorides (**49**), and aliphatic/aromatic thiols (**50**) in the presence of palladium catalyst (**Scheme 1.14**).[45] The mechanism of reaction was confirmed by control experiments and product (**51**) was confirmed by X-ray crystal and spectroscopic data.



Scheme 1.14: MCR of alkynes, carbonyl chlorides and aromatic thiols

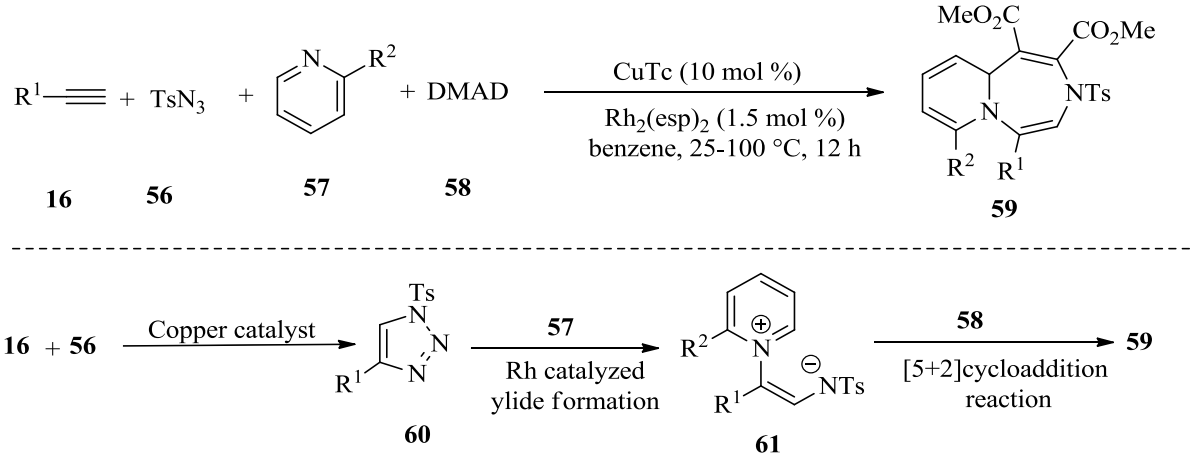
Jana *et al.* reported synthesis of complex pyrrolo[1,2-*a*]quinoline derivatives (**56**) by the reaction of 2-(phenylethynyl)aniline (**52**), nitroalkene (**53**) and 1,3-dicarbonyl compound (**54**) with iron-catalyst followed by gold-catalyzed intermolecular 6-*endo*-*dig* cyclization (**Scheme 1.15**).[46] The tandem product was achieved by sequential reactions that involved an iron(III)-catalyzed synthesis of *N*-(2-alkynylaryl)pyrroles (**55**) and gold(III)-catalyzed intramolecular hydroarylation reaction. Preliminary photophysical study of synthesized compounds exhibited good fluorescence activity.



Scheme 1.15: Synthesis of pyrrolo[1,2-*a*]quinolines through multi-component and sequential reactions

Yoo *et al.* described the catalytic reaction of pyridines (**57**) and 1-sulfonyl-1,2,3-triazoles (**60**) for the formation of azomethine ylides (**61**) which are isolable and air-stable 1,5-dipoles. The developed strategy was further utilized for multi-component [5 + 2] cycloaddition reactions by adding activated alkynes (dimethyl acetylenedicarboxylate) (**58**) in reaction mixture for the synthesis of 1,4-diazepines molecules (**59**) in the presence of rhodium catalyst (**Scheme 1.16**).[47]

The reaction was smoothly proceeded with four components in one-pot to give straightforward route for the synthesis of 1,4-diazepines in good yield.



Scheme 1.16: Four component reaction for the synthesis of 1,4-diazepines

With our interest in the synthesis of novel heterocyclic compounds using transition metal catalyzed multi-component, tandem and C–H functionalization approach through C–C coupling as well as C–N coupling reaction,[48-51] in this chapter we describe the synthesis of 3-aroylimidazo[1,2-*a*]pyridines by employing copper catalyst.

Chapter I

PART-A

Synthesis of 3-Aroylimidazo[1,2-*a*]pyridines by the Reaction of Chalcones and 2-Aminopyridines

1.2. Introduction

Heterocyclic moieties have gained much interest of synthetic organic chemist due to its wide variety of applications in pharmaceutical, veterinary and agrochemical.[52] Especially large class of nitrogen-containing heterocyclic molecules is extremely valuable for drug discovery programme.[53-54] Imidazole and pyridine fused heterocyclic compounds are found in various natural and synthetic unnatural biologically active molecules and also play an important role as intermediate in synthetic chemistry.[55-58] These compounds are also found to show interesting optical properties.

Bridged nitrogen heterocyclic compounds are widely studied for various biologically active compounds.[59-62] Among the class of bridged heterocyclic compounds, imidazopyridines which contain imidazole moiety fused pyridine ring is an important biologically active nitrogen containing heterocycle.[63-64] Different structural isomers of imidazopyridines are possible depending on the site of the attachment of the pyridine and imidazole scaffold (**Figure 1.3)**.[65]

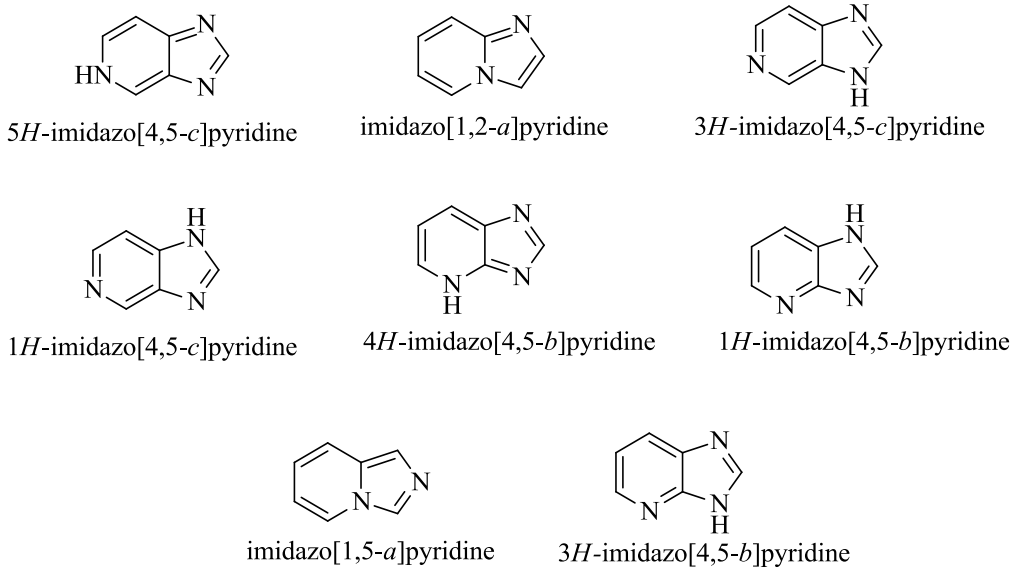


Figure 1.3: Different structural isomer of imidazopyridines scaffold

1.2.1. Biological applications of imidazo[1,2-*a*]pyridines

Among various imidazopyridine derivatives, imidazo[1,2-*a*]pyridine moiety is the most important in the area of natural products and pharmaceuticals as well as material science. The chemical structure of imidazo[1,2-*a*]pyridines are different from benzodiazepines but they show similar pharmacological properties to that of benzodiazepine drugs, hence they are termed as

nonbenzodiazepines. These scaffolds have shown many interesting biological activities such as hypnoselective, anxioselective, antiepileptic, antiulcer, antiviral, anticancer, antibacterial, antifungal, antiprotozonal, anti-inflammatory, anticonvulsant, antipyretic, antituberculosis, anthelmintic and analgesic,.[66-79] These compounds have been exclusively studied for GABA receptor agonists, 5-lipoxygensase inhibition, cyclic dependent kinase inhibition, HIF-1α prolyl hydroxylase inhibition, MCH1R antagonism, histamine H2 receptor antagonism and β-amyloid detecting ligands.[80-83] The imidazo[1,2-*a*]pyridine system is also present in pharmacologically important drugs such as Alpidem (for the treatment of anxiety), Necopidem and Saripidem (anxiolytic), and Zolpidem (to treat insomnia). Further the molecular core structure is also present in Olprinone (cardiotonic agent), Miroprofen (analgesic), DS-1 (GABA receptor agonist), GSK812397 (candidate for the treatment of HIV infection), Minodronic acid (for treating osteoporosis) and Zolimidine (to treat peptic ulcers). The core structure of imidazo[1,2-*a*]pyridine has also been studied in the field of optoelectronics, for example imidazo[1,2-*a*]pyridine bearing the 2-hydroxyphenyl substituent at C2-position of imidazole ring exhibits good excited state intramolecular proton transfer (ESIPT) (**Figure 1.4**).[84-85]

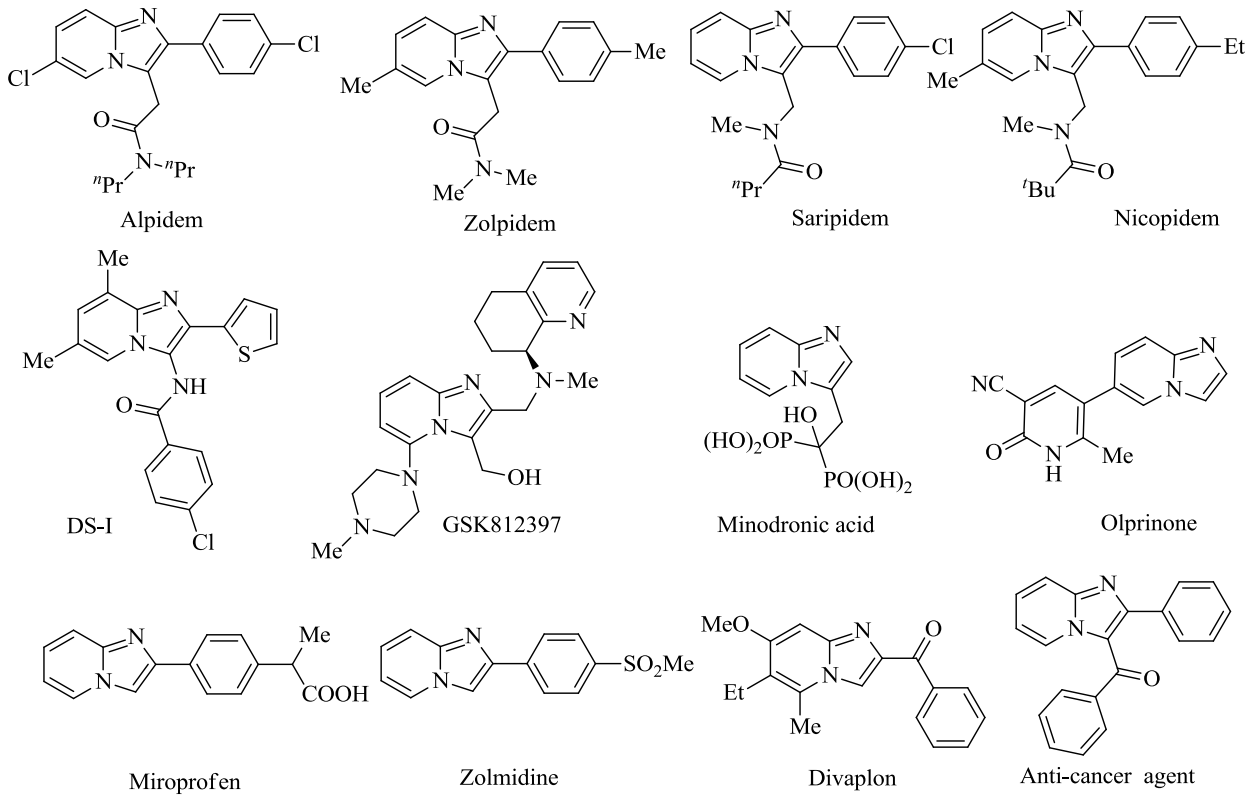


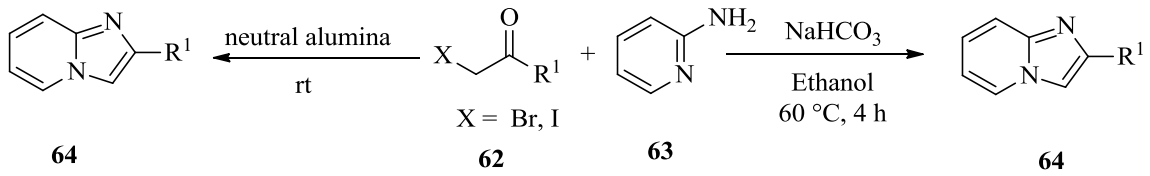
Figure 1.4: Bio-active imidazo[1,2-*a*]pyridine derivatives.

1.2.2. Synthesis of imidazo[1,2-*a*]pyridines

Not surprisingly, because of applications of imidazo[1,2-*a*]pyridine in variety of fields, extensive efforts have been directed to develop different synthetic strategies for this privileged structure.[86-87] Particularly, the last decade has been witnessed remarkable progress in the synthesis of imidazo[1,2-*a*]pyridines by employing several interesting approaches, such as multi-component reactions, tandem sequences, and transition-metal-catalyzed C–H functionalizations. These methods offer easy access to imidazo[1,2-*a*]pyridines from simple and readily available precursors without the necessity for pre-functionalities and with variety of substituents at the 2 and 3-positions of this moiety.[88] Various catalytic and non-catalytic systems have been developed by the different groups over the years for the synthesis of imidazo[1,2-*a*]pyridine.[89-90]

1.2.2.1. Metal-free synthesis of imidazo[1,2-*a*]pyridines

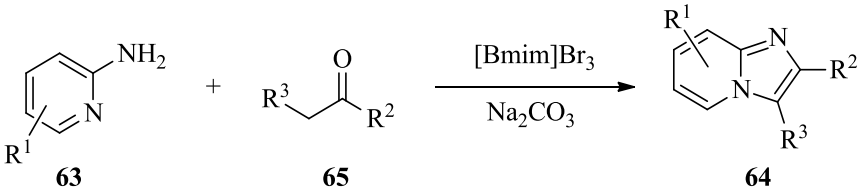
Condensation of *α*-haloketones (**62**) with 2-aminopyridines (**63**) is a traditional method for the synthesis of imidazo[1,2-*a*]pyridine derivatives (**64**).[91] Sahu *et al.* reported modified synthesis of variety of imidazo[1,2-*a*]pyridines (**64**) using alumina at room temperature (**Scheme 1.17**).[92] The lachrymatory nature of *α*-haloketones (especially phenacyl bromides) has restricted their use in organic reactions, particularly in bulk processes. From this perspective, great advances have been made over the last decade to improve the synthesis of imidazo[1,2-*a*]pyridines by replacing *α*-halocarbonyl compounds with environmentally benign reagents such as α-tosyloxy ketones or *α*-diazo ketones.[93-94]



Scheme 1.17: Synthesis of imidazo[1,2-*a*]pyridine derivatives from *α* -haloketones

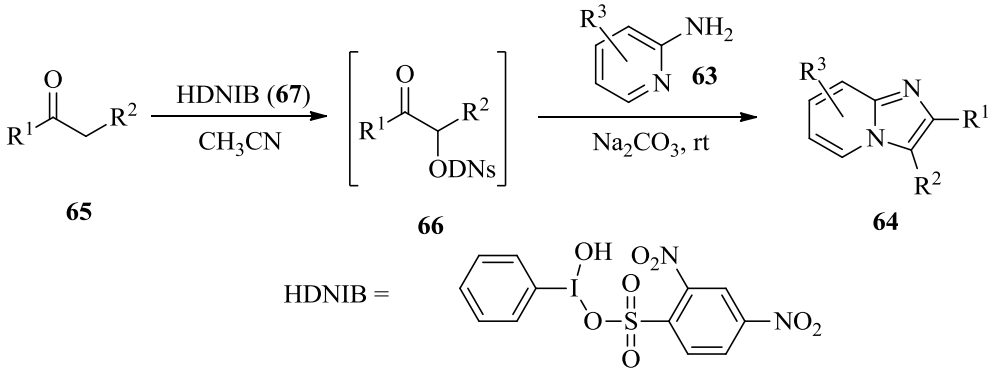
Zhang *et al.* improved the methodology for solvent-free synthesis of imidazo[1,2-*a*]pyridines (**64**) by the reaction of *in situ* activated ketone (**65**) through [Bmim]Br_3 and 2-aminopyridine (**63**) in the presence of Na_2CO_3 (**Scheme 1.18**).[95] The method avoided the use of toxic solvent and

catalyst and lachrymatory phenacyl bromides, and provided high yield of product under environmentally benign conditions.



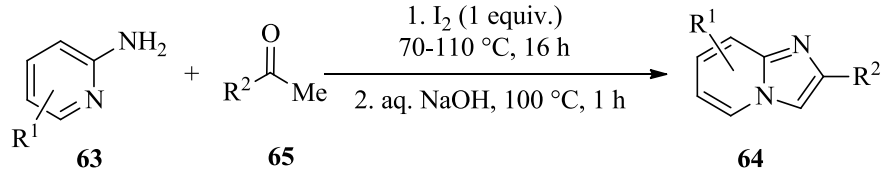
Scheme 1.18: Solvent-free synthesis of imidazo[1,2-*a*]pyridine

Chen and coworkers described an efficient approach for the synthesis of imidazo[1,2-*a*]pyridines (**64**) by the reaction of aryl methyl ketones (**65**) with hypervalent iodine(III) sulfonate (HDNIB) (**67**) (**Scheme 1.19**).[96] Reaction is believed to proceed through formation of *α*-organosulfonyloxy ketones (**66**) by the reaction of [hydroxy(2,4-dinitrobenzenesulfonyloxy)-iodo]benzene (HDNIB) and their subsequent cyclocondensation with 2-aminopyridines (**63**) produces final product.



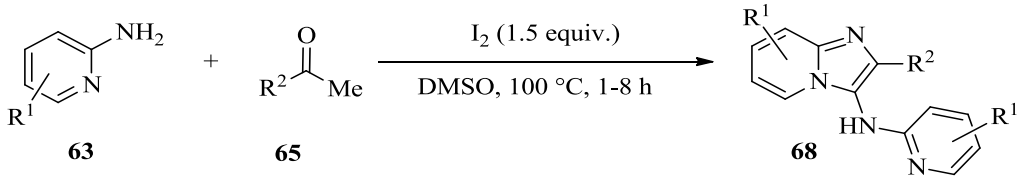
Scheme 1.19: Hypervalent iodine mediated synthesis of imidazo[1,2-*a*]pyridines

Stasyuk group reported the Ortoleva–King-type reaction of ketones (**65**) and 2-aminopyridines (**63**) using iodine to give imidazo[1,2-*a*]pyridines (**64**) (**Scheme 1.20**).[97] The reaction proceeds *via* pyridinium salts which undergo efficient ring-closure in the presence of base. The reaction is applicable for wide range of functional group and allows for the preparation of imidazo[1,2-*a*]pyridines including compounds bearing strongly electron-donating group at different position.



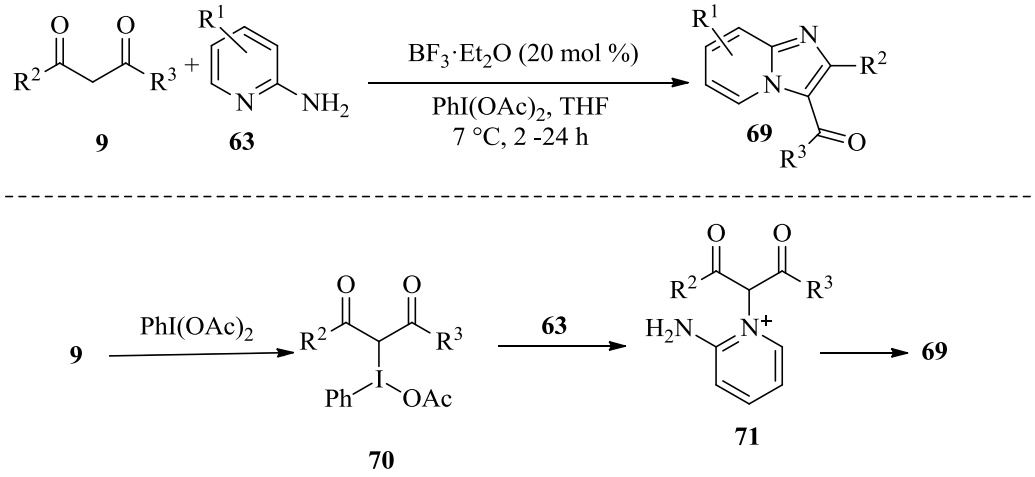
Scheme 1.20: Ortoleva−King reaction for synthesis of imidazo[1,2-*a*]pyridines

Wu *et al.* also reported iodine promoted reaction of ketones (**65**) and 2-aminopyridines (**63**) for the synthesis of 2-aryl-3-(2-pyridylamino)imidazo[1,2-*a*]pyridines (**68**) (**Scheme 1.21**).[98] This protocol allows the synthesis of 3-[(heteroaryl)amino]imidazo[1,2-*a*]pyridine in single step without using metal, base, or ligand.



Scheme 1.21: Iodine promoted reaction of ketones and 2-aminopyridine

Imidazo[1,2-*a*]pyridine-3-carboxylates (**69**) have been prepared by (diacetoxyiodo)benzene mediated oxidative coupling between 2-aminopyridines (**63**) and *β*-keto esters (**9**) (**Scheme 1.22**).[99] Reaction of *β*-keto esters with $PhI(OAc)_2$ generates intermediate **70** which on reaction with pyridinium endocyclic nitrogen gives **71**. Intermediate **71** on intramolecular condensation and subsequent aromatization produces the desired imidazo[1,2-*a*]pyridines (**69**). The use of excess of $BF_3{\cdot}Et_2O$ hampers the function of 2-aminopyridine by acid base reaction as nucleophile, and this leads to the formation of by-product resulting lower yield of imidazo[1,2-*a*]pyridine-3-carboxylates.



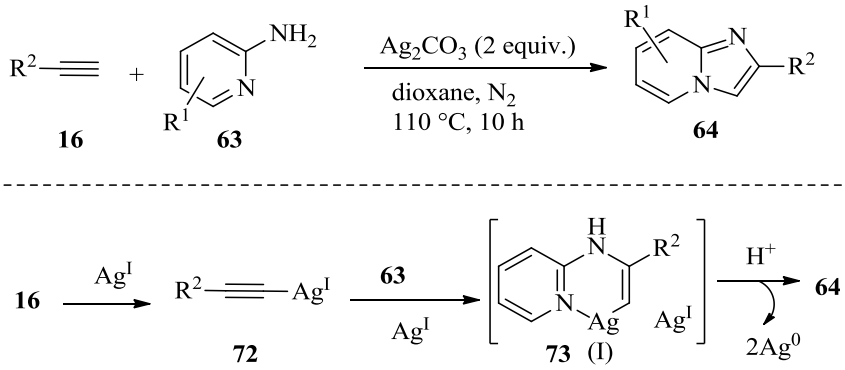
Scheme 1.22: Synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates

1.2.2.2. Transition metal-catalyzed synthesis of imidazo[1,2-*a*]pyridines

The last decade has witnessed remarkable advancement in the synthesis of imidazo[1,2-*a*]pyridines by employing several interesting approaches, such as multi-component reactions,

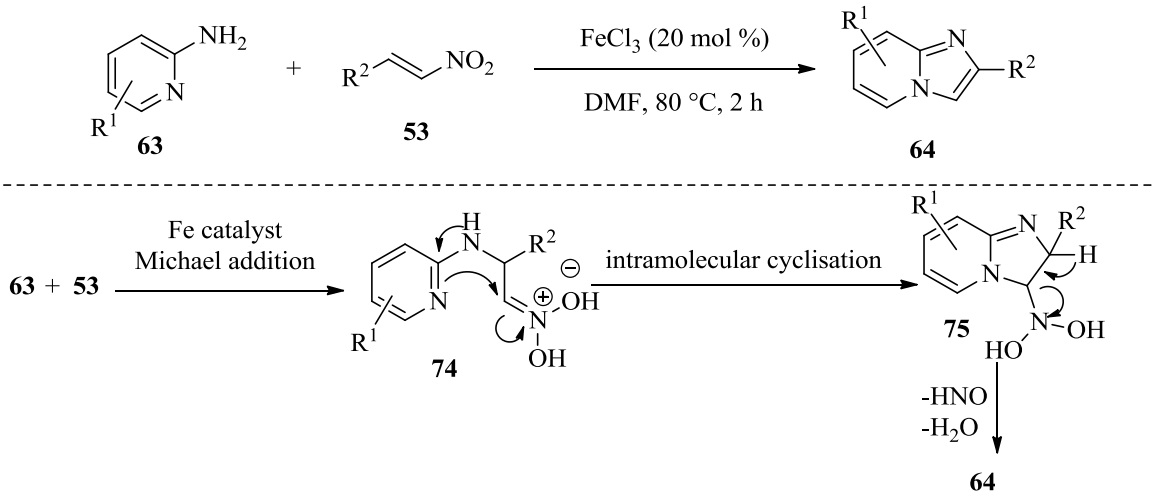
tandem sequences, and transition-metal-catalyzed C–H functionalizations. These methods offer easy access to imidazo[1,2-*a*]pyridines from simple and readily available precursors.

Lei group reported convenient method for the synthesis of imidazo[1,2-*a*]pyridines (**64**) by oxidative cross-coupling between 2-aminopyridines (**63**) and terminal alkynes (**16**) in the presence of silver carbonate (**Scheme 1.23**).[100] Various 2-aminopyridines reacted smoothly with wide range of terminal alkynes in perfect selectivity with moderate to good yields, although internal alkynes such as prop-1-ynylbenzene, 1,2-diphenylethyne could not produce the corresponding product. Reaction started with the formation of silver acetylide complex **72** followed by nucleophilic attack of 2-aminopyridine resulted intermediate **73**. Finally, silver-induced oxidative cyclization of **73** afforded the product *via* two single-electron oxidation.



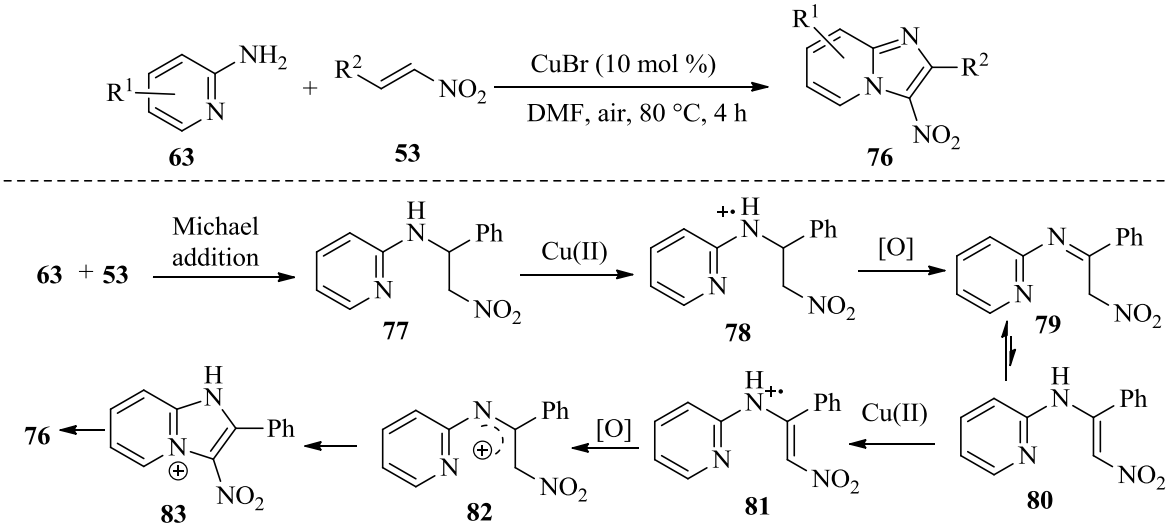
Scheme 1.23: Silver-mediated synthesis of imidazo[1,2-*a*]pyridines *via* C–H/N–H oxidative cross-coupling/cyclization

Hajra *et al.* developed simple and efficient method for the synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines (**64**) by the cascade reaction between nitroolefins (**53**) and 2-aminopyridines (**63**) (**Scheme 1.24**).[101] $FeCl_3$-catalyzed reaction is applicable for both the aromatic as well as aliphatic nitroolefins and for various substituted 2-aminopyridines to generate the corresponding product in good to excellent yield. The reaction mechanism is proposed through the formation of Michael adduct (**74**) by the reaction of 2-aminopyridine (**63**) with nitroolefin (**53**) which undergoes intramolecular cyclization involving the pyridine nitrogen in regioselective 5-*exo-trig* manner to produce the intermediate **75**. Finally elimination of water and nitroxyl (HNO) produces the final product. Lewis acid catalyzed coupling between 2-aminopyridine and nitroolefin in this reaction afforded 3-unsubstituted imidazopyrines *via* sequential Michael addition/ cyclization/denitration.[102-103]



Scheme 1.24: $FeCl_3$-catalyzed reaction of nitroolefins and 2-aminopyridines

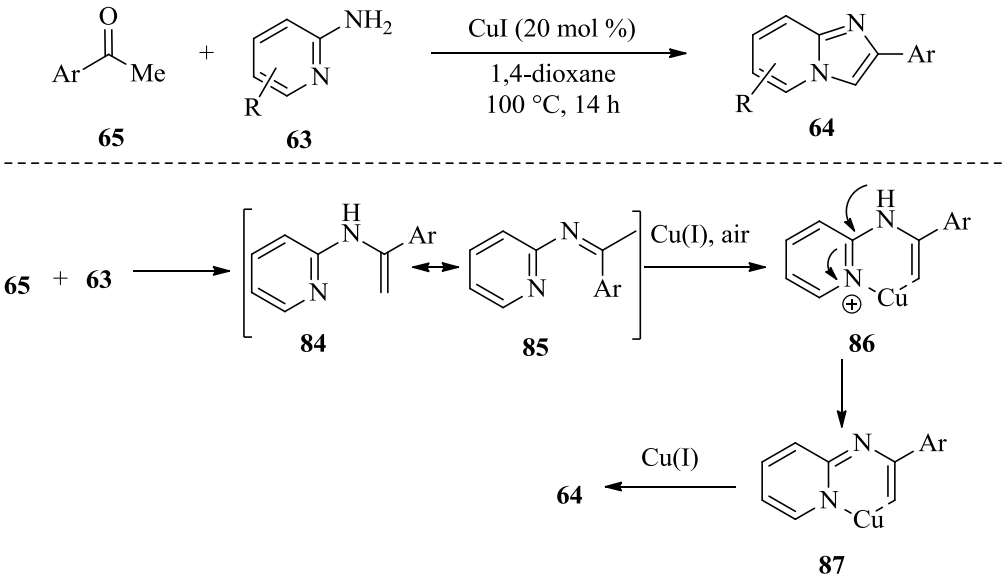
Interestingly, copper-catalyzed oxidative coupling of nitroolefins (**53**) with 2-aminopyridines (**63**) produced 3-nitroimidazo[1,2-*a*]pyridines (**76**) in the presence of air as oxidant. Copper bromide was the most efficient catalyst in DMF solvent at 80 °C (**Scheme 1.25**).[104] A wide range of substrate with electron withdrawing groups as well as electron donating groups resulted good to excellent yield of corresponding product. The reaction proceeded through Michael addition followed by intramolecular cyclization involving formation of two nitrenium ions.



Scheme 1.25: Copper-catalyzed synthesis of 3-nitroimidazo[1,2-*a*]pyridines

Our group reported ligand and additive-free copper-catalyzed synthesis of imidazo[1,2-*a*]pyridines (**64**) in good to excellent yield by using cheaper and readily available substrates such as acetophenones (**65**) and 2-aminopyridines (**63**) (**Scheme 1.26**).[105] In the reported methodology copper salts have been proved as an efficient catalyst for direct C–C and C–N bond

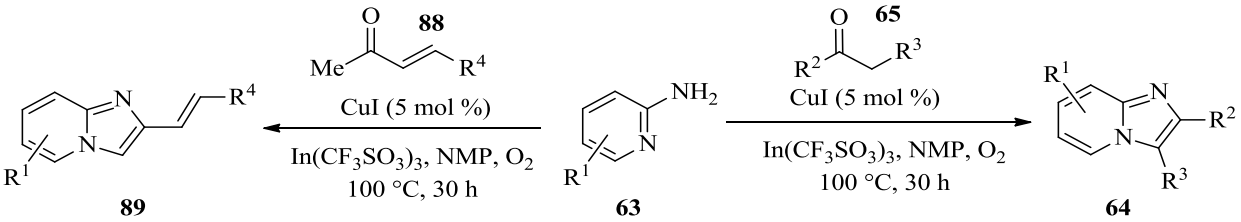
formations *via* oxidative cyclizations, cross-dehydrogenative couplings. Diversely substituted 2-aminopyridines and wide range of acetophenones were used for the synthesis of library of imidazo[1,2-*a*]pyridine derivatives. The developed method was also validated by synthesizing Zolimidine drug used for peptic ulcers, in single step. Reaction occurred through the formation of enamine (**84, 85**) by the reaction of ketone and 2-aminopyridine followed by intra-molecular cyclisation and reductive elimination to produce the final product.



Scheme 1.26: CuI-catalyzed tandem synthesis of substituted imidazo[1,2-*a*]pyridines

Hajra group and Adimurthy group independently reported the synthesis of 2-arylimidazo[1,2-*a*]pyridines by the reaction of 2-aminopyridines with acetophenones using combination of $Cu(OAc)_2$/Phen/ZnI_2 and CuI/$BF_3{\cdot}Et_2O$ catalytic system, respectively. These methods were applicable for the synthesis of wide range of functionalized imidazo[1,2-*a*]pyridine moieties. Using reported methodology the reaction was also validated with large scale synthesis of antiulcer drug Zolimidine in one-pot.[106-107]

Zhang *et al.* reported an excellent method for the synthesis of 2-alkenylimidazo[1,2-*a*]pyridines (**64**) *via* copper-catalyzed aerobic oxidative cyclization of methyl vinyl ketones (chalcone) (**88**) and 2-aminopyridines (**63**) (**Scheme 1.27**).[108] Reaction of ketone (**65**) and 2-aminopyridine (**63**) resulted aryl substituted imidazoheterocyles (**64**) under the same reaction conditions. The reaction methodology was further utilized for the synthesis of marketed drug Zolimidine in gram scale.

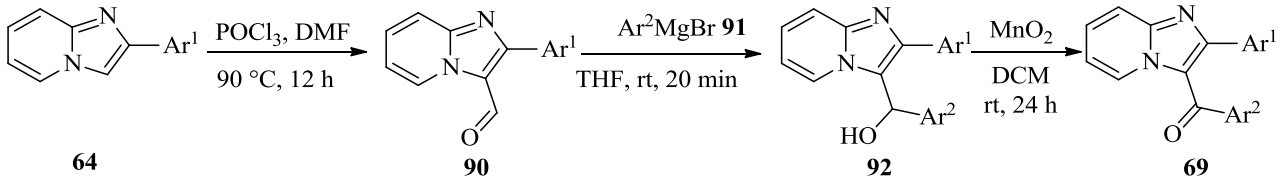


Scheme 1.27: Synthesis of aryl and alkenyl substituted imidazo[1,2-*a*]pyridine

1.2.2.3. Synthesis of 3-aroylimidazo[1,2-*a*]pyridines

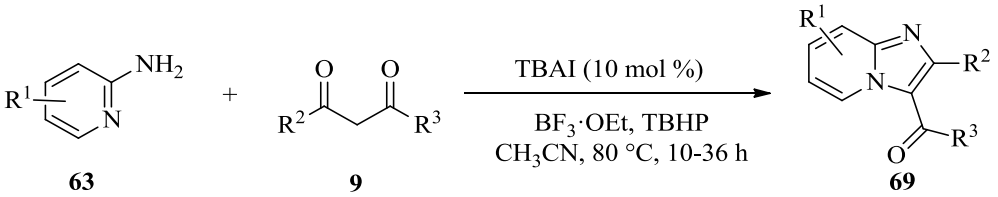
The biological activities of imidazo[1,2-*a*]pyridines has proved to be greatly dependent on substituent at the C-2 and C-3 positions. For example, 3-aroylimidazo[1,2-*a*]pyridines have been studied as anticancer and antitumor agents.[109-110] Direct functionalization of imidazo[1,2-*a*]pyridines with aroyl chloride *via* Friedel-Crafts acylation to get 3-aroylimidazo[1,2-*a*]pyridines was unsuccessful.

3-Aroylimidazo[1,2-*a*]pyridines derivatives were synthesized by Hsieh *et al*. using sequence of reactions in three steps; a) formylation of imidazo[1,2-*a*]pyridines (**64**) with $POCl_3$ in DMF at 90 °C for 12 h , b) Grignard reaction of 3-formylimidazo[1,2-*a*]pyridines (**90**) with arylmagnasium bromide (**91**) in THF at room temperature for 20 minutes and c) oxidation of generated alcohol (**92**) in the presence of MnO_2 in DCM for 24 h (**Scheme 1.28**).[111]



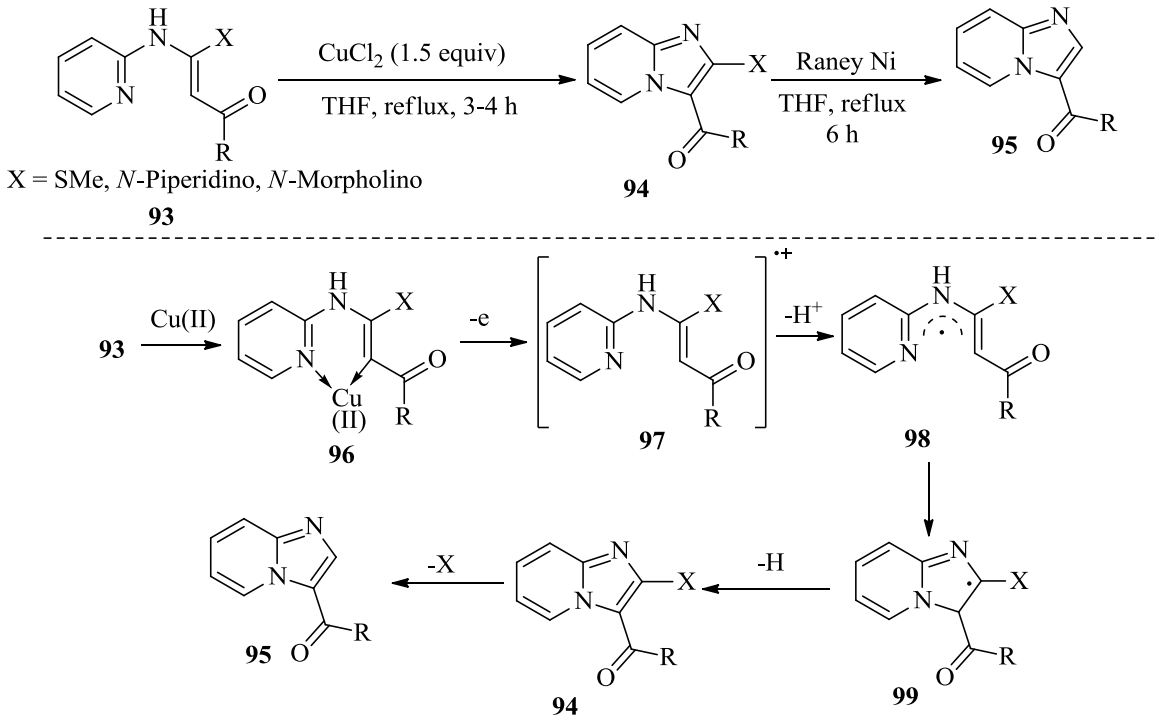
Scheme 1.28: Synthesis of 3-aroylimidazo[1,2-*a*]pyridines *via* sequence of reactions

Han and co-worker synthesized 2-arylimidazo[1,2-*a*]pyridine-3-carboxylates derivative (**69**) in the presence of $BF_3{\cdot}Et_2O$ using TBAI as the catalyst and TBHP as the terminal oxidant by the reaction of 2-aminopyridines (**63**) and *β*-keto esters or 1,3-diketones (**9**) (**Scheme 1.29**).[112]



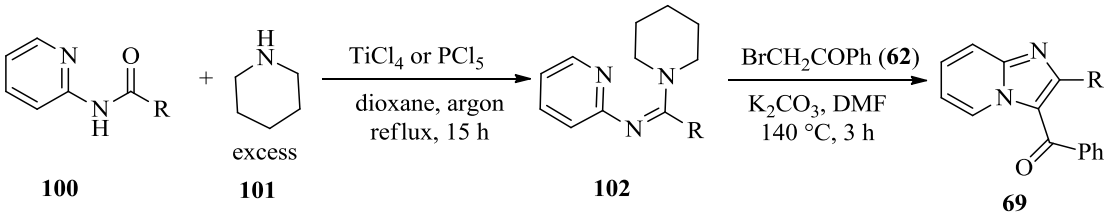
Scheme 1.29: TBAI-mediated reaction of 2-aminopyridine and 1,3-diketone

Ila group has reported an efficient method for the synthesis of biologically important 3-functionalized imidazo[1,2-*a*]pyridines (**95**) *via* $CuCl_2$ catalyzed oxidative ring closure of novel *α*-oxoketene (**93**), *S-*, *N*, *O-*, and *N*,*N*-acetal intermediates (**Scheme 1.30**).[113] The developed methodology allows regiospecific introduction of alkylthio, alkoxy, primary, and secondary amino group at the 2-position and aroyl group at the 3-position of imidazopyridine ring which could be further utilized for the synthesis of novel fused heterocyclic ring systems. Reaction mechanism is depicted in **scheme 1.30** and it starts with abstraction of hydrogen by copper *via* cation radical intermediate followed by resonance to aminyl radical (**98**). Aminyl radical undergoes intramolecular addition to the enamine followed by elimination of hydrogen radical to give the final product (**95**).



Scheme 1.30: Copper-promoted synthesis of 3-aroylimidazo[1,2-*a*]pyridines

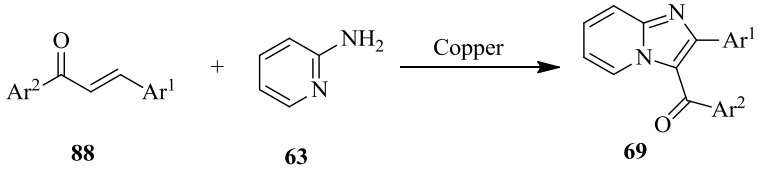
Schmitt *et al.* synthesized 2-functionalized 3-aroylimidazo[1,2-*a*]pyridines (**69**) from activated amidines (**102**) resulting from the activation of secondary amides (**100**) with $TiCl_4$ or PCl_5 in the presence of excess of piperidine (**101**) as fragile functional groups. The activated amidines (**102**) was further subjected to phenacyl bromides (**62**) in the presence of base K_2CO_3 for 3 h to give the corresponding product (**69**) (**Scheme 1.31**).[114]



Scheme 1.31: Synthesis of 3-aroylimidazo[1,2-*a*]pyridine from amidines

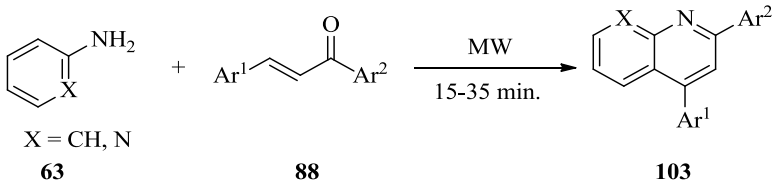
In spite of these efforts, reports for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines under ligand/additive-free aerobic conditions are rare. Thus, there is an intrinsic need to develop straightforward method for the synthesis of these biologically significant structures. With the multiple reactive sites, chalcones have been proven to be important organic scaffolds. Particularly, copper-catalyzed oxidative cyclizations of chalcones delivered variety of heterocycles with high regioselectivities.

In the pursuit of our ongoing interest for the synthesis and functionalization of imidazo[1,2-*a*]pyridines,[51, 105, 115-119] we focused our attention towards the synthesis of 3-aroylimidazo[1,2-*a*]pyridines (**69**) *via* copper-catalyzed tandem reaction between chalcones (1-aryl-3-arylprop-2-en-1-one) (**88**) and 2-aminopyridines (**63**) (**Scheme 1.32**).



Scheme 1.32: Copper catalyzed reaction of chalcones and 2-aminopyridines

Goswami *et al.* used variety of aryl or heteroaryl amines (**63**) and aryl vinyl ketones (**88**) for the synthesis of series of functionalized, aryl substituted naphthyridines (X = N) (**103**) and quinolines (X = CH) (**103**) using microwave-assisted one-pot two-component solvent-free reaction conditions (**Scheme 1.33**).[120] Reaction mechanism was believed to proceed by the Michael addition followed by ring-closing condensation and spontaneous aromatization to afford the functionalized aryl substituted 1,8-naphthyridines and quinolines.



Scheme 1.33: Microwave-assisted synthesis of quinolines and 1,8-naphthyridines

We envisioned that the reaction between chalcones and 2-aminopyridines in the presence of copper catalyst could lead to the formation of 2-aryl-3-aroylimidazo[1,2-*a*]pyridines by oxidative cyclization, which could be potential alternative for the synthesis of these motifs, as Friedel-Crafts aroylations of imidazo[1,2-*a*]pyridines were unsuccessful.[121]

1.3. Results and discussion

A model reaction was conducted using 1,3-diphenylprop-2-en-1-one (**88a**) and 2-aminopyridine (**63a**) in the presence of catalytic amount of copper iodide in toluene at 120 °C for 12 h (**Table 1.1**, entry 1). To our delight, 2-phenyl-3-benzoylimidazo[1,2-*a*]pyridine (**69a**) was isolated in 14% yield. Interestingly, neither the Michael adduct (**104a**) nor the 1,8-naphthyridine derivative (**103**) were detected in the reaction under these conditions. The structure of **69a** was elucidated by IR and NMR spectroscopic data. In the IR spectrum of **69a**, a strong peak appeared at 1597 cm^{-1} for C=O (stretching) (**Figure 1.5**) and in the ^{1}H NMR spectrum characteristic doublet appeared at δ 9.55 for the C-5 proton and the carbonyl carbon appeared at δ 187.36 along with all other expected carbons in the ^{13}C NMR spectrum (**Figure 1.6**). The HRMS of **69a** displayed peak at 299.1184 for $[M+H]^{+}$ ion that confirmed the structure of the product (**Figure 1.7**).

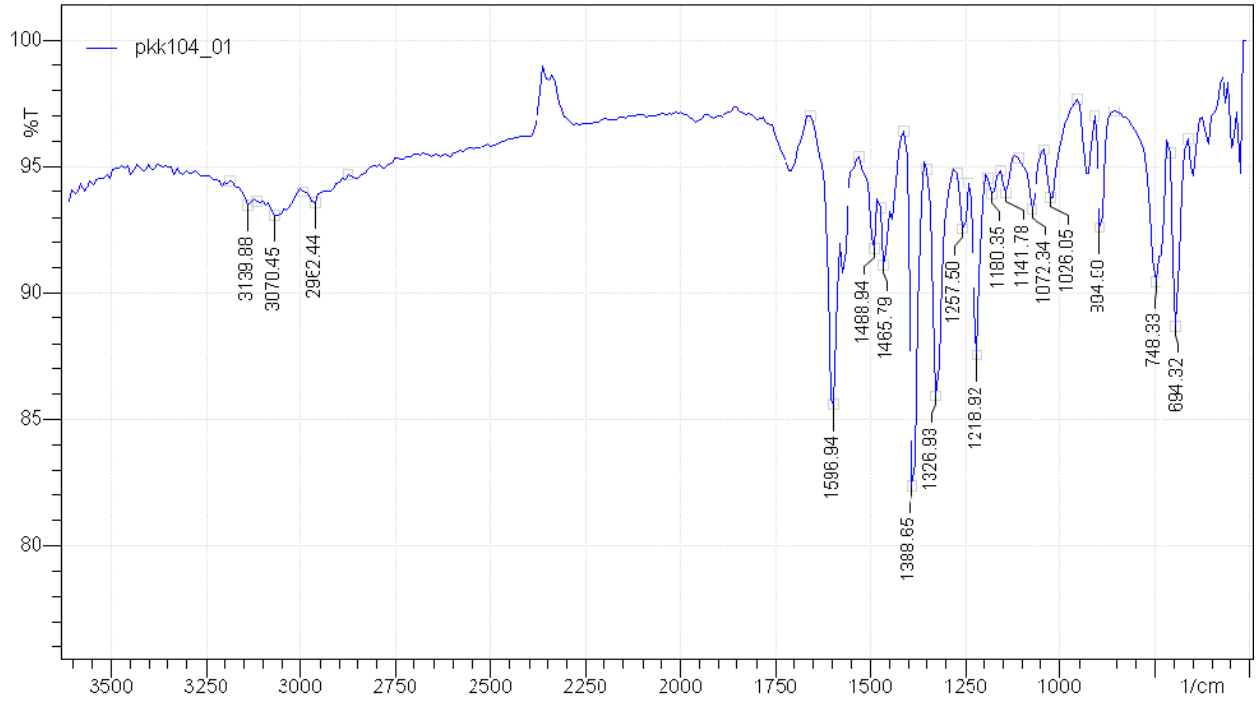


Figure 1.5: IR Spectrum of **69a**

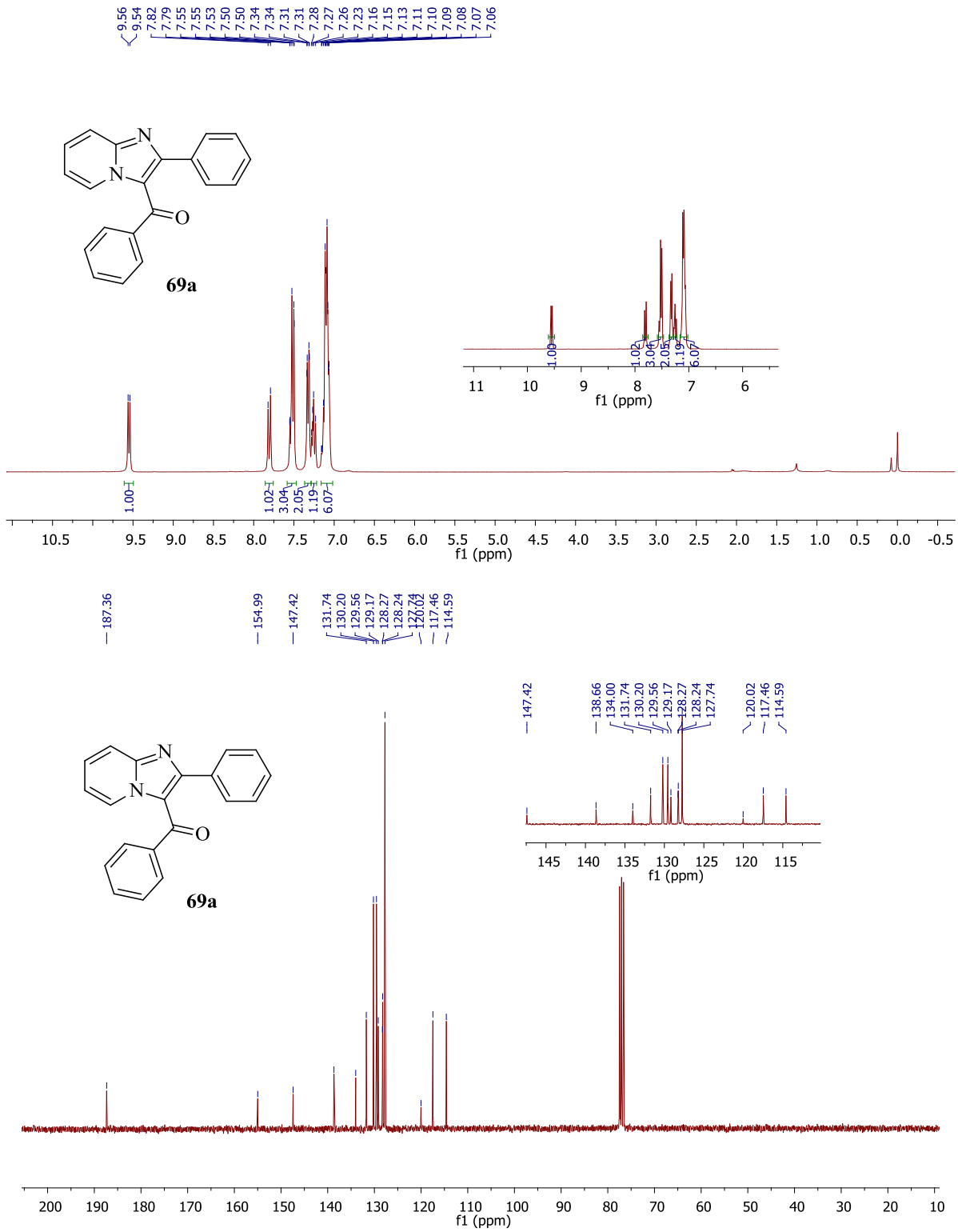


Figure 1.6: ^{1}H and ^{13}C NMR spectra of **69a**

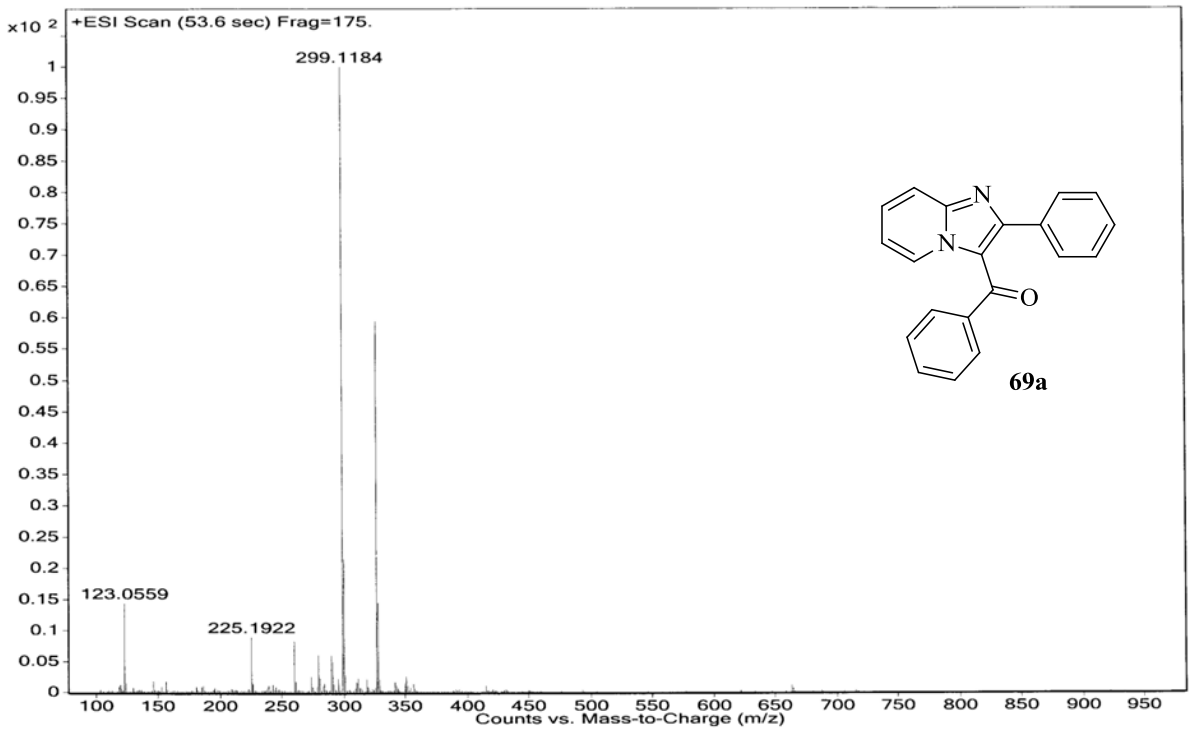
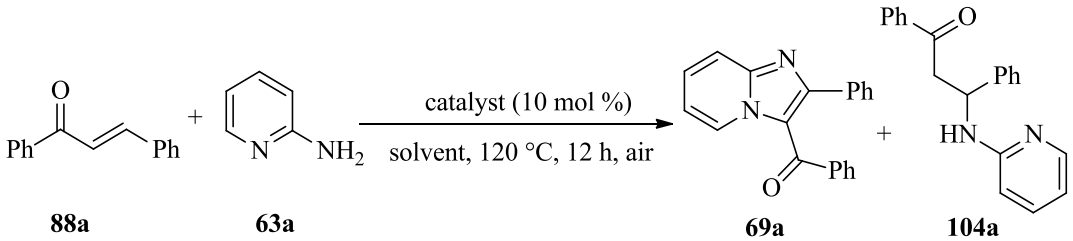


Figure 1.7: HRMS of **69a**

With these results in hand, we further undertook the optimization of reaction condition by varying catalysts in conjunction with different solvents for the tandem reaction (**Table 1.1**). After screening of set of different copper catalysts for the synthesis of **69a**, $CuCl_2.2H_2O$ was found to give the highest yield (81%) of tandem product **69a** (**Table 1.1**, entry 7). Among other copper salts screened, $CuBr_2$, $Cu(OTf)_2$, $Cu(OAc)_2$ and CuOTf resulted in moderate to good yields of **69a**, whereas only Michael adduct (**104a**) was obtained in the case of CuO (**Table 1.1**, entries 2-6). CuBr and $CuSO_4$ produced only traces of **69a** with major amount being unreacted substrates (**Table 1.1**, entries 8-9). With an ambiguity, some Lewis as well as Bronsted acids were screened for the tandem cyclization. It was realized that $Sc(OTf)_3$, TFA, and AcOH were completely ineffective for this transformation while in case of $BF_3.Et_2O$, traces of **69a** was observed (**Table 1.1**, entries 10-13). These results indicated that the copper catalyst was crucial for the success of the tandem cyclization. With $CuCl_2.2H_2O$ as the optimum catalyst, we further focussed on finding the effect of solvent for the tandem process. Excitingly, toluene was proved to be an ideal choice among the solvents investigated, while other solvents were proved to be less effective for the tandem cyclization (**Table 1.1**, entries 14-18).

Table 1.1: Optimization of reaction conditions for the synthesis of **69a**[a]



88a **63a** **69a** **104a**

Entry	Catalyst	Solvent	Yield (%)[b]
1	CuI	Toluene	14
2	$CuBr_2$	Toluene	60
3	$Cu(OTf)_2$	Toluene	76
4	$Cu(OAc)_2$	Toluene	67
5	CuO	Toluene	45[c]
6	CuOTf	Toluene	34
7	**$CuCl_2{\cdot}2H_2O$**	**Toluene**	**81**
8	CuBr	Toluene	traces
9	$CuSO_4$	Toluene	traces
10	$Sc(OTf)_3$	Toluene	NR[d]
11	CF_3CO_2H	Toluene	NR[d]
12	CH_3CO_2H	Toluene	NR[d]
13	$BF_3.Et_2O$	Toluene	traces
14	$CuCl_2{\cdot}2H_2O$	Benzene	15
15	$CuCl_2{\cdot}2H_2O$	DMF	14
16	$CuCl_2{\cdot}2H_2O$	THF	44
17	$CuCl_2{\cdot}2H_2O$	1,4-Dioxane	32
18	$CuCl_2{\cdot}2H_2O$	MeCN	40
19	$CuCl_2{\cdot}2H_2O$	Toluene	60
20	$CuCl_2{\cdot}2H_2O$	Toluene	82[e]
21	$CuCl_2{\cdot}2H_2O$	Toluene	87[f]
22	$CuCl_2{\cdot}2H_2O$	Toluene	50[g]
23	$CuCl_2{\cdot}2H_2O$	Toluene	54[c,h]

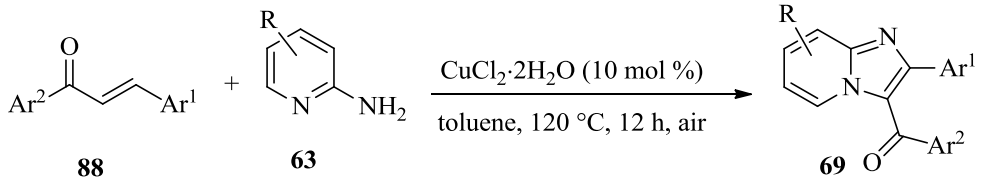
[a]Reaction conditions: **88a** (1.0 mmol), **63a** (1.2 mmol), catalyst (10 mol %), solvent (5 mL), 120 °C, 12 h, air.
[b]Isolated yields.
[c]Yield corresponds to **104a**.
[d]No reaction.
[e]20 mol % of catalyst was used.
[f]30 mol % of catalyst was used.
[g]5 mol % of catalyst was used.
[h]MW (120 °C, 30 min, 250 psi, 300 W).

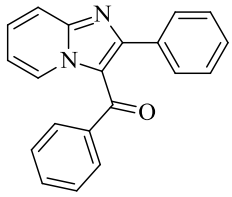
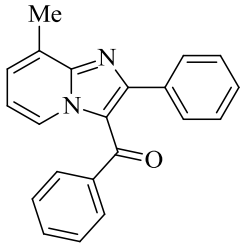
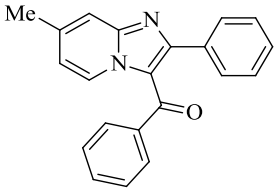
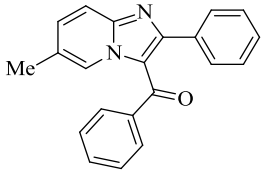
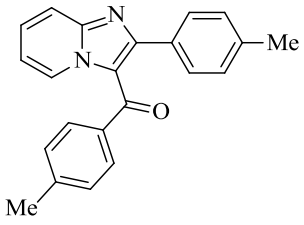
Subsequently, effect of catalyst loading was also investigated. With increasing $CuCl_2.2H_2O$ loading from 10 mol % to 30 mol % there was slight improvement in the yield of **69a** (**Table 1.1**, entries 20-21). However, decreasing $CuCl_2.2H_2O$ loading from 10 mol % to 5 mol % resulted in reduction of the yield of **69a** to 50% (**Table 1.1**, entry 22). It should be noted that the same reaction under microwave irradiation resulted Michael adduct (**104a**) as major product (**Table 1.1**, entry 23).

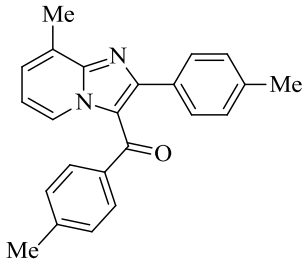
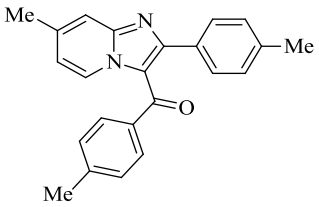
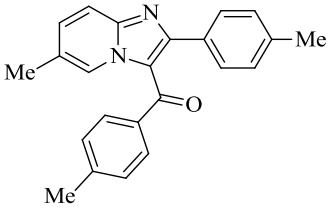
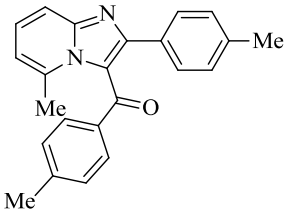
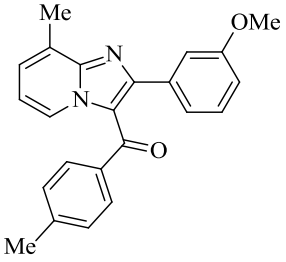
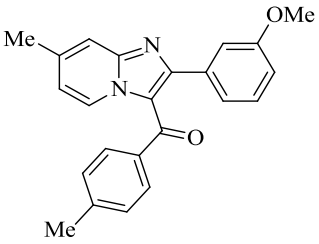
The standardized condition is inherently modular and allowed assimilation of substituents at any site of imidazo[1,2-*a*]pyridines (**Table 1.2**). Initially, wide variety of 2-aminopyridines (**63**) with substitutions at various positions were reacted with **88a** under the optimized reaction conditions, and moderate to high yields of tandem oxidative cyclization products were obtained. A labile bromo substituent at the C-5 position was well tolerated under the reaction conditions to afford the tandem products in good yields (**Table 1.2, 69m** and **69p**). Lower yields of 3-aroylimidazo[1,2-*a*]pyridines were observed for 2-amino-6-methylpyridine; this may be due to the steric congestion (**Table 1.2, 69i**). Unfortunately, desired product was not observed when 2-amino-5-nitropyridine was reacted with **88a**.

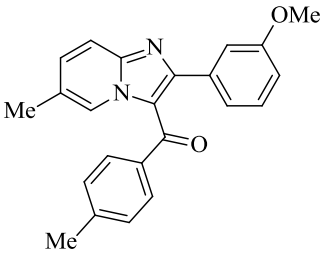
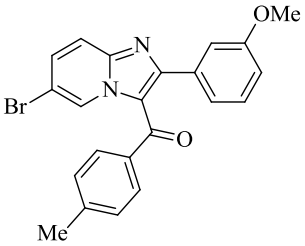
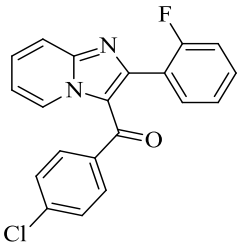
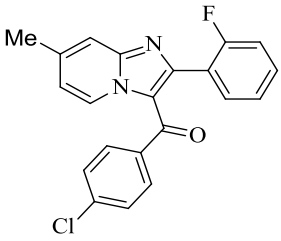
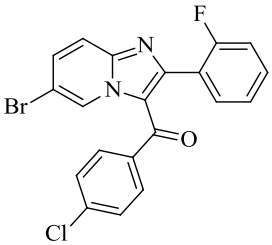
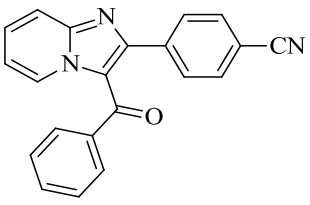
With regard to substitutions of aryl rings on chalcones, range of diverse groups could be employed, which demonstrates the high level of flexibility of the present approach. For example, chalcone derivatives (**88**) bearing substituents like methyl, methoxy, fluoro, chloro, bromo, nitro and cyano at *ortho*, *meta* and *para* positions on aryl rings (Ar^1 and Ar^2) were well tolerated to afford the desired products in good yields (**Table 1.2**, entries 5-9). Generally, chalcones bearing electron donating substituents on the Ar^1 and/or Ar^2 rings afforded higher yields of tandem products **69** as compared with the chalcones bearing electron withdrawing groups. The electron withdrawing substituents such as nitro and cyano on Ar^1 of chalcones greatly influenced the yields of tandem products (**Table 1.2**, entries 17-19). It was also observed that the chalcones with *ortho*-substituted aryl rings (Ar^1) produced lower yields of tandem product (**Table 1.2**, entries 14-16). Structures of all the synthesized 3-aroylimidazo[1,2-*a*]pyridines (**69**) were confirmed by IR, NMR spectroscopy and HRMS data.

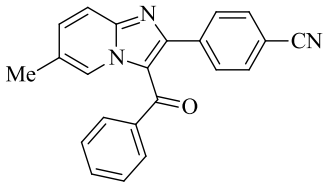
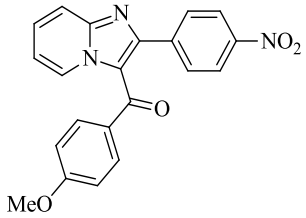
Table 1.2: Synthesis of 3-aroylimidazo[1,2-*a*]pyridines **69**[a]



Entry	Ar^1	Ar^2	R	Product		% Yield[b]
1	C_6H_5	C_6H_5	H		**69a**	81
2	C_6H_5	C_6H_5	8-Me		**69b**	76
3	C_6H_5	C_6H_5	7-Me		**69c**	60
4	C_6H_5	C_6H_5	6-Me		**69d**	62
5	4-MeC_6H_4	4-MeC_6H_4	H		**69e**	86

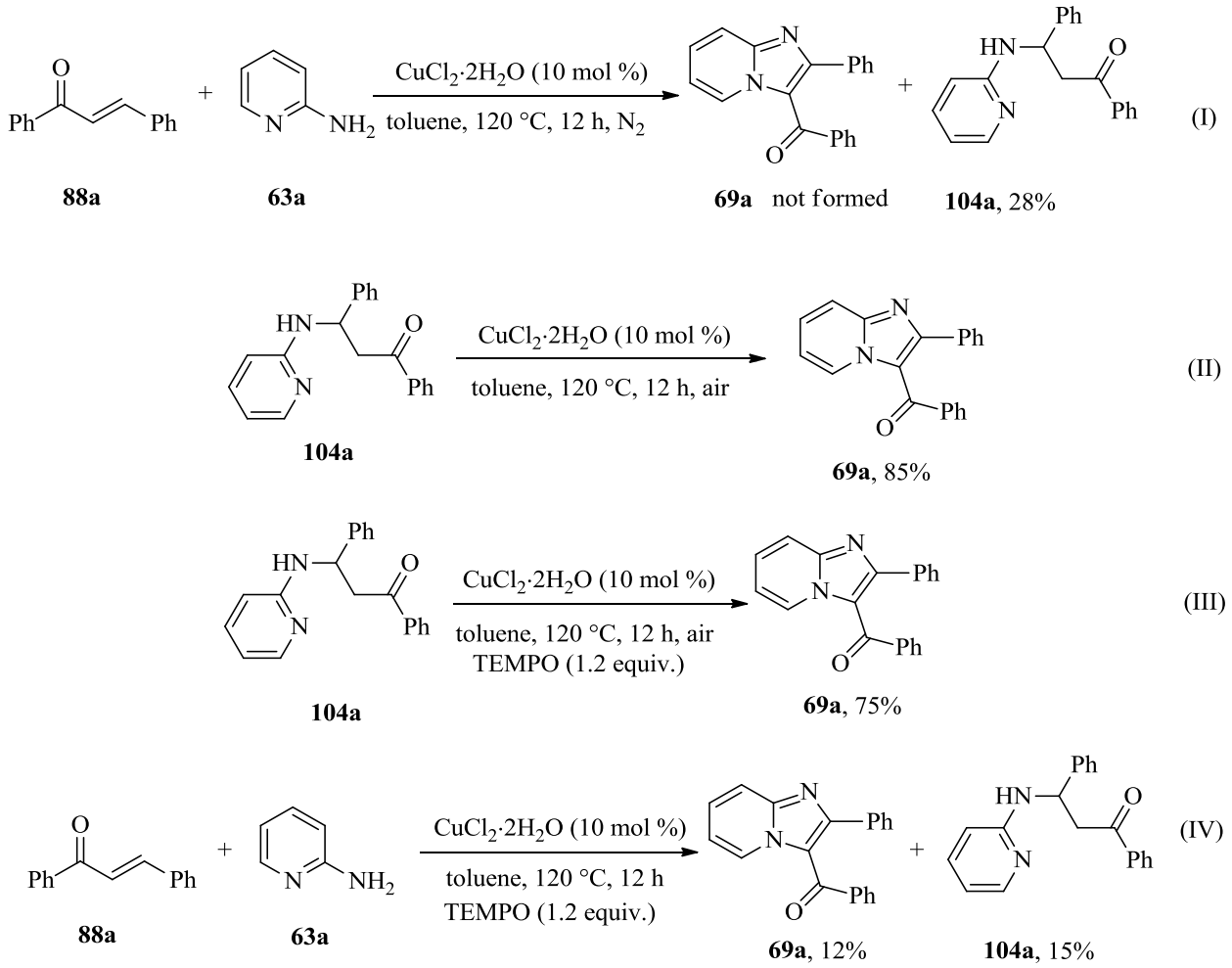
Entry	Ar^1	Ar^2	R	Product		% Yield[b]
6	4-MeC_6H_4	4-MeC_6H_4	8-Me		**69f**	80
7	4-MeC_6H_4	4-MeC_6H_4	7-Me		**69g**	64
8	4-MeC_6H_4	4-MeC_6H_4	6-Me		**69h**	76
9	4-MeC_6H_4	4-MeC_6H_4	5-Me		**69i**	45
10	3-$OMeC_6H_4$	4-MeC_6H_4	8-Me		**69j**	76
11	3-$OMeC_6H_4$	4-MeC_6H_4	7-Me		**69k**	59

Entry	Ar^1	Ar^2	R	Product		% Yield[b]
12	3-$OMeC_6H_4$	4-MeC_6H_4	6-Me		**69l**	75
13	3-$OMeC_6H_4$	4-MeC_6H_4	6-Br		**69m**	61
14	2-FC_6H_4	4-ClC_6H_4	H		**69n**	62
15	2-FC_6H_4	4-ClC_6H_4	7-Me		**69o**	55
16	2-FC_6H_4	4-ClC_6H_4	6-Br		**69p**	57
17	4-CNC_6H_4	C_6H_5	H		**69q**	56

Entry	Ar^1	Ar^2	R	Product		% Yield[b]
18	4-CNC_6H_4	C_6H_5	6-Me		**69r**	51%
19	4-$NO_2C_6H_4$	4-$OMeC_6H_4$	H		**69s**	38

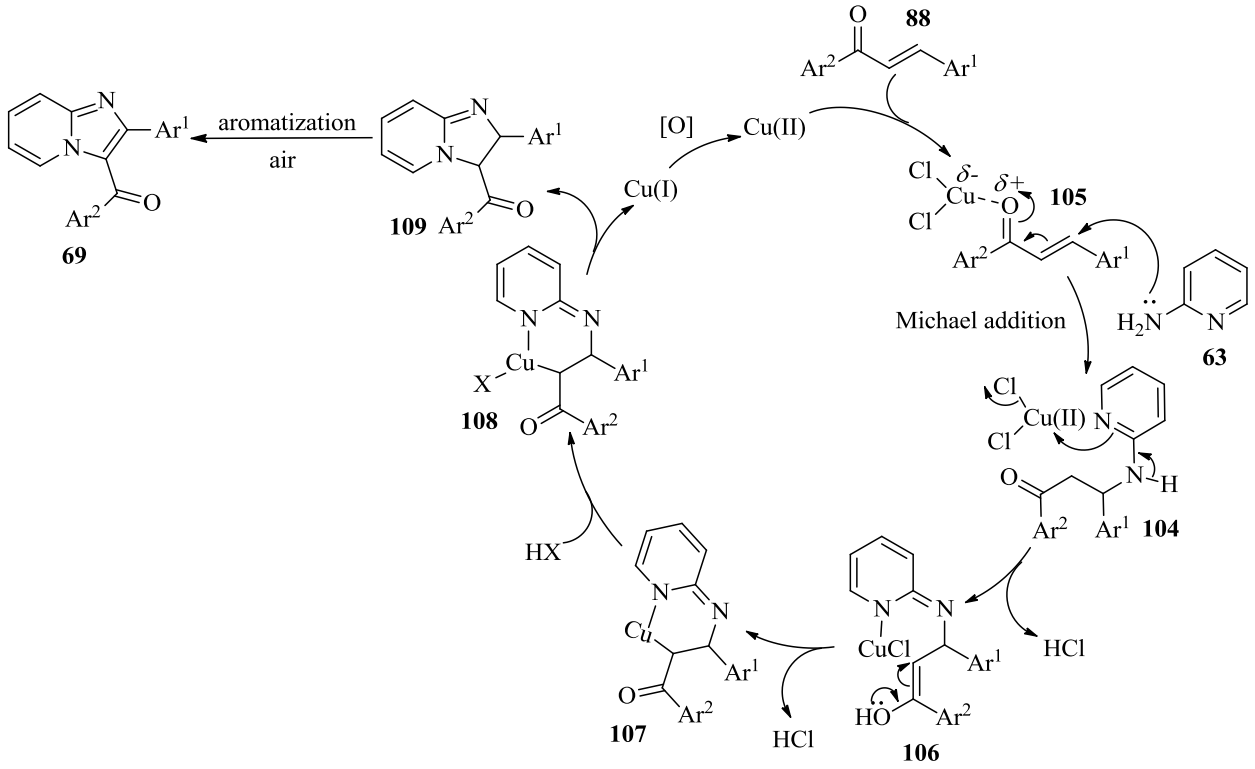
[a]Reaction conditions: **88** (1.0 mmol), **63** (1.2 mmol), $CuCl_2.2H_2O$ (10 mol %), toluene (5 mL), 120 °C, 12 h, air.
[b]Isolated yields.

Some control experiments were performed to explore the mechanism for the proposed tandem reaction (**Scheme 1.34**). When the chalcone (**88a**) was reacted with **63a** in the presence of nitrogen atmosphere, moderate yield of Michael adduct (**104a**) was obtained without formation of the cyclized product (**69a**) clarifies the crucial role of aerobic conditions for the success of tandem reaction (**Scheme 1.34, eq I**). When Michael adduct (**104a**) was subjected to the optimized reaction conditions, quantitative conversion was observed (isolated yield 85%, **Scheme 1.34, eq II**). This observation suggests that the key intermediate in the reported tandem process is **104a**. When radical scavenger TEMPO (1.2 equiv.) was used in the oxidative cyclization of the Michael adduct (**104a**), the minimal reduction in yield was observed, which confirms that the oxidative cyclization proceeds through non-radical mechanism pathway (**Scheme 1.34, eq III**). Surprisingly, only traces of product (**69a**) was observed, together with low yields of the Michael adduct (**104a**), when TEMPO was used in the standard reaction (**Scheme 1.34, eq IV**).



Scheme 1.34: Control experiments

Based on the results obtained and recent literature,[8] the plausible mechanism for the formation of 3-aroylimidazo[1,2-*a*]pyridines (**69**) is shown in **Scheme 1.35**. It is believed that initially $CuCl_2$ assists in the Michael addition of 2-aminopyridine (**63**) to give the Michael adduct, 1,3-diaryl-3-(pyridin-2-ylamino)propan-1-one (**104**). Concurrent binding of pyridinium nitrogen followed by the enolic carbon to the copper salt provides intermediate **107**. Oxidation of **107** to **108** followed by reductive elimination produces intermediate **109**, which on rapid oxidative aromatization under aerobic conditions leads to the tandem product, 3-aroylimidazo[1,2-*a*]pyridines (**69**). Regeneration of Cu(II) from Cu(I) under aerobic oxygen completes the catalytic cycle.[15]



Scheme 1.35: Plausible mechanism for the formation of **69** by copper-catalyzed tandem reaction between **88** and **63**

1.4. Conclusion

In summary, we have demonstrated straightforward, atom-economical, high yielding one-pot procedure for the synthesis of bioactive 3-aroylimidazo[1,2-*a*]pyridines from chalcones and 2-aminopyridines *via* unprecedented $CuCl_2.2H_2O$ catalyzed tandem aza-Michael addition and oxidative C−N coupling. The catalytic amount of copper catalyst was found to be crucial for the success of the tandem reaction that altered the synthetic pathway of the reaction to give the aforementioned tandem products, whereas entirely dissimilar products were reported in the earlier methods with the same precursors, but in the absence of copper catalyst. The method allows regioseletive introduction of an aryl ring at the C-2 position and an aroyl group at the C-3 position in single step. The reported novel tandem approach is practical and expected to proceed *via* initial 1,4-Michael addition followed by copper catalyzed oxidative C−N bond formation to provide medicinally important 2-aryl-3-aroylimidazo[1,2-*a*]pyridines in one-step. Dual C−N bond formation in 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.

1.5. Experimental section

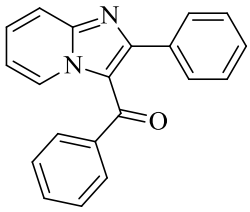
1.5.1. General

Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) using Bruker AV NMR 300 MHz, Bruker AV 400 MHz and Varian 500 MHz spectrometers. ^{13}C NMR spectra are fully decoupled. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (internal) as the standard. The HRMS data were recorded in ESI mode using Agilent Q-TOF mass spectrometer, and IR spectra were obtained an using ABB Bomen MB 3000 FTIR instrument. The *α,β*-unsaturated ketones (chalcones) **88** were prepared by the treatment of an appropriate acetophenone with benzaldehydes in the presence of sodium hydroxide as reported in literature.[122] All other chemicals were obtained from the commercial suppliers and used without further purification.

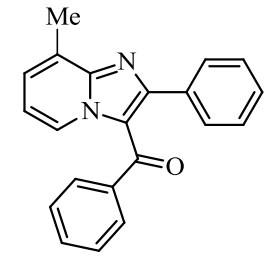
1.5.2. Procedure for synthesis of 3-aroylimidazo[1,2-*a*]pyridine (69a) A clean oven-dried 10 mL RB flask was charged with chalcone (**88a**) (200 mg, 0.961 mmol), 2-aminopyridine (**63a**) (108 mg, 1.15 mmol), $CuCl_2.2H_2O$ (16 mg, 0.096 mmol) and toluene (5.0 mL). The resulting solution was stirred at 120 °C for 12 h under ambient air. On completion, the reaction mixture was evaporated to dryness. The crude residue was purified by column chromatography (EtOAc: Hexanes, 2: 3) to obtain phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**69a**).

1.5.3. Physical and spectral data of 69a-s

Phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (69a): Yield 81%; Colourless solid; mp 124-127 °C; IR (KBr) *v*: 3070, 1597 (C=O$_{str}$), 1388, 1326, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.55 (d, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.32 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.29 – 7.21 (m, 1H), 7.17 – 7.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 187.4, 155.0, 147.4, 138.7, 134.0, 131.7, 130.2, 129.6, 129.2, 128.3, 128.2, 127.7, 120.0, 117.5, 114.6; HRMS (*m/z*) calcd for $C_{20}H_{15}N_2O$ 299.1179, found 299.1184 $[M+H]^+$.

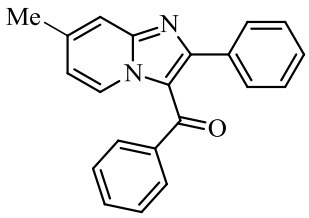


(8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69b): Yield 76%;



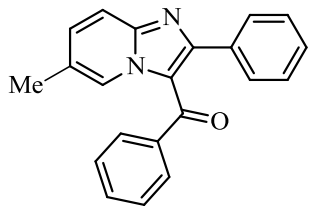
Colourless solid; mp 139-141 °C; IR (KBr) *v*: 3063, 1606 ($C=O_{str}$), 1466, 1388, 1250, 910, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, J = 4.9 Hz, 1H), 7.53 (d, J = 6.5 Hz), 7.40 – 7.32 (m, 3H), 7.31 – 7.24 (m, 1H), 7.17 – 7.07 (m, 5H), 7.06 – 7.03 (m, 1H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 154.6, 147.7, 138.9, 134.3, 131.6, 130.3, 129.6, 128.1, 127.8, 127.7, 127.5, 126.0, 120.5, 114.6, 17.2; HRMS (*m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1333 $[M+H]^+$.

(7-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69c): Yield 60%; Off-



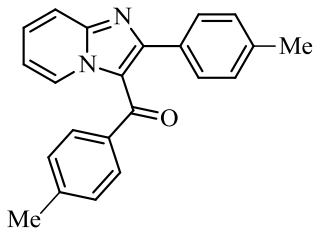
white solid; mp 140-142 °C; IR (KBr) *v*: 3060, 1605 ($C=O_{str}$), 1466, 1396, 918, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, J = 3.0 Hz, 1H), 7.59 (s, 1H,), 7.52 (d, J = 6.2 Hz, 2H), 7.34 (t, J = 11.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.18 – 7.06 (m, 5H), 6.97 (d, J = 0.9 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 155.4, 147.9, 140.9, 138.8, 134.2, 131.6, 130.2, 129.5, 128.2, 127.8, 127.7, 127.5, 117.1, 116.1, 21.6; HRMS (*m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1335 $[M+H]^+$.

(6-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69d): Yield 62%;



Colourless solid; mp 156-158 °C; IR (KBr) *v*: 3063, 1605 ($C=O_{str}$), 1466, 1389, 903, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 6.7 Hz, 2H), 7.31 – 7.24 (m, 1H), 7.17 – 7.06 (m 5H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 154.9, 146.4, 138.8, 134.2, 132.1, 131.7, 130.2, 129.6, 128.1, 127.7, 127.7, 126.2, 124.6, 119.9, 116.7, 18.5; HRMS (*m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1339 $[M+H]^+$.

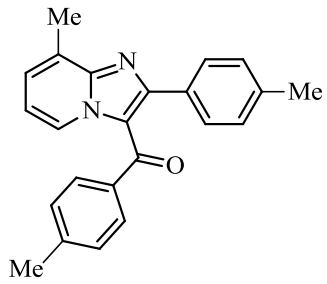
***p*-Tolyl(2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)methanone (69e):** Yield 86%; Colourless solid;



mp 111-114 °C; IR (KBr) *v*: 3063, 1605 ($C=O_{str}$), 1504, 1412, 1381, 903, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, J = 6.4 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.07 (t, J = 6.3 Hz, 1H), 6.93 – 6.85 (m, 4H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 154.5,

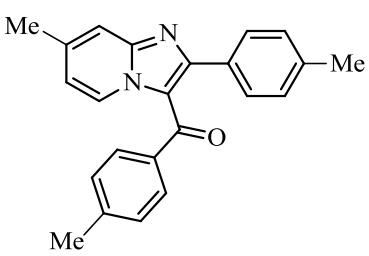
147.3, 142.5, 138.1, 136.0, 131.1, 130.1, 129.8, 128.8, 128.4, 128.1, 120.0, 117.3, 114.3, 21.5, 21.2; HRMS (*m/z*) calcd for $C_{22}H_{19}N_2O$ 327.1492, found 327.1500 $[M+H]^+$.

(8-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69f): Yield 80%;



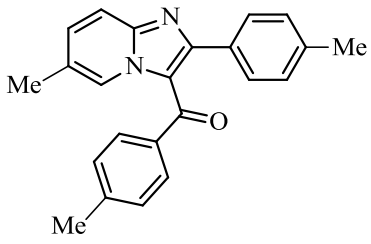
Colourless solid; mp 127-129 °C; IR (KBr) *v*: 3060, 1605 ($C=O_{str}$), 1381, 910, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 5.5 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.20 (m, 3H), 7.00 – 6.96 (m, 1H), 6.93 – 6.85 (m, 4H), 2.75 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 154.1, 147.5, 142.3, 137.9, 136.1, 131.5, 130.2, 129.8, 128.4, 128.4, 127.7, 127.3, 125.8, 120.4, 114.3, 21.5, 21.2, 17.1; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O$ 341.1648, found 341.1659 $[M+H]^+$.

(7-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69g): Yield 64%; Pale



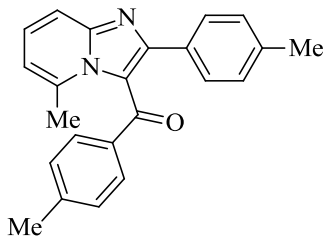
yellow solid; mp 190-192 °C; IR (KBr) *v*: 3024, 1597 ($C=O_{str}$), 1474, 1227, 926, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, *J* = 6.9 Hz, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 2H), 6.92 – 6.83 (m, 5H), 2.52 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 154.9, 147.8, 142.2, 140.4, 138.0, 136.2, 131.3, 130.1, 129.7, 128.4, 127.4, 119.7, 116.8, 116.0, 21.6, 21.4, 21.2; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O$ 341.1648, found 341.1647 $[M+H]^+$.

(6-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69h): Yield 76%;



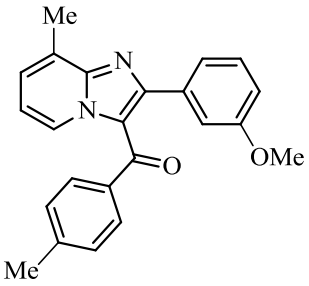
Colourless solid; mp 149-151 °C; IR (KBr) *v*: 3063, 1605 ($C=O_{str}$), 1504, 1412, 1381, 903, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 2H), 6.92 – 6.85 (m, 4H), 2.44 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 154.4, 146.3, 142.3, 137.9, 136.1, 131.7, 131.3, 130.1, 129.8, 128.4, 126.0, 124.2, 119.8, 116.6, 21.5, 21.2, 18.5; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O$ 341.1648, found 341.1657 $[M+H]^+$.

(5-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69i): Yield 45%;



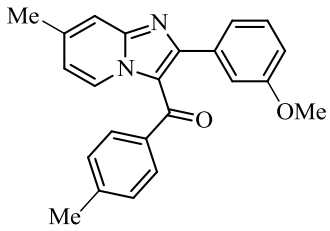
Colourless solid; mp 134-136 °C; IR (KBr) *v*: 3063, 1651, 1597 ($C=O_{str}$), 1474, 1381, 1234, 926, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.68 (m, 3H), 7.47 (d, *J* = 3.6 Hz, 2H), 7.39 – 7.25 (m, 1H), 7.09 – 6.90 (m, 4H), 6.75 (s, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 149.0, 147.5, 144.4, 137.9, 137.5, 136.0, 130.7, 130.5, 129.3, 129.0, 128.8, 127.0, 120.1, 115.2, 114.5, 22.1, 21.7, 21.2; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O$ 341.1648, found 341.1652 $[M+H]^+$.

(2-(3-Methoxyphenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69j): Yield



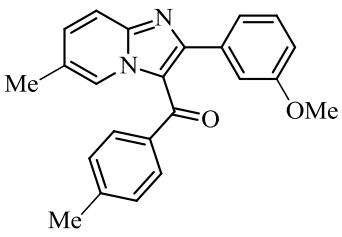
76%; Red viscous liquid; IR (CCl_4) *v*: 3055, 2955, 1606 ($C=O_{str}$), 1474, 1285, 803, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 6.6 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.31 (dd, *J* = 9.0, 4.1 Hz, 1H), 7.02 – 6.94 (m, 3H), 6.94 (d, *J* = 7.4 Hz, 2H), 6.89 (s, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 3.66 (s, 3H), 2.75 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 159.0, 153.7, 147.5, 142.4, 136.2, 135.6, 129.7, 128.9, 128.4, 127.8, 127.5, 125.9, 123.0, 120.6, 115.0, 114.8, 114.5, 55.2, 21.5, 17.1; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1602 $[M+H]^+$.

(2-(3-Methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69k): Yield



59%; Pale yellow sold; mp 110-112 °C; IR (KBr) *v*: 3063, 2955, 1606 ($C=O_{str}$), 1455, 1281, 833, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 – 9.41 (m, 1H), 7.58 – 7.56 (m, 1H), 7.47 (d, *J* = 3.4 Hz, 2H), 7.11 – 6.92 (m, 5H), 6.87 (s, 1H), 6.75 (d, *J* = 0.4 Hz, 1H), 3.66 (s, 3H), 2.54 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 159.0, 154.5, 147.7, 142.4, 140.6, 136.2, 135.5, 129.7, 128.8, 128.4, 127.4, 122.9, 119.9, 117.0, 116.0, 115.0, 114.8, 55.2, 21.6, 21.5; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1598 $[M+H]^+$.

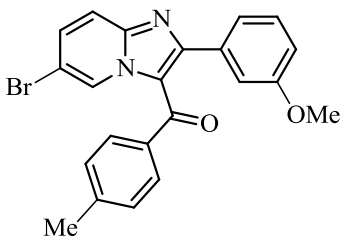
(2-(3-Methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69l)*:* Yield



75%; Off-white solid; mp 83-85 °C; IR (KBr) *v*: 3055, 2955, 1606 ($C=O_{str}$), 1474, 1281, 833, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 6.4 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.10 – 6.92 (m, 4H), 6.89 (s, 1H), 6.74 (d, *J* =

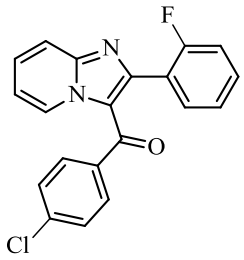
5.9 Hz, 1H), 3.66 (s, 3H), 2.46 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 159.0, 154.0, 146.2, 142.5, 136.2, 135.4, 131.9, 129.7, 128.8, 128.5, 126.0, 124.4, 122.9, 119.9, 116.7, 115.0, 114.7, 55.2, 21.5, 18.5; HRMS (*m/z*) calcd for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1597 $[M+H]^+$.

(6-Bromo-2-(3-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)(*p*-tolyl)methanone (69m): Yield



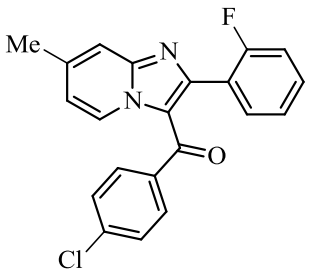
61%; Yellow liquid; IR (CCl_4) *v*: 3060, 2955, 1606 ($C=O_{str}$), 1474, 1381, 910, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 9.4 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.97 – 6.89 (m, 3H), 6.88 (s, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 159.1, 154.0, 145.6, 143.1, 135.6, 134.8, 132.3, 129.7, 129.0, 128.6, 128.2, 122.9, 120.2, 118.0, 115.3, 114.7, 109.2, 55.2, 21.5; HRMS (*m/z*) calcd for $C_{22}H_{18}BrN_2O_2$ 421.0546, found 421.0546 $[M+H]^+$ 423.0524 $[M+H+2]^+$.

(4-Chlorophenyl)(2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69n*):* Yield



62%; Off-white solid; mp 144-146 °C; IR (KBr) *v*: 3055, 2924, 1612 ($C=O_{str}$), 1481, 1227, 1080, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, *J* = 6.6 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 5.4 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.72 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 159.1 (d, *J* = 248.7 Hz), 148.5, 147.7, 137.8, 136.9, 131.2 (d, *J* = 2.4 Hz), 131.0, 130.7 (d, *J* = 8.3 Hz), 129.3, 128.3, 127.7, 124.2 (d, *J* = 3.5 Hz), 122.8, 122.8 (d, *J* = 14.1 Hz), 117.7, 115.2 (d, *J* = 22.0 Hz), 114.98; HRMS (*m/z*) calcd for $C_{20}H_{13}ClFN_2O$ 351.0695, found 351.0698 $[M+H]^+$.

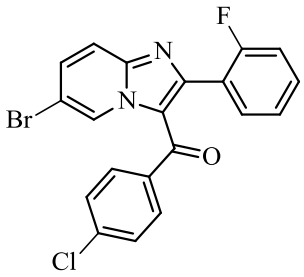
(4-Chlorophenyl)(2-(2-fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (69o):



Yield 55%; Off-white solid; mp 157-159 °C; IR (KBr) *v*: 3055, 2965, 1612 ($C=O_{str}$), 1481, 1227, 1076, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 7.1 Hz, 1H), 7.59 (s, 1H), 7.49 (td, *J* = 7.4, 1.7 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.26 – 7.19 (m, 1H), 7.12 – 7.04 (m, 3H), 6.99 (dd, *J* = 7.1, 1.6 Hz, 1H), 6.74 – 6.65 (m, 1H), 2.54 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 159.1 (d, *J* = 248.7 Hz), 148.8, 148.2, 141.1, 137.6, 137.0, 131.3 (d, *J* = 2.5 Hz), 130.8 (d, *J* = 8.3 Hz), 130.5, 127.6,

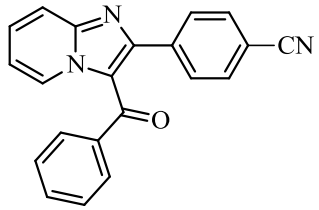
127.5, 124.1 (d, *J* = 3.4 Hz), 122.9 (d, *J* = 14.3 Hz), 120.6, 117.5, 116.2, 115.2 (d, *J* = 22.0 Hz), 21.6; HRMS (*m/z*) calcd for $C_{21}H_{15}ClFN_2O$ 365.0851, found 365.0851 $[M+H]^+$.

(6-Bromo-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(4-chlorophenyl)methanone (69p):

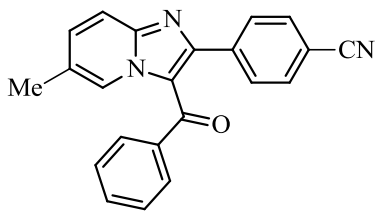


Yield 57%; Off-white solid; mp 172-175 °C; IR (KBr) *v*: 3101, 3055, 2924, 1612 ($C=O_{str}$), 1481, 1389, 1227, 1080, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.75 (d, *J* = 9.3 Hz, 1H), 7.64 (d, *J* = 9.4 Hz, 1H), 7.54 (t, *J* = 6.9 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 5.4 Hz, 1H), 7.15 – 7.06 (m, 3H), 6.73 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 159.1 (d, *J* = 249.1 Hz), 148.3, 146.07, 138.2, 136.4 (d, *J* = 1.9 Hz), 132.7, 131.2, 131.1, 130.5, 128.3, 127.8, 124.3 (d, *J* = 3.5 Hz), 122.3 (d, *J* = 14.0 Hz), 120.9, 118.1, 115.3 (d, *J* = 22.0 Hz), 109.87; HRMS (*m/z*) calcd for $C_{20}H_{12}BrClFN_2O$ 428.9800, found 428.9801 $[M+H]^+$ 430.9780 $[M+H+2]^+$.

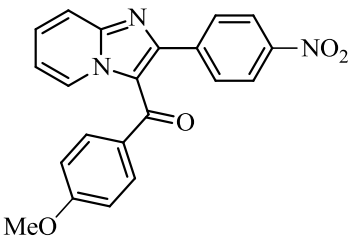
4-(3-Benzoylimidazo[1,2-*a*]pyridin-2-yl)benzonitrile (69q): Yield 56%; Off-white solid; mp 173-175 °C; IR (KBr) *v*: 3109, 3070, 2222 ($C\equiv N_{str}$), 1612 ($C=O_{str}$), 1474, 1227, 933, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 4.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 6.5 Hz, 2H), 7.45 (d, *J* = 5.7 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 6.9 Hz, 1H), 7.18 – 7.12 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 152.4, 147.5, 138.7, 138.4, 132.4, 131.4, 130.7, 129.7, 129.5, 128.3, 128.0, 120.4, 118.6, 117.7, 115.2, 111.7; HRMS (*m/z*) calcd for $C_{21}H_{14}N_3O$ 324.1131, found 324.1131 $[M+H]^+$.



4-(3-Benzoyl-6-methylimidazo[1,2-*a*]pyridin-2-yl)benzonitrile (69r): Yield 51%; Pale yellow solid; mp 179-182 °C; IR (KBr) *v*: 3102, 3059, 2222 ($C\equiv N_{str}$), 1608 ($C=O_{str}$), 1478, 1232, 933, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.73 – 7.71 (m, 1H), 7.50 – 7.32 (m, 8H), 7.15 (d, *J* = 5.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 152.2, 146.5, 138.9, 138.6, 132.7, 132.3, 131.4, 130.6, 129.6, 128.0, 126.1, 120.2, 118.7, 116.9, 111.6, 18.6; HRMS (*m/z*) calcd for $C_{22}H_{16}N_3O$ 338.1288, found 338.1292 $[M+H]^+$.



(4-Methoxyphenyl)(2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69s): Yield



38%; Pale yellow solid; mp 199-202 °C; IR (KBr) *v*: 3102, 1597 ($C=O_{str}$), 1512, 1342, 1227, 1026, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.03 (d, J = 6.9 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.64 – 7.51 (m, 5H), 7.13 – 7.09 (m, 1H), 6.66 (d, J = 6.8 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 163.4, 150.3, 147.3, 147.2, 140.7, 132.0, 130.9, 130.8, 129.2, 127.9, 123.0, 120.6, 117.7, 114.9, 113.5, 55.5; HRMS (*m/z*) calcd for $C_{21}H_{16}N_3O_4$ 374.1135, found 374.1132 $[M+H]^+$.

Chapter I

PART-B

Three-Component Reaction of 2-Aminopyridines, Acetophenones and Aldehydes: Synthesis of 3-Aroylimidazo[1,2-*a*]pyridines

1.6. Introduction

Construction of bioactive fused heterocycles by exploiting transition metal-catalyzed coupling reactions is highly challenging and attractive task in organic synthesis.[123-125] The achievement of making multiple bonds in one-pot *via* multi-component coupling reaction promotes sustainable synthetic approach to new molecule discovery. The basic concepts of disconnections are generally overruled for the synthesis of molecules following the combination of MCRs and tandem processes. Several innovative strategies have been witnessed in last decade where coupling reactions have been amalgamated with MCRs/tandem reactions.[16, 32, 42]

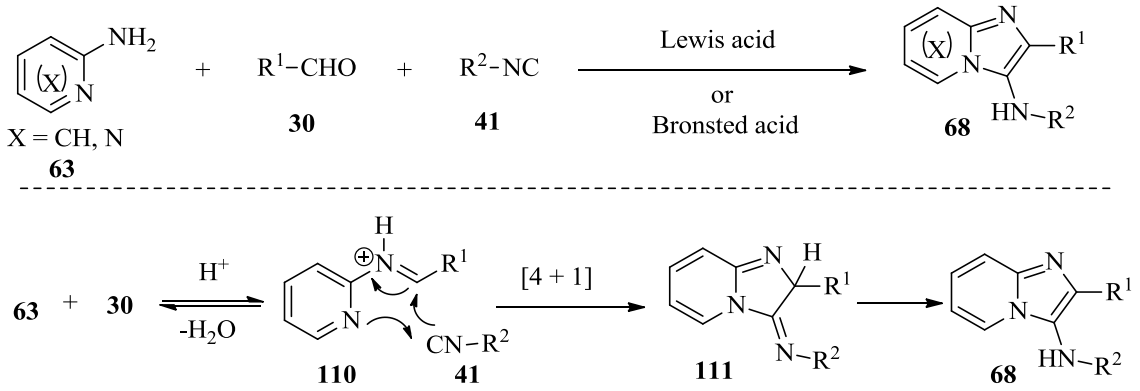
Synthesis and functionalization of imidazo[1,2-*a*]pyridines have gained great interest in recent years because of their significance in medicinal chemistry, material science and organometallics.[126-130] Several drugs such as alpidem, zolpidem, zolimidine, saripidem, and necopidem contain imidazo[1,2-*a*]pyridine skeleton as core with slight variations. In addition, several novel molecules with imidazo[1,2-*a*]pyridine as core structure have been synthesized and studied for their activity against various biological targets.[77, 131-134] Among them, 3-aroylimidazo[1,2-*a*]pyridines are the interesting structures with anticancer activities.[121] Aroyl functionality has also been reported to be highly responsible for the elevated biological applications of various other heterocycles.[135] Boykin with his coworkers reported the synthesis of aroylsubstituted heterocycles using sequential reactions and studied their antiproliferative activity, and structure–activity relationships. The synthesized aroyl substituted heterocycles includes 3-aroyl pyridine, 2-aroylindole, 3-aroylindole and 5-aroylindoles.[136] In this context, direct methods toward the synthesis of 3-aroylimidazo[1,2-*a*]pyridines is highly desirable.

1.6.1. Synthesis of imidazo[1,2-*a*]pyridines through multi-component reactions

Diversity-oriented synthesis of fused heterocycles entities has been emerged as possible tool for exploring the intersections between chemistry and biology.[6, 137] Multi-component reactions (MCRs) together with tandem sequences have been recognized as powerful tool in modern organic chemistry for the synthesis of fused heterocyclic compounds with diverse substitutions.[26, 43, 138-145] Some of the examples of this class include the Passerini reaction,[146]

Ugi reaction,[30] Biginelli reaction,[31] Morita-Baylis-Hillman reaction,[147] Groebke-Blackburn-Bienayme (GBB) reaction.[148]

Groebke-Blackburn-Bienayme (GBB) reaction was disclosed independently in 1998 by three research groups; Katrin Groebke (Switzerland), Christopher Blackburn (Cambridge, USA) and Hugues Bienayme (France). The GBB reaction is a four-centre, three-component reaction, which involves reaction between an aldehyde (**30**), 2-aminoazine (**63**), and an isonitrile (**41**) in the presence of catalyst (**Scheme 1.36**).[149] The GBB reaction affords highly substituted and fused imidazole derivatives and the catalyst usually used are Lewis acids or Bronsted acids.

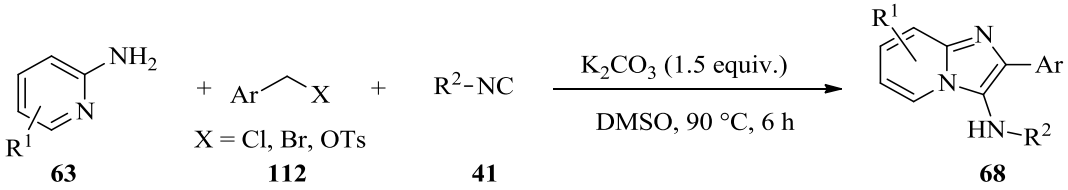


Scheme 1.36: General representation of the Groebke-Blackburn-Bienayme-reaction

The reaction mechanism of GBB starts with the formation of Schiff base (**110**) (which has both the electrophile and nucleophile) *via* the condensation of aldehyde (**30**) and amine (**63**). Further the cycloaddition reaction between the protonated Schiff base (**110**) and the isonitrile (**41**) generate intermediate **111** and subsequent prototropic shift results in the formation of final aromatic fused 3-aminoimidazopyridines (**68**) (**Scheme 1.36**).[150]

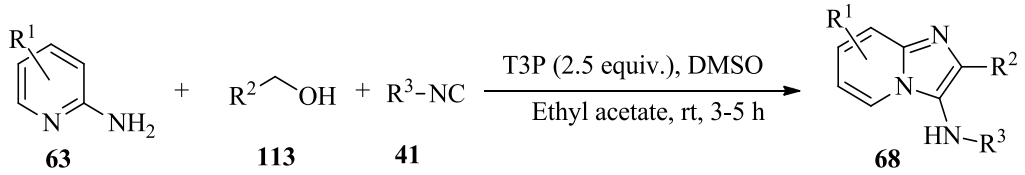
Adib group developed new and efficient approach for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines (**68**) *via* one-pot, three-component condensation reaction between 2-aminopyridines (**63**), benzyl halides or benzyl tosylates (**112**) and isocyanides (**41**) in the presence of K_2CO_3 (**Scheme 1.37**).[151] Simple benzyl halides/tosylates were oxidized to the corresponding aldehydes under mild oxidative conditions. Replacement of aldehyde by the use of benzylic substrates is the main advantage of reported reaction. Various benzylic substrates such as benzyl chlorides, benzyl bromides and benzyl tosylates reacted well under the standard reaction

conditions, but simple alkyl halides or alkyl tosylates did not react under the standard reaction conditions.



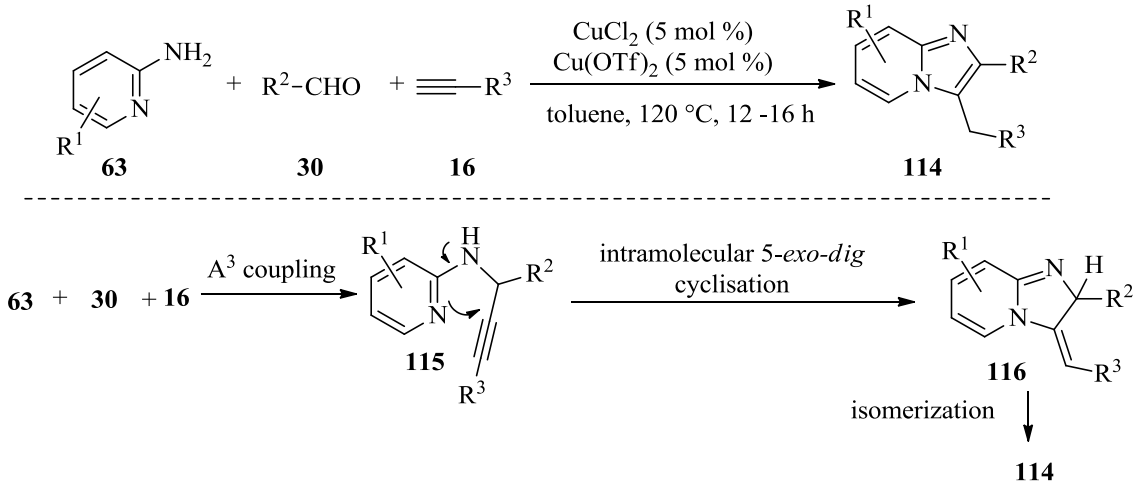
Scheme 1.37: Synthesis of 3-aminoimidazo[1,2-*a*]pyridine from benzyl halides/tosylates

Owing to the importance of 3-aminoimidazo[1,2-*a*]pyridine motifs in medicinal chemistry, several groups have modified the reaction condition for conventional GBB reaction by varying the catalyst and the solvent. Reaction of 2-aminopyridine (**63**) and isocynide (**41**) were also reported with benzyl alcohol (**113**) and benzyl halide (**112**) which *in situ* generates aldehyde (**Scheme 1.38**).[151-154]



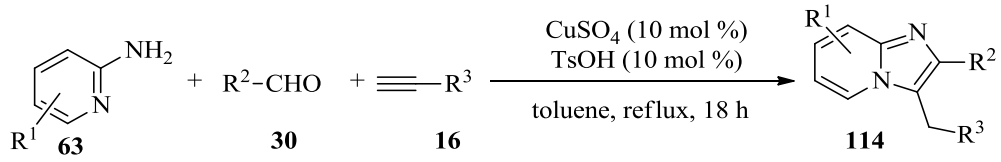
Scheme 1.38: Synthesis of 3-aminoimidazo[1,2-*a*]pyridine using benzyl alcohol

A tandem reaction of aldehyde, amine, and alkyne commonly known as A^3 coupling is an efficient approach to access propargylamines.[155] The A^3-coupling has been successfully employed for the construction of 3-alkylimidazo[1,2-*a*]pyridines (**114**) (**Scheme 1.39**).[156-157] This method was greatly extended to synthesize imidazopyridine-based drugs Alpidem and Zolpidem in good yields. Initial A^3 coupling between 2-aminopyridines (**63**), aldehydes (**30**), and alkynes (**16**) gives propargylamines (**115**) that undergoes intramolecular cyclization in 5-*exo-dig* fashion to generate intermediate **116** which finally on isomerization gives 3-alkylimidazo[1,2-*a*]pyridines (**114**) (**Scheme 1.39**).



Scheme 1.39: Synthesis of 3-alkylimidazo[1,2-*a*]pyridine *via* A^3 coupling reaction

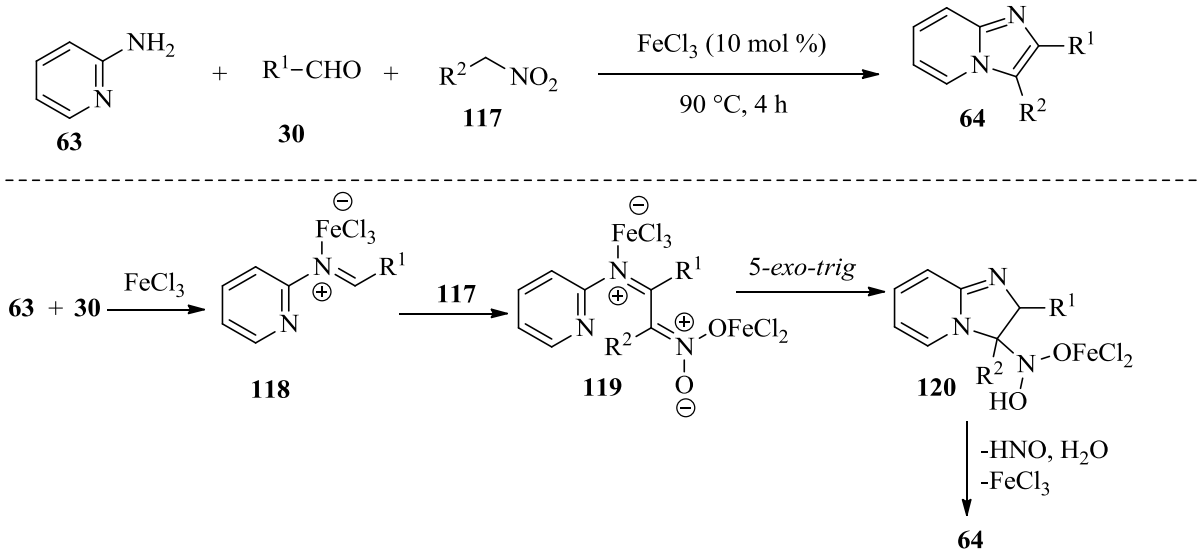
Lin group utilized A^3 coupling reaction for the synthesis of imidazopyridine derivatives using $CuSO_4$/TsOH catalytic system (**Scheme 1.40**)[157]. The use of Brönsted acid (TsOH) facilitated the alkyne addition through the protonation of the imine or by inhibiting the coordination of pyridine nitrogen to copper. The methodology was applicable to various aminopyridines (**63**), alkynes (**16**) and aldehydes (**30**) having different steric effect, electron withdrawing, electron donating group as well as with sensitive functional groups.



Scheme 1.40: Copper-catalyzed synthesis of 3-alkylimidazo[1,2-*a*]pyridine *via* A^3 coupling reaction

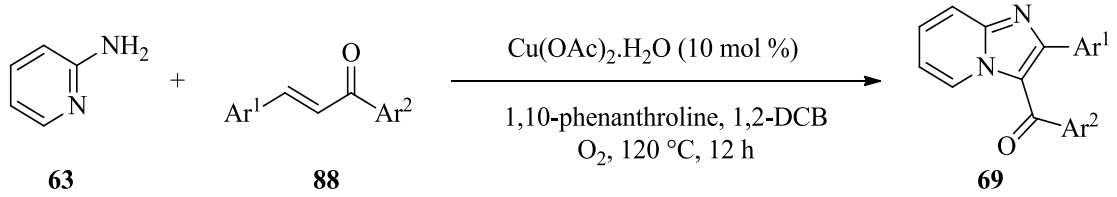
Huang *et al.* recently described one-pot, multi-component reaction for the synthesis of imidazopyridines. The Fe(III)-catalyzed three-component cross-coupling reaction of 2-aminopyridine (**63**), aldehyde (**30**) and nitroalkane (**117**) offered new strategy for the straight forward access to imidazo[1,2-*a*]pyridine (**64**) (**Scheme 1.41**)[103]. Aldehydes containing electron-withdrawing as well as electron donating groups were well tolerated under the standard reaction condition to afford 2,3-disubstituted imidazo[1,2-*a*]pyridine. Heteroaryl as well as aliphatic aldehydes also afforded the products in good yield. 2-Aminopyridine with electron-withdrawing groups afforded higher yield as compared to the electron-donating group.

Nitropropane and nitromethane required the presence of TBAI with the optimized reaction conditions.



Scheme 1.41: Three component reaction for synthesis of imidazo[1,2-*a*]pyridine

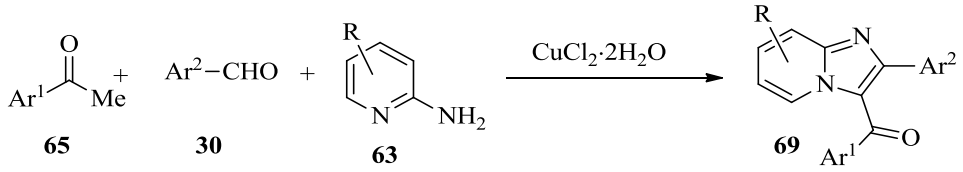
A new methodology has been independently developed by our group (as reported in part A)[158] and Hajra *et al.* for the construction of 3-aroylimidazo[1,2-*a*]pyridines (**69**) by the copper-catalyzed oxidative coupling between 2-aminopyridines (**63**) and chalcones (**88**) under oxygen atmosphere (**Scheme 1.42**).[159] Reaction is suitable for wide range of 2-aminopyridines and chalcones and can be applied for gram-scale synthesis. This simple strategy offers new route for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines employing oxygen as an oxidant. The tandem reaction is supposed to proceed through the Michael addition followed by intramolecular oxidative C–N bond formation.



Scheme 1.42: Synthesis of 3-aroylimidazo[1,2-*a*]pyridines

To the best of our knowledge there is no report available for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines *via* one-pot, three-component tandem approach. With our continuous interest in synthesis and functionalizations of imidazo[1,2-*a*]pyridines,[105, 115-119] we developed an efficient synthesis of 3-aroylimidazo[1,2-*a*]pyridines (**69**) *via* one-pot, three-component copper-catalyzed

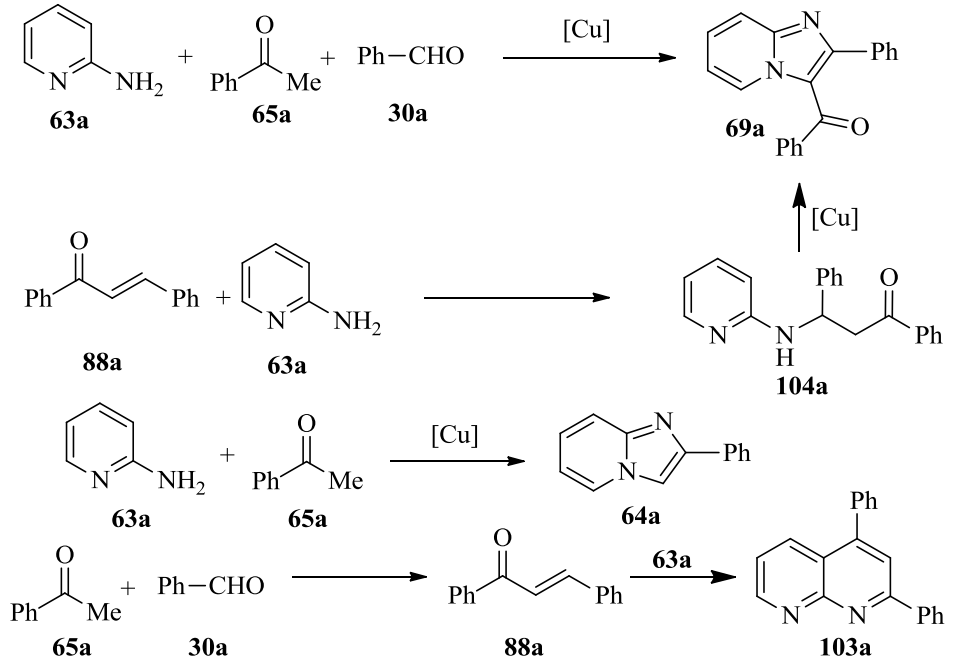
tandem reaction of acetophenones (**65**), arylaldehydes (**30**) and 2-aminopyridines (**63**) with air as sole oxidant (**Scheme 1.43**).



Scheme 1.43: Three component copper-catalyzed synthesis of 3-aroylimidazo[1,2-*a*]pyridine

1.7. Results and discussion

In our initial study, acetophenone (**65a**), benzaldehyde (**30a**) and 2-aminopyridine (**63a**) were chosen as model substrates for the screening of reaction conditions to obtain phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**69a**). Based on literature survey, several competing reactions could be expected with the present set of substrates and other parameters, which includes 1,3-diphenyl-3-(pyridin-2-ylamino)propan-1-one (**104a**),[11] 2-phenylimidazo[1,2-*a*]pyridine (**64a**),[105] chalcone (**88a**), 2,4-diphenyl-1,8-naphthyridine (**103a**) (**Scheme 1.44**).[120] With these concerns in mind, **63a** (1.0 mmol) was treated with **65a** (1.0 mmol) and **30a** (1.0 mmol) in the presence of $CuCl_2.2H_2O$ in toluene for 12 h at reflux condition. As expected, phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**69a**) was obtained in 35% yield along with other by-products such as **64a** and **88a** in minor quantities (**Table 1.3**, entry 1). However, Michael adduct (**104a**) and naphthyridine (**103a**) were not detected in the reaction mass.



Scheme 1.44 Competing reactions with selected set of precursors

The structure of **69a** was characterized by spectral data IR, NMR and mass. In the IR spectrum of **69a**, strong peak appeared at 1597 cm^{-1} for C=O stretching (**Figure 1.8**). In the ^{1}H NMR spectrum of **69a**, doublet appeared at δ 9.55 ppm for highly deshielded C_5-H along with other protons at their respective positions (**Figure 1.9**). The ketonic carbon of **69a** appeared at δ 187.36 along with all other expected carbons in the ^{13}C NMR spectrum (**Figure 1.9**). The peak at 299.1162 for $[M+H]^+$ ion in the HRMS mass spectrum of **69a** further confirmed its structure. The spectral data for the product was in agreement with **69a**, prepared in part A of this chapter.

The formation of by-product **64a** by the reaction of **65a** and **63a** in the presence of copper was also confirmed by ^{1}H NMR, ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **64a**, a doublet appeared at δ 8.11 ppm for highly deshielded C_5-H and characteristic singlet appeared at δ 7.85 ppm for C_3-H along with other protons at their respective positions. Total 11 peaks appeared in ^{13}C NMR with well agreement of given structure of **64a** (**Figure 1.10**).

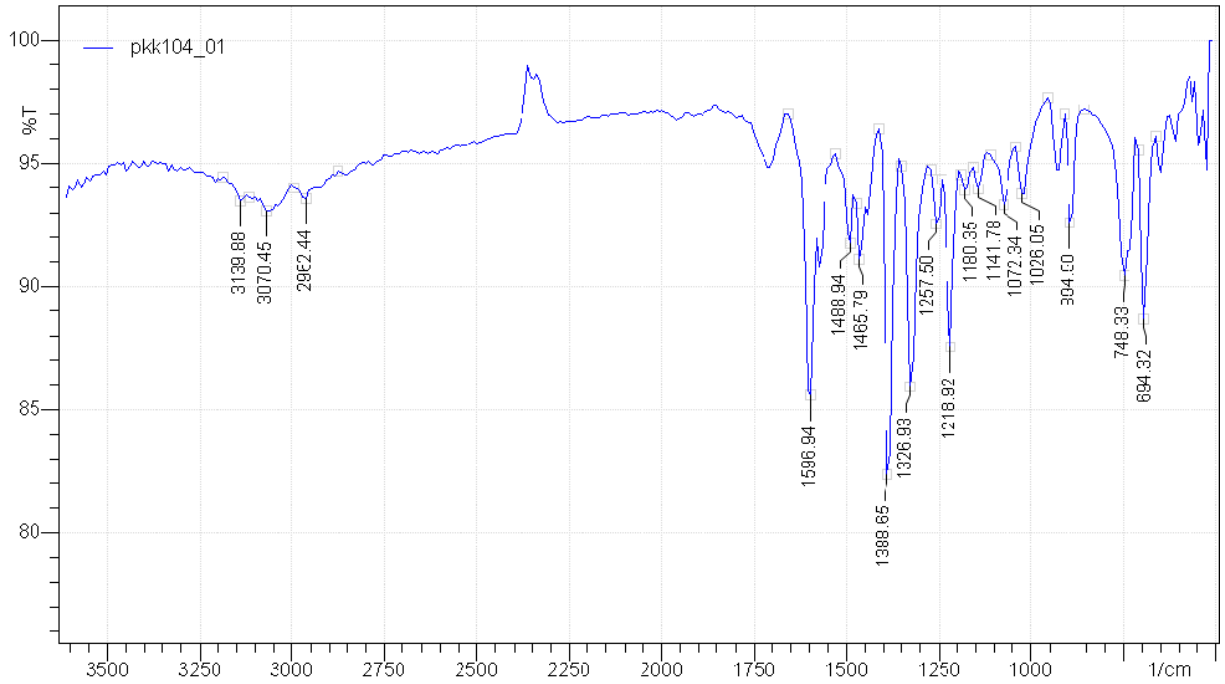


Figure 1.8: IR spectrum of **69a**

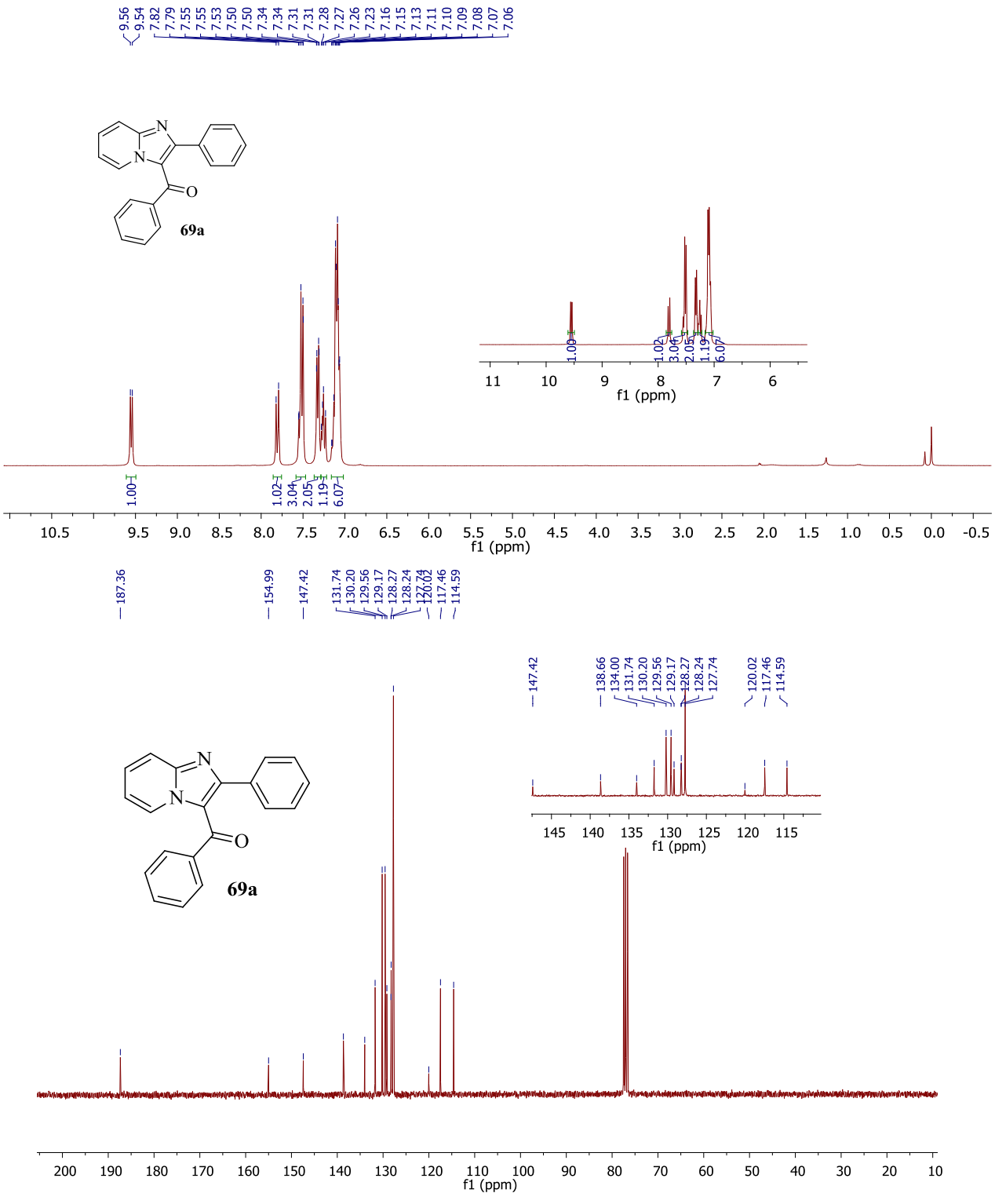


Figure 1.9: ^{1}H and ^{13}C NMR spectra of **69a**

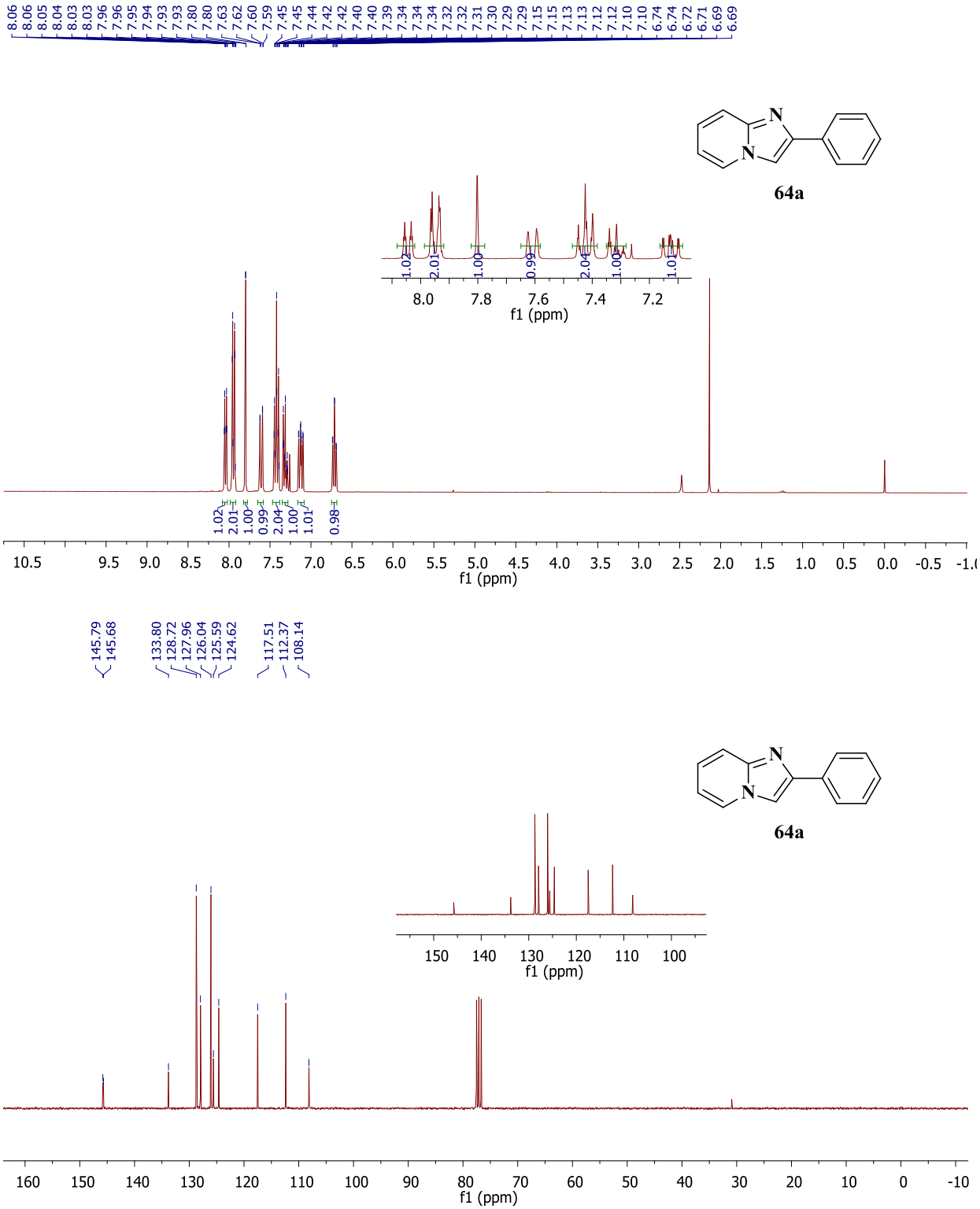
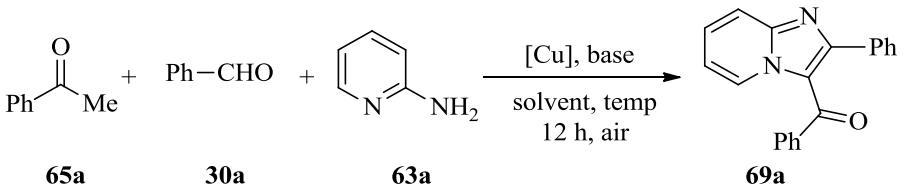


Figure 1.10: ^{1}H and ^{13}C NMR spectra of **64a**

To enhance the yields of tandem product, we turned our focus on minimization of unwanted products by varying the molar ratios of precursors. It was observed that the formation of by-product **64a** could be reduced if rate of reaction between **65a** and **30a** to give **88a** is faster than the rate of reaction between **65a** and **63a**. We succeeded in eliminating the formation of **64a** in the reaction by keeping **65a** as limiting agent with other substrates (**30a** and **63a**) in 1.2 equivalents. Addition of K_2CO_3 to the reaction keeping other parameters same resulted in slight improvement in the yield of **69a** (**Table 1.3**, entry 2). A smooth enhancement in yield of **69a** was observed with DMF as solvent (**Table 1.3**, entry 3). With the encouraging result in hand, we next increased the reaction temperature to 150 °C keeping other parameters constant. Gratifyingly, excellent yield of **69a** was observed at 150 °C (**Table 1.3**, entry 4). Among other solvents, good yields of **69a** were obtained in polar solvents like DMA and DMSO (**Table 1.3**, entries 6-7) while moderate yields of **69a** was obtained in water (**Table 1.3**, entry 5). Desired product **69a** was not obtained when 1,4-dioxane and ethanol were used as solvents (**Table 1.3**, entries 9-10). Simultaneously, various bases were screened for the model reaction and the use of K_2CO_3 gave the optimum result for the tandem process among other bases like Cs_2CO_3, K_3PO_4 and KOH which also offered good yields of tandem products (**Table 1.3**, entries 10 and 12-13). However, no product was noticed in case of $NaHCO_3$ (**Table 1.3**, entry 11). Other copper salt such as $Cu(OAc)_2.H_2O$, $Cu(OTf)_2$, CuI, were also screened and resulted lower yield of **69a** and CuBr failed to give the product. So attempts were failed to replace the copper catalyst to facilitate higher yields of tandem products (**Table 1.3**, entries 14-17).

Table 1.3: Optimization of reaction conditions for the synthesis **69a**[a]



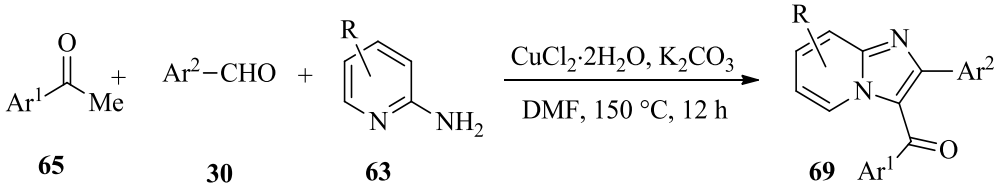
65a **30a** **63a** **69a**

Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$CuCl_2{\cdot}2H_2O$	-[c]	toluene	120	35
2	$CuCl_2{\cdot}2H_2O$	K_2CO_3	toluene	120	38
3	$CuCl_2{\cdot}2H_2O$	K_2CO_3	DMF	120	45
4	**$CuCl_2{\cdot}2H_2O$**	**K_2CO_3**	**DMF**	**150**	**81**
5	$CuCl_2{\cdot}2H_2O$	K_2CO_3	water	reflux	55
6	$CuCl_2.2H_2O$	K_2CO_3	DMA	150	72
7	$CuCl_2{\cdot}2H_2O$	K_2CO_3	DMSO	150	63
8	$CuCl_2{\cdot}2H_2O$	K_2CO_3	1,4-dioxane	reflux	-[d,e]
9	$CuCl_2{\cdot}2H_2O$	K_2CO_3	EtOH	reflux	-[d,e]
10	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3	DMF	150	52
11	$CuCl_2{\cdot}2H_2O$	$NaHCO_3$	DMF	150	-[d,e]
12	$CuCl_2{\cdot}2H_2O$	KOH	DMF	150	46
13	$CuCl_2{\cdot}2H_2O$	K_3PO_4	DMF	150	64
14	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	150	38
15	$Cu(OTf)_2$	K_2CO_3	DMF	150	66
16	CuBr	K_2CO_3	DMF	150	-[d,e]
17	CuI	K_2CO_3	DMF	150	48

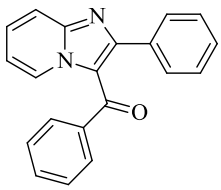
[a]Reaction conditions: **65a** (1.0 mmol), **30a** (1.2 mmol), **63a** (1.2 mmol), catalyst (20 mol %), base (2.0 mmol), solvent (4 mL), 12 h, air.
[b]Isolated yields.
[c]No base was present in the reaction and **65a**, **30a**, and **63a** were used 1 mmol each.
[d]Starting materials were recovered.
[e]**69a** not detected.

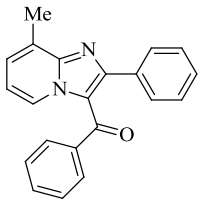
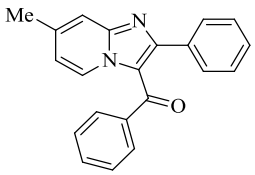
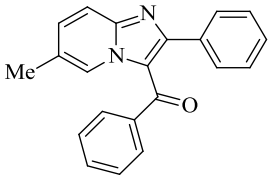
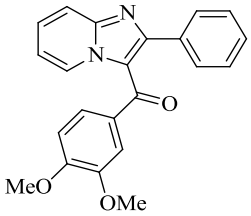
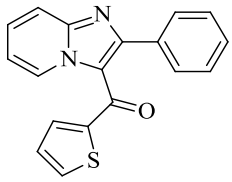
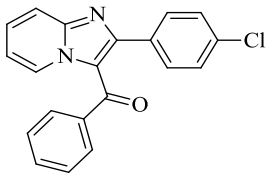
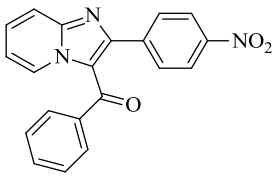
With optimized reaction conditions in hand (**Table 1.3**, entry 4), substrate scope for cascade process was evaluated and the results are summarized in **table 1.4**. In early experiments, diversely substituted 2-aminopyridines were tested that offered moderate to good yields of 3-aroylimidazo[1,2-*a*]pyridines (**Table 1.4**, entries 2-4 and 15). It is worth to mention that highly sensitive bromo substitution, towards transition metal-catalyzed transformations was well tolerated under the optimized conditions and afforded good yields of tandem product (**Table 1.4**, entry 15). Aryl aldehydes substituted with electron-withdrawing groups such as 4-Cl, 2-F and 4-NO_2 offered high yields of tandem products (**Table 1.4**, entries 7-8 and 10-16). On the other hand, reactions involving aryl aldehydes with electron rich substituent produced 2-arylimidazo[1,2-*a*]pyridines instead of tandem product (**Table 1.4**, entry 17). This may be due to the fact that under these reaction conditions, reaction of acetophenones and 2-aminopyridines is faster as compared to the tandem reaction to give corresponding 2-arylimidazo[1,2-*a*]pyridines.[105-106, 160-161] In the case of aryl ketones electron withdrawing group as well as electron donating group afforded moderate yield of the products. To our delight, heterocyclic ketones and aldehydes such as 2-acetylthiophene and thiophene-2-carbaldehyde reacted smoothly under the optimized conditions to give corresponding tandem products in moderate yields (**Table 1.4**, entries 6 and 9).

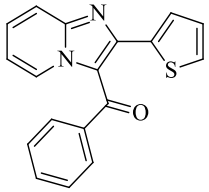
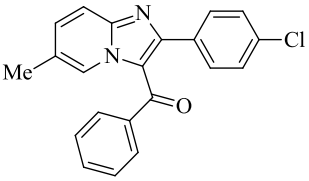
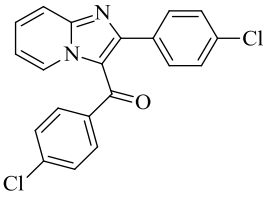
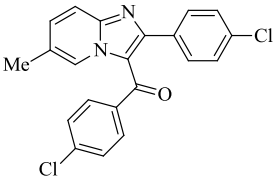
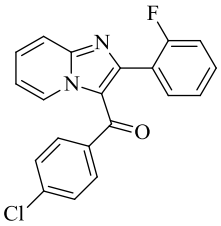
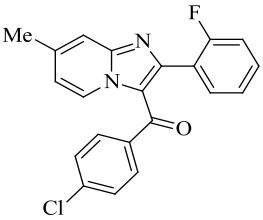
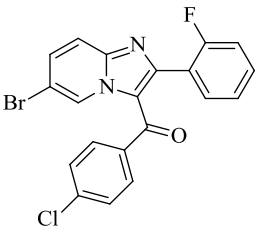
Table 1.4 Substrate scope for one-pot, three-component tandem reaction for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines[a]

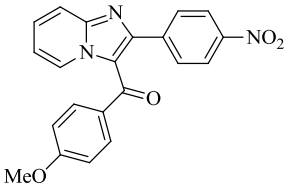
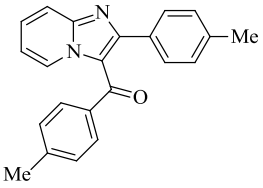


65 **30** **63** **69**

Entry	Ar^1	Ar^2	R	Product	Yield (%)[b]
1.	C_6H_5	C_6H_5	H	 **69a**	81

Entry	Ar^1	Ar^2	R	Product		Yield (%)[b]
2.	C_6H_5	C_6H_5	3-Me		**69b**	62
3.	C_6H_5	C_6H_5	4-Me		**69c**	26
4.	C_6H_5	C_6H_5	5-Me		**69d**	63
5.	3,4-$(OMe)_2C_6H_3$	C_6H_5	H		**69t**	47
6.	2-thienyl	C_6H_5	H		**69u**	36
7.	C_6H_5	4-ClC_6H_4	H		**69v**	52
8.	C_6H_5	4-$NO_2C_6H_4$	H		**69w**	76

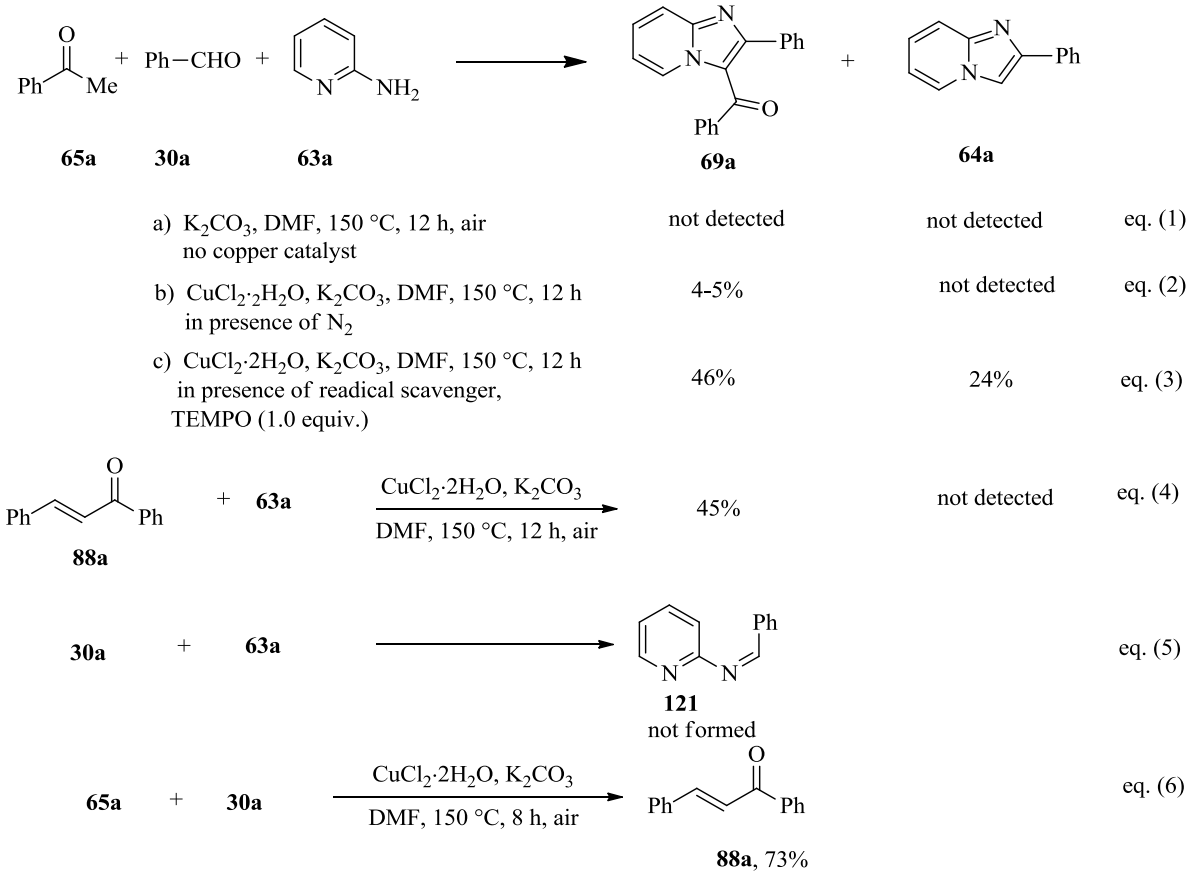
Entry	Ar^1	Ar^2	R	Product		Yield (%)[b]
9.	C_6H_5	2-thienyl	H		**69x**	46
10.	C_6H_5	4-ClC_6H_4	5-Me		**69y**	82
11.	4-ClC_6H_4	4-ClC_6H_4	H		**69z**	63
12.	4-ClC_6H_4	4-ClC_6H_4	5-Me		**69ab**	75
13.	4-ClC_6H_4	2-FC_6H_4	H		**69n**	45
14.	4-ClC_6H_4	2-FC_6H_4	4-Me		**69o**	42
15.	4-ClC_6H_4	2-FC_6H_4	5-Br		**69p**	51

Entry	Ar^1	Ar^2	R	Product		Yield (%)[b]
16.	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	H		**69ac**	44
17.	4-MeC_6H_4	4-MeC_6H_4	H		**69ad**	-[c,d]

[a]Reaction conditions: **65** (1.0 mmol), **30** (1.2 mmol), **63** (1.2 mmol), $CuCl_2.2H_2O$ (20 mol %), K_2CO_3 (2.0 mmol), DMF (4 mL), 150 °C, 12 h, air.
[b]Isolated yields.
[c]**69ad** was not formed.
[d]2-(*p*-tolyl)imidazo[1,2-*a*]pyridine was isolated in 56% yield.

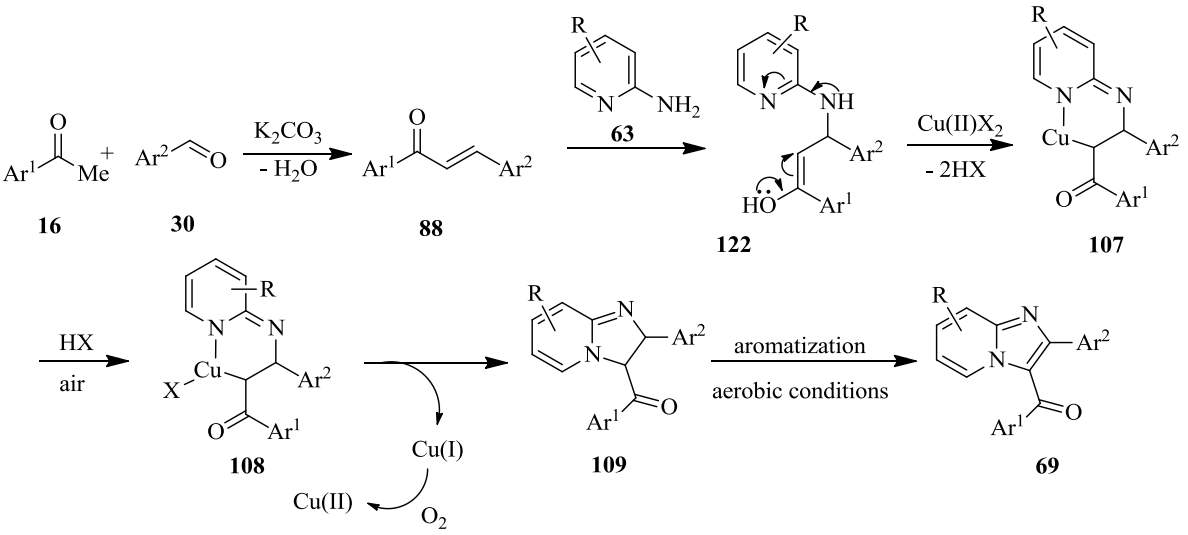
Next, we performed some control experiments to understand the synthetic sequence and plausible mechanism of the protocol (**Scheme 1.45**). In the absence of copper catalyst, no product formation was observed (**eq. 1, Scheme 1.45**) which confirmed the crucial role of copper catalyst for the successful formation of **69a**. When the model reaction was performed under nitrogen atmosphere, only catalytic amount of product was formed which confirmed the necessity of aerobic conditions for the current transformation (**eq. 2, Scheme 1.45**). Reaction performed in the presence of radical scavenger, (2,2,6,6-tetramethylpiperdin-1-yl)oxy (TEMPO), produced both tandem product **69a** and **64a** in 46% and 24% isolated yields, respectively (**eq. 3, Scheme 1.45).** It was concluded that both **69a** and **64a** were formed *via* non-radical pathway as reported earlier for **64a**.[9] Two synthetic routes could be possible to attain the tandem product **69** from corresponding substrates *via* a) chalcone intermediate and b) *via* imine intermediate. However, formation of imine was not observed from the reaction of **30a** with **63a** in the absence of **65a** under these conditions (**eq. 5, Scheme 1.45**). This excludes the possibility of imine as intermediate in this tandem process. In other experiment **65a** and **30a** were reacted under the same standard reaction condition to result chalcone (**88a**) which confirm reaction path through chalcone intermediate (**eq. 6, Scheme 1.45**). Thus, it is believed that the probable pathway for this transformation is *via* chalcone intermediate which is formed through the crossed aldol condensation between **65a** and **30a.** This was further supported by the fact that reaction of pre-

synthesized chalcone **88a** with **63a** under similar conditions afforded good yield of tandem product **69a** (**eq. 4, Scheme 1.45**). It is important to mention that the yield of **69a** was higher from tandem reaction than that of step-wise approach under these conditions.



Scheme 1.45: Control experiments

Based on literature reports[162] and findings from the control experiments, the mechanism of the tandem process for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines is proposed (S**cheme 1.46**). It is believed that initially chalcone (**88**) is generated by the crossed aldol condensation of **65** and **30** which then undergoes Michael addition with **63** to afford intermediate **122**. Interaction of **122** with copper salt through pyridinium nitrogen and enolic carbon simultaneously affords intermediate **107**.[159] Oxidation of copper (II) to copper (III)[106, 163] gives intermediate **108,** which on reductive elimination may result in the formation dihydro imidazopyridine **109**. Rapid aromatization of intermediate **109** under aerobic conditions affords the desired product **69**. Oxidation of Cu(I) to Cu(II) in the presence of air completes the catalytic cycle.[164] Reaction of 2-aminopyridine (6**3**) with methylketones (**65**) in the presence of copper results the formation of 2-arylimidazo[1,2-*a*]pyridines (**64**).[105-106, 160-161]



Scheme 1.46: Plausible mechanism for the synthesis of 3-aroylimdazo[1,2-*a*]pyridines

1.8. Conclusion

In summary, we have developed straightforward method for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines through one-pot three-component tandem process. This protocol makes the use of simple and readily available precursors like acetophenones, aldehydes and 2-aminopyridines to deliver highly functionalized bio-active 3-aroylimidazo[1,2-*a*]pyridines in single step. Atom and step-economy, use of economically attractive and readily available precursors, simple isolation procedures, moderate to good yields of tandem products, air as sole oxidant, and good functional group tolerance are the salient features of the method.

1.9. Experimental Section

1.9.1. General

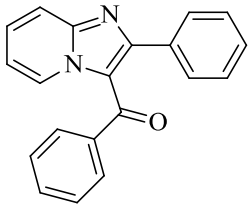
Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by their NMR spectra (^{1}H and ^{13}C NMR). Chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. The HRMS data were recorded on mass spectrometer with electrospray ionization and TOF mass analyzer. IR spectra were recorded on FTIR spectrophotometer and the ν_{max} is expressed in cm^{-1}. All chemicals were obtained from the commercial suppliers and used without further purification.

1.9.2. Procedure for synthesis of 69a

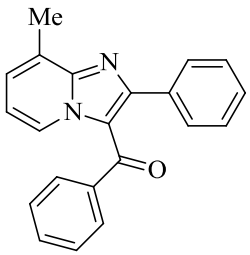
An oven-dried 10 mL RB flask was charged with acetophenone (120 mg, 1.0 mmol), benzaldehyde (122 mg, 1.2 mmol), 2-aminopyridine (113 mg, 1.2 mmol), K_2CO_3 (276 mg, 2.0 mmol), $CuCl_2.2H_2O$ (34 mg, 20 mol %) and DMF (4 mL). The resulting solution was stirred at 150 °C for 12 h. On completion of the reaction, the reaction mass was allowed to cool to ambient temperature and then diluted with water (10 mL). The mixture was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc: Hexanes, 2: 3) to afford **69a**.

1.9.3. Physical and spectral data of 69a-d, 69t-z, 69ab-ac and 64a

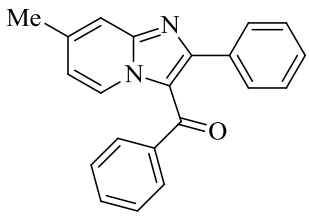
Phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**69a):** Yield 81%; Colourless solid; mp 124-127 °C; IR (KBr) *v:* 3070, 1597, 1388, 1326, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, J = 7.0 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.32 (dd, J = 7.8, 1.4 Hz, 2H), 7.29 – 7.21 (m, 1H), 7.17 – 7.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 155.0, 147.4, 138.7, 134.0, 131.7, 130.2, 129.6, 129.2, 128.3, 128.2, 127.7, 120.0, 117.5, 114.6; HRMS (ESI, *m/z*) calcd for $C_{20}H_{15}N_2O$ 299.1179, found 299.1162 $[M+H]^+$.



(8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69b): Yield 62%; Colourless solid; mp 140-143 °C; IR (KBr) *v*: 3063, 1606, 1466, 1388, 1250, 910, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, J = 4.9 Hz, 1H), 7.51 (d, J = 6.5 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.30 – 7.22 (m, 1H), 7.15 – 7.06 (m, 5H), 7.04 – 6.98 (m, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 154.6, 147.7, 138.9, 134.4, 131.7, 130.4, 129.6, 128.2, 127.8, 127.8, 127.6, 126.1, 120.6, 114.7, 17.2; HRMS (ESI, *m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1352 $[M + H]^+$.

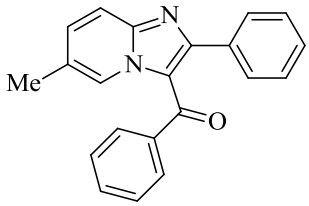


(7-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69c): Yield 26%; Off-white solid; mp 137-140 °C; IR (KBr) *v*: 3060, 1605, 1466, 1396, 918, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 3.0 Hz, 1H), 7.63 (s, 1H), 7.56 (d, J = 6.2 Hz, 2H), 7.41 – 7.28 (m, 3H), 7.20 – 7.11 (m, 5H), 7.01 (d, J = 0.9 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz,



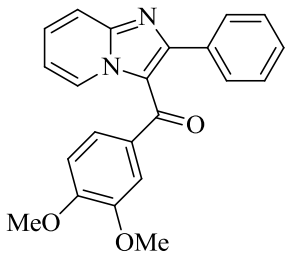
$CDCl_3$) δ 187.1, 155.4, 147.9, 140.9, 138.8, 134.2, 131.6, 130.2, 129.1, 128.2, 127.7, 127.7, 127.5, 117.1, 116.1, 21.6; HRMS (ESI, *m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1321 $[M + H]^+$.

(6-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69d): Yield 63%;



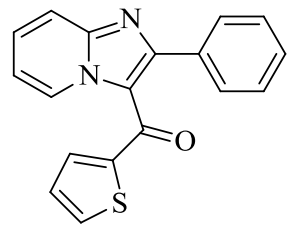
Colourless solid; mp 156-158 °C; IR (KBr) *v*: 3063, 1605, 1466, 1389, 903, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 6.7 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.14 – 7.04 (m, 5H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 154.9, 146.5, 138.8, 134.2, 132.2, 131.7, 130.2, 129.6, 128.2, 127.8, 127.8, 126.2, 124.6, 119.9, 116.7, 18.6; HRMS (ESI, *m/z*) calcd for $C_{21}H_{17}N_2O$ 313.1335, found 313.1348 $[M + H]^+$.

(3,4-Dimethoxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (69t): Yield 47%;



Gummy mass; IR (KBr) *v*: 3073, 2947, 1605, 1466, 1389, 1227, 913, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 7.0 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.34 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.11 – 7.06 (m, 3H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.98 (t, *J* = 6.9 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 153.4, 152.5, 148.3, 147.3, 134.2, 131.1, 130.1, 128.7, 128.4, 128.0, 127.9, 124.5, 119.9, 117.4, 114.3, 112.4, 110.0, 56.0, 55.7; HRMS (ESI, *m/z*) calcd for $C_{22}H_{19}N_2O_3$ 359.1390, found 359.1385 $[M + H]^+$.

Phenyl(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69u): Yield 36%; Pale



yellow solid; mp 122-124 °C; IR (KBr) *v*: 3078, 2947, 1589, 1466, 1389, 1227, 795, 756, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.45 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.18 – 7.12 (m, 3H), 7.02 (dd, *J* = 3.7, 0.7 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.63 – 6.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 153.2, 147.2, 143.6, 134.5, 134.2, 133.1, 130.0, 128.8, 128.5, 128.1, 127.8, 127.4, 119.8, 117.5, 114.3; HRMS (ESI, *m/z*) calcd for $C_{18}H_{13}N_2OS$ 305.0743, found 305.0749 $[M + H]^+$.

(2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (69v): Yield 52%; Off-white solid; mp 132-134 °C; IR (KBr) *v*: 3070, 1605, 1489, 1466, 1389, 1327, 1227, 933, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.82 (d, *J* = 9.0, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.52 (m, 1H), 7.51 (d, *J* = 1.3 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.28 (t, *J* = 1.5 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.18 – 7.12 (m, 3H), 7.10 – 7.08 (m, 1H), 7.07 – 7.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 153.5, 147.4, 138.5, 134.5, 132.5, 132.0, 131.4, 129.4, 129.4, 128.3, 182.0, 120.1, 117.5, 114.8; HRMS (ESI, *m/z*) calcd for $C_{20}H_{14}ClN_2O$ 333.0789, found 333.0795 $[M + H]^+$.

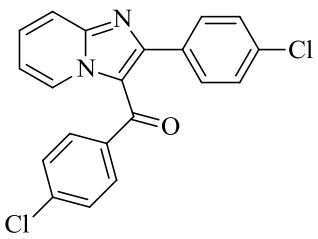
(2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (**69w):** Yield 76%; Pale yellow solid; mp 241-243 °C; IR (KBr) *v*: 3078, 1605, 1512, 1466, 1389, 1250, 1227, 856, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, *J* = 6.9 Hz, 1H), 7.98 – 7.89 (m, 3H), 7.78 – 7.69 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.28 (m, 2H), 7.19 – 7.16 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 186.7, 151.7, 147.2, 147.1, 141.2, 138.9, 132.5, 131.6, 130.7, 130.6, 129.9, 128.4, 128.4, 123.0, 117.9, 116.1; HRMS (ESI, *m/z*) calcd for $C_{20}H_{14}N_3O_3$ 344.1030, found 344.1025 $[M + H]^+$.

(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)(thiophen-2-yl)methanone (69x): Yield 46%; Off-white solid; mp 118-120 °C; IR (KBr) *v*: 3078, 2947, 1603, 1466, 1389, 1227, 748, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 – 7.28 (m, 1H), 7.21 – 7.19 (m, 1H), 7.18 – 7.16 (s, 1H), 7.17 – 7.15 (m, 1H), 6.98 (td, *J* = 6.9, 1.2 Hz, 1H), 6.63 – 6.58 (m, 1H), 6.56 – 6.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 147.5, 147.2, 138.6, 135.8, 132.3, 130.1, 129.5, 129.3, 128.2, 128.0, 127.7, 127.2, 117.3, 114.6, 100.0; HRMS (ESI, *m/z*) calcd for $C_{18}H_{13}N_2OS$ 305.0743, found 305.0746 $[M + H]^+$.

(2-(4-Chlorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (**69y):** Yield 82%; Off-white solid; mp 148-150 °C; IR (KBr) *v*: 3089, 2947, 1612, 1458, 1389, 1227, 1088, 795, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.39 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.33 (t, *J* = 7.4 Hz,

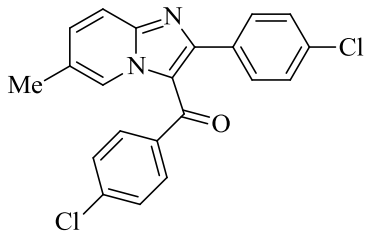
1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 153.4, 146.4, 138.7, 134.3, 132.7, 132.3, 131.9, 131.3, 129.6, 127.9, 126.1, 124.8, 119.9, 116.7, 18.5; HRMS (ES, *m/z* I) calcd for $C_{21}H_{16}ClN_2O$ 347.0946, found 347.0956 $[M + H]^+$.

(4-Chlorophenyl)(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69z): Yield



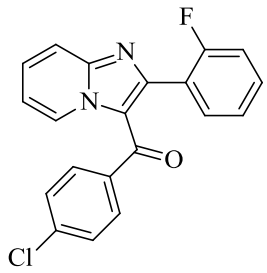
63%; Off-white solid; mp 192-194 °C; IR (KBr) *v*: 3086, 1612, 1496, 1404, 1335, 1227, 795, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.61 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 7.30 – 7.24 (m, 2H), 7.17 – 7.09 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 153.6, 147.5, 138.5, 136.9, 134.9, 132.4, 131.4, 130.9, 129.6, 128.2, 128.2, 119.9, 117.6, 115.0; HRMS (ESI, *m/z*) calcd for $C_{20}H_{13}Cl_2N_2O$ 367.0399, found 367.0387 $[M + H]^+$.

(4-Chlorophenyl)(2-(4-chlorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methanone



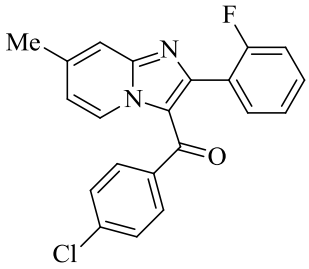
(69ab): Yield 75%; Off-white solid; mp 154-156 °C; IR (KBr) *v*: 3063, 2955, 1605, 1466, 1381, 1335, 1242, 957, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.8, Hz, 1H), 7.71 (dd, *J* = 9.1, 0.5 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.45 – 7.39 (m, 2H), 7.28 – 7.23 (m, 2H), 7.15 – 7.10 (m, 4H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 153.5, 146.5, 138.3, 137.2, 134.7, 132.6, 132.5, 131.3, 130.9, 128.2, 128.1, 126.1, 125.0, 119.7, 116.8, 18.5; HRMS (ESI, *m/z*) calcd for $C_{21}H_{15}Cl_2N_2O$ 381.0556, found 381.0551 $[M + H]^+$.

(4-Chlorophenyl)(2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69n): Yield



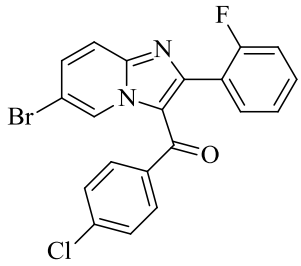
45%; Off-white solid; mp 144-146 °C; IR (KBr) *v*: 3055, 2924, 1612, 1481, 1389, 1227, 1080, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 6.6 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 5.4 Hz, 1H), 7.21 – 7.05 (m, 4H), 6.74 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.75, 159.11 (d, *J* = 248.7 Hz), 148.4, 147.7, 137.8, 136.9, 131.2 (d, *J* = 2.4 Hz), 130.9, 130.9 (d, *J* = 8.3 Hz), 129.3, 128.2, 127.7, 124.2 (d, *J* = 3.5 Hz), 122.8, 122.7, 120.9, 117.6, 115.2 (d, *J* = 22.0 Hz), 115.0; HRMS (ESI, *m/z*) calcd for $C_{20}H_{13}ClFN_2O$ 351.0695, found 351.0698 $[M + H]^+$.

(4-Chlorophenyl)(2-(2-fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (69o):



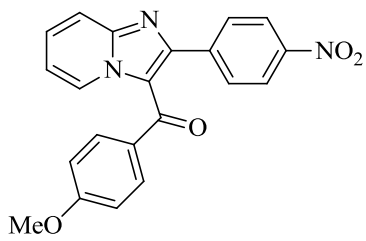
Yield 42%; Off-white solid; mp 147-149 °C; IR(KBr) *v*: 3055, 2965, 1612, 1481, 1227, 1076, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 7.1 Hz, 1H), 7.59 (s, 1H), 7.49 (td, *J* = 7.4, 1.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.26 – 7.19 (m, 1H), 7.12 – 7.04 (m, 3H), 7.00 – 6.96 (m, 1H), 6.75 – 6.65 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 159.2 (d, *J* = 248.7 Hz), 148.8, 148.2, 141.1, 137.6, 137.0, 131.2 (d, *J* = 2.5 Hz), 130.8 (d, *J* = 8.3 Hz), 130.5, 127.6, 127.5, 124.1 (d, *J* = 3.5 Hz), 123.0, 122.8, 120.6, 117.5, 116.2, 115.2 (d, *J* = 22.0 Hz), 21.6; HRMS (ESI, *m/z*) calcd for $C_{21}H_{15}ClFN_2O$ 365.0851, found 365.0835 $[M + H]^+$.

(6-Bromo-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(4-chlorophenyl)methanone (69p):



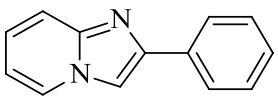
Yield 51%; Off-white solid; mp 173-175 °C; IR (KBr) *v*: 3101, 3055, 2924, 1612, 1481, 1389, 1227, 1080, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.73 (d, *J* = 9.3 Hz, 1H), 7.63 (d, *J* = 9.4 Hz, 1H), 7.53 (t, *J* = 6.9 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 5.4 Hz, 1H), 7.15 – 7.05 (m, 3H), 6.71 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 159.1 (d, *J* = 249.1 Hz), 148.3, 146.1, 138.2, 136.4, 136.4, 132.7, 131.2 (d, *J* = 6.4 Hz), 131.1, 130.4, 128.3, 127.8, 124.3 (d, *J* = 3.5 Hz), 122.3 (d, *J* = 14.0 Hz), 120.9, 118.1, 115.3 (d, *J* = 22.0 Hz), 109.9; HRMS (ESI, *m/z*) calcd for $C_{20}H_{12}BrClFN_2O$ 428.9800, found 428.9822 $[M+H]^+$.

(4-Methoxyphenyl)(2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (69ac): Yield



44%; Pale yellow solid; mp 199-201 °C; IR (KBr) *v*: 3109, 3070, 2222, 1612, 1512, 1478, 1342, 1026, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.07 (d, *J* = 6.9 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.67 – 7.57 (m, 5H), 7.18 – 7.16 (m, 1H), 6.70 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 163.4, 150.3, 147.2, 147.2, 140.7, 132.0, 130.9, 130.8, 129.2, 127.9, 123.0, 120.6, 117.7, 114.9, 113.5, 55.5; HRMS (ESI, *m/z*) calcd for $C_{21}H_{16}N_3O_4$ 374.1135, found 374.1123 $[M + H]^+$.

2-Phenylimidazo[1,2-*a*]pyridine (64a): Off-white solid; mp 134-136 °C;[105] ^1H NMR (300



MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.85 (s, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.30

(m, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.78 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 138.0, 133.7, 128.7, 128.0, 126.1, 125.6, 124.8, 117.6, 112.5, 108.2.

1.10. References:

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