Synthesis of Novel Fused Azaheterocycles by One-pot, Tandem and Multicomponent Reactions

THESIS

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Dedicated to

My family

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
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<u>CERTIFICATE</u>

This is to certify that the thesis entitled **"Synthesis of Novel Fused Azaheterocycles by One-pot, Tandem and Multicomponent Reactions"** submitted by **Mr. Kasiviswanadharaju Pericherla** ID No **2010PHXF415P** for the award of Ph. D. Degree of the Institute embodies the original work done by him under our supervision.

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Kasiviswanadharaju Pericherla

ABSTRACT

Nitrogen containing heterocyclic compounds have been known to have a tremendous potential in multidisciplinary fields. The thesis entitled "**Synthesis of Novel Fused Azaheterocycles by One-pot, Tandem and Multicomponent Reactions**" deals with the synthesis of some selected *N*-fused heterocycles by employing the multi-bond forming procedures like tandem sequences, multicomponent reactions, and also utilizing transition metal catalyzed C−H functionalizations. The thesis is divided into five chapters.

The first chapter of thesis describes the brief literature overview on recent progress in the construction of imidazo[1,2-*a*]pyridine scaffolds through various techniques such as multi-component reactions, tandem processes, rearrangement reactions, transition metal catalyzed C−H functionalizations, inter and intramolecular oxidative/reductive cyclizations. A detailed mechanisms have been discussed for the selected transformations.

The second chapter of the thesis describes the synthesis of *N*-fused bicyclic heterocycles, imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines by tandem reactions. The chapter is divided in two parts. In part-A, a simple and convenient strategy is described for the synthesis of imidazo[1,2-*a*]pyridines *via* inexpensive copper catalyzed tandem imine formation and intramolecular aerobic oxidative C–H bond amination/cyclizations. An array of imidazo[1,2-*a*]pyridines were prepared by the reaction of readily available acetophenones and 2-aminopyridines in good to excellent yields (48-92%). The scope of method was validated by single step synthesis of zolimidine, drug used for peptic ulcers, in 61% yield. In part-B, an efficient procedure has been developed for the regioselective synthesis of pyrazolo[1,5-*a*]pyrimidines through the tandem reaction of 3-aminopyrazoles and chalcones in presence of catalytic amount of KOH. The reported method offers highly regioselective access to 5,7-diarylpyrazolo[1,5-*a*]pyrimidines in good to excellent yields (41-89%). A gram-scale reaction has been performed to demonstrate the potency of optimized procedure for the scale-up processes.

 The third chapter of the thesis describes the functionalization of imidazo[1,2-*a*]pyridines and pyrazolo-[1,5-*a*]pyrimidines by multicomponent protocol. An efficient one-pot condensation reaction of imidazo-[1,2-*a*]pyridine/pyrazolo[1,5-*a*] pyrimidines, aldehydes and acetamide has been investigated using Yb(OTf)$_3$ as a catalyst in 1,4-dioxane. The reaction furnished good to excellent yield of imidazo[1,2-*a*]pyridine based drug like structures, 1-amidomethyl-imidazo[1,2-*a*]pyridines and 1-amidomethyl-pyrazolo[1,5-*a*]pyrimidines. The outcome of the three-component reaction was found to be dependent on the nature of imidazo[1,2-*a*]pyridine/ pyrazolo[1,5-*a*]pyrimidines and aldehydes. The reaction of pyrazolo[1,5-*a*]pyrimidine with aldehydes resulted in formation of two new symmetrical and unsymmetrical aryl methylene-*bis*-pyrazolo[1,5-*a*]pyrimidines while imidazo[1,2-*a*]pyridine gave symmetrical aryl methylene-*bis*(imidazo[1,2-*a*]pyridine) together with expected three-component products. A plausible mechanism has been proposed based on the product distribution.

The fourth chapter of thesis describes the synthesis azole fused imidazo[1,2-*a*]pyridines by employing transition metal catalyzed C−H functionalizations. The chapter is divided in two parts. In part-A, an efficient one-pot protocol has been developed using sequential C−N coupling and intramolecular dehydrogenative cross-couplings for the synthesis of azole fused imidazo[1,2-*a*]pyridine derivatives in good yields (62-78%). An interesting result on regioselectivity of imidazo[1,2-*a*]pyridines towards copper catalyzed Ullmann-type C−N coupling has been discussed. In part-B, a ligand-free copper-catalyzed tandem azide-alkyne cycloaddition (CuAAC), Ullmann-type C−N coupling and intramolecular direct arylation has been described. The designed strategy resulted in the construction of novel triazole-fused azaheterocyclic frameworks in good yields (59-77%).

Finally overall thesis work is summarized in the chapter five. The future scope of the research work have also been highlighted in this chapter.

TABLE OF CONTENTS

Chapter V: Conclusions

Appendices

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
Δ	Delta
°C	Degree centigrade
Å	Angstrom
Ac	Acetyl
ACN	Acetonitrile
Ar	Aryl
[Bmim][Br]	1-Butyl-3-methylimidazolium bromide
[Bmim][Br$_3$]	1-Butyl-3-methylimidazolium tribromide
[Bmim][BF$_4$]	1-Butyl-3-methylimidazolium tetrafluoroborate
[Bmim][PF$_6$]	1-Butyl-3-methylimidazolium hexafluorophosphate
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
Calcd.	Calculated
^{13}C	Carbon-13
Cat.	Catalyst
CAN	Ceric ammonium nitrate
CDCl$_3$	Deuterated chloroform
Chalcones	1,3-Diarylprop-2-en-1-ones
Conc	Concentration
COSY	Correlation Spectroscopy (NMR)

CuAAC	Copper catalyzed Azide-Alkyne Cycloaddition
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N,N*-Dimethylacetamide
DMAD	Dimethyl acetylene dicarboxylate
DMF	*N,N*-Dimethylformamide
DMSO-*d₆*	Deuterated dimethylsulfoxide
DOS	Diversity oriented synthesis
EI	Electron Ionization
[Emim]OTs	1-Ethyl-3-methylimidazolium tosylate
ESI	Electron Spray Ionization (MS)
ESIPT	Excited state intramolecular proton transfer
EtOAc	Ethyl acetate
Equiv	Equivalent
G	Gram
h	Hours
[Hbim][BF₄]	1-*n*-Butylimidazolium tetrafluoroborate
HDNIB	[Hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene,
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectra
HSQC	Heteronuclear Single Quantum Correlation

HTIB	(Hydroxy(tosyloxy)iodo)benzene
IBX	2-Iodoxybenzoic acid
ILs	Ionic liquids
IR	Infrared
Hz	Hertz
J	Coupling constant
Lit.	Literature
MCR	Multi component reaction
Me	Methyl
MS	Mass spectrometry
M.P	Melting point
m	Multiplet
MBHAs	Morita-Baylis-Hillman acetates
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave
N_2	Nitrogen gas
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect (NMR)
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
O_2	Oxygen gas
PEG	Polyethylene glycol

PIDA	Phenyl iodonium diacetate
Ph	Phenyl
ppm	Parts per million
PS	Polymer supported
%	Percentage
psi	Per square inch
p-TsOH	*p*-Toluenesulfonic acid
R	Hydrocarbon
rt	Room temperature
s	Singlet
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
t	Triplet
T3P	Propylphosphonic anyhydride
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
OTf	Triflouromethanesulfonate
δ	Parts per million
w	Watt

Chapter I

Introduction

A Brief Overview on Chemistry of Imidazo[1,2-*a*]pyridines

1.1 Introduction

A cyclic organic compound, in general termed as carbocyclic compound comprises a ring system containing all the carbon atoms in its skeleton. When at least one of the carbon atom in the carbocyclic ring is replaced by other atom (referred as heteroatom) then they are stated as heterocyclic compounds.[1-3] The chemistry of heterocycles has great theoretical as well as practical importance. In fact, heterocyclic compounds filled more than half basket of the total chemical inventory of organic molecules. These structures form the basis for numerous pharmaceutical, agrochemical and biologically active compounds. Diverse compounds like alkaloids, antibiotics, essential amino acids, vitamins, haemoglobin, hormones and many synthetic drugs and dyes contains heterocyclic rings as core skeletons.[3-4]

Though heterocyclic compounds with several heteroatoms are known in the literature, nitrogen is the most common which follows oxygen and sulfur among the others.[5-6] Nitrogen-containing heterocycles has importance in medical as well as organic chemistry because they constitute the main structure within a huge number of natural products and also because of their broad range of biological properties.[7] Particularly, condensed heterocycles act as synthetic building blocks and pharmacophores. Fused azaheterocycles comprise a family of biological agents with particularly interesting pharmacological properties related to planarity of the system and consequently to its DNA-chain intercalating ability, which make them suitable for anti-neoplastic and mutagenic applications.[8-11] Because of their useful applications in the biological field, synthesis of fused heterocycles has attracted the interest in modern drug discovery.[12-16]

Benzodiazepine, the diazepine ring fused with benzene, is the core structure of an array psychoactive drugs like diazepam, lorazepam, flunitrazepam, alprazolam, triazolam and midazolam (**Figure 1.1**). These motifs enhances the effect of the neurotransmitter gamma-amino butyric acid (GABA) at the $GABA_A$ receptor which results sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties.[17-18]
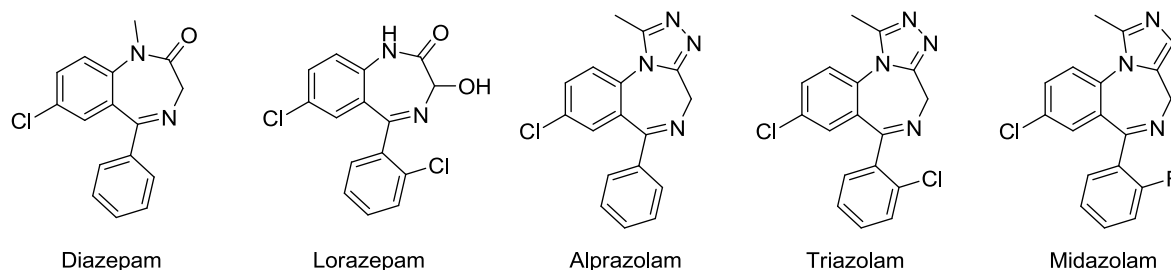
Figure 1.1 Structures of psychoactive benzodiazepine drugs

Interestingly, there is an another class of psychoactive drugs collectively termed as non-benzodiazepines.[19-20] Although, they are structurally unrelated to benzodiazepines on a molecular level but their pharmacodynamics are quite similar to that of benzodiazepine drugs. The key structures which includes in this category are imidazopyridines, pyrazolopyrimidines, cyclopyrrolones and β-carbolines (**Figure 1.2**).[20-24] The marketed drugs, currently leading in the market under this category are

- Zolpidem, Alpidem, Necopidem and Saripidem (contains imidazo[1,2-*a*]pyridine skeleton)
- Zaleplon, Devaplon, Lorediplon and Ocinaplon (with pyrazolo[1,5-*a*]pyrimidine skeleton)
- Eszopiclone, Zopiclone, Pagoclone and Suproclone (contains cyclopyrrolone motif)
- Abecarnil, Gedocarnil and ZK-93423 (contains β-carboline moiety)
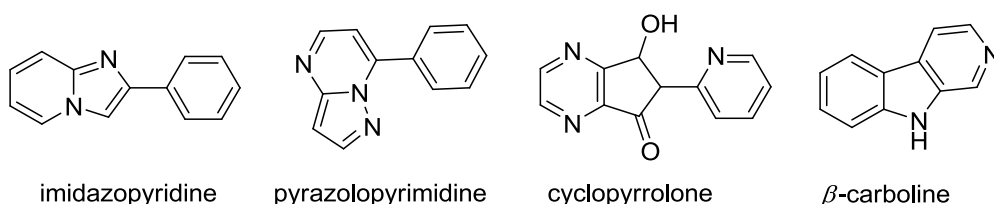
Figure 1.2 Key structures of non-benzodiazepine drugs

As the thesis is mainly focused on chemistry of imidazo[1,2-*a*]pyridines, diverse procedures reported for the synthesis of imidazo[1,2-*a*]pyridines are briefly reviewed. Additionally, functionalization of these motifs have also been discussed systematically.

1.2 Biological Significance of Imidazo[1,2-*a*]pyridines

Among *N*-fused azoles, imidazo[1,2-*a*]pyridines have taken a lead role in the recent literature because of their wide variety of applications in various disciplines like medicinal chemistry,

organometallics and material science.[25-29] Molecules with imidazo[1,2-*a*]pyridine moiety have shown wide range of biological properties such as antifungal, antiviral, antibacterial, anticancer, antiprotozonal, anti-inflammatory, anticonvulsant, antipyretic, anthelmintic, analgesic, anti-epileptic, antituberculosis, antiulcer, hypno-selective and anxioselective.[30-37] They have also been studied as $GABA_A$ receptor agonists, 5-lipoxygensase inhibitors, cyclic dependent kinase inhibitors, MCH1R antagonists, *β*-amyloid detecting ligands, HIF-1α prolyl hydroxylase inhibitors, and histamine H2 receptor antagonists.[38-41] This moiety is also present in a number of commercially available drugs such as alpidem and zolpidem (for the treatment of anxiety and insomnia), saripidem and necopidem (anxiolytic), olprinone (cardiotonic agent), miroprofen (analgesic), DS-1 ($GABA_A$ receptor agonist), zolimidine (for peptic ulcers), GSK812397 (candidate for the treatment of HIV infection) and minodronic acid (for treating osteoporosis) (**Figure 1.3**).
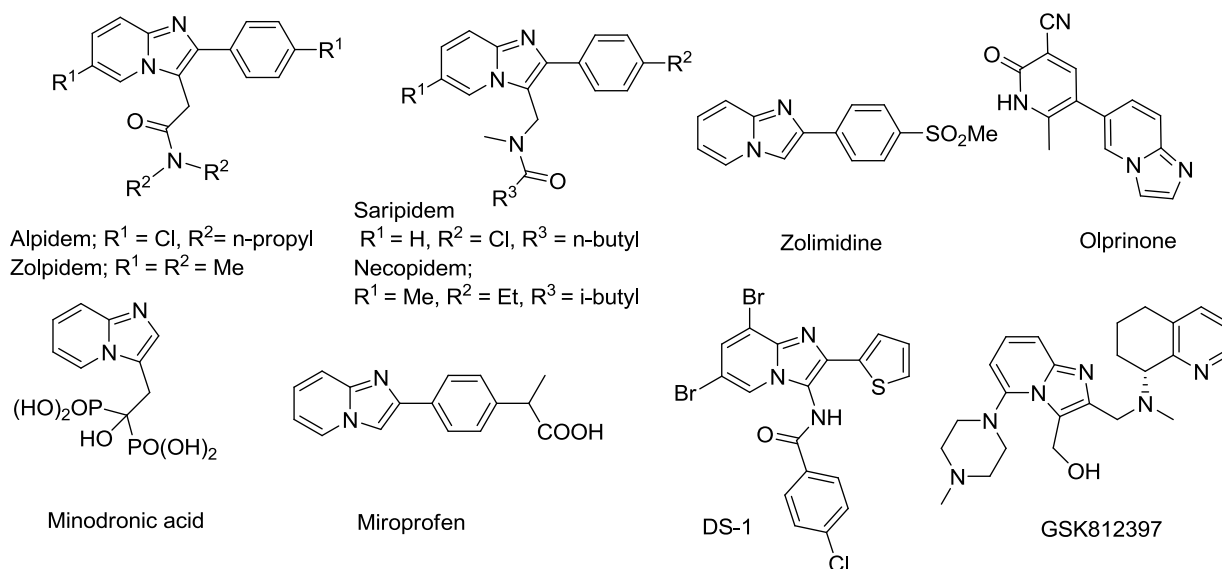
Figure 1.3 Marketed drugs with imidazo[1,2-*a*]pyridine skeleton

Not surprisingly, because of their applications in a variety of fields, several synthetic routes have been developed to achieve imidazo[1,2-*a*]pyridine motif. Particularly, last decade has witnessed a remarkable advancement in the synthesis of imidazo[1,2-*a*]pyridines by employing several interesting approaches such as multi-component reactions, tandem sequences and C−H functionalizations. These methods offer an easy access to imidazo[1,2-*a*]pyridine skeletons by means of simple and readily available precursors without the need of any pre-functionalities.

1.3 Synthesis of Imidazo[1,2-*a*]pyridines from 2-Aminopyridines

2-Aminopyridines (**1**) have been exploited as a key substrates for the synthesis of imidazo[1,2-*a*]pyridine nucleus. Tschitschibabin reported a pioneering method for the synthesis of imidazo[1,2-*a*]pyridines (**3**) in 1925 (**Scheme 1.1**).[42] Reaction of 2-aminopyridine (**1**) with bromo acetaldehyde (**2**) at 150-200 °C in a sealed tube resulted the formation of imidazo[1,2-*a*]pyridine (**3**), albeit in low yields. In the following years, several synthetic groups had eventually adapted the Tschitschibabin's method to achieve imidazo[1,2-*a*]pyridines (**3**) under mild conditions with higher efficiencies. It was realized that, efficiency of Tschitschibabin's protocol could be drastically enhanced in the presence of mild base, sodium bicarbonate which offered higher yields of imidazo[1,2-*a*]pyridines (**3**) under mild reaction conditions.

R^2 = H, alkyl, aryl; X = Cl, Br, I
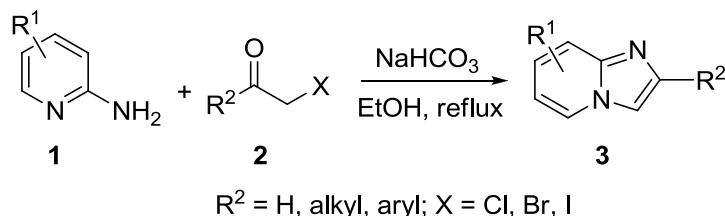
Scheme 1.1 Conventional synthesis of imidazo[1,2-*a*]pyridines

1.3.1 Revisiting traditional cyclocondensation

The lachrymatory nature of phenacyl bromides has strictly restricted their use in organic reactions, particularly in bulk processes. In this perspective, tremendous achievements have been made in the last decade to renew the traditional cyclocondensation procedure for the synthesis of imidazo[1,2-*a*]pyridines.[43-46] Few groups have reported an efficient alternatives like α-halo carbonyl compounds were replaced with environmentally benign reagents such as *α*-tosyloxy ketones,[47-48] *α*-diazo ketones[49] to offer imidazo[1,2-*a*]pyridines in good yields. In other hand, carbonyl compounds are activated *in situ* through the reagents such as [Bmim]Br$_3$,[50] hypervalent iodine agents[51] then treated with 2-aminopyridines to obtain the imidazo[1,2-*a*]pyridines. In some cases flow chemistry has been applied for the synthesis of these pharmacologically potent motifs starting from readily available materials.[52-53] Recently, Donohoe and co-workers disclosed an effective method to generate *α*-halo carbonyl compounds (**2**) by the reaction of

alkenes (**4**) with IBX/I$_2$/DMSO (**Scheme 1.2**). The *in situ* generated reactive α-iodo ketones (**2**) were utilized for the synthesis of thiazoles, imidazoles and imidazo[1,2-*a*]pyridines.[54]
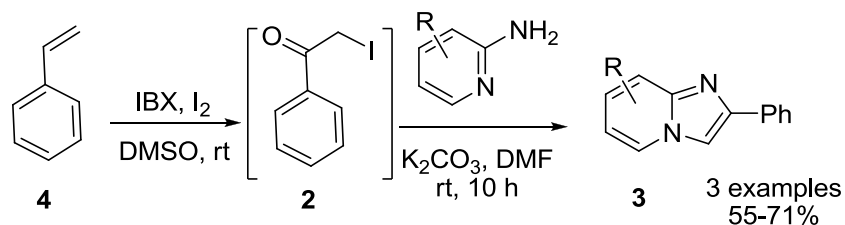
Scheme 1.2 Synthesis of imidazo[1,2-*a*]pyridines through *in situ* generated α-iodo ketones

Togo and collaborators reported a direct method for the synthesis of α-tosyloxy carbonyl compounds from alcohols (**5**) with iodosylbenzene and *p*-TSA (**Scheme 1.3**).[55] This method was smoothly employed for the direct synthesis of heteroaromatics from alcohols. Initially, (hydroxy(tosyloxy)iodo)benzene (HTIB) was generated *in situ* by the reaction of iodosylbenzene and *p*-TSA. Then, alcohols underwent oxidation in presence of HTIB to deliver the carbonyl compounds. These carbonyl compounds tautomerized to enol form in the presence of *p*-TSA which reacted with HTIB to produce α-tosyloxy carbonyl compounds. These intermediates were reacted with 1,3-binucleophiles such as thioamides, amidines and 2-aminopyridines and offered good yields of thiazoles, imidazoles, and imidazo[1,2-*a*]pyridines respectively. Recently, Chen and co-workers generated HTIB *in situ* and treated with ketones and 2-aminopyridines in [emim]OTs ionic liquid to achieve 2-arylimidazo[1,2-*a*]pyridines in good yields. As previous case, α-tosyloxy carbonyl compounds have generated and involved in cyclocondensation.[56]
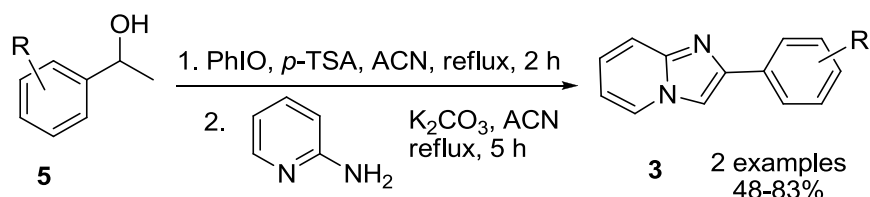
Scheme 1.3 Oxidative construction of imidazo[1,2-*a*]pyridines using HTIB

Yu *et al*. developed an effective one-pot procedure for an access to imidazo[1,2-*a*]pyridine-3-carboxylates (**7**) from 2-aminopyridines (**1**) and *β*-keto esters (**6**) *via* phenyl-iodonium diacetate (PIDA) mediated direct oxidative coupling in presence of BF$_3$.Et$_2$O (**Scheme 1.4**).[57] Amount of catalyst played a crucial role in the success of oxidative cyclization. When BF$_3$.Et$_2$O was used in

stoichiometric amount, α-acetoxylation of β-keto ester was predominated over imidazo[1,2-a]pyridines. 20 mol % of catalyst was found to be optimum which resulted good yields of desired imidazo[1,2-a]pyridines (**7**). It was proposed that reaction among active methylene compound (**6**) and PIDA resulted in activated intermediate **8** which is then attacked by **1** through its endocyclic pyridinium nitrogen to afford **9**. Finally, intramolecular condensation of **9** with subsequent aromatization gave the desired fused azoles (**7**).
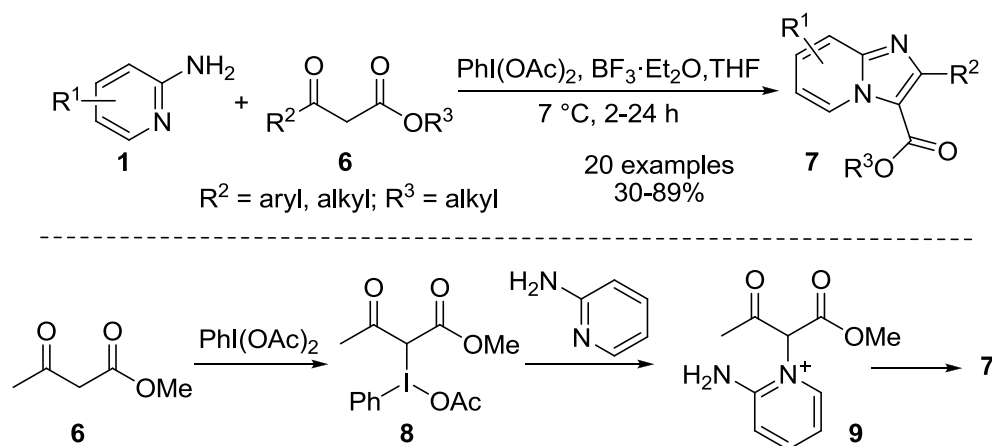
Scheme 1.4 PIDA mediated synthesis of imidazo[1,2-a]pyridines

Ma *et al.* achieved these molecules by TBAI catalyzed reaction of 2-aminopyridines and β-keto esters (**6**) or 1,3-diones (**10**) in TBHP oxidizing media (**Scheme 1.5**). Catalytic amount of BF$_3$.Et$_2$O was used to promote the reaction. An array of imidazo[1,2-a]pyridines (**7** and **11**) were synthesized by varying 2-aminopyridines and 1,3-diones in good yields.[58]
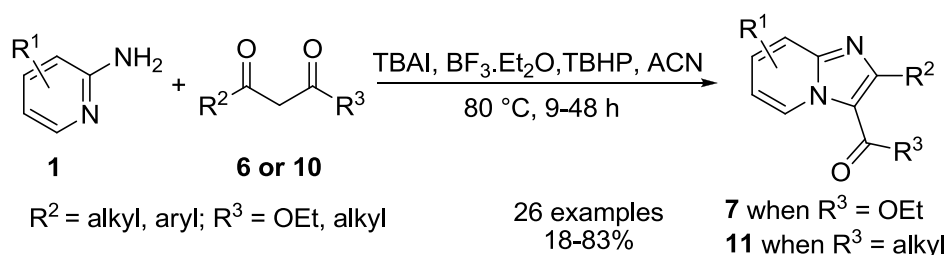
Scheme 1.5 TBAI promoted synthesis of imidazo[1,2-a]pyridines

Stasyuk *et al.* disclosed a short and efficient one-pot method for the synthesis of imidazo[1,2-a]pyridines *via* Ortoleva-King reaction followed by ring closure (**Scheme 1.6a**). A wide variety of 2-aminopyridines (**1**) and acetophenones (**12**) reacted in presence of I$_2$ and NaOH to deliver

moderate to good yields of imidazo[1,2-*a*]pyridines (**3**). This method is compatible with various reactive functionalities such as OH, NEt$_2$, Br, and OMe. This article mainly focussed on synthesis of imidazo[1,2-*a*]pyridines bearing *ortho*-hydroxy aryl substituent at *C-2* position. These motifs have displayed excited state intramolecular proton transfer (ESIPT).[29] Fei *et al.* disclosed a simple method for the synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridines (**13**) by I$_2$ catalyzed reaction of aryl ketones (**12**) and 2-aminopyridines (**1**) (**Scheme 1.6b**). This method is interesting as 3-heteroarylamino substituted imidazo[1,2-*a*]pyridines (**13**) can be obtained in single step without using metal, base and ligand.[59]
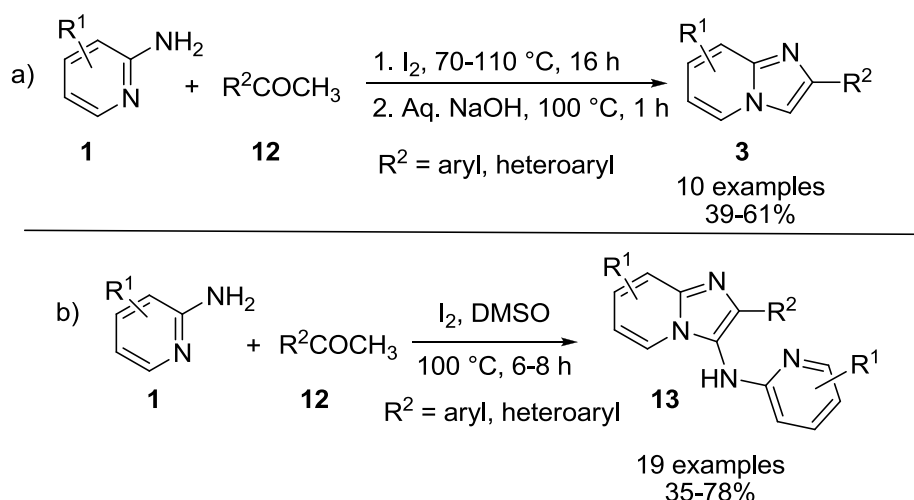
Scheme 1.6 Iodine mediated synthesis of imidazo[1,2-*a*]pyridines

1.3.2 Cyclocondensation associated with the cross-coupling reactions

Recently, a few reports have appeared where traditional cyclocondensation was amalgamated with transition metal catalyzed cross coupling reactions which offered substituted imidazo[1,2-*a*]pyridines in single step. Raboin and collabarators reported microwave assisted Suzuki coupling and heteroarylations for the synthesis of substituted imidazo[1,2-*a*]pyridines. Moreover, one-pot, cyclization, Suzuki reaction and palladium-catalyzed regioselective heteroarylation of 2-amino-5-bromopyridine were performed for the synthesis of 2,3,6-triarylimidazo[1,2-*a*]pyridines.[60] Recently, the same group has demonstrated PEG 400 as a suitable media for cyclocondensation of 2-aminopyridines (**1**) with phenacyl halides (**2**) to achieve 2-arylimidazo[1,2-*a*]pyridines (**3**) in shorter reaction times under microwave irradiation. Furthermore, one-pot protocol was attempted to achieve 2,3-diarylimidazo[1,2-*a*]pyridines (**14**) directly from 2-aminopyridines (**1**)

through initial cyclization followed by palladium catalysed direct arylation under ligand-free conditions (**Scheme 1.7a**).[61] Very recently, Li group disclosed a straightforward one-pot approach for the synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines (**14**) *via* palladium catalyzed three-component reaction under microwave irradiation (**Scheme 1.7b**).[62]
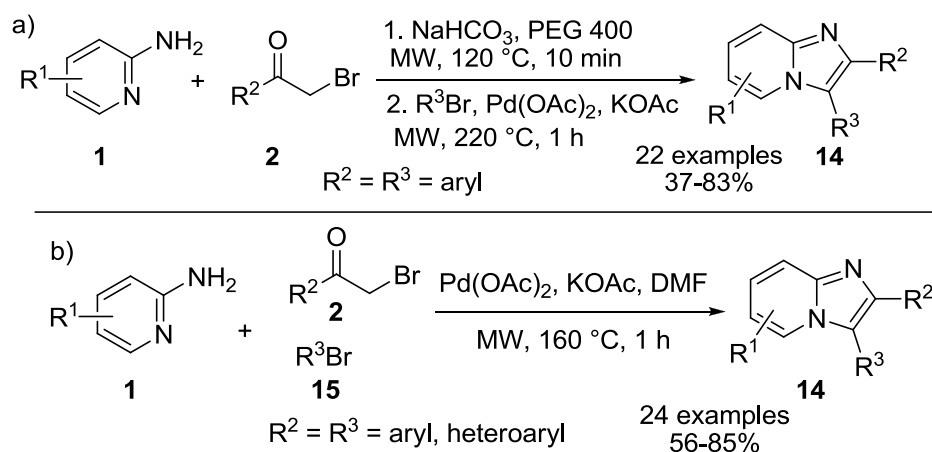
Scheme 1.7 One-pot access to 2,3-diarylimidazo[1,2-*a*]pyridines

1.3.3 Regioselectivity in cyclocondensation

In the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), the fate of historic reaction has been inverted as phenacyl bromides (**2**) and 2-aminopyridines (**1**) delivered 3-arylimidazo[1,2-*a*]pyridines (**16**) instead of 2-aryl counterparts (**3**) in aqueous media (**Scheme 1.8**). This method was conveniently applied to other heterocyclic amines such as 2-aminothiazoles to afford the respective imidazo fused motifs in high yields. Under the present environment, water soluble quaternary salt of DABCO with phenacyl bromide (**17**) was formed. Then, primary amine of compound **1** reacted with **17** and results **18**. Finally, cyclization followed by dehydration leads 3-arylimidazo[1,2-*a*]pyridines (**16**). The high regioselectivity was due to the fact that quaternary salt of DABCO predominate over pyridinium salt and favoured the attack of primary amine on carbon near to quaternary nitrogen instead of carbonyl carbon.[63]

1.3.4 Reactions of un-activated carbonyl compounds

2,3-Disubstituted imidazo[1,2-*a*]pyridines (**19 & 20**) are prepared in presence of acid catalyst by the reaction of 2-aminopyidines with carbonyl compounds (**Scheme 1.9**). Specifically, *α*-activation of carbonyl group is not a part of the reported annulation procedure. Formation of

products were greatly dependent on catalyst and substitution on aryl ketones. *p*-TSA smoothly catalyzed the reaction of 2-aminopyridine with ketones like 4-methyl and 4-fluoroacetophenone and 1-acetylnaphthalene to afford high yields of 2-aryl-3-(1-arylethyl)imidazo[1,2-*a*]pyridines (**19**). When *p*-TSA was replaced with H_2SO_4, mixture of **19** and 2-pheyl-3-(1-phenylethenyl)imidazo[1,2-*a*]pyridines (**20**) were obtained as major products.[64] The same group further extended their investigations on mechanism of the aforesaid reaction. The formation of multiple products was explained through ketimine and Ortoleva-King type reaction intermediates.[65]
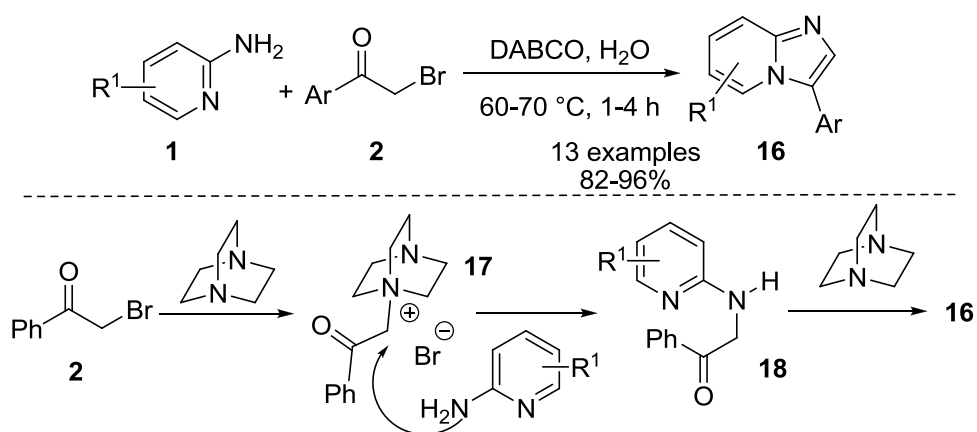
Scheme 1.8 Regioselective synthesis of 3-arylimidazo[1,2-*a*]pyridines
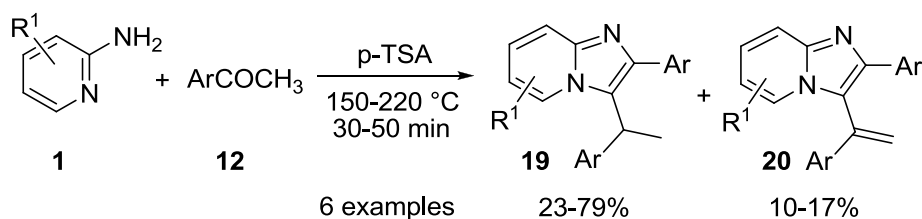
Scheme 1.9 *p*-TSA catalyzed synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines

1.3.5 Reactions of α,β-unsaturated carbonyl compounds

Jorgensen and co-workers developed an efficient one-pot cascade enantioselective organocatalytic [3 + 2] annulation for the synthesis of optically active hydroxyalkyl imidazo[1,2-*a*]pyridines (**22**) by reacting α,β-unsaturated aldehydes (**21**) and 2-aminopyridines (**1**) (**Scheme 1.10**). α,β-Unsaturated, linear and γ-branched aliphatic aldehydes (**21**) were well tolerated under the reaction conditions but cinnamaldehyde failed to give target molecule. This methodology

was smoothly applied for the synthesis of 3-aminoalkylimidazo[1,2-*a*]pyridines (**22**) with high enantioselectivities using 2,3-aziridine aldehydes.[66]
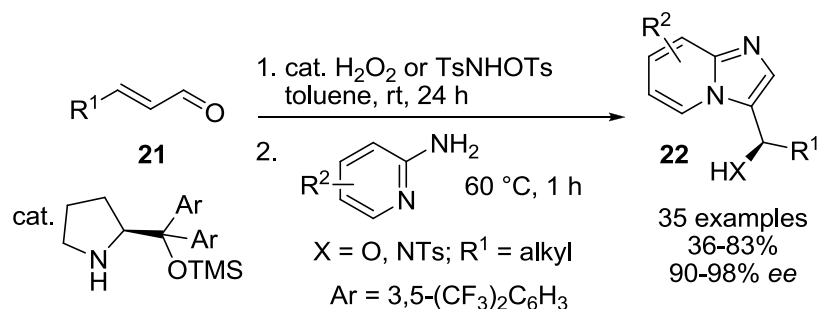
Scheme 1.10 Enantioselective synthesis of 3-hydroxyalkyl imidazo[1,2-*a*]pyridines

Very recently, Hajra group reported an efficient aerobic oxidative coupling between 2-aminopyridines (**1**) and chalcones (**23**) to afford bioactive 3-aroylimidazo[1,2-*a*]pyridines (**11**) in a single step (**Scheme 1.11**). Cu(OAc)$_2$ efficiently catalyzed the oxidative cyclization and produced good yields of substituted imidazo[1,2-*a*]pyridines under O$_2$ environment. It was proposed that Michael addition of 2-aminopyridine to chalcones results the adduct **24**. The Michael adduct in its enol form reacts with copper salt through pyridinium nitrogen to give **25** followed by enolic carbon to afford six membered intermediate **26**. Oxidation of intermediate **26** in presence of O$_2$ and AcOH produces Cu(III) intermediate **27**. Finally, reductive elimination (**28**) and spontaneous aromatization led to the desired tandem products (**11**).[67]

1.3.6 Reactions of olefins

Nitroolefins are reported as a valuable synthons for imidazo[1,2-*a*]pyridines syntheses. An interesting fact about these dienophiles is that in presence of Lewis acid, they reacted with 2-aminopyridines and offered 2-substituted imidazo[1,2-*a*]pyridines (**3**) through denitration. When transition metal salts are used as catalysts, nitro group retained at *C*-3 position of imidazo[1,2-*a*]pyridines (**34**) which can be useful for post-functionalizations.

Yan *et al*. disclosed the synthesis of imidazo[1,2-*a*]pyridines (**3**) by FeCl$_2$ catalyzed denitration reaction (**Scheme 1.12**). This method enabled an easy access to imidazo[1,2-*a*]pyridines (**3**) by the reaction of 2-aminopyridines (**1**) with nitroolefins (**29**). It was expected that 5-*exo-trig*

cyclization of Michael adduct (**30**) afforded the intermediate **31** which on HNO_2 elimination led to the title compound **3**.[68]
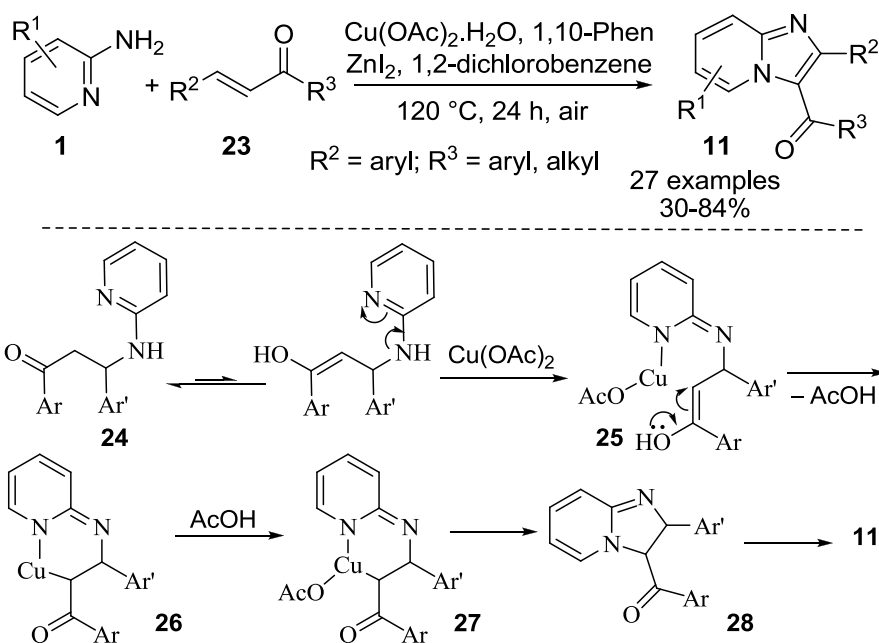
Scheme 1.11 Copper catalyzed synthesis of 3-aroylimidazo[1,2-*a*]pyridines
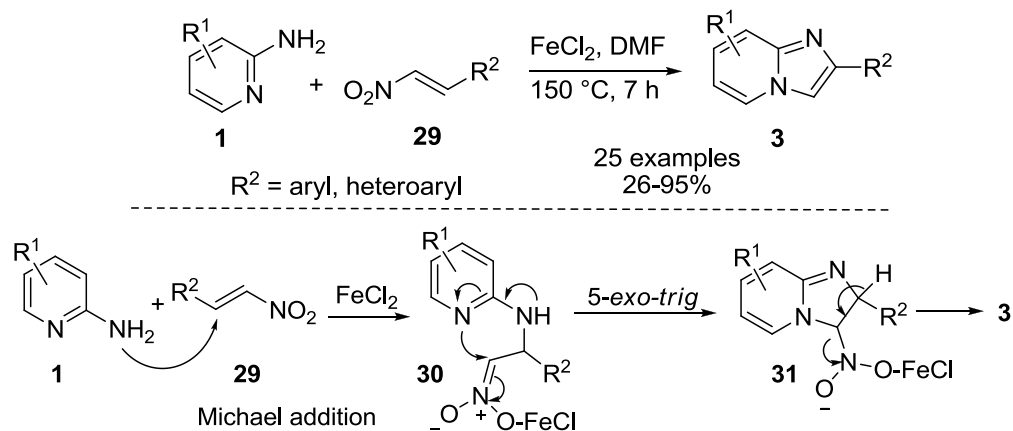
Scheme 1.12 FeCl$_2$ catalyzed denitration reaction for the synthesis of imidazo[1,2-*a*]pyridines

Recently, Hajra group reported FeCl$_3$ catalyzed domino approach for the synthesis of 2-arylimidazo[1,2-*a*]pyridines (**3**) by the reaction of 2-aminopyridines (**1**) and nitroolefins (**29**). This methodology was extended to the gram-scale synthesis of imidazo[1,2-*a*]pyridine based drug, zolimidine in two steps with good yields.[69] The same group further synthesized these motifs in a three component domino strategy. The reaction of 2-aminopyridines, aldehydes and

nitroalkanes led to imidazo[1,2-*a*]pyridines *via* aza-Henry reaction, cyclization and finally denitration.[70] Haung group disclosed a highly efficient approach for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines *via* FeCl₃ catalyzed three-component denitration reaction of 2-aminopyridines, aldehydes and nitroalkanes. This protocol was found to have broad scope as a wide range of aromatic amidines, aldehydes and nitroalkanes smoothly participated in one-pot reaction and resulted moderate to good yields of tandem products.[71]

Very recently, Meshram and co-workers disclosed a simple method to synthesize imidazo[1,2-*a*]pyridine-2-caboxylates (**33**) by the reaction of 2-aminopyridines (**1**) and *β*−nitro acrylates (**32**) in ionic liquid, [Hbim]BF₄ at room temperature (**Scheme 1.13**). The catalyst and solvent-free conditions as well as excellent yields of imidazo[1,2-*a*]pyridines (**33**) were the salient features of this methodology. Moreover, the optimized method was greatly extended to the synthesis of various imidazo fused thiazoles in good yields.[72]
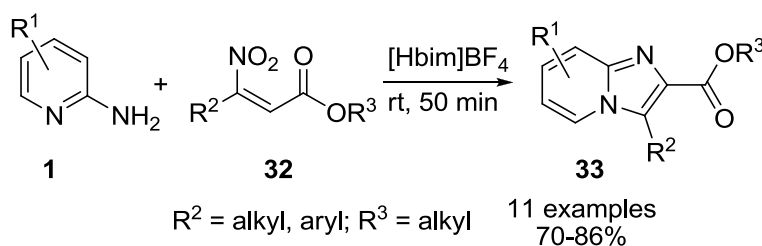
Scheme 1.13 Catalyst-free synthesis of imidazo[1,2-*a*]pyridine-2-carboxylates

Yan *et al.* employed copper catalysis for the reaction of nitroolefins (**29**) and 2-aminopyridines (**1**) which offered high yields of 3-nitroimidazo[1,2-*a*]pyridines (**34**) through oxidative cyclization (**Scheme 1.14**). The developed method utilized air as an oxidant and expected to proceed *via* initial Michael addition followed by oxidation and intramolecular annulation in presence of copper(I) bromide. The same group further extended their previous report to its fundamental level, a one-pot three-component reaction (3CR) where 2-aminopyridines, aldehydes and nitromethane reacted in presence of CuBr to afford 3-nitroimidazo[1,2-*a*]pyridines (**34**) in good yields under aerobic conditions.[73-74] Very recently, Pitchumani group synthesized these motifs (**34**) through a 3CR of 2-aminopyridines, aldehydes and nitroalkane catalyzed by a reusable copper terephthalate metal–organic frameworks.[75]
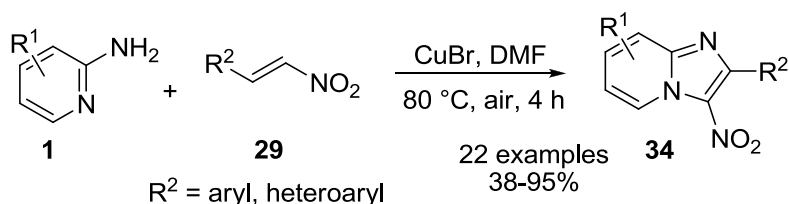
Scheme 1.14 Copper catalyzed synthesis of 3-nitro imidazo[1,2-*a*]pyridines

Besides nitroolefins, Morita-Baylis-Hillman acetates (MBHAs) are proven to be suitable synthons for the synthesis of imidazo[1,2-*a*]pyridines. Namboothiri group disclosed the reaction of MBHAs of nitroalkenes (**35**) with 2-aminopyridines (**1**) for the synthesis of imidazo-[1,2-*a*]pyridines (**36**) through inter-intra molecular double aza-Michael addition (**Scheme 1.15**). This tandem protocol has several advantages as reaction proceeds without any catalyst at room temperature and results in high regioselectivities. This protocol was effectively adapted to the synthesis of imidazo[1,2-*a*]pyridine based drugs, alpidem and zolpidem in good overall yields. It was proposed that Michael addition of 2-aminopyridine on MBHA followed by acetate group elimination in a overall S_N^2 reaction results the intermediate **37**. Next, regioselective Michael addition of pyridine nitrogen *via* 5-*exo-trig* fashion offers **38** which on HNO_2 elimination affords the desired imidazo[1,2-*a*]pyridines (**36**).[76]
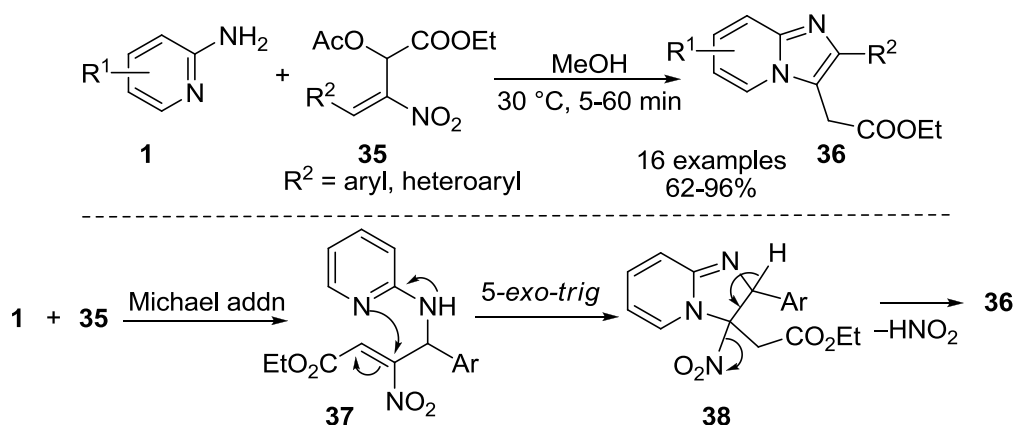
Scheme 1.15 Synthesis of imidazo[1,2-*a*]pyridines using MBHAs

Zou and co-workers demonstrated the potential utility of MBHAs for the synthesis of structurally diversified heterocyclic motifs by varying the nucleophilic partners (**Scheme 1.16**). The developed method was highly efficient and verified the reactivity of all the electrophilic sites (α, β, γ and δ) of MBHAs to deliver imidazo[1,2-*a*]pyridines, indolizines, pyrroles, pyrazoles and

benzo[b][1,6]oxazocin-2-ones with the respective coupling partners. It was found that MBHAs bearing electron-withdrawing substituents offered good yields of substituted imidazo[1,2-a]pyridines (**7**) when compared to MBHAs of electron-rich groups. Michael-elimination, rearrangement provides the intermediate **40**. Subsequent Michael addition at α-position (**41**) followed by elimination afforded the desired imidazo[1,2-a]pyridines (**7**).[77]
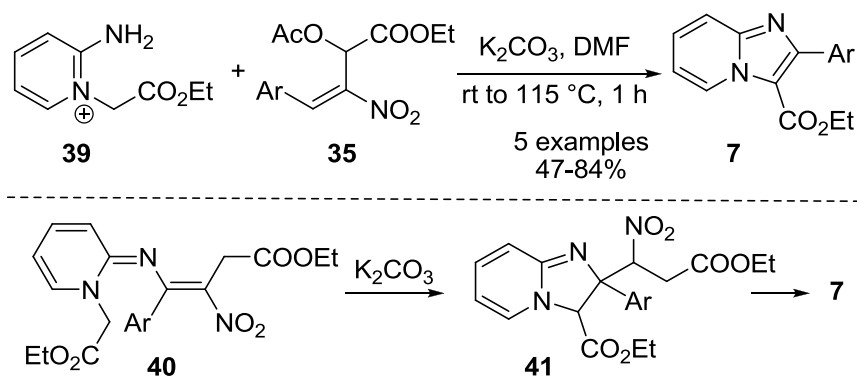
Scheme 1.16 Synthesis of imidazo[1,2-a]pyridine-3-carboxylates using MBHAs

1.3.7 Reactions of alkynes

Transition metal catalyzed oxidative annulations of alkyne with diverse coupling partners have received much attention because they evade pre-activation or functionalization of starting materials. Lei group demonstrated a convenient method for the synthesis of imidazo[1,2-a]pyridines by the oxidative cross coupling among 2-aminopyridines (**1**) and terminal alkynes (**42**) in presence of Ag_2CO_3 (**Scheme 1.17**). The imidazo[1,2-a]pyridine based anti-ulcer drug, zolimidine was synthesized in a concise route with good yields by employing the optimized conditions. It was expected that silver acetylide (**43**) could be generated which follows the silver promoted nucleophilic attack of 2-aminopyridine (**1**) produces intermediate **44**. Finally, silver induced oxidative cyclization furnished the products (**3**) *via* two single electron oxidation.[78]

Very recently, Toste group disclosed a novel route to access imidazo[1,2-a]pyridines (**3**) through $PicAuCl_2$ catalyzed redox reaction of 2-aminopyridine *N*-oxides (**45**) and alkynes (**42**) in presence of TFA (**Scheme 1.18**). Various aliphatic, aromatic, heterocyclic alkynes well reacted under the reaction conditions to afford substituted imidazo[1,2-a]pyridines (**3**) in good yields. It was proposed that addition of pyridine *N*-oxide (**45**) to the pre-activated alkyne (**46**) produces

vinyl gold intermediate (**47**) which rearranges to form gold-carbenoid intermediate **48**. Finally, reaction of 2-aminopyridine with gold-carbenoid (**48**) to form pyridinium salt (**49**) and subsequent condensation results the formation of desired products (**3**).[79]
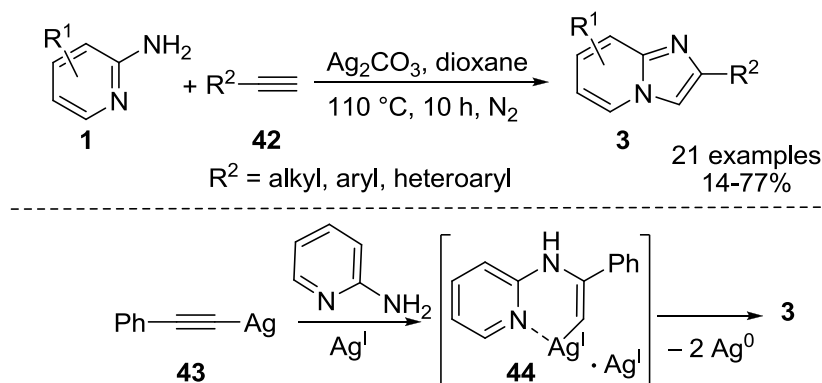
Scheme 1.17 Silver mediated oxidative cyclizations for the synthesis of imidazo[1,2-*a*]pyridines
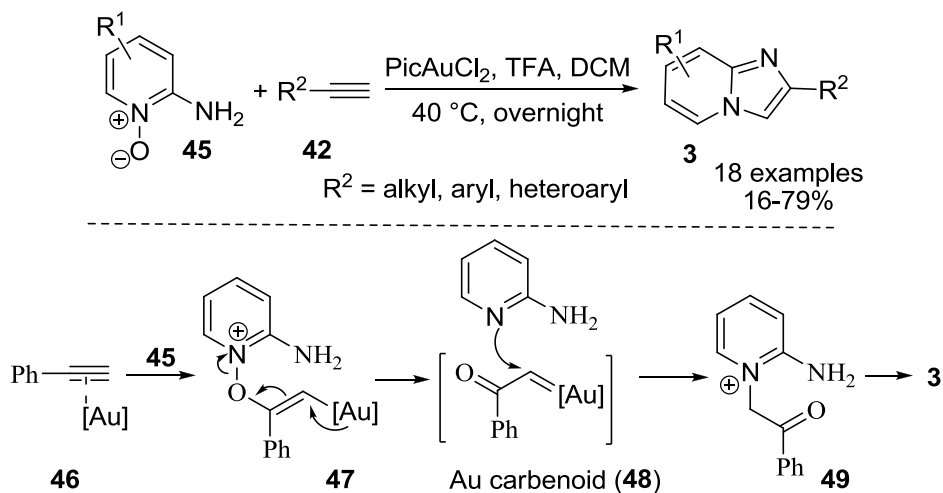
Scheme 1.18 Gold catalyzed synthesis of imidazo[1,2-*a*]pyridines

Gao *et al.* reported an efficient copper catalyzed intermolecular oxidative cyclization of haloalkynes (**50**) with 2-aminopyrdines (**1**) which offered 2-haloimidazo[1,2-*a*]pyridines (**51**) in good yields (**Scheme 1.19**). This method was systematically extended to various aromatic amidines such as pyrazines, pyrimidines, pyridazines, and isoquinolines to access the corresponding imidazo-fused heterocycles in good yields. Post functionalization of these halo bicyclic-imidazoles have been demonstrated by Suzuki, Sonogashira and Kumada reactions. Haloalkyne insertion into 2-aminopyridine:Cu(OTf)$_2$ co-ordinated complex leads to intermediate

52 with new C−N bond. Deprotonation and further oxidation of **52** affords **53**. Finally, reductive elimination affords the desired imidazo[1,2-*a*]pyridines (**51**).[80]

R² = alkyl, aryl; X = Br, I, Cl

36 examples
49-80%
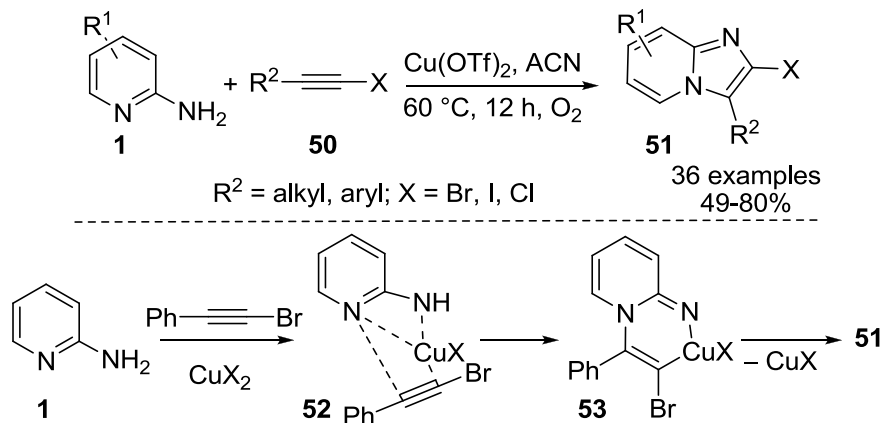
Scheme 1.19 Synthesis of 2-halo imidazo[1,2-*a*]pyridines

Liu and co-workers reported a facile construction of imidazo[1,2-*a*]pyridine skeleton (**33**) *via* Cu(II)/Fe(III) co-catalyzed oxidative diamination of internal alkynes (**54**) with 2-aminopyridines (**1**)(**Scheme 1.20**). A wide range of aminopyridines and isoquinolines as well as internal alkynes were well tolerated under the reaction conditions and offered fused imidazoles with high levels of regio- and chemoselectivities.[81]

Ar = aryl, heteroaryl; R₂ = CO₂Et

17 examples
22-92%
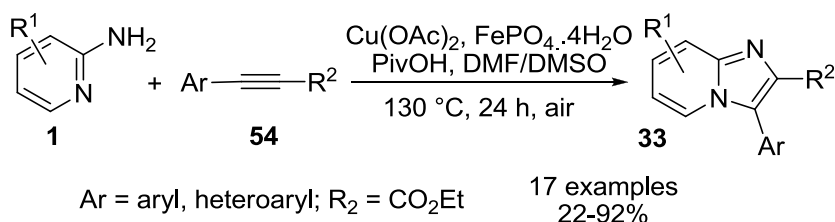
Scheme 1.20 Cu(II)/Fe(III) co-catalyzed synthesis of imidazo[1,2-*a*]pyridines

A couple of groups have effectively used iodonium salts for the synthesis of imidazo[1,2-*a*]pyridines. In the first case, 2-aminopyridines (**1**) reacted with alkynyl-(phenyl)iodonium salts (**55**) in the presence of K_2CO_3 and delivered good yields of imidazo[1,2-*a*]pyridines (**3**) (**Scheme 1.21**). It was proposed that attack of pyridine nitrogen on iodonium salt affords an adduct **56**, which on polyhetero Claisen rearrangement (**57**) and 1,1-elimination of iodobenzene results a reactive carbene intermediate (**58**). Finally, cycloaromatization resulted the desired fused imidazoles (**3**) through the intermediate **59**.[82]

In other case, Carroll and co-workers revealed that the regioselectivity of aforementioned reaction was counter-ion as well as concentration dependent (**Scheme 1.22**). Tosylate and triflate counter-ions greatly favoured the formation of 3-arylimidazo[1,2-*a*]pyridines (**16**) whereas trifluoro-acetate ion reversed the selectivity towards 2-arylimidazo[1,2-*a*]pyridines (**3**). Moreover, higher dilutions favoured the selective formation of **3**.[83]
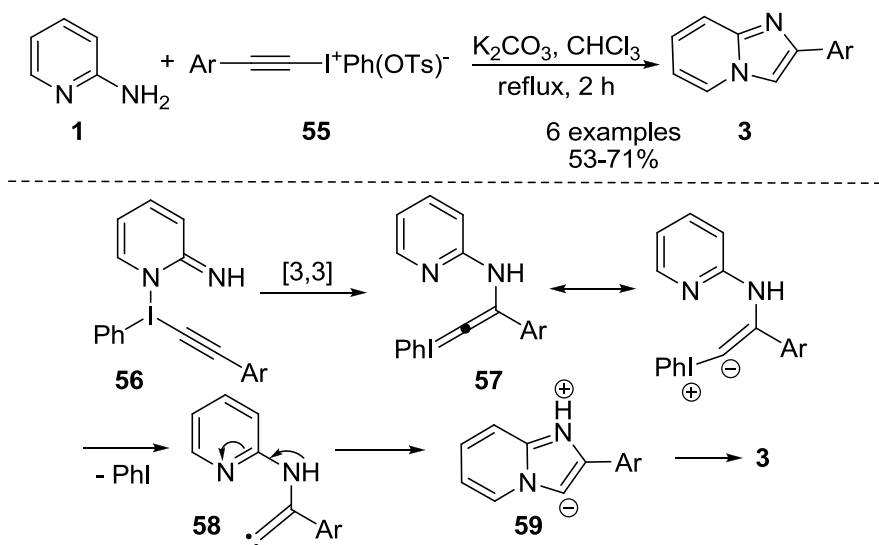
Scheme 1.21 Synthesis of imidazo[1,2-*a*]pyridines starting from alkynyl iodonium salts
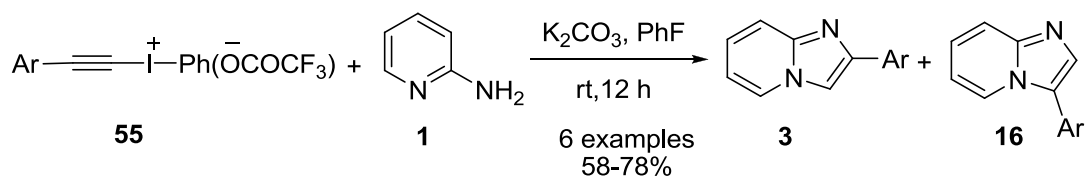
Scheme 1.22 Synthesis of imidazo[1,2-*a*]pyridines starting from alkynyl iodonium salts

Liu *et al.* explored $ZnCl_2$/CuCl catalyzed tandem synthesis of imidazo[1,2-*a*]pyridines (**61**) using 2-aminopyridines (**1**) and propargylic alcohols (**60**) (**Scheme 1.23a**). The cascade process was expected to proceed *via* amination followed by intramolecular cyclization and isomerization to afford the desired products.[84] When phenylpropynal (**62**) and 2-aminopyridine (**1**) reacted in presence of HCl, 3-(2-pyridylamino(phenyl)methyl)imidazo[1,2-*a*]pyridine (**63**) was isolated in good yield (**Scheme 1.23b**).[85] Adib group described a simple and efficient synthesis of imidazo[1,2-*a*]pyridin-3(2*H*)-ones (**65**) from 2-aminopyridines (**1**) and diaroylacetylenes (**64**) (**Scheme 1.23c**).[86]
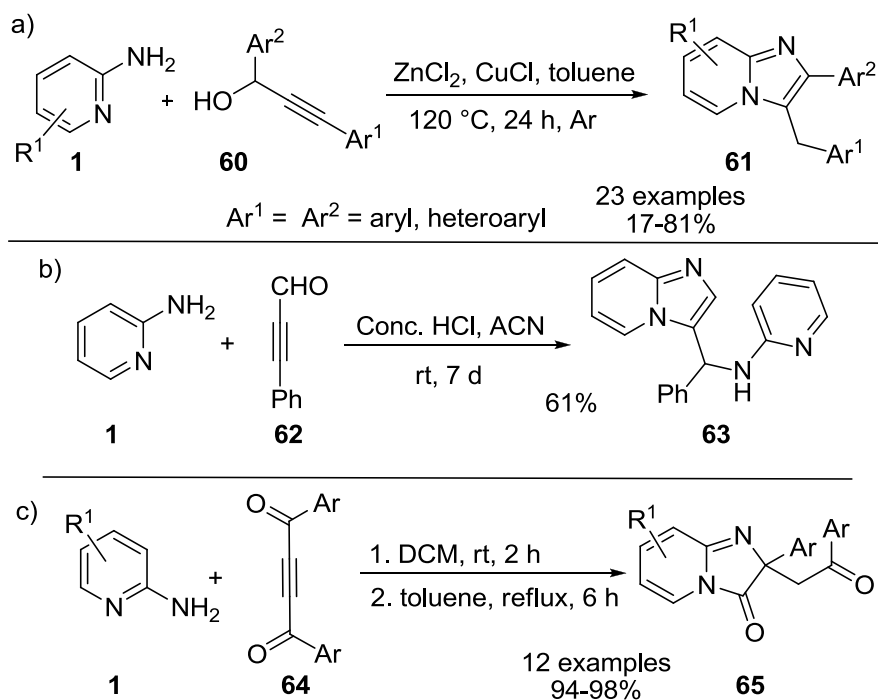
Scheme 1.23 Synthesis of imidazo[1,2-*a*]pyridines from alkyne analogues

1.3.8 Through Multi-component reactions

Multicomponent reactions are an efficient surrogates to linear multi-step conventional synthesis. They retain majority of the atoms of starting materials and thus provide high atom economy and complexity in the products in a single step. Moreover, low cost, reduction in overall reaction time and operational simplicity are the other advantages of multi-component reactions.

1.3.8.1 Three-component reaction of 2-aminopyridine (1), aldehyde (66) and isonitrile (67)

A Lewis/Bronsted acid catalyzed three-component reaction (3CR) of aldehyde, 2-aminopyridine and isonitrile known as Groebke–Blackburn–Bienaymé (GBB) reaction is an established method for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines (**13**) (**Scheme 1.24**).[87-89]
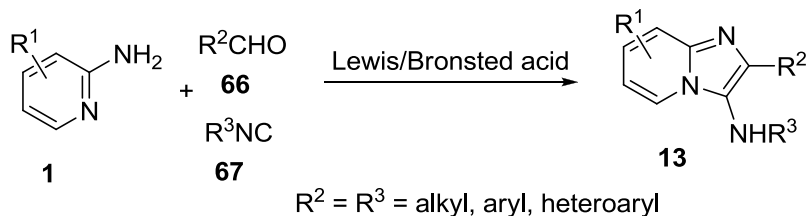
Scheme 1.24 Three component synthesis of 3-aminoimidazo[1,2-*a*]pyridines

Owing to the importance of these motifs in medicinal chemistry, several groups have modified the conventional procedure by varying the catalyst and reaction conditions.[90-107] For example, glyoxylic acid (**68**) was used as formaldehyde equivalent in the three-component reaction both in solution and solid-phase (**Scheme 1.25**).[108-109]
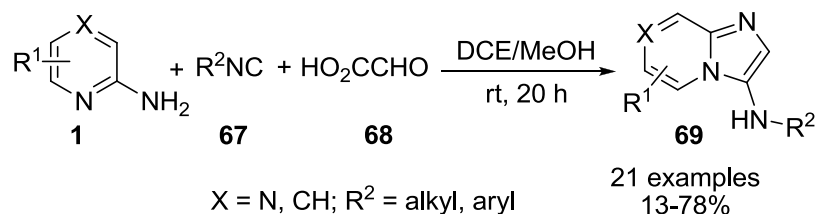
Scheme 1.25 3CR synthesis of imidazo[1,2-*a*]pyridines with glyoxylic acid as aldehyde

Propylphosphonic anhydride (T3P) was used as an effective and mild reagent for the one-pot synthesis of 3-aminoimidazo[1,2-*a*]pyridines (**13**) *via* 3CR (**Scheme 1.26a**). Alcohols (**70**) have been used in this strategy which were oxidized *in situ* to aldehydes by T3P/DMSO system and participated in three component reaction.[110] A three component reaction of benzyl halides/tosylates (**71**), 2-aminopyridines (**1**) and isocyanides (**67**) in presence of potassium carbonate was reported to yield imidazo[1,2-*a*]pyridines (**13**)(**Scheme 1.26b**). The benzyl halides are first converted to corresponding aldehydes under Kornblum oxidation conditions and the later was then involved in the 3CR.[111] Marandi and co-workers reported that simply heating the mixture of 2-amino-3-pyridinecarboxylic acid (**72**), aldehydes (**66**) and isonitriles (**67**) leads to the formation of corresponding 3-(alkylamino)imidazo[1,2-*a*]pyridine-8-carboxylic acids (**73**) in good to excellent yield (**Scheme 1.26c**).[112] The reaction proceeds under catalyst-free conditions as carboxylic acid attached to aminopyridine nucleus promoted the Ugi-type condensation. DiMauro and Kennedy have synthesized 5-boronic acid pinacol esters of imidazo[1,2-*a*]pyridine *via* microwave-assisted 3CR using MgCl$_2$ as catalyst (**Scheme 1.26d**). The resulted 5-boronic acid pinacol esters of imidazo[1,2-*a*]pyridines were subjected to Suzuki coupling with aryl halides to give 5-aryl-3-aminoimidazo[1,2-*a*]pyridines (**75**).[113]
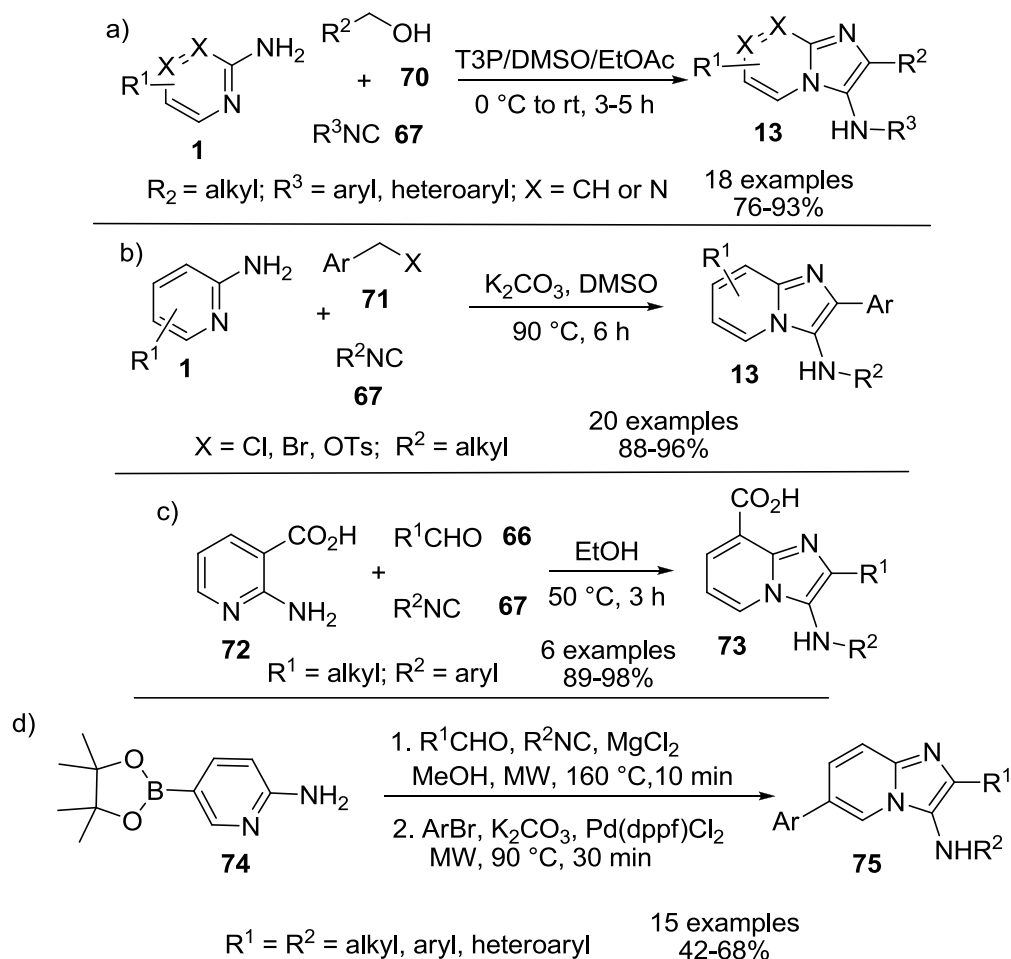
Scheme 1.26 3CR for the synthesis of 3-aminoimidazo[1,2-*a*]pyridine analogues

Hulme and group reported microwave-assisted polymer bounded Sc(OTf)$_3$ catalyzed syntheses of 3-iminoarylimidazo[1,2-*a*]pyridines (**76**) and imidazo[1,2-*a*]pyridyn-3-ylamino-2-acetonitriles (**77**) by employing 3-center-4-component and 3-center-5-component reactions where TMSCN was used as equivalent of isocyanide (**Scheme 1.27**).[114] The sequential 3CR reaction and Strecker reaction resulted the aforesaid motifs (**76 & 77**) in good yields. Outcome of the reaction was found to be depends on stoichiometry of reactants and reaction times. Other acidic reagents such as silica supported H$_2$SO$_4$,[115] MCM-41 supported boron trifluoride[116] and (bromodimethyl-sulfonium)bromide[117] have also been found to catalyze this reaction effectively to give 3-iminoarylimidazo[1,2-*a*]pyridines in good yields. A catalyst and solvent-free 3CR of 2-aminopyridines, aldehydes and imidazoline-2,4,5-trione (**78**) have also been reported to give excellent yield of 3-iminoarylimidazo[1,2-*a*]pyridines (**76**) (**Scheme 1.28**).[118]
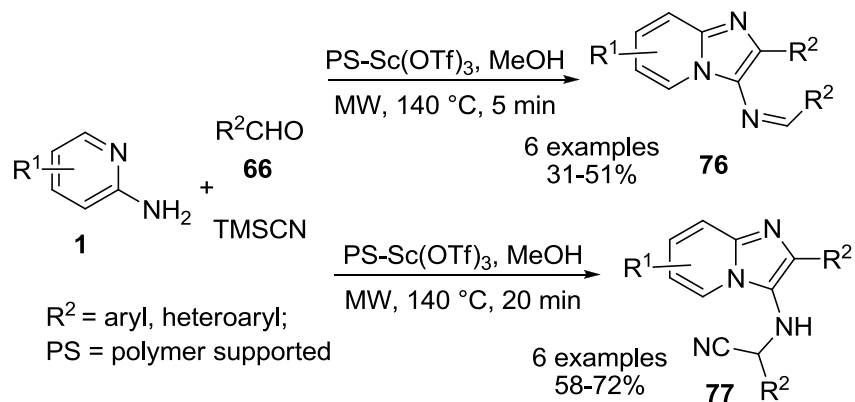
Scheme 1.27 Synthesis of imidazo[1,2-*a*]pyridines catalyzed by polymer supported Sc(OTf)$_3$
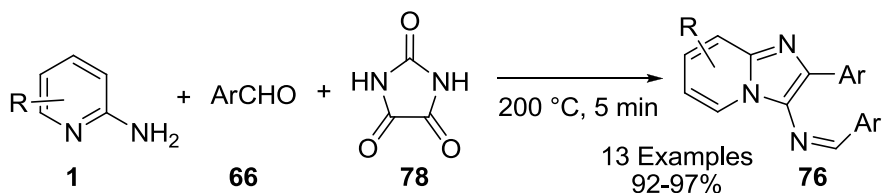
Scheme 1.28 3CR for the synthesis of 3-iminoarylimidazo[1,2-*a*]pyridines

1.3.8.2 Three component reaction of 2-aminopyridine, aldehyde and alkyne

A tandem reaction of aldehyde, amine and alkyne, commonly known as A^3-coupling is an efficient approach to access propargylamines.[119] The A^3-coupling has been successfully applied to access 3-alkylimidazo[1,2-*a*]pyridines (**61**) using catalytic amount of copper (**Scheme 1.29**).[120],[121] High functional group tolerance was observed in this method and it was extended to synthesize imidazopyridine based drugs, alpidem and zolpidem in good yields. It is believed that initially propargylamines (**79**) are formed from A^3 coupling and they further undergo an intramolecular cyclization through 5-*exo-dig* fashion followed by isomerisation to give imidazo[1,2-*a*]pyridine skeleton (**61**).

Recently, several reports have appeared with improved conditions of 3CR of aldehydes, alkynes and 2-aminopyridines for the synthesis of imidazo[1,2-*a*]pyridines.[122-127] Lee group disclosed a modified approach for the synthesis of imidazo[1,2-*a*]pyridines (**61**) *via* decarboxylative three-component reaction of 2-aminopyridines (**1**), aldehydes (**66**) and alkynecarboxylic acids (**80**) in presence of two fold copper catalytic system CuI/Cu(OTf)$_2$ (**Scheme 1.30**). The decarboxylative coupling proceeds smoothly with various alkynoic acids which are efficient surrogates of low-

molecular weight alkynes such as acetylene, propyne and butyne as they are gases at room temperature. When aryl alkynoic acids were synthesized *in situ* using standard palladium catalyzed cross-coupling conditions and then subjected to present protocol, good yields of 2-aryl-3-benzylimidazo[1,2-*a*]pyridines (**61**) were obtained. The one-pot procedure avoids the isolation of aryl alkynecarboxylic acids (**80**). Deuterated experiments have been performed to understand main reaction site of propiolic acid since there are two active positions present, terminal alkyne carbon and decarboxylative carbon. It was concluded that two pathways (I and II) are involved in the mechanism but path I, decarboxylative addition predominates over the other possibility.[128]
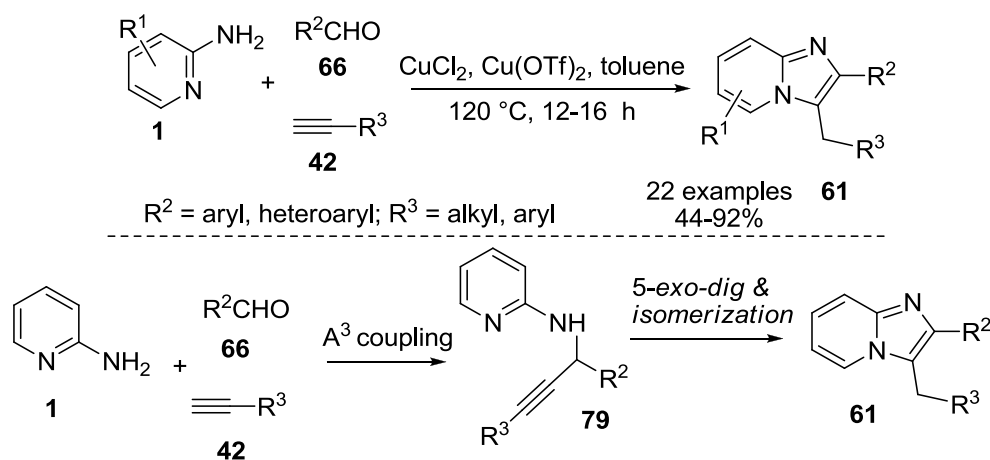
Scheme 1.29 Three component synthesis of 3-alkylimidazo[1,2-*a*]pyridines

1.3.8.3 Other multi-component procedures

Wei and colleagues disclosed a modified approach employing 3CR of 2-aminopyridines (**1**), ketones (**12**) and disulfides (**85**) for the synthesis of 3-sulfenylimidazo[1,2-*a*]pyridines (**86**) using CeCl$_3$.7H$_2$O/NaI catalytic system (**Scheme 1.31**).[129] In earlier methods, these motifs have been prepared from *pre*-synthesized imidazo[1,2-*a*]pyridines. High yields of 2-substituted imidazo[1,2-*a*]pyridines (**3**) were obtained in the absence of disulfides. It is believed that phenacyl iodide (**2**) is generated *in-situ* which then reacts with **1** and produces **3**. On other side, the disulfide (**85**) reacts with I$_2$ and generates electrophilic R^{3}SI species, which undergoes S$_E$Ar with imidazo[1,2-*a*]pyridines (**3**) to give desired frameworks (**86**).[129] Adimurthy and colleagues have synthesized these molecules through copper catalyzed aerobic oxidative C−H activation strategy.[130]
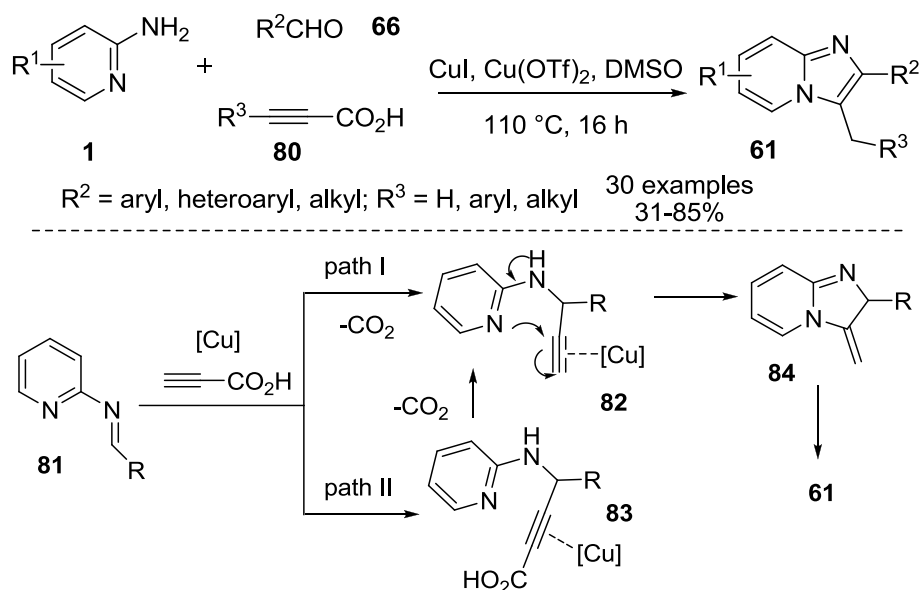
Scheme 1.30 Decarboxylative 3CR for the synthesis of imidazo[1,2-*a*]pyridines
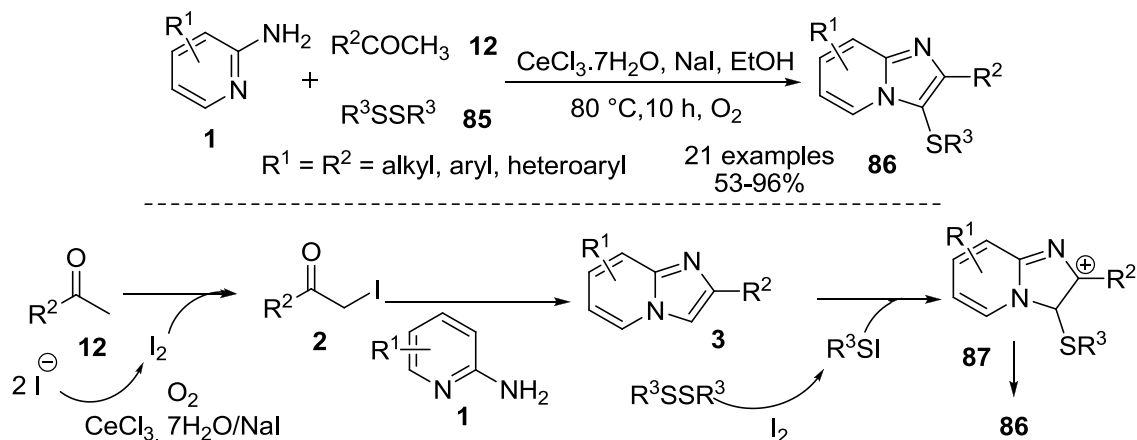
Scheme 1.31 3CR for the Synthesis of 3-sulfenylimidazo[1,2-*a*]pyridines

Li group proposed a novel one-pot method to construct imidazo[1,2-*a*]pyridines with hydroxy substitution at *C-3* position (**89**) by employing Petasis based tandem reaction (**Scheme 1.32**). It is proposed that the Petasis reaction between 2-aminopyridine (**1**), glyoxylic acid (**68**) and phenyl boronic acid (**88**) followed by intramolecular nucleophilic cyclization, dehydroxylation and aromatization results in the formation of 3-hydroxyimidazo[1,2-*a*]pyridines (**89**).[131]

Regiospecific synthesis of 3-functionalized imidazo[1,2-*a*]pyridines (**22**) was achieved by Cao and colleagues through three-component reaction of 2-aminopyridines (**1**), alkynals (**62**) and

alcohols (**90**) in the presence of acetic acid (**Scheme 1.33**). When alcohols were replaced with thiols and amines, the 3CR proceeded smoothly to furnish corresponding imidazo[1,2-*a*]pyridines (**22**) in excellent yields. Initially, ynal (**62**) and **1** reacts to give corresponding imine **91** in presence of AcOH, which is attacked by ethanol in Michael addition fashion leading to intermediate **92**. Intramolecular cyclization and proton transfer of **93** promoted by AcOH results the intermediate **94**, which on aromatization affords the target molecule (**22**).[132]
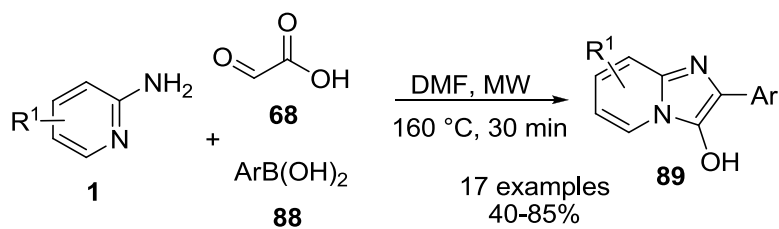
Scheme 1.32 Synthesis of 3-hydroxyimidazo[1,2-*a*]pyridines
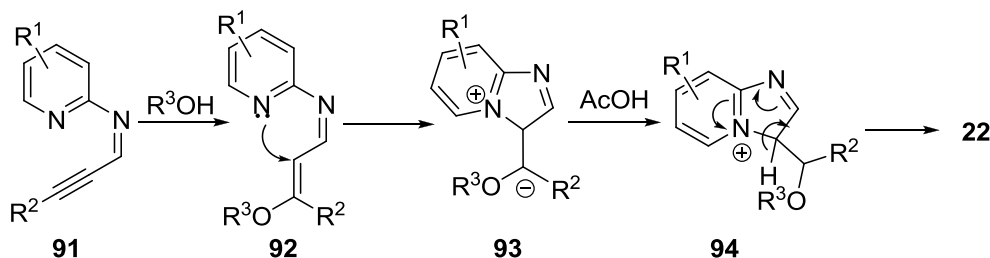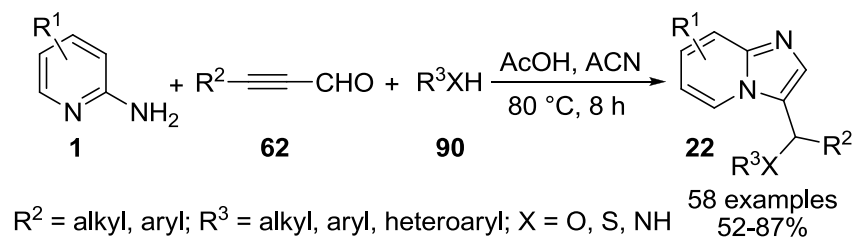
Scheme 1.33 Regiospecific synthesis of 3-functionalized imidazo[1,2-*a*]pyridines

1.3.9 Miscellaneous methods of 2-aminopyridines

Some other approaches where 2-aminopyridine was used as substrate for the synthesis of imidazo[1,2-*a*]pyridine skeleton are shown in **Scheme 1.34**. The reaction of amine **1** and hexafluoroacetone (**95**) followed by treatment with trimethylphosphite gave moderate to good yield of 3-fluoro-2-(trifluoromethyl)imidazo[1,2-*a*]pyridines (**96**) (**Scheme 1.34a**).[133] A [3+2] cyclizations of 2-aminopyridines (**1**) and 1,2-bis(benzotriazolyl)-1,2-(dialkyl-amino)ethanes (**97**)

resulted in the regioselective synthesis of 3-substituted imidazo[1,2-*a*]pyridines (**98**) (**Scheme 1.34b**).[134] Hamdouchi group disclosed a novel method to access 2-aminoimidazo[1,2-*a*]pyridines and studied their cyclin dependent kinase inhibition activities. Amine **1** was treated with *p*-tolylsulfonyl chloride followed by iodoacetamide in the presence of Hunig's base which afforded corresponding carbomide. By treating these carbomides with trifluorotoacetic anhydride offered 2-(*N*-trifluoro acetylamino)imidazopyridine (**99**) (**Scheme 1.34c**). Further reactions on these molecules resulted the functionalized scaffolds for biological evaluation.[135] Matsumoto group also synthesized these motifs (**99**) and evaluated them as a novel dual c-Met and VEGFR2 kinase inhibitors.[136] Rozentsveig *et al*. reported a highly efficient one-pot unprecedented protocol for the synthesis of *N*-(imidazo[1,2-*a*]pyridin-3-yl)sulfonamides (**101**) starting from 2-aminopyridines (**1**) (**Scheme 1.34d**). Nucleophilic addition of compound **1** to the azomethine group of *N*-(2,2-dichloro-2-phenylethylidene)arene sulfonamides (**100**) gave the *N*-[2,2-dichloro-2-phenyl-1-(2-pyridinylamino)-ethyl]sulfonamides which on smooth cyclization in alkali medium resulted to *N*-(imidazo[1,2-*a*]pyridin-3-yl)sulfonamides (**101**). However, expected *N*-(imidazo[1,2-*a*]pyridin-2-yl)sulfonamides were not detected in the reaction. Furthermore, the two step procedure has been carried out in one-pot to afford the imidazo[1,2-*a*]pyridines (**101**) in good yields.[137]

1.3.10 From *N*-substituted-2-aminopyridines

An efficient procedure for the synthesis of 2-methylthio/alkoxy/amino-3-aroylimidazo[1,2-*a*]pyridines (**103**) through copper catalyzed intramolecular oxidative cyclization of α-oxoketene *N,S-*, *N,O-*, and *N,N*-acetals (**102**) has been developed by Ila and co-workers (**Scheme 1.35**).[138] The acetals could be accessed conveniently by the displacement reactions of α-oxoketene *S,S*-acetals with the nucleophiles in presence of strong base such as *n*-BuLi and NaOMe. Initially, formation of radical cation intermediate **104** in presence of copper followed by proton loss affords the resonance stabilized aminyl radical **105**. Intramolecular cyclization of aminyl radical (**106**) followed by the elimination of hydrogen radical results in the formation of imidazo[1,2-*a*]pyridine derivatives (**103**).
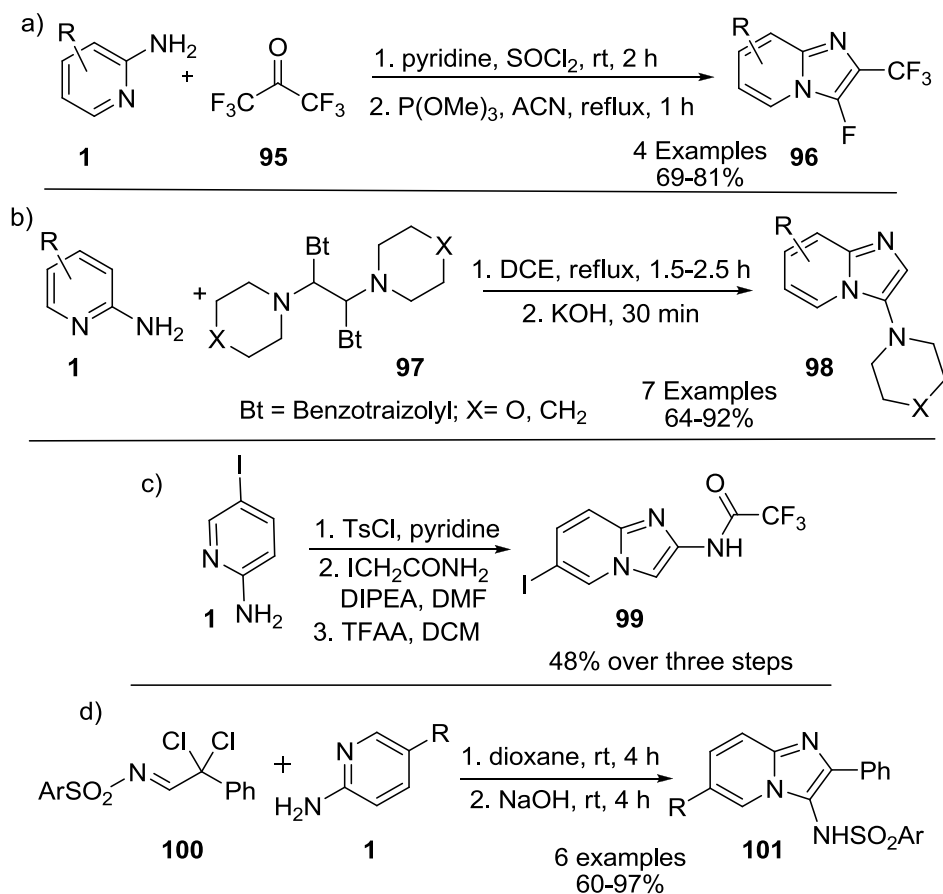
Scheme 1.34 Synthesis of diversely substituted imidazo[1,2-*a*]pyridines
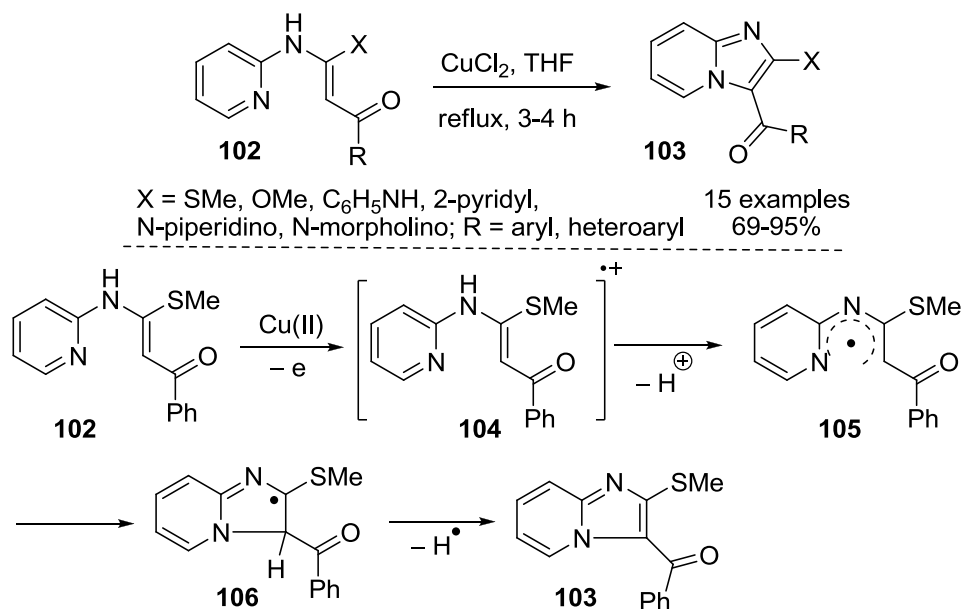
Scheme 1.35 Synthesis of 3-acetylimidazo[1,2-*a*]pyridines

Chioua *et al*. have described a silver catalyzed intramolecular cycloisomerization of *N*-(prop-2-yn-1-yl)pyridin-2-amines (**107**) as an efficient method to access 3-methylimidazo[1,2-*a*]pyridines (**108**) (**Scheme 1.36**).[139] Interestingly, *N*-Boc-*N*-propargyl-aminopyridines (**107**) underwent *in situ* deprotection and participated in annulation to offer good yields of fused azoles. The reported protocol is highly regioselective which afforded imidazo[1,2-*a*]pyridines (**108**) through *exo-dig* cyclization. However, precursors with internal alkynes followed *endo-dig* cyclization and delivered pyrido[1,2-*a*]pyrimidine analogues. Synthesis of 3-methylimidazo[1,2-*a*]pyridines (**108**) have also been achieved through a potassium *tert*-butoxide promoted intramolecular cyclization of the compound **107**.[140]
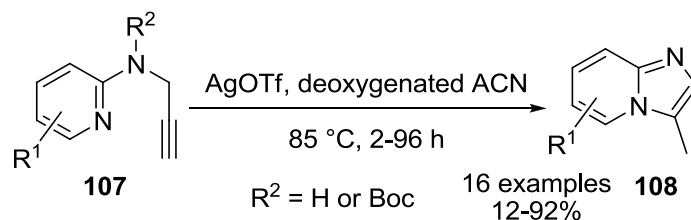
Scheme 1.36 Synthesis of imidazo[1,2-*a*]pyridines from *N*-propargyl 2-aminopyridines

An unexpected synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes (**110**) have been reported by intra-molecular dehydrogenative aminooxygenation of *N*-allyl-2-aminopyridines (**109**) in the presence of copper complex (**Scheme 1.37**).[141] This protocol has been successfully employed for the gram scale synthesis of imidazo[1,2-*a*]pyridine based drug, necopidem in a concise route. It is expected that copper coordinated *N*-(1-phenylallyl)-2-aminopyridine (**111**) forms peroxycopper(III) intermediate **112** in the presence of oxygen. Further, isomerization of **112** followed by elimination gives 2,3-dihydroimidazo[1,2-*a*]pyridine-3-carbaldehyde (**115**) which on aerobic oxidation results in the formation of imidazo[1,2-*a*]pyridine-3-carbaldehydes (**110**).

3-Alkylimidazo[1,2-*a*]pyridines (**108**) could be easily accessed by deprotective hydroamination of *N*-propargylaminopyridines (**107**) promoted by water.[142] The substrates with electron releasing groups on pyridine ring provided almost quantitative yields of corresponding 3-alkylimidazo[1,2-*a*]pyridines (**108**). On the other hand, imidazo[1,2-*a*]pyridine-3-carbaldehydes (**110**) were obtained when **107** was treated with AgNO$_3$, TMEDA in acetonitriles under oxygen atmosphere (**Scheme 1.38**).[143] It was proposed that the reaction of **107** with Ag$^+$ forms metal-

alkyne π-complex **116**, which on cyclization leads to intermediate **117**. Addition of oxygen to **117** generates organo silver peroxide **118**. Aromatization, subsequent isomerization and elimination of Ag(I) species produced the 3-formyl imidazo[1,2-*a*]pyridines (**110**).
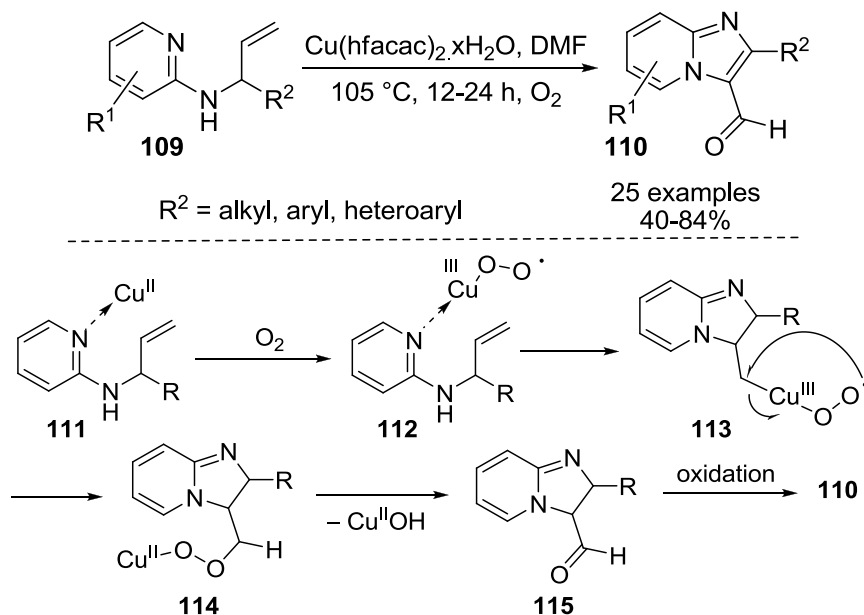
Scheme 1.37 Synthesis of imidazo[1,2-*a*]pyridines from *N*-allyl 2-aminopyridines
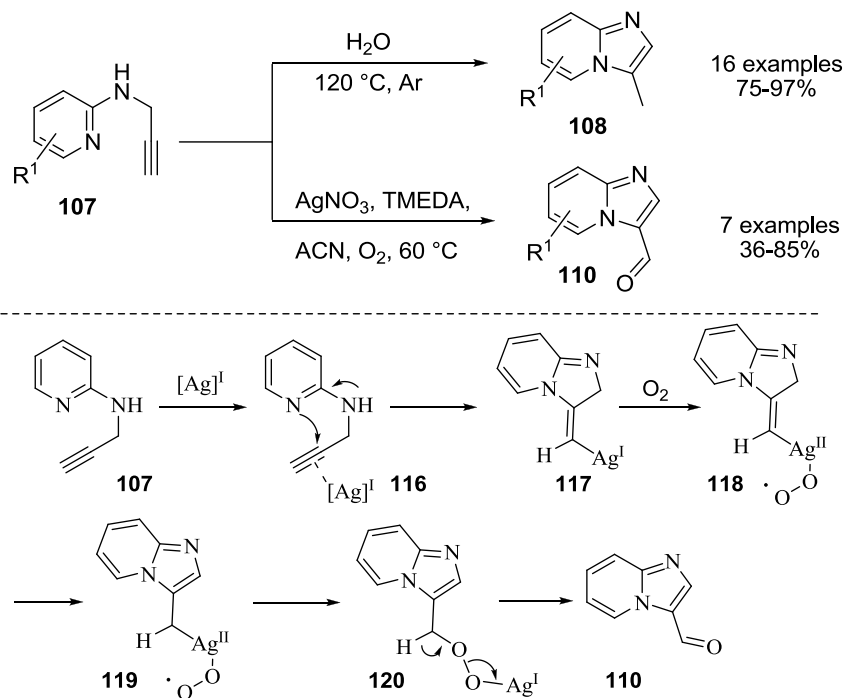
Scheme 1.38 Silver mediated synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes

Contelles *et al.* used a new and versatile precursor, *N*-(prop-2-yn-1-ylamino)pyridine-2-amine (**121**) for the synthesis of (*E*)-exo-halomethylene bicyclic pyridone containing imidazo[1,2-*a*]pyridines (**122**) *via* Sandmeyer reaction in presence of organic nitrite (**Scheme 1.39a**). It was also shown that these precursors led to good yields of *exo/endo*-methylene bicyclopyridones in the presence of Pd(OAc)$_2$, NaAuCl$_4$, PtCl$_2$, NIS or HCl/H$_2$O.[144] Bakherad and group reported tandem Sonogashira coupling and heterocyclisation for the synthesis of 2-benzylimidazo[1,2-*a*]pyridines (**124**) (**Scheme 1.39b**). The quaternization of 2-aminopyridine with propargyl bromide afforded 2-amino-1-(2-propynyl)pyridinium bromide (**123**). These salts on successive Sonogashira coupling followed by intramolecular cyclization offered the 2-benzyl imidazo[1,2-*a*]pyridines (**124**). It was found that electron withdrawing groups on aryl iodide was essential for the success of this reaction because in case of iodobenzene, 2-methylimidazo[1,2-*a*]pyridine is the major product which is the heterocyclization product without Sonogashira coupling.[145] The same group further extended their investigations and realized that this transformation can be performed in aqueous media in presence of sodium lauryl sulfate as a surfactant.[146]
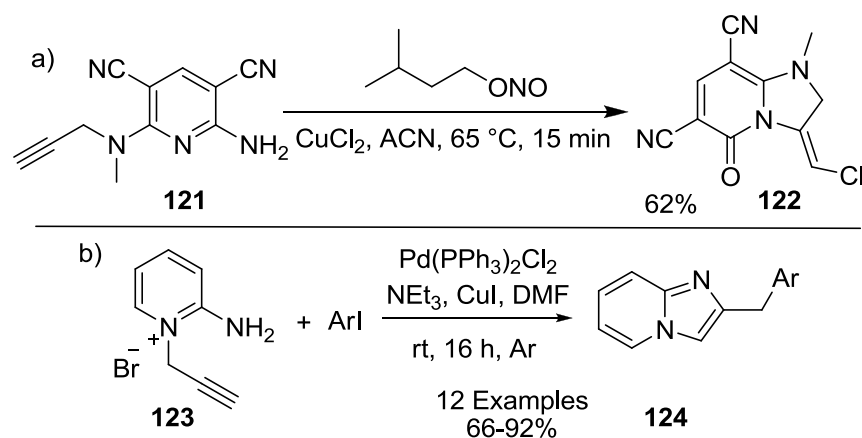
Scheme 1.39 Synthesis of imidazo[1,2-*a*]pyridines from diverse *N*-propargyl pyridyl amines

Zalesov and group synthesized imidazo[1,2-*a*]pyridine analogues (**126**) through the reaction of *N*-(2-pyridyl)-amides of *Z*-4-aryl-2-hydroxy-4-oxobut-2-enoic acids (**125**) and diazomethane (**Scheme 1.40**).[147] A reaction of 2-pyridylimines of methyl trifluoropyruvate (**127**) with trimethylphosphite resulted methyl 3-fluoro imidazo[1,2-*a*]pyridine-2-carboxylates (**128**) *via* deflourination of trifluoromethyl group and intramolecular ring closure (**Scheme 1.41a**).[148] On the other side, 3-fluoro-2-(diethoxy-phosphoryl)imidazo[1,2-*a*]pyridines (**130**) were obtained in

a one-pot reaction of *N*-(pyridin-2-yl)-2,2,2-trifluoroacetimidoyl chloride (**129**) with triethylphosphite (**Scheme 1.41b**).[149] The fluoro group at *C-3* position of imidazo[1,2-*a*]pyridines could be easily replaced by amines without the necessity of additional catalyst.
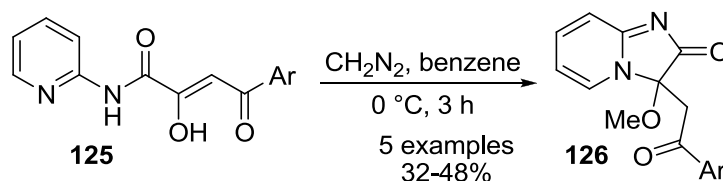
Scheme 1.40 Synthesis of imidazo[1,2-*a*]pyridines from CH_2N_2 and pyridyl amine analogues
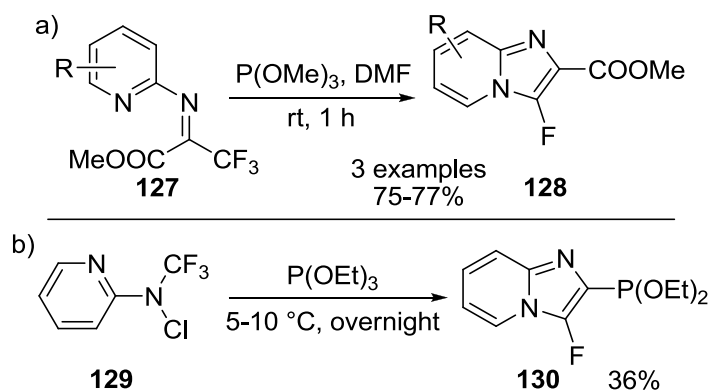
Scheme 1.41 Synthesis of 3-fluoro imidazo[1,2-*a*]pyridines

Zamora and co-workers synthesized 3-aroylimidazo[l,2-*a*]pyridines (**11**) by the treatment of *N'*-pyridylformamidine (**131**) with phenacyl bromides (**2**) (**Scheme 1.42a**). High yields have been obtained in DMF or under solvent-free conditions.[150] Schmitt and co-workers reported a novel method for the synthesis of functionalized imidazo[1,2-*a*]pyridines (**7** or **11**) (**Scheme 1.42b**). This procedure involved the activation of secondary amide of 2-aminopyridine (**132**) by $TiCl_4$ or PCl_5 followed by reacting with α-halo active methylene compounds like ethyl bromoacetate and phenacyl bromides to deliver 3-acyl/aroyl functionalized imidazo[1,2-*a*]pyridines (**11**) in good yields.[151]

1.4 Synthesis of Imidazo[1,2-*a*]pyridines from Pyridines

Imidazo[1,2-*a*]pyridines are synthesized by the reaction of pyridines (**133**) with *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines (**134**) through a copper catalyzed cascade reaction involving N−N

bond cleavage of *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amine and C$_2$−H activation of pyridine ring (**Scheme 1.43**).[152]
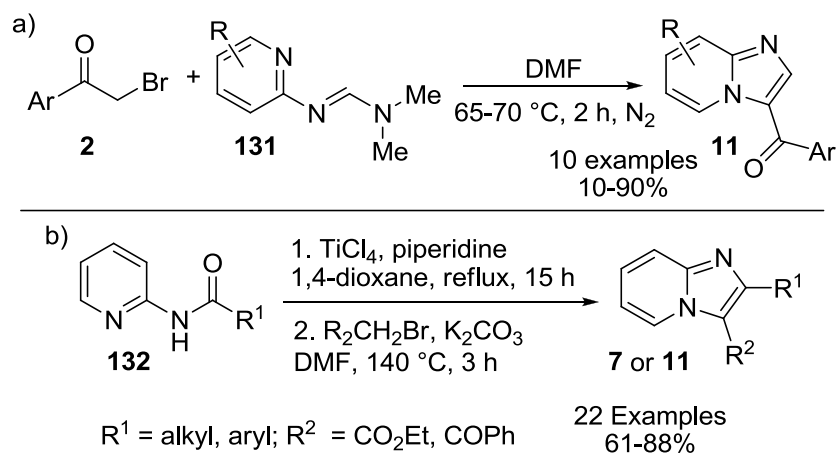
Scheme 1.42 Synthesis of 3-aroylimidazo[1,2-*a*]pyridines
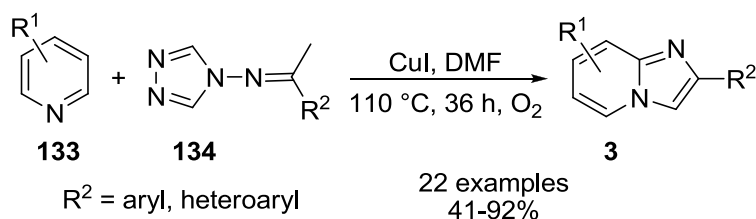
Scheme 1.43 Synthesis of imidazo[1,2-*a*]pyridines from pyridines and triazolylamines

Mantellini *et al.* reported a solvent-free synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates (**7**) by reacting pyridines (**133**) with 1,2-diaza-1,3-dienes (**135**) (**Scheme 1.44**).[153] When quinolines and isoquinolines were used in place of pyridine corresponding imidazo[1,2-*a*]quinolines, and imidazo[2,1-*a*]isoquinolines were obtained in good yields. The reaction is believed to proceed *via* Michael-type nucleophilic addition of pyridine nitrogen to 1,2-diaza-1,3-dienes giving non-isolable zwitter ionic hydrazone intermediate **136**. Proton transfer followed by nucleophilic attack of hydrazone to the pyridinium ion leads to imidazoline derivative **138**. Finally, aromatization by the elimination of carbomate through N−N bond cleavage affords substituted imidazo[1,2-*a*]pyridines (**7**). Despite two suitable *α*-positions in isoquinolines, cyclization occurred at C-1 position regioselectively to give imidazo[2,1-*a*]isoquinolines as a single product. Imidazo[1,2-*a*]pyridines (**140**) have been synthesized by a copper catalyzed aerobic dehydrogenative cyclization of pyridines (**133**) and ketone oxime esters (**139**) (**Scheme 1.45**). An

array of imidazo[1,2-*a*]pyridines and imidazo[2,1-*a*]isoquinolines with diverse substitutions were obtained by direct C−H functionalization of pyridines and isoquinolines. Oxidative insertion of Cu[I] to oxime esters affords intermediate **141**. Insertion of **133** into **141** with a new Cu−N bond formation gives **143**. Tautomerization followed by C-Cu bonding leads to six-membered copper ring **144**. Finally, reductive elimination and oxidative aromatization results in formation of imidazo[1,2-*a*]pyridines (**140**).[154]
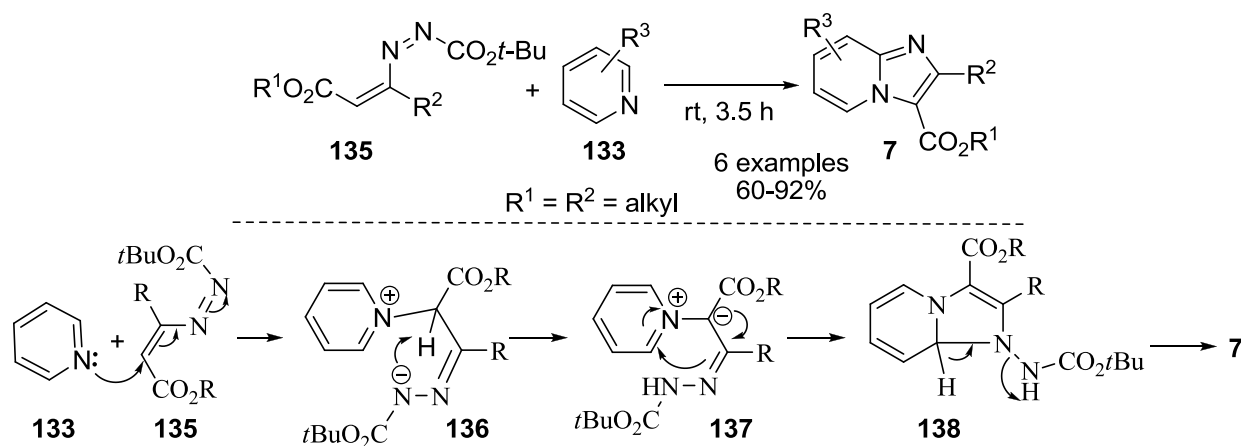
Scheme 1.44 Synthesis of imidazo[1,2-*a*]pyridines from pyridines and 1,2-diaza-1,3-dienes

Imidazo[1,2-*a*]pyridines and indolizines were prepared through the cyclization of *in-situ* generated aromatic cyclo iminium ylides with electron deficient nitriles and alkynes, respectively in the presence of K$_2$CO$_3$ (**Scheme 1.46**).[155] Initially, phenacyl bromides (**2**) were treated with pyridine (**133**) to obtain pyridinium salt which produced ylide in presence of base. These ylides underwent smooth cyclization with nitriles and alkynes followed by aromatization affording highly substituted imidazo[1,2-*a*]pyridines and indolizines in good yields.

1.4.1 MCR involving pyridines

Motevalli group disclosed an interesting method for the construction of imidazo[1,2-*a*]pyridine skeleton (**3**) by one-pot solvent-free, three component reaction of phenacyl bromide (**2**), pyridine (**133**) and urea or thiourea (**147**) as a source of nitrogen under microwave irradiation (**Scheme 1.47**).[156] It was proposed that nucleophilic attack of pyridine to phenacyl bromide produces pyridinium salt **148** which on subsequent reaction with urea affords intermediate **149**. Finally,

cyclization by elimination of HBr (**150**) and aromatization by the removal of formamide furnishes imidazo[1,2-*a*]pyridines (**3**).
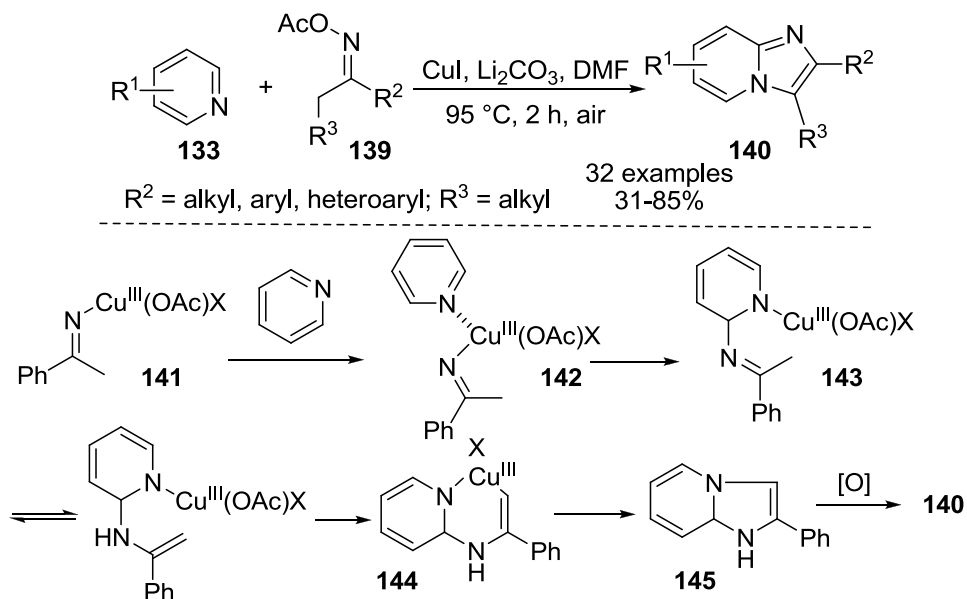
Scheme 1.45 Synthesis of imidazo[1,2-*a*]pyridines from pyridines and ketone oxime esters
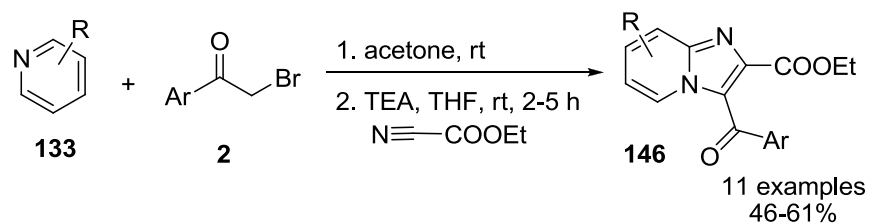
Scheme 1.46 Synthesis of imidazo[1,2-*a*]pyridines through cyclic iminium ylides
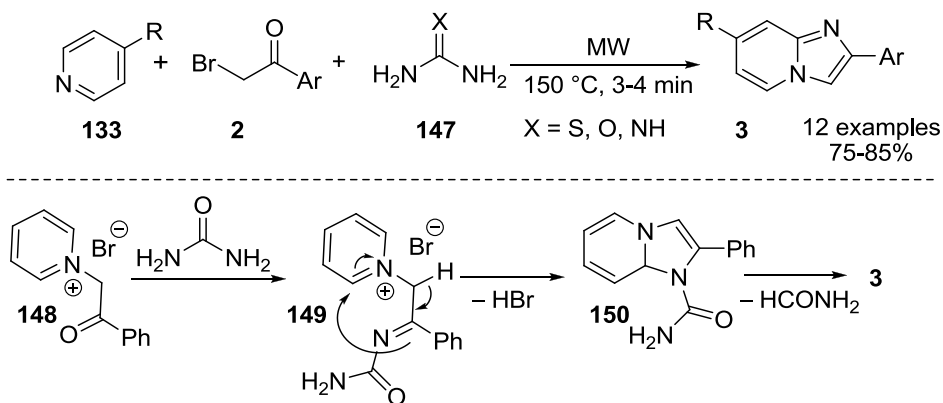
Scheme 1.47 Synthesis of imidazo[1,2-*a*]pyridines by urea as a nitrogen source

A one-pot, 3CR of pyridine (**133**), phenacyl bromide (**2**) and thiocyanate (**151**) have been developed for the synthesis of 2-(alkylsulfinyl)-3-aroylimidazo[1,2-*a*]pyridines (**152**) (**Scheme 1.48a**).[157] In case of 3-substitued pyridines the hindered *ortho*-position was attacked by the imine anion for the construction of an imidazole ring. Perumal and co-workers reported a one-pot, three component reaction of pyridine (**133**), phenacyl bromide (**2**) and (*E*)-*N*-hydroxyarylimidoyl chloride (**153**) in the presence of triethylamine to yield imidazo[1,2-*a*]pyridines (**3**) in excellent yield (**Scheme 1.48b**).[158]
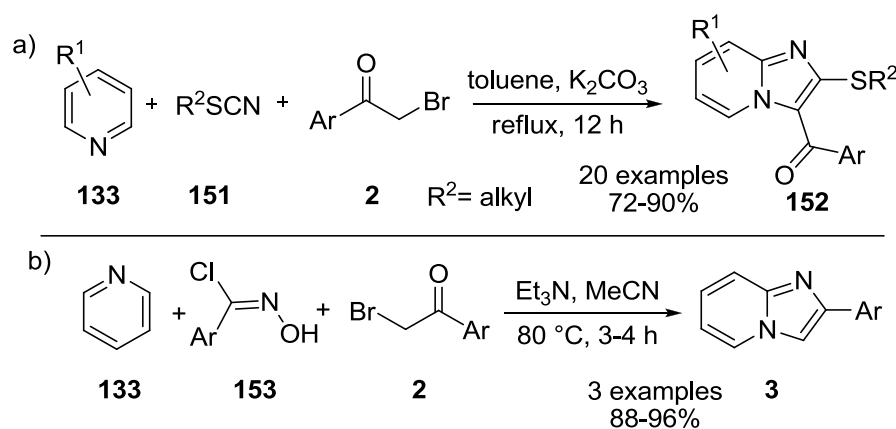
Scheme 1.48 Synthesis of imidazo[1,2-*a*]pyridine analogues using 3CR

N-Fluoropyridinium salts are versatile and reactive species used for introducing various functionalities such as hydroxy, amido, phosphonio, heteroaryl and aryloxy groups at C-2 position of pyridines. Kiselyov reported a new route for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines by the 3CR reaction of *N*-fluoropyridinium salts (**154**), isonitriles (**67**) and acetonitrile/propionitrile (**155**) in the presence of NaBH(OAc)$_3$ (**Scheme 1.49**).[159] 2-Acetamidopyridines were found to be major by-products in this reaction. Substitutions on nitriles and isonitriles did not affect the outcome of three-component process but strong electron donating as well as withdrawing groups on *N*-fluoropyridinium salt highly influenced the yield of desired products through the formation of byproduct, 2-acetamidopyridines. This protocol was successfully applied to quinolinium and isoquinolinium salts to afford corresponding fused imidazoles in good yields. It was proposed that proton abstraction from C-2 of pyridinium salt by base leads to reactive carbene intermediate **156**. Then, carbene undergoes subsequent reaction with nitrile to afford nitrilium ylide **157**. Addition of isonitrile followed by cyclization affords

bicyclic pyridinium species **159**. Zwitter ion is generated by reduction of **159** with NaBH(OAc)$_3$ followed by aromatization to give the desired fused imidazoles (**13**).[160]
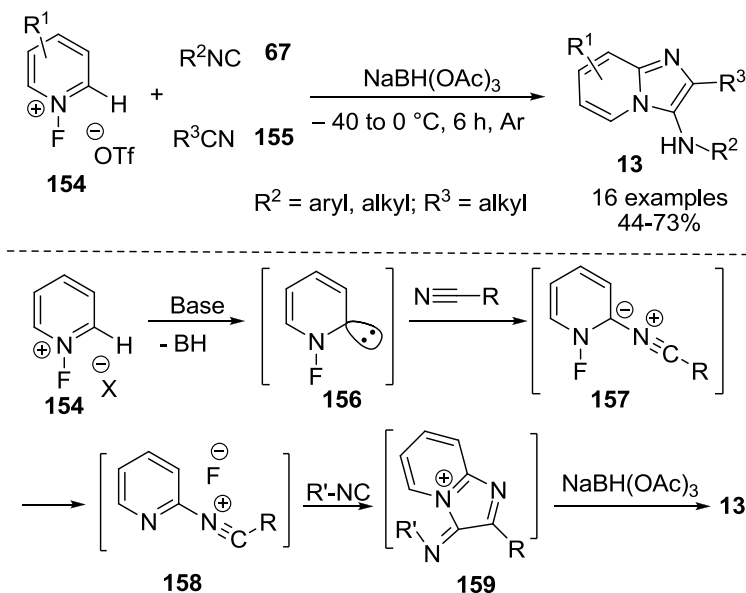
Scheme 1.49 Synthesis of imidazo[1,2-*a*]pyridines from *N*-Fluoropyridinium salts

Deyanov and Konshin synthesized 3-hydroxy imidazo[1,2-*a*]pyridines (**89**) by the reaction of 2-chloro-5-ethoxycarbonyl-6-methylnicotinonitrile (**160**) with *α*-amino acids (**161**) (**Scheme 1.50a**).[162] Cheng and co-workers developed a novel one-pot procedure by utilizing *β*-lactam carbenes (**162**) and 2-pyridyl isonitriles (**163**) for the synthesis of 2-carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines (**164**) (**Scheme 1.50b**). These motifs have been studied as an efficient fluorescent probes for mercury ion.[163]

1.5 Synthesis of Imidazo[1,2-*a*]pyridines from Imidazoles

A few reports have appeared for the synthesis of imidazo[1,2-*a*]pyridines starting from imidazole analogues. Dong *et al.* developed rhodium catalyzed direct oxidative coupling between alkenes (**165**) and internal alkynes (**54**) for the synthesis of aza-fused heterocycles, imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]benzimidazoles (**166**) through sp^2 C−H functionalization (**Scheme 1.51**). The reported protocol has found broad substrate scope as alkynes with aryl, alkyl and heteroaryl groups smoothly participated to produce respective fused azoles in excellent yields. Moderate regioselectivities were found in the case of unsymmetrical alkynes.[164]
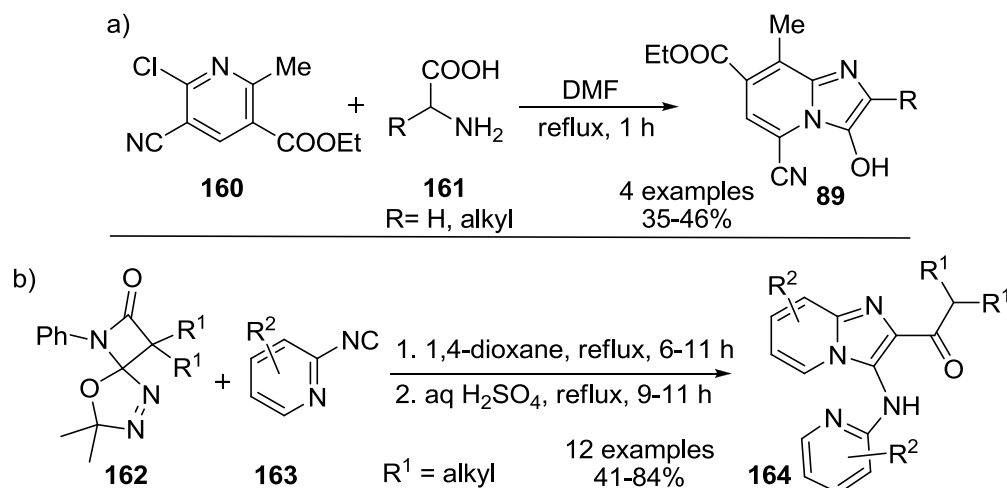
Scheme 1.50 Synthesis of imidazo[1,2-*a*]pyridines starting from pyridine analogues
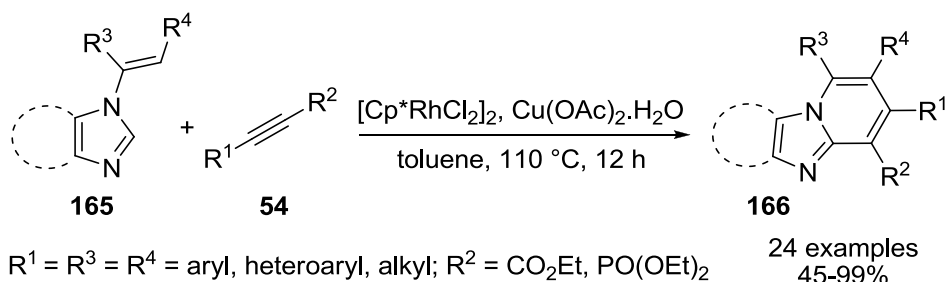
Scheme 1.51 Rhodium catalyzed oxidative coupling to access imidazo[1,2-*a*]pyridines

Muthusubramanian group presented an effective catalyst and solvent-free procedure for the synthesis of 2,8-diaryl-6-aminoimidazo[1,2-*a*]pyridines (**169**) through microwave assisted benz-annulation of dialkylamines (**168**) and imidazole analogues (**167**) (**Scheme 1.52a**). This method has found wide substrate scope and also applied to the synthesis of indolizines.[165] Kerwin and Nadipuram synthesized imidazo[1,2-*a*]pyridines (**171**) by thermal cyclisation of dialkynyl imidazoles (**170**) in presence of chlorinated solvents (**Scheme 1.52b**). These products were also obtained in presence of HCl/DMF or TFA/Me4NCl/DMF system. Longer reaction times and formation of byproducts are the major disadvantages of this method.[166]

Kiselyov described regioselective synthesis of imidazo[1,2-*a*]pyridines (**175**) from α,β-unsaturated imines (**173**) (generated *in situ* by the reaction of aldehyde and nitriles) and dianions (**174**) derived from methyl azolyl acetates (**Scheme 1.53**). It was believed that the reaction proceeds through initial formation of α,β-unsaturated imines (**173**) that undergoes nucleophilic

attack by 1,3-dianion (**174**). This is followed by cyclisation and aromatization to yield polysubstituted imdazo[1,2-*a*]pyridine derivatives (**175**). This protocol was further extended to the synthesis of fused tricyclic systems (**177**) by reaction of the intermediate (**173**) with dianions (**176**) derived from 2-indolyl/benzimidazolyl methyl acetates.[167]
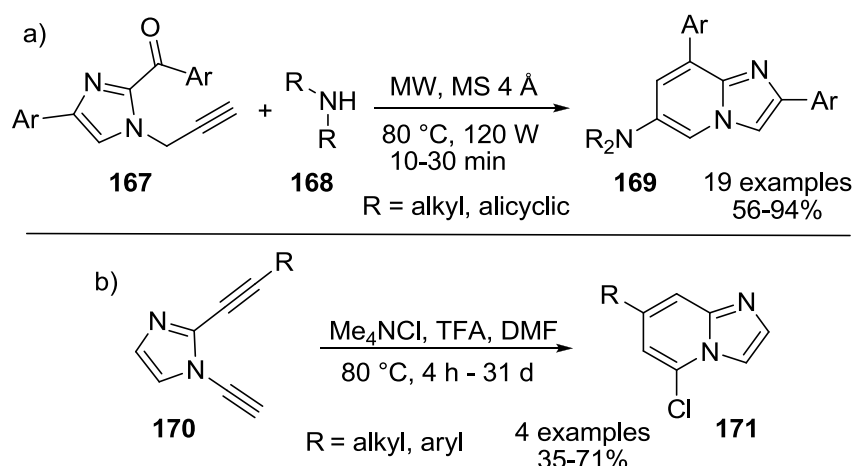
Scheme 1.52 Synthesis of imidazo[1,2-*a*]pyridines from alkynyl imidazoles
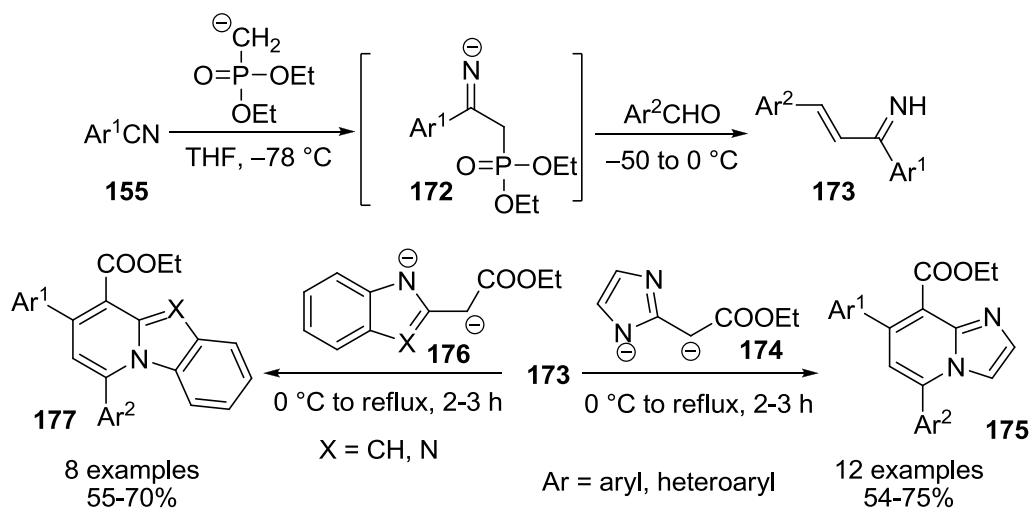
Scheme 1.53 Synthesis of imidazo[1,2-*a*]pyridines from α,β-unsaturated imines

Heterocyclic ketene aminals (HKAs) have been thoroughly employed for the construction of imidazo[1,2-*a*]pyridines. Ram and colleagues disclosed the synthesis of imidazo[1,2-*a*]pyridine derivatives (**180**) by the reaction of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles (**178**) with imidazoliden-2-ylidene nitromethane (**179**) (**Scheme 1.54**).[168]
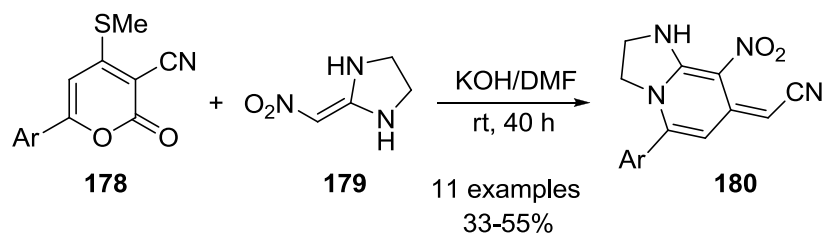
Scheme 1.54 Synthesis of imidazo[1,2-*a*]pyridines from HKAs

Li and Wen group has published several articles for the synthesis of imidazo[1,2-*a*]pyridines starting from HKAs. An efficient four-component cascade reaction of HKAs (**181**), diketene (**183**), aldehydes (**66**) and amines (**182**) in presence of Et₃N afforded imidazo[1,2-*a*]pyridine analogues (**184**) in moderate to good yields (**Scheme 1.55**). The proposed cascade reaction was expected to proceeds *via* diketene ring opening by amines followed by Knoevenagel condensation, aza-ene reaction, and cyclization. This methodology was smoothly extended to the one-pot synthesis of imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives (**186**).[169] The same group has developed a DABCO catalyzed tandem annulations of HKAs (**185**) and electron-deficient allenic esters (**187**) to access imidazo/pyrido[1,2-*a*]pyridines (**188**), which can be further cyclized in presence of base to give imidazo/pyrido[3,2,1-*ij*][1,8]naphthyridines (**189**) (**Scheme 1.56**).[141]
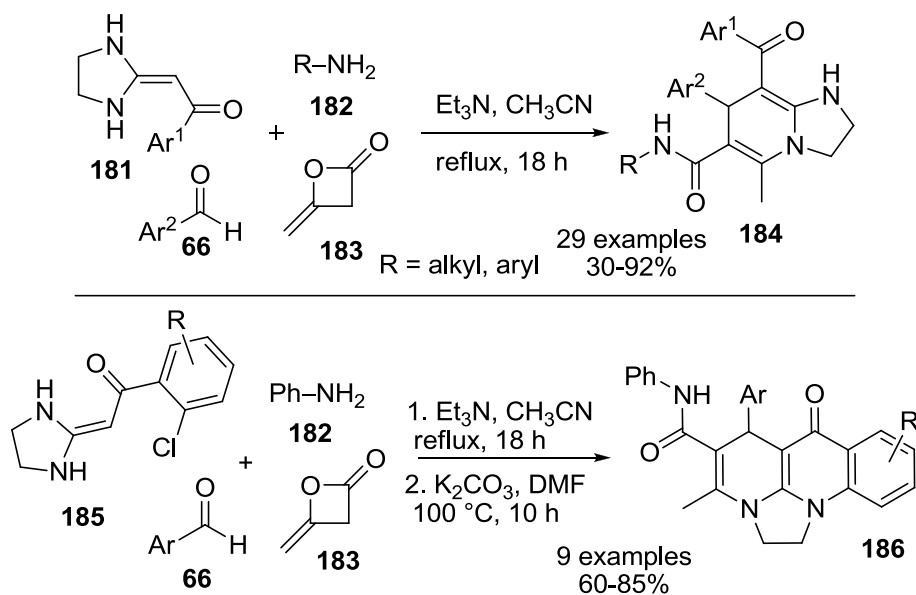
Scheme 1.55 Four component cascade synthesis of imidazo[1,2-*a*]pyridines
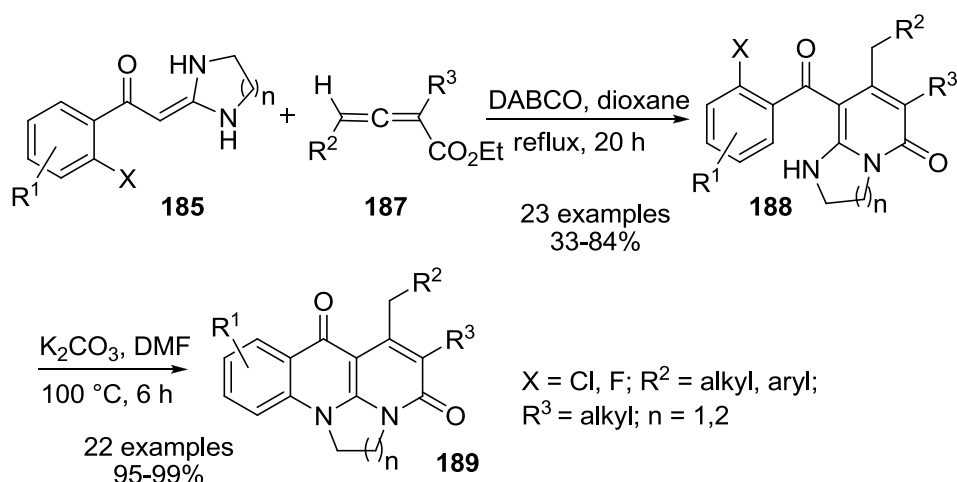
Scheme 1.56 DABCO catalyzed annulation of HKAs to access imidazo[1,2-*a*]pyridines

In other case, when ortho-haloaryl HKAs (**185**) reacted with aldehydes (**66**) and active methylene compounds (**190**) in presence of triethylamine, tetrahydroimidazo[1,2-*a*]pyridines (**191**) are obtained in good yields. These products on further cyclization afforded benzo-[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines (**192**) *via* nucleophilic substitution in presence K_2CO_3 (**Scheme 1.57a**).[170] They further described a highly efficient and regioselective method for the synthesis of imidazo[1,2-*a*]pyridines (**194**) through cyclization of HKAs (**181**) with β-oxodithioesters (**192**) and aldehydes (**66**) in presence of Et_3N under solvent-free conditions (**Scheme 1.57b**).[171]
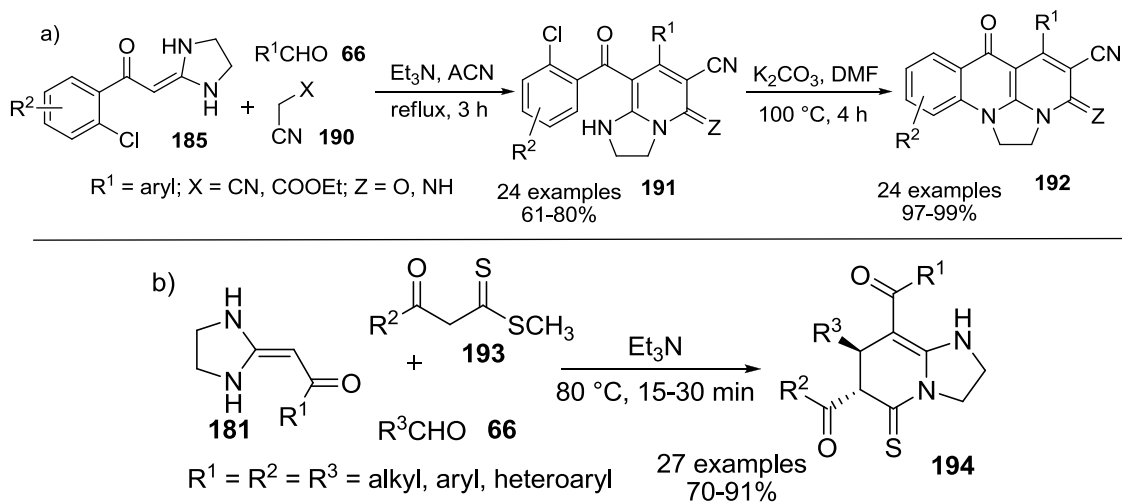
Scheme 1.57 Three-component synthesis of imidazo[1,2-*a*]pyridines from HKAs

Lin group demonstrated an acetic acid promoted one-pot reaction of heterocyclic ketene aminals (**181**) and 4-arylmethylene-2-phenyloxazol-5(4*H*)-ones (**195**) for the synthesis of imidazo[1,2-*a*]pyridine derivatives (**196**) under mild reaction conditions (**Scheme 1.58a**).[172] It was mentioned that HKAs bearing electron-withdrawing groups offered higher yields of fused heterocycles than those with electron-rich substituents. The optimized method was greatly extended to six and seven membered HKA to deliver pyrido[1,2-*a*]pyrimidines and pyrido[1,2-*a*][1,3]diazepine analogues in good yields. Recently, the same group presented an efficient method for the synthesis of tetrahydro imidazo[1,2-*a*]pyridines (**198**) *via* three-component reaction of HKAs (**181**), triethylorthoformate (**197**) and nitroolefins (**29**) under catalyst and solvent-free conditions. This method was practical and offered an array of imidazo[1,2-*a*]pyridine analogues (**198**) in good to excellent yields (**Scheme 1.58b**).[173]

Orlov group presented a novel approach to access imidazo[1,2-*a*]pyridine analogues (**200**) by reacting HKAs (**181**) with dimethyl acetylenedicarboxylate (**199**) (**Scheme 1.58c**).[174] Hammouda *et al.* disclosed a straightforward access to *N*-fused heterocycles (**202**) through the reaction of arylidene-malononitriles (**201**) with nitromethylene substituted cyclic diaminals (**179**) (**Scheme 1.58d**).[175] Gratifyingly, these imidazo[1,2-*a*]pyridines could be prepared in good yields by the one-pot reaction of aldehydes (**66**), malononitrile (**190**) and 2-(nitromethylene) imidazolidine (**179**).

Dabiri and co-workers developed a four-component approach for the synthesis of imidazo[1,2-*a*]pyridines (**206**) by condensing ethane-1,2-diamine (**205**), 1,1-bis(methyl-thio)-2-nitroethene (**203**), aldehydes (**66**) and active methylene compounds (**204**) under catalyst-free conditions (**Scheme 1.59a**). HKAs were generated *in situ* and reacted with Knoevenagel adduct, of **66** and **204**, followed by cyclization and dehyration resulted in the formation of imidazo[1,2-*a*]pyridines (**206**) in good yields.[176] Barluenga *et al.* reported regio- and stereoselective [6+3] heterocyclization of readily available 6-dimethylamino-1,4-diazafulvene (**207**) with alkenyl Fischer carbene complexes (**208**) to access dihydroimidazo[1,2-*a*]pyridines followed by acid promoted amine elimination to give aromatic imidazo[1,2-*a*]pyridines (**209**) (**Scheme 1.59b**).[177]

a)

R[1] = aryl; R[2] = aryl, heteroaryl

32 examples
71-90%

b)

25 examples
73-90%

c)

4 examples
50-92%

d)

4 examples
67-83%
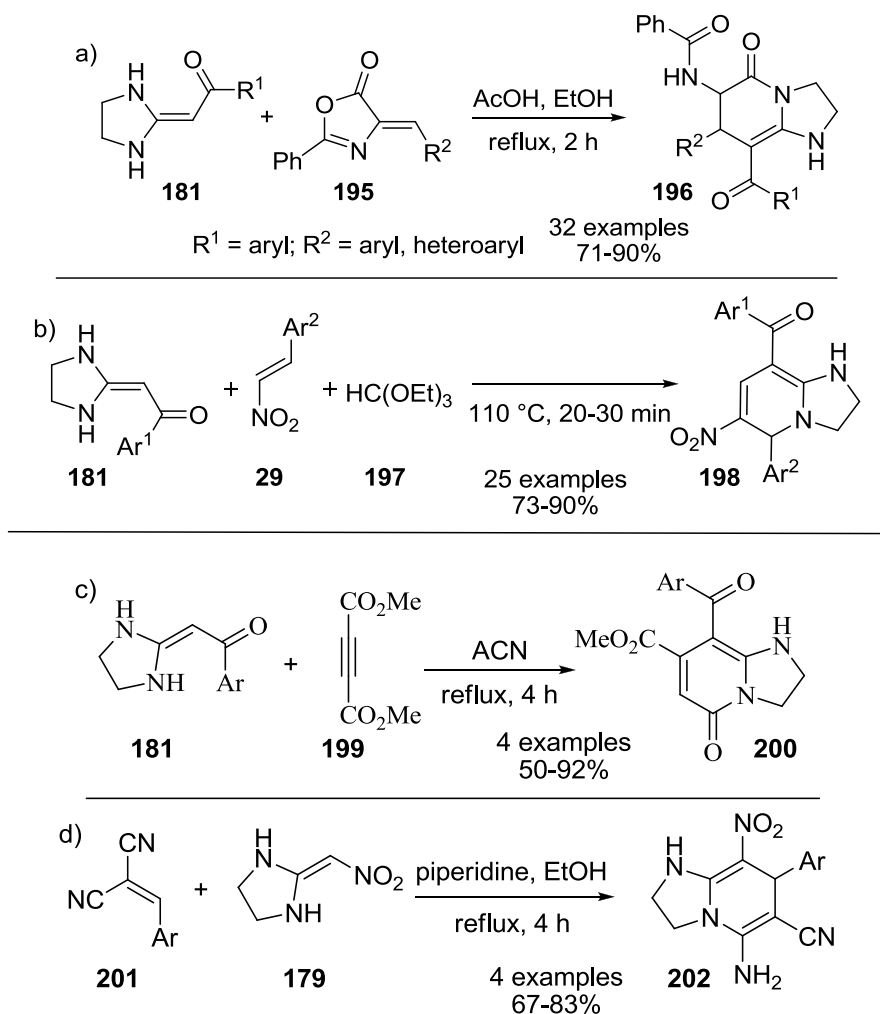
Scheme 1.58 Synthesis of imidazo[1,2-*a*]pyridine analogues from HKAs

a)

4 examples
65-83%

b)

R = 2-furyl; M = Cr

62% overall yield
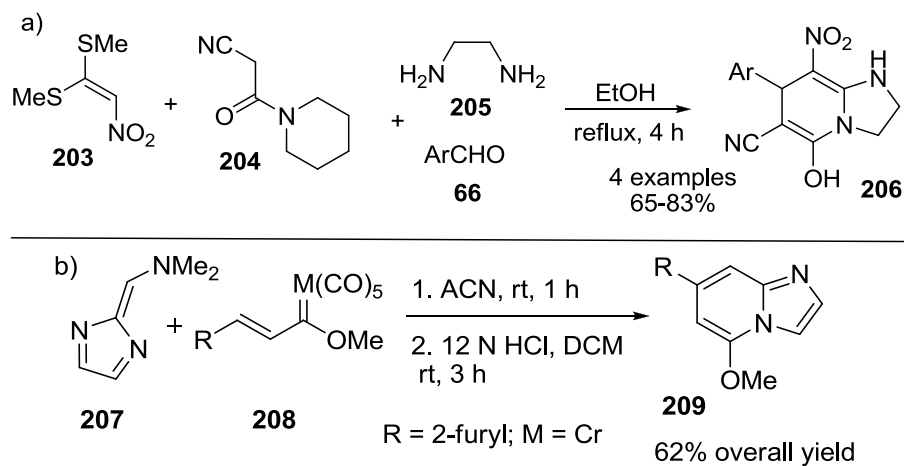
Scheme 1.59 Synthesis of imidazo[1,2-*a*]pyridines using HKAs

1.6 Other Miscellaneous Procedures

A set of reports have collectively shown that when aminoisooxazolones with *N*-pyridyl substitution (**210**) are heated in presence of mild base such as K_2CO_3 or Et_3N, they rearrange to imidazo[1,2-*a*]pyridines through ring opening mechanism. Prager *et al.* reported K_2CO_3 mediated rearrangement of 2-aryl-3-arylaminoisoxazol-5(2*H*)-ones (**210**) to imidazo[1,2-*a*]pyridines (**211**) and indoles (**214**) (**Scheme 1.60**). The substituents on aryl ring was greatly influenced the mode of cyclization. The major product of this rearrangement reaction was imidazo[1,2-*a*]pyridines (**211**). When substrates with electron rich aryl ring was subjected, indoles (**214**) have obtained in significant quantities together with imidazo[1,2-*a*]pyridines (**211**). It was reported that weak base favours tautomerism of **210** to **212** which follows the solvolysis to afford 1,3-dipolar intermediate **213**. Charge delocalization of substituent group will influence the cyclization at either side to produce imidazo[1,2-*a*]pyridine (**211**) and indole (**214**).[178] The same year, Khalafy and group reported the triethylamine catalyzed rearrangement of 2-(5-nitropyrid-2-yl)-3-(4-aryl)aminoisoxazol-5(2*H*)-ones (**210**) for the synthesis of imidazo[1,2-*a*]pyridine (**211**) and indoles (**214**).[179]
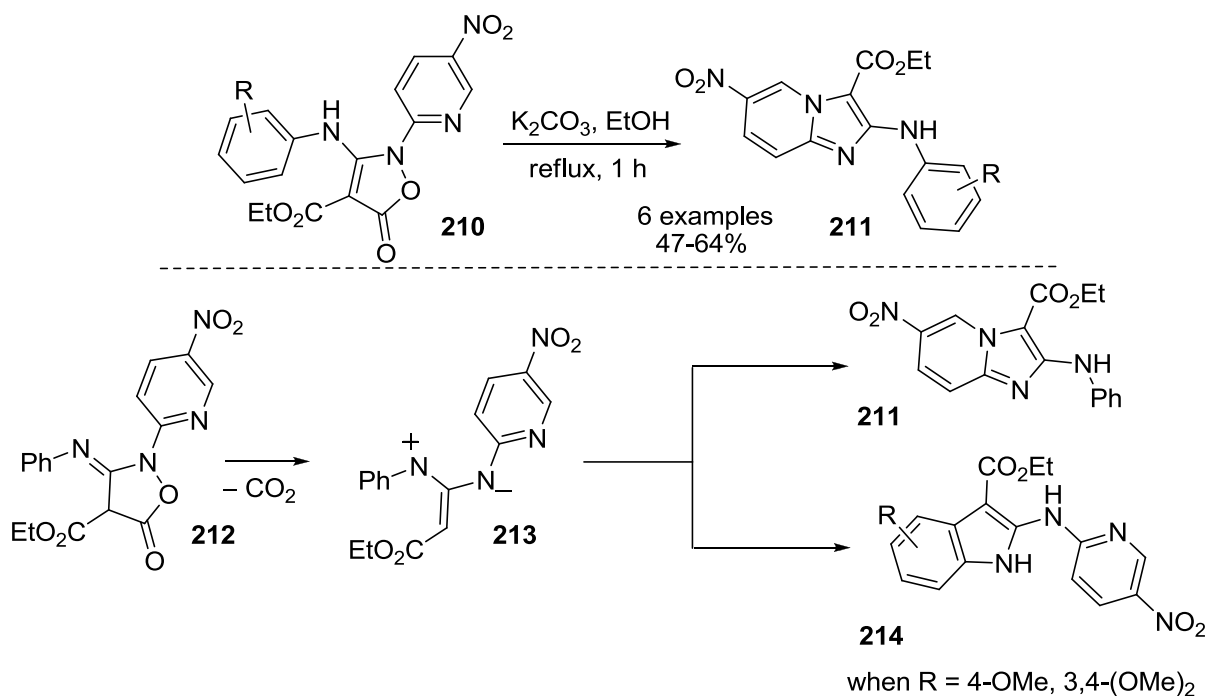
Scheme 1.60 Rearrangement of isooxazolines to imidazo[1,2-*a*]pyridines

Few other reports have also found for the aforesaid rearrangement with an improved reaction conditions.[180-182] Li and co-workers disclosed the synthesis of imidazo[1,2-*a*]pyridine derivatives (216) *via* DABCO catalyzed 3CR of ethyl 2-(3-oxo-3-arylpropanethioamido)-acetates (215), malanonitrile (190) and aldehydes (66) under microwave irradiation (**Scheme 1.61**).[183]
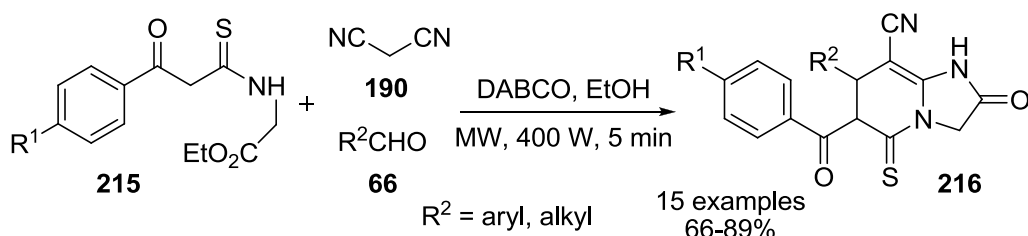
Scheme 1.61 3CR for the synthesis of imidazo[1,2-*a*]pyridine analogues

1.7 Functionalization of Imidazo[1,2-*a*]pyridines

Imidazo[1,2-*a*]pyridine skeleton was used as a synthon for the construction of a variety of azafused polyheterocyclic molecules. This section deals with some interesting reports where imidazo[1,2-*a*]pyridine analogues underwent inter/intramolecular cyclizations, multicomponent reactions, tandem sequences together with C−H functionalizations and offered a new class of fused heterocyclic scaffolds. In each of the following reactions, either imidazo[1,2-*a*]pyridine was used as a substrate or it was built internally and reacted further to give the corresponding polycyclic structures.

1.7.1 Functionalization of imidazo[1,2-*a*]pyridine skeleton

When imidazo[1,2-*a*]pyridines (3) are treated with aldehydes (60) in presence of NaOAc, 3,3'-(arylmethylene)diimidazo[1,2-*a*]pyridines (217) are formed with high yields (**Scheme 1.62**).[184] Surprisingly the expected product, 3-hydroxyalkylimidazo[1,2-*a*]pyridine (218) was not detected in the reaction. As the C-3 position of imidazo[1,2-*a*]pyridine is more prone towards the electrophilic substitution resembling indole, most of the functionalizations of imidazo[1,2-*a*]pyridine skeleton are based on either C-3 substitutions or initiates from C-3 functionalized imidazo[1,2-*a*]pyridines. Particularly, cross-coupling reactions at C-3 of imidazo[1,2-*a*]pyridine are more common in the literature. For the arylation at C-3 position, various protocols were

available and recent developments in the field of transition metal catalyzed cross-coupling reaction allowed C-3 aryl bond formations without the necessity of pre-activation of either of the substrate. These developments from the initial days were reviewed very briefly. In 2000, Gueiffier group employed Suzuki-Miyaura cross coupling for the C-3 arylation of imidazo[1,2-a]pyridines (**Scheme 1.63**).[185] Here, 3-bromoimidazo[1,2-a]pyridines (**219**) were reacted with aryl boronic acids (**88**) which offered 3-arylimidazo[1,2-a]pyridines (**14**) in good yields.
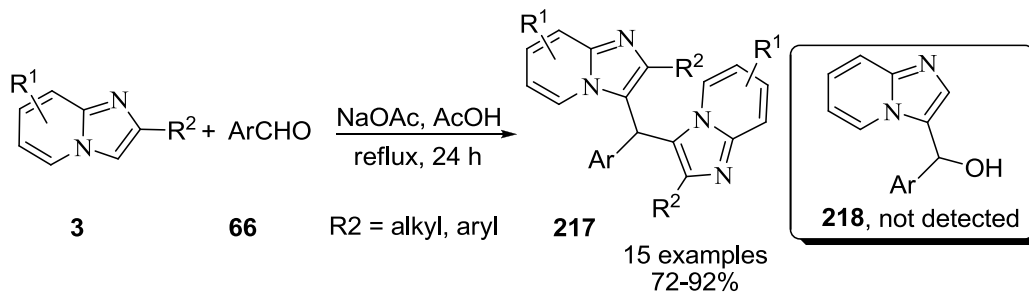
Scheme 1.62 Formation of *bis*-imidazo[1,2-a]pyridines
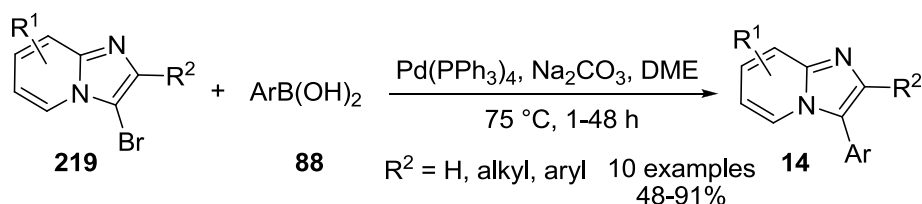
Scheme 1.63 Suzuki coupling on 3-iodo imidazo[1,2-a]pyridines

Later in 2006, a couple of groups independently reported the direct arylation of imidazo[1,2-a]pyridines (**3**) by employing the concept of C−H functionalization.[186-187] In this protocol, unactivated imidazo[1,2-a]pyridines (**3**) were smoothly reacted with various aryl halides (**15**) in presence of palladium catalyst and offered good yields of corresponding C-3 arylated imidazo[1,2-a]pyridines (**14**) (**Scheme 1.64**).[188-189] Cao *et al*. disclosed an efficient method for the direct arylation of imidazo[1,2-a]pyridines (**3**) in presence of highly abundant and inexpensive copper catalyst.[190] Recently, the same group reported the direct arylation of imidazo[1,2-a]pyridines (**3**) using inexpensive and highly challenged aryl chlorides (**15**).[191]

Very recently, Wang *et al*. synthesized these motifs through palladium catalyzed oxidative coupling of imidazo[1,2-a]pyridines (**3**) and arenes (**220**) *via* double C−H activation (**Scheme**

1.65).[192] This method has shown high functional group compatibilities, reaction efficiencies, regioselectivities together with good yields of arylated products (**16**).

R² = H, alkyl, aryl; X = Br, I, Cl
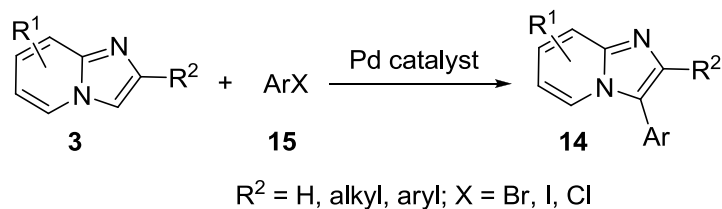
Scheme 1.64 Direct arylation of imidazo[1,2-*a*]pyridines

R² = H, alkyl, aryl   20 examples
43-79%
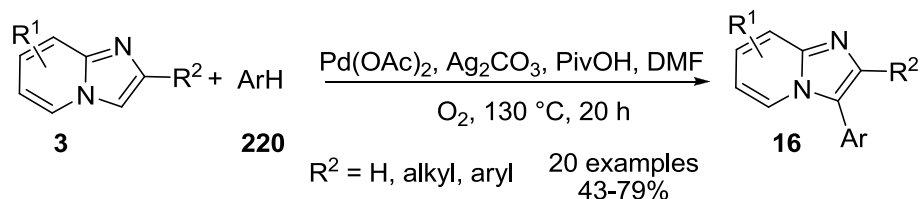
Scheme 1.65 Arylation of imidazo[1,2-*a*]pyridines through double C−H activation

Raboin and colleagues disclosed palladium catalyzed regio-controlled Suzuki and Sonogashira couplings of 3,6-dihalo imidazo[1,2-*a*]pyridines (**221**) (**Scheme 1.66**).[193] This report focussed on dissimilarly difunctionalization of imidazo[1,2-*a*]pyridines (**221**) by utilizing the reactivity of halo groups. For example, when 6-iodo-3-bromo imidazo[1,2-*a*]pyridine (**221**) was treated with alkynes (**42**) or aryl boronic acids (**88**) under milder Sonogashira or Suzuki reaction conditions, they underwent smooth coupling with iodo group selectively and offered Sonogashira/Suzuki coupled products, 6-alkynyl/aryl-3-bromo imidazo[1,2-*a*]pyridines in high yields (**222** or **223**). These products were further treated under either Suzuki or Sonogashira reaction conditions to afford the corresponding difuctionalized compounds in good yields. Authors have succeeded in di-functionalization of these precursors under microwave irradiation in one-pot manner (**224**).

Adhikari group synthesized 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines (**226**) through a multistep protocol (**Scheme 1.67**).[36] Propargyl functionality was attached to the imidazo[1,2-*a*]pyridines which on [3+3] cycloaddition with alkyl azides offered the targeted molecules (**226**). These motifs (**226**) were evaluated for their antiepileptic properties.
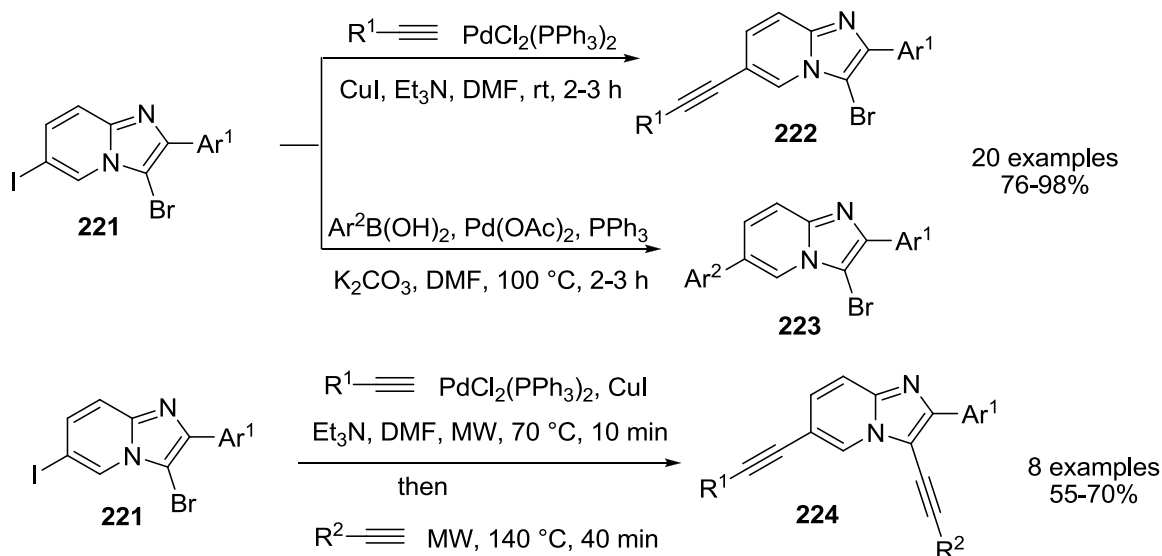
Scheme 1.66 Regio-controlled difunctionalizations of imidazo[1,2-*a*]pyridines
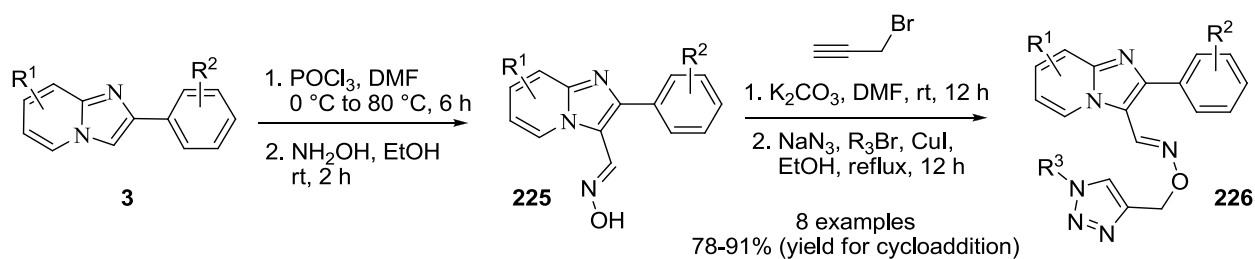
Scheme 1.67 Synthesis of 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines

Recently, our group has reported the synthesis of 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines (**229**) where azide group was condensed to imidazo[1,2-*a*]pyridine skeleton (**228**) at C-3 position (**Scheme 1.68**).[194] The developed procedure was simple and offered good yields triazolyl imidazo[1,2-*a*]pyridines (**229**). Urge group reported the parallel synthesis of 3-imidazo[1,2-*a*]pyridin-3-yl-propionic acids (**232**) using a three-step protocol (**Scheme 1.69**).[195] The key step in this report was the three-component Michael-type reaction of imidazo[1,2-*a*]pyridines (**3**), aldehydes (**66**) and Meldrum's acid (**230**). This method has found broad substrate scope and these products on further transformations gave imidazopyridine based drug like structures in reduced number of synthetic steps.
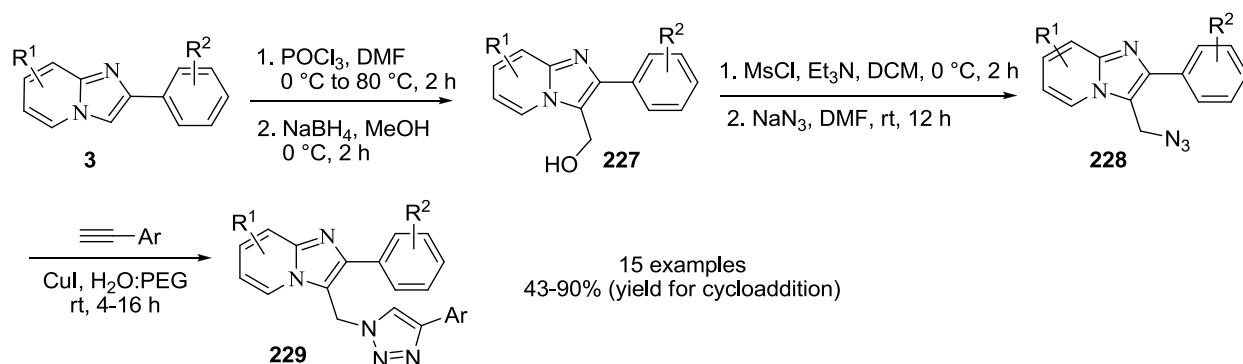
Scheme 1.68 Synthesis of 1,2,3-triazole substituted imidazo[1,2-a]pyridines
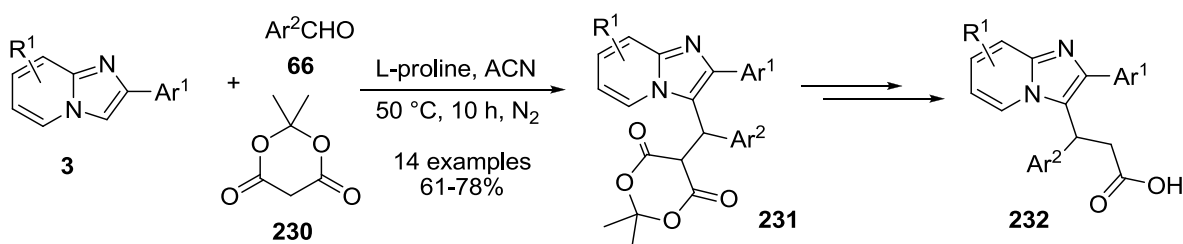
Scheme 1.69 3CR of imidazo[1,2-a]pyridines, aldehydes and Meldrums acid

1.7.2 Synthesis fused heterocycles starting from imidazo[1,2-a]pyridines

Raboin group employed intramolecular direct arylation conditions for the synthesis of fused imidazo[1,2-a]pyridine scaffolds, pyrido[2',1':2,3]imidazo[5,4-c]quinolin-6(5H)-ones (**234**) through C−H functionalization at C-3 position of imidazo[1,2-a]pyridines (**233**) (**Scheme 1.70**).[196] This methodology was smoothly extended to the construction of seven membered ring fused products in good yields.
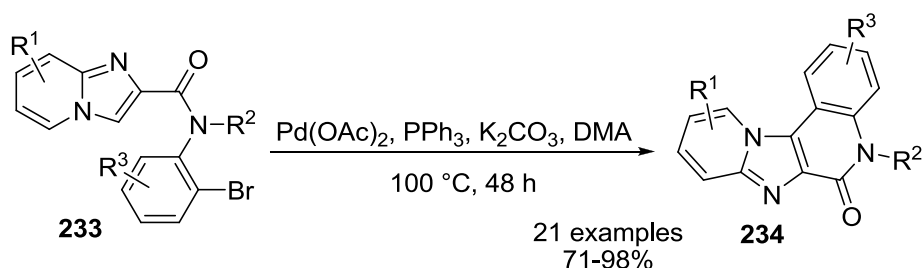
Scheme 1.70 Intramolecular direct arylation of imidazo[1,2-a]pyridine derivatives

Stasyuk *et al.* disclosed the reaction of imidazo[1,2-a]pyridines (**3**) with benzynes which offered good yields of benzo[a]imidazo[5,1,2-cd]indolizines (**236**) through tandem [8+2]cycloaddition–

[2+6+2]dehydrogenation (**Scheme 1.71**).[197] Benzynes were generated *in situ* by reacting 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**235**) in presence of CsF, 18-crown-6 under microwave irradiation then fused with imidazo[1,2-*a*]pyridines (**3**) at C-3 and C-5 position. The precursors, 2-(2-hydroxyphenyl)imidazo[1,2-*a*]pyridines (**3**) were achieved through Ortoleva-King reaction followed by Chichibabin ring closure of 2'-hydroxyacetophenones (**12**) and 2-aminopyridines (**1**) (**Scheme 1.6a**). The synthesized tetracyclic fused structures (**236**) have displayed excited state intramolecular proton transfer (ESIPT).
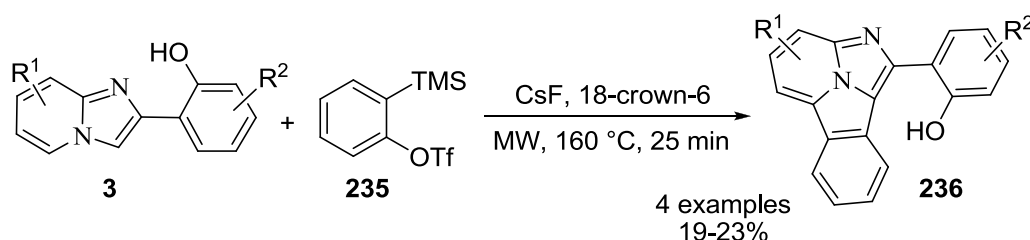
Scheme 1.71 Synthesis of fused imidazo[1,2-*a*]pyridines from benzynes

Zamora and colleagues disclosed a convenient method for the synthesis of novel 1,2,3-triazinone fused imidazo[1,2-*a*]pyridines, Pyrido(1',2':1,2)imidazo[5,4-*d*]-1,2,3-triazinones (**238**) from imidazo[1,2-*a*]pyridines (**237**) (**Scheme 1.72**).[198] The key precursors **237** are synthesized from ethyl 3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate. Diazotization of **237** with sodium nitrite in dilute HCl then on treatment with NaHCO$_3$ (pH ≈ 7) offered the triazinone fused imidazo[1,2-*a*]pyridines (**238**) in good yields.
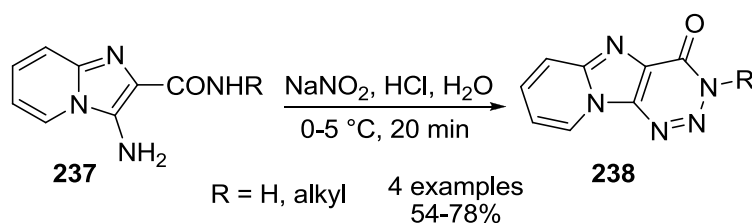
Scheme 1.72 Synthesis of 1,2,3-triazinone fused imidazo[1,2-*a*]pyridines

Teulade and co-workers described the synthesis of a new class of dipyrido[1,2-*a*;3',4'-*d*]imidazoles (**240**), dipyrido[1,2-*a*;4',3'-*d*]imidazoles (**243**) and pyrido[1',2';1,2]imidazo[4,5-*d*]pyridazines (**242**) starting from imidazo[1,2-*a*]pyridine analogues (**239** and **241**) (**Scheme 1.73**).[199] These targeted skeletons were achieved in two different synthetic routes. 3-

Alkenylimidazo[1,2-*a*]pyridine-2-oximes (**239**) underwent smooth electrocyclization under thermal conditions and offered good yields of dipyridoimidazoles (**240**). In other hand, condensation of 2,3-dicarbonyl imidazo[1,2-*a*]pyridines (**241**) with ethylglycinate and hydrazine afforded fused imidazo[1,2-*a*]pyridines (**240**, **242** and **243**) in good yields.

1.7.3 Synthesis fused heterocycles through *in situ* generated imidazo[1,2-*a*]pyridines

This section deals with some interesting reports where inter/intramolecular cyclizations resulted in the arrangement of fused azoles. In each of these reactions imidazo[1,2-*a*]pyridine skeleton was built internally. Recently, Arnould *et al.* disclosed the synthesis of novel fused imidazo[1,2-*a*]pyridines, pyrido[2',1':2,3]imidazo[4,5-*b*]quinolines (**245**) through diversity oriented strategy (DOS) (**Scheme 1.74**). Initially, three-component Groebke–Blackburn–Bienaym reaction of 2-amino-pyridines (**1**), ynals (**62**) and isonitriles (**67**) in presence of perchloric acid produced imidazo[1,2-*a*]pyridines (**244**) which on intramolecular electrophilic cyclization in presence of DBU offered pyrido [2',1':2,3]imidazo [4,5-*b*]quinolines (**245**) in good yields. The developed DOS strategy offers a novel heterocyclic libraries (**245**) in two-steps under metal-free conditions using readily available precursors.[200]

Recently, Siddiqui group disclosed the synthesis novel fused imidazo[1,2-*a*]pyridines (**247**) through basic ionic liquid, [bmim]OH promoted cyclocondensation of 2-aminopyridines (**1**) with *N*-methylisatin (**246**) (**Scheme 1.75**). [Bmim]OH was acted as a base, catalyst and solvent and afforded good yields of fused imidazo[1,2-*a*]pyridines (**247**) at room temperature.[201]

Ila group reported an efficient intramolecular *N*-arylation of heterocyclic arenes (**248**) in presence palladium for the synthesis of benzo-fused imidazo[1,2-*a*]pyridines (**249**) (**Scheme 1.76**). The key precursors, 2-(2-bromoanilino)quinolines (**248**) were readily obtained by oxidation of 2-(methylthio)quinolines in presence of *m*-CPBA followed by nucleophilic displacement of methylsulfonyl group with 2-bromoanilines in overall good yields. When NaHCO$_3$ was used as a base in DMF, indolo[2,3-*b*]quinoline formation was also observed together with fused imidazo[1,2-*a*]pyridines (**249**) which might have produced *via* palladium catalyzed intramolecular C−H functionalization.[202]
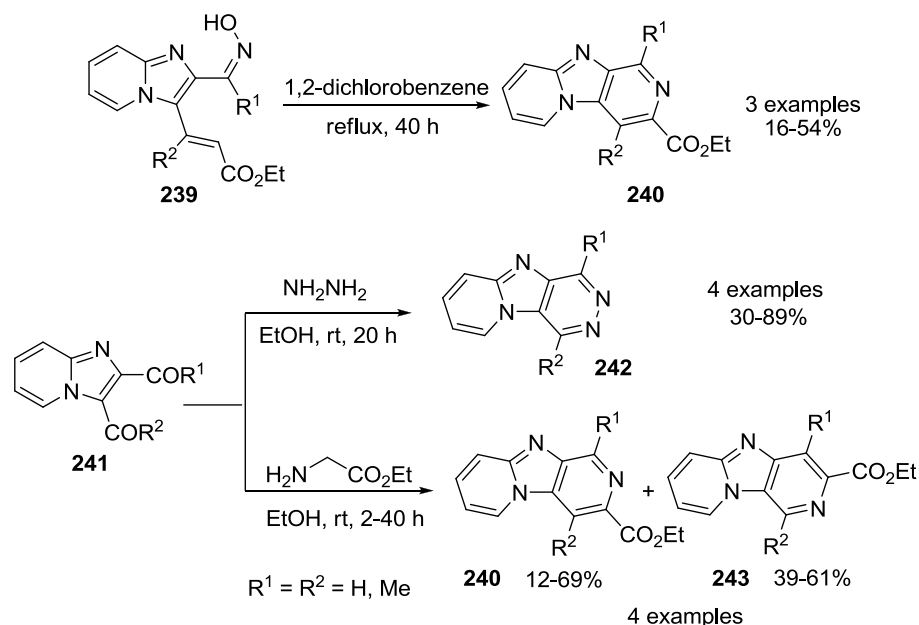
Scheme 1.73 Synthesis of pyrido fused imidazo[1,2-a]pyridines
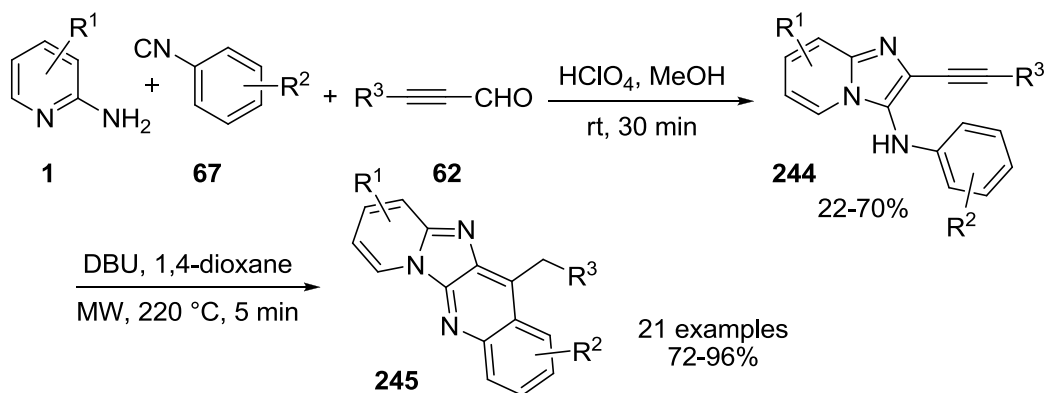
Scheme 1.74 Synthesis of quinoline fused imidazo[1,2-a]pyridines
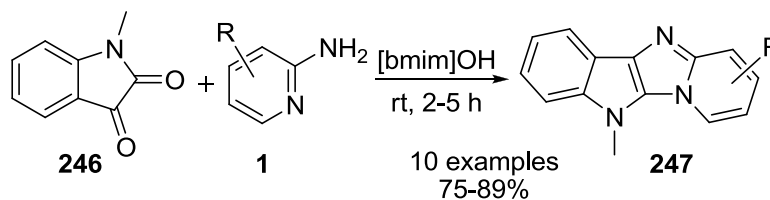
Scheme 1.75 Synthesis of fused imidazo[1,2-a]pyridines from *N*-methyl isatins

Very recently, Yang *et al.* reported an one-pot sequential method for the construction of functionalized cyclazines, 2,2a^1,4-triazacyclopenta[*cd*]indenes (**252**) through Yb(OTf)$_3$/ Pd(OAc)$_2$ catalyzed three component tandem process (**Scheme 1.77**). A well established 3CR of

2-amino-6-halopyridine (**1**), aldehydes (**66**) and isonitriles (**250**) in presence of Yb(OTf)$_3$ resulted 3-aminoimidazo[1,2-*a*]pyridines (**251**). These products then reacted in presence of Pd(OAc)$_2$ to give corresponding cyclazines (**252**) in good yields *via* intramolecular cyclization by C−H activation.[203]
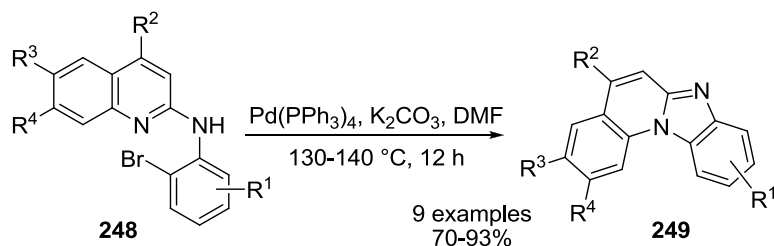
Scheme 1.76 Synthesis of benzo-fused imidazo[1,2-*a*]pyridines
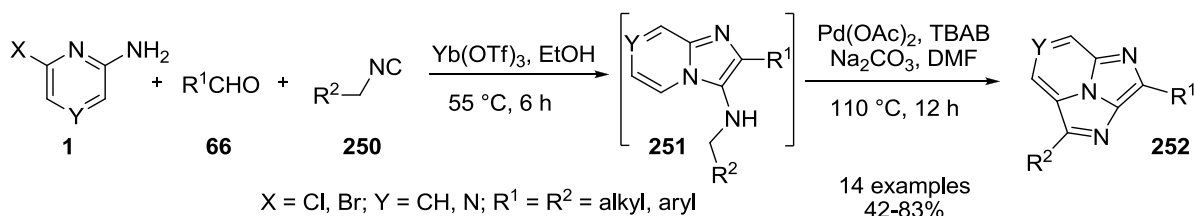
Scheme 1.77 Synthesis of functionalized cyclazine through imidazo[1,2-*a*]pyridines

Other report by Sun *et al.* revealed an effective one-pot sequential three-component reaction for the synthesis of 3*H*-1,2a^1,3-triazaacenaphthylenes (**254**) (**Scheme 1.78**). The tandem 3CR involves Yb(OTf)$_3$ catalyzed Groebke−Blackburn −Bienayme like condensation of 6-alkynyl-2-amino pyridines (**253**), aldehydes (**66**) and isonitriles (**67**) which follows the intramolecular nucleophilic attack of amine through 6-*endo-dig* fashion in presence Ag$_2$CO$_3$. A wide range of aldehydes (**66**), isonitriles (**67**) and aromatic amidines (**253**) participated in tandem 3CR protocol and delivered structurally diverse cyclazines (**254**) in good yields.[204]

Raboin *et al*. disclosed the synthesis of indole fused imidazo[1,2-*a*]pyridines (**257**) through a sequential three-component Bienayme reaction and copper catalyzed *N*-arylation (**Scheme 1.79**). 2-bromobenzalydes (**255**) were treated with 2-aminopyridines (**1**) and isonitriles (**67**) in the presence of HClO$_4$ to afford 3-aminoimidazo[1,2-*a*]pyridines (**256**) in good yields. These products underwent intramolecular *N*-arylation reaction in presence of CuI/TMEDA in dioxane or aqueous media to deliver good yields of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles (**257**).[205]
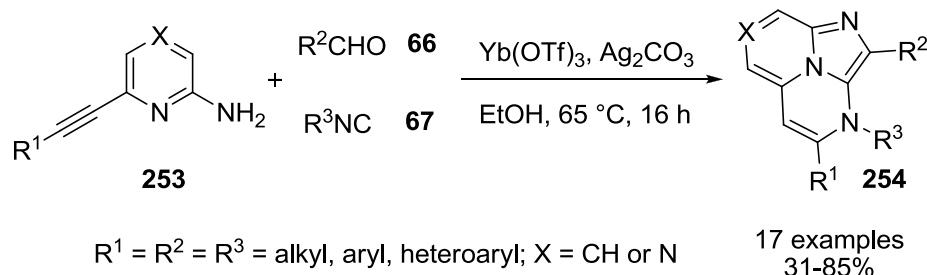
Scheme 1.78 Synthesis of cyclazines through imidazo[1,2-*a*]pyridines
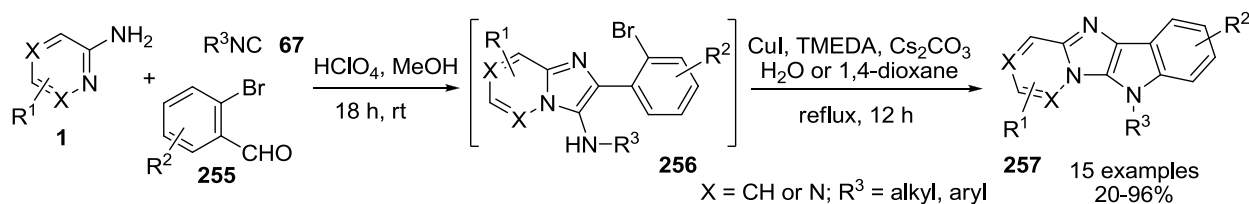
Scheme 1.79 Synthesis of indole fused imidazo[1,2-*a*]pyridines

Kumar group has reported the synthesis of fused imidazo[1,2-*a*]pyridines (**259**) through the tandem aldol condensation of 2-(1*H*-imidazol/benzimidazolyl-1-yl)-1-arylethanones (**258**) and 2-bromoarylaldehydes (**255**) followed by palladium catalyzed intramolecular direct arylation (**Scheme 1.80**).[206] The key precursors (**258**) for these studies have been achieved in a single step by the reaction among phenacyl bromides and azoles. This method offered good yields of fused imidazo[1,2-*a*]pyridines with aroyl substitutions (**259**).
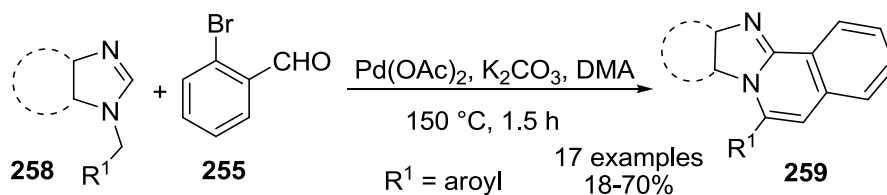
Scheme 1.80 Synthesis of fused imidazo[1,2-*a*]pyridines from imidazole analogues

1.8 Conclusions

Thus, a tremendous recent development shows an augmented interest in the chemistry of imidazo[1,2-*a*]pyridines might be due to their utility in various fields particularly in medicinal chemistry. This overview summarized the diverse procedures reported for the synthesis of imidazo[1,2-*a*]pyridine skeleton over last decade. Owing to the increased interest of these

skeletons in various fields such as medicinal chemistry, material science and organometallics, more advanced methods to access these skeletons in a simple manner and obviously from readily available precursors are highly warranted. Since fused heterocycles are found to have applications in diverse disciplines, synthesis of novel fused heterocyclic libraries containing highly valuable imidazo[1,2-*a*]pyridine motifs are highly desirable.

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Chapter II

Synthesis of Fused Azaheterocycles by Tandem Reactions

From the standpoint of green chemistry, development of organic transformations for the construction of bioactive heterocyclic scaffolds in reduced number of synthetic steps with high molecular complexity and diversity is an everlasting demand in organic chemistry. Tandem reactions are one of the finest choice which fulfils the above discussed requirements.[1-2]

Dictionary portrays the term *tandem* as a bicycle with seats and pedals for two riders, one behind the other. This can be comprehended for chemical reactions as two or more reactions which follow one another. They are also termed as cascade or domino processes which can be defined as the reactions in which several bonds are formed in a sequence without isolating intermediates, changing reaction conditions or adding reagents. In other words, these are a class of reactions where sequential transformation of substrate occurs *via* two or more mechanically distinct processes. A simple representation of tandem process is shown in **Scheme 2.1**. 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 a single step starting from the precursors **A** and **B**.
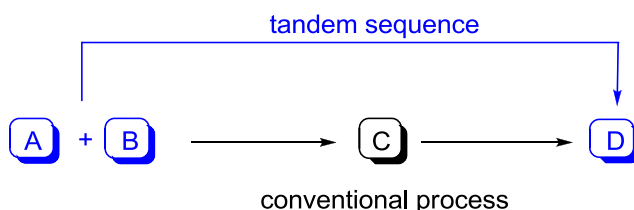
Scheme 2.1 Illustration of tandem reaction

The major advantages of tandem reactions are that they

- avoid isolation of intermediates whereby reduces the labor and time required for the given target molecules
- reduce the waste generation
- build a large number of complexity in a single step

Several research groups have successfully employed tandem sequences for the synthesis of diverse heterocyclic molecules. For example, Kundu *et al.* synthesized a new class of *N*-fused heterocycles, indolo[2,3-*c*][1,2,3]triazolo[1,5-*a*][1]benzazepines (**3**) by Yb(OTf)$_3$ catalyzed tandem reaction among nitroolefin substituted arylazides (**1**) and indole analogues (**2**) (**Scheme 2.2**). The tandem reaction involved intermolecular Michael addition followed by intramolecular azide/alkyne 1,3-dipolar cycloaddition.[3] Gratifyingly, several bonds are formed in a sequence with a simple and inexpensive Lewis acid catalyst.
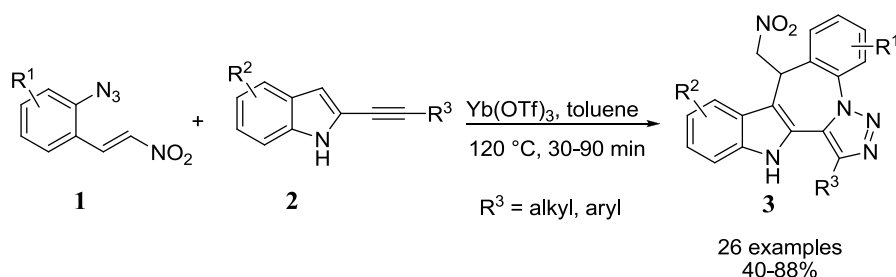
Scheme 2.2 Yb(OTf)$_3$ catalyzed tandem synthesis of *N*-fused heterocycles

Povarov reaction is a well documented method for the synthesis of 2,4-disubstituted quinolines. This method offers dihydroquinolines by the reaction of aldehydes, alkynes and anilines in presence of Lewis acid. In some cases, dihydroquinolines undergo aerobic oxidation to result aromatized quinolines. In other cases, additional oxidant such as DDQ was employed for the oxidation of dihyroquinolines. Jha *et al.* has reported Yb(OTf)$_3$ as an auto-tandem catalyst for the tandem three-component reaction of 1,4-phenylenediamine (**4**), arylaldehydes (**5**) and alkynes (**6**) to access novel *N*-arylmethyl-6-amino-2,4-diarylquinolines (**7**) (**Scheme 2.3**).[4] The tandem process proceeded *via* Povarov reaction, dihydroquinoline oxidation and imine reduction.
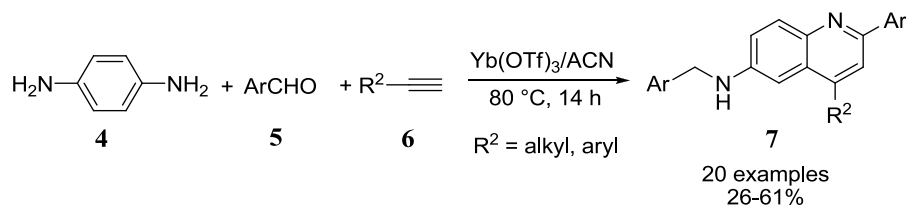
Scheme 2.3 Yb(OTf)$_3$ catalyzed tandem synthesis of 6-aminoquinolines

Yokomatsu and colleagues disclosed a novel method for the synthesis of benzimidazo[1,2-*a*]quinolines (**10**) through the tandem reaction of 2-methylbenzimidazoles (**8**) and 2-fluoroarylaldehydes (**9**) in presence of Cs$_2$CO$_3$ (**Scheme 2.4**). The domino sequence involved

aromatic nucleophilic substitution (S_NAr) followed by intramolecular Knoevenagel condensation. Variously substituted azoles and aldehydes including heterocyclic frameworks, such as nicotinaldehyde and pyrazole-4-carboxaldehyde smoothly participated under the reaction conditions and offered the fused azoles (**10**) in high yields. Gratifyingly, Knoevenagel condensation proceeded without the necessity of any direct-activating group.[5]

R² = Me, OMe, SMe, 4-morpholinyl;

24 examples
39-86%
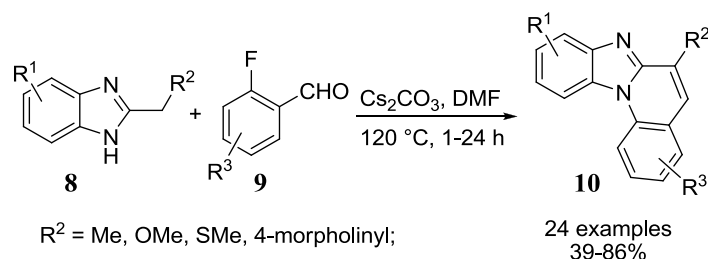
Scheme 2.4 Base mediated tandem synthesis of benzimidazo[1,2-*a*]quinolines

Cai and co-workers reported an efficient copper catalyzed cascade approach for the synthesis of azole-fused quinolines (**13**) (**Scheme 2.5**). The developed tandem approach involved intermolecular Knoevenagel condensation followed by Ullmann-type C−N coupling of azoles with active methylene group at C_2 position (**11**) and 2-haloarylaldehydes (**12**). Various substituted 2-iodo/bromo benzaldehydes as well as highly challenging 2-chlorobenzaldehyde participated in tandem reaction with slight modifications in reaction temperatures.[6]

R¹ = CN, COPh, SO₂Ph, CO₂Et; X = Cl, Br, I; Y = CH or N

30 examples
25-91%
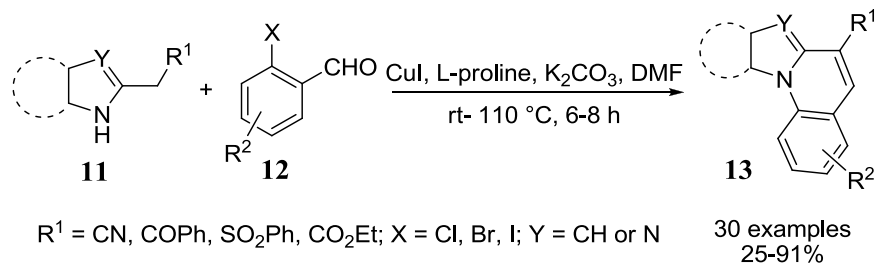
Scheme 2.5 Copper catalyzed synthesis of azole-fused quinolines through a tandem sequence

With our interest in synthesizing heterocyclic molecules with an improved procedures, in this chapter we described the synthesis of imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines by employing tandem reaction sequences.

67

Chapter II

PART-A

Copper Catalyzed Tandem Oxidative C–H Amination and Cyclization: Direct Access to Imidazo[1,2-*a*]pyridines

2.1 Introduction

Transition metal catalyzed C–H activation reactions have emerged as an active field of research in organic synthesis.[7-9] These reactions are most ideal for forming carbon-carbon (C–C) or carbon-heteroatom bonds from the viewpoint of synthetic simplicity, atom-economy and efficiency. Moreover, this activation of C–H bond avoids pre-functionalization of the substrates prior to the coupling reactions and provides a more efficient and straightforward access to the target molecules. Over the last decade, excellent efforts have been made towards the synthesis of ample number of bioactive heterocyclic molecules and natural products through direct C–C or C–X (X = N, O, S) bond formations.[10-13] Efficiency of copper catalysts is well demonstrated in literature since last century where these salts are proved to catalyze plethora of cross-coupling reactions to form C–C as well as C–X bonds for the synthesis of natural products and bioactive molecules.[14-17] Because of their economical attractiveness, low toxicity and good functional group tolerance, copper salts have became potential alternative to their expensive counterparts such as palladium, rhodium and ruthenium catalysts.[2, 18-19] In this context, copper salts are also proved as an efficient catalysts for the direct C–C as well as C–X bond formations *via* oxidative cyclizations and cross dehydrogenative couplings (CDC).[20-25]

A brief overview of some recent copper catalysed oxidative cyclization reactions

Zhu group reported an efficient Cu/Fe co-catalysed direct C−H amination of *N*-aryl-2-amino pyridines (**14**) for the synthesis of pyrido[1,2-*a*]benzimidazoles (**15**) under dioxygen atmosphere (**Scheme 2.6**). Sensible functionalities in cross-coupling conditions such as bromo and chloro groups remained intact under the reaction conditions. When regioselectivity was concerned, sterically less hindered products were dominated over their counterparts. This method has found excellent functional group tolerance and offered good yields of fused azoles.[22]
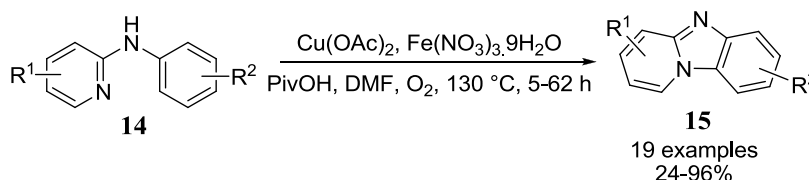
Scheme 2.6 Cu/Fe co-catalyzed synthesis of pyrido[1,2-*a*]benzimidazoles

Two different mechanisms were proposed with/without the assistance of iron catalyst. In the absence of Fe catalyst, Cu(II) adduct (**16**) was formed by the reaction of pyridinium endocyclic nitrogen with copper acetate which followed the C−Cu bond with aryl ring through electrophilic substitution fashion to give intermediate **17**. Reversible protonation and further oxidation of Cu(II) to Cu(III) results **19**, finally reductive elimination affords the desired products (**15**). The resultant Cu(I) was regenarated to Cu(II) in presence of O_2 which completes the catalytic cycle. When $Fe(NO_3)_3$ was present, Cu(II) species (**16**) oxidizes to Cu(III) (**20**) which undergoes electrophilic substitution more readily to give **21**. Elimination of proton through six membered transition state offered the Cu(III) intermediate (**19**), which on reductive elimination results into the desired fused azoles (**Scheme 2.7**).
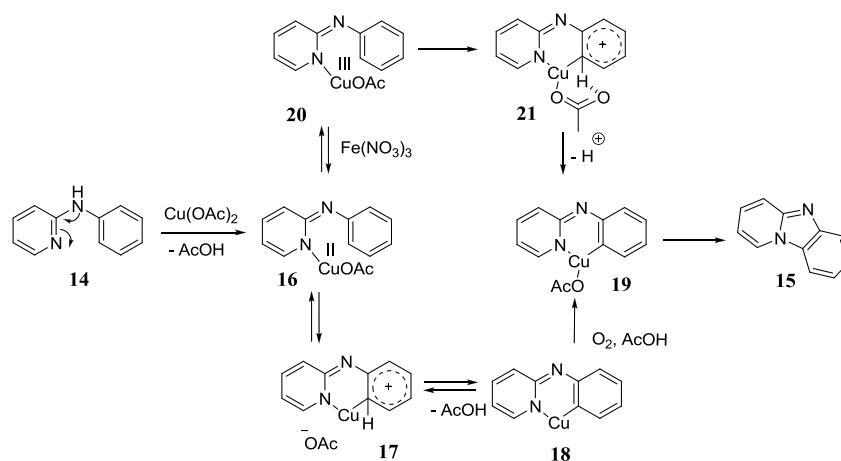
Scheme 2.7 Mechanism for Cu/Fe co-catalyzed synthesis of pyrido[1,2-*a*]benzimidazoles

At the similar time of Zhu and Zhang group, Maes group also reported direct C−H amination of *N*-aryl-2-aminopyridines (**14**) to access pyrido[1,2-*a*]benzimidazoles (**15**) using a catalytic amount of copper acetate in presence of oxygen for the regeneration of copper catalyst (**Scheme 2.8**). A detailed investigations on the influence of acid additive has been carried out while considering various aliphatic, aromatic carboxylic as well as non-carboxylic acids. These studies concluded that catalytic amount of 3,4,5-trifluorobenzoic acid was a superior additive which facilitated complete conversion of **14** in shorter reaction times. This protocol has found good functional group tolerance and also high regioselectivities when meta-substituted aryl ring was involved in cyclization.[23]
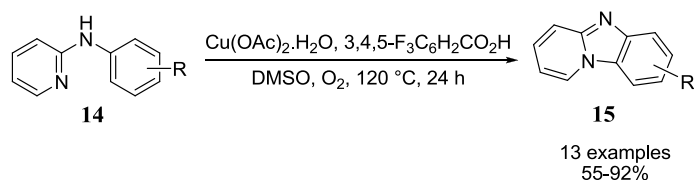
Scheme 2.8 Copper catalyzed synthesis of pyrido[1,2-*a*]benzimidazoles

The proposed mechanism was suggested based on experimental observations. Intramolecular nucleophilic attack of endocyclic nitrogen of pyridine on activated arene complex results in intermediate **22**. Subsequent *β*-hydride elimination produces desired fused azoles (**15**) and Cu^{II}-hydride. Reductive elimination of RCO_2H from $RCO_2Cu^{II}H$ yields Cu^0. Re-oxidation of Cu^0 to $Cu(OCOR)_2$ in presence of oxygen and acid additive completes the catalytic cycle (**Scheme 2.9**).
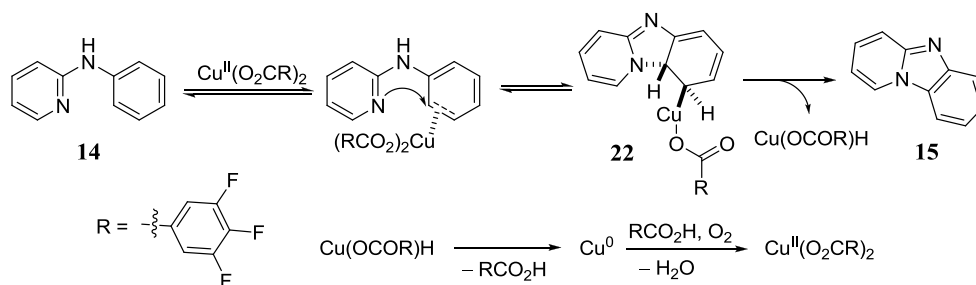
Scheme 2.9 Mechanism for copper catalyzed synthesis of pyrido[1,2-*a*]benzimidazoles

Fu and colleagues successfully employed copper catalyzed aerobic oxidative intramolecular C−H amination strategy for the synthesis of *N*-fused polyheterocyclic motifs (**24**) starting from 3-benzylidene-2-pyridin-2-ylmethyl-2,3-dihydro-isoindol-1-ones (**23**) (**Scheme 2.10**). A variety of inexpensive and commercially available copper salts such as CuI, CuBr, CuCl, $Cu(OAc)_2$, $CuSO_4.5H_2O$, $CuCl_2$, $CuBr_2$ and $Cu(O_2CCF_3)_2$ efficiently catalyzed the oxidative coupling reaction. Among the copper salts screened, $Cu(O_2CCF_3)_2$ offered high yields of fused heterocycles (**24**).[26]
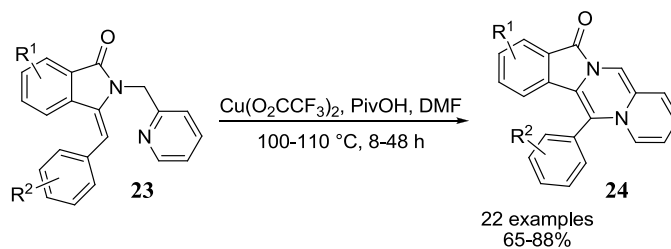
Scheme 2.10 Copper catalyzed synthesis of *N*-fused polyheterocycles

It was proposed that coordination of pyridine nitrogen with copper catalyst results **25**. Then isomerization of pyridine ring and complexation with copper through elimination of TFA leads to **26**. Intramolecular addition of alkene bond in **26** afforded **27**. Finally aerobic oxidation of **27** in presence of acid furnishes desired fused heterocyclic motifs (**24**) (**Scheme 2.11**).
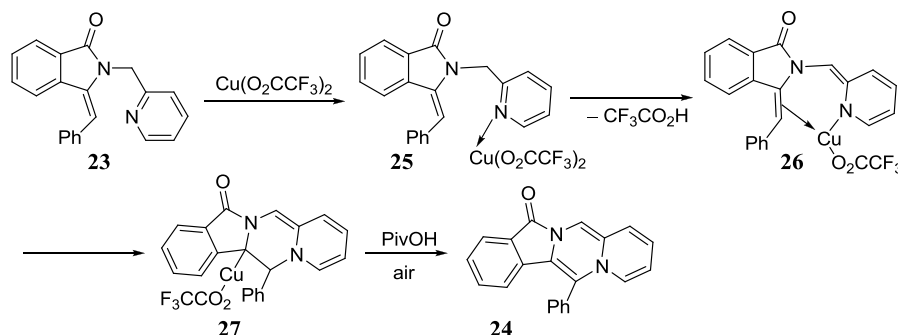
Scheme 2.11 Mechanism for copper catalyzed synthesis of *N*-fused polyheterocycles

Imidazo[1,2-*a*]pyridines are the privileged structural motifs in bioactive compounds, pharmaceuticals and organic functional materials. Compounds with imidazo[1,2-*a*]pyridine structures have been studied for various biological properties such antiviral,[27-28] antibacterial,[29]antifungal,[30-31] K^{+}-stimulated ATPase inhibition,[32] bradykinin B2 receptor antagonists,[33] anti-rhinoviral,[34-35] antiulcer,[36] and antihelminthics .[30] Moreover, 2-(2-hydroxy phenyl)imidazo[1,2-*a*]pyridines have displayed excellent excited state intramolecular proton transfer (ESIPT).[37-39] Ubiquity of these skeletons in biologically active compounds continues to give an impetus to develop novel methods for their synthesis.

The most convenient method to attain imidazo[1,2-*a*]pyridine nucleus is the reaction between 2-aminopyridines and α-halo carbonyl compounds.[40] However, the use of lachrymatory phenacyl bromides makes this method less preferred in present era of green chemistry. Other methods, which result substituted imidazo[1,2-*a*]pyridines are

 (a) Three component reaction of 2-aminopyridines, aldehydes and isonitriles also referred as Groebke-Blackburn-Bienayme reaction[41-43]

(b) Three component reaction of 2-aminopyridines, aldehydes and alkynes[44-45]

 (c) *via* Ortoleva-king type reaction[38]

(d) Using bielectrophilic nitro-alkene precursors[46-48]

(e) Oxidative cross-coupling reaction using alkynes[49-50] as well as β-ketoesters or 1,3-diones[51] as electrophiles.

Although, several synthetic methodologies have been exploited towards the synthesis of imidazo[1,2-*a*]pyridines,[52-53] there have been no reports of a ligand free catalyst system that can effectively synthesize imidazo[1,2-*a*]pyridines from acetophenones and 2-aminopyridines. Thus, there is an intrinsic need to develop a novel method to construct these significant bioactive motifs from commercially available precursors. With our interest towards the synthesis of heterocyclic molecules by employing advanced methodologies, we have synthesized 2-aryl imidazo[1,2-*a*]pyridines by the reaction of acetophenones and 2-aminopyridines *via* tandem oxidative C–H amination/cyclizations catalyzed by copper iodide (CuI) in the absence of external ligand and additives using air as a sole oxidant (during the course of publishing our results, we have found that a few other groups also reported the synthesis of imidazo[1,2-*a*]pyridines through copper catalyzed oxidative cyclizations at similar time boundaries. However, the reported procedures employed additional ligands, Lewis acids and oxygen atmosphere).[54-56]

2.2 Results and Discussion

We envisioned that the use of lachrymatory phenacyl bromides in the synthesis of imidazo[1,2-*a*]pyridines can be replaced by simple acetophenones using copper catalysts as they can enable the C–N bonding by oxidative C–H aminations.[22-23] Acetophenone (**28a**), and 2-aminopyridine (**29a**) were chosen as the model substrates for the initial investigations to optimize the reaction conditions, and the results are summarized in Table 2.1. A mixture of **28a** (1 mmol), **29a** (1.2 mmol), and Cu(OTf)$_2$ (0.1 mmol) in 1,4-dioxane was stirred at 100 °C for 14 h. Unfortunately, no reaction occurred in presence of Cu(OTf)$_2$ (entry 1, Table 2.1). However, to our delight, when the starting materials were treated with dual catalytic system, Cu(OTf)$_2$ (10 mol %) and CuI (10 mol %), the product 2-phenylimidazo[1,2-*a*]pyridine (**30aa**) was isolated in 45% yield (entry 2, Table 2.1) (**Scheme 2.12**).
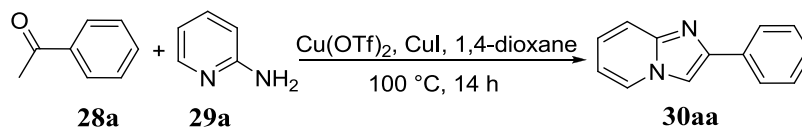
Scheme 2.12 Copper catalyzed tandem synthesis of imidazo[1,2-*a*]pyridines

The structure of **30aa** was characterized by NMR data and compared with previous reports. Characteristic singlet at δ 7.85 ppm corresponding to C-3 proton of imidazole ring, a doublet and triplet at δ 8.11 and 6.78 ppm (with J = 6.6 Hz) for C-4 and C-5 proton of pyridine ring appeared in the ^{1}H NMR of **30aa**. All other protons were located at their respective positions. Additionally, ^{13}C NMR and melting point were in agreement with literature reports. A representative ^{1}H and ^{13}C NMR of **30aa** is shown in **Figure 2.1**.

We then attempted the same conversion with only 10 mol % of CuI, which resulted the product (**30aa**) in 48% isolated yield (entry 3, Table 2.1). From these observations, CuI was found to be effective catalyst for this transformation. When the catalyst loading was increased to 20 mol %, the target molecule **30aa** was isolated in 71% yield (entry 4). Further increase in the catalyst loading did not influence the yields of tandem product. Other catalysts examined were either poorly effective (CuBr, CuCl, Cu(OAc)$_2$.H$_2$O, CuBr$_2$, CuCl$_2$.2H$_2$O, entries 5-8, and 9 respectively, Table 2.1) or entirely ineffective (Cu(OTf) and CuSO$_4$.5H$_2$O, entries 10-11, Table 2.1). During the examination of the effect of solvent using 20 mol % of CuI, we found that solvents like *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and toluene gave moderate yields of tandem product (entries 12-14 respectively, Table 2.1), while 1,2-dichloroethane (DCE), acetonitrile (ACN) and ethanol produced good yields of **30aa** (entries 15-17 respectively, Table 2.1). It is noteworthy that use of water as reaction medium was found less effective for this transformation (entry 18, Table 2.1). Among the solvents screened, 1,4-dioxane was found to be best solvent for the synthesis of **30aa** (entry 4, Table 2.2). The results showed that the reaction proceeded optimally with 20 mol % CuI in 1,4-dioxane.
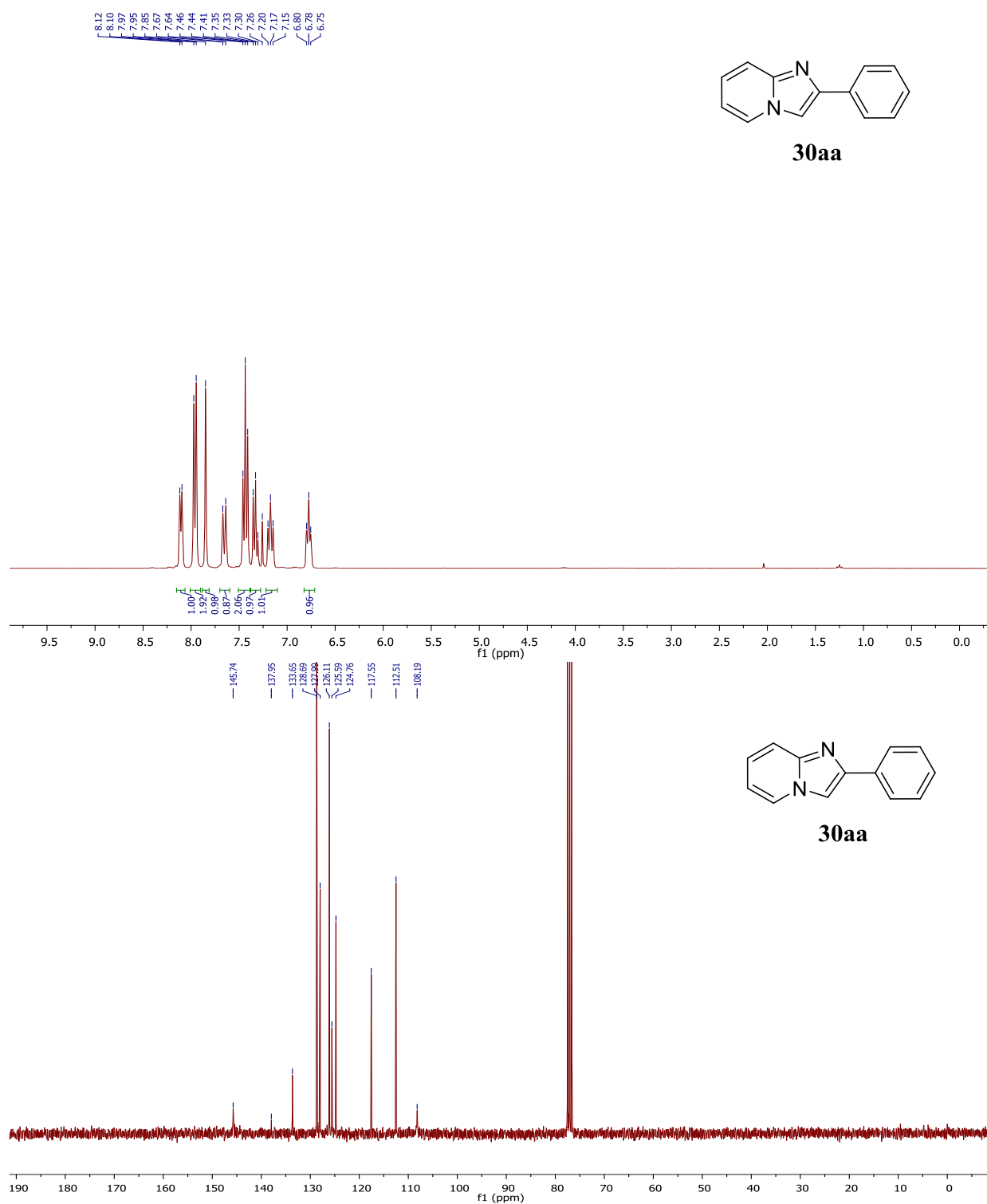
Figure 2.1 ^{1}H and ^{13}C NMR spectra (in CDCl$_3$; recorded on a Bruker AV 300 spectrometer) of 2-phenylimidazo[1,2-a]pyridine (**30aa**)

Table 2.1 Optimization of reaction conditions for the synthesis of **30aa**[a]
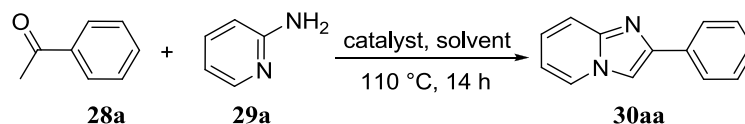
Entry	Catalyst	Solvent	% Yield[b]
1.	$Cu(OTf)_2$	1,4-Dioxane	NR[c,d]
2.	$Cu(OTf)_2$/ CuI	1,4-Dioxane	45[c]
3.	CuI	1,4-Dioxane	48[c]
4.	**CuI**	**1,4-Dioxane**	**71**
5.	CuBr	1,4-Dioxane	35
6.	CuCl	1,4-Dioxane	26
7.	$Cu(OAc)_2.H_2O$	1,4-Dioxane	22
8.	$CuBr_2$	1,4-Dioxane	16
9.	$CuCl_2.2H_2O$	1,4-Dioxane	31
10.	CuOTf	1,4-Dioxane	NR[d]
11.	$CuSO_4.5H_2O$	1,4-Dioxane	NR[d]
12.	CuI	DMF[e]	48
13.	CuI	DMSO[f]	42
14.	CuI	Toluene	46
15.	CuI	DCE[g]	67
16.	CuI	ACN[h]	62
17.	CuI	EtOH	65
18.	CuI	H_2O	12

[a]Reaction conditions: **28a** (1.0 mmol), **29a** (1.2 mmol), Catalyst (0.2 mmol), Solvent (3.0 mL), 100 °C, 14 h. [b]Isolated yields. [c]10 mol % of catalyst was used. [d]NR= no reaction. [e]*N, N*-Dimethylformamide. [f]Dimethyl sulfoxide. [g]1,2-Dichloroethane. [h]Acetonitrile.

With the optimized conditions in hand (entry 4, Table 2.1), we next explored the generality of the reaction, and the results are summarized in Table 2.2. Diversely substituted 2-aminopyridines reacted smoothly to give tandem products in good yields (60-79%, entries 1, 2, 4, and 6, Table 2.2). The results demonstrated that a wide range of acetophenones regardless of electron-rich and electron-deficient groups on *ortho*-, *meta*-, *para*- position of aryl ring were suitable substrates for the tandem cyclization reaction and gave corresponding imidazo[1,2-*a*]pyridines in moderate to excellent yields. For example, acetophenones bearing electron rich groups such as methyl, methoxy, dimethoxy provided good yields (48-79%) of tandem products (entries 5-14, Table 2.2). Acetophenones with halo substitutions like fluoro, chloro, and bromo were well tolerated
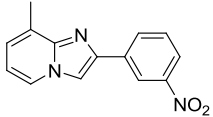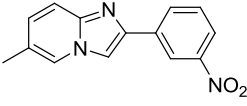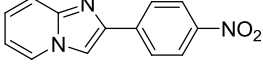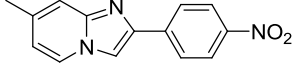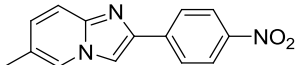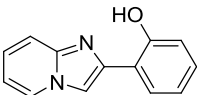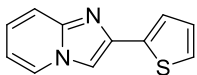
under the reaction conditions and gave good yields (56-87%) of tandem products (entries 15-22, Table 2). When 2'-bromo acetophenone was used as a substrate, reactions proceeded smoothly with the quantitative conversions but traces of debrominated product were observed (entries 19-20, Table 2.2). Acetophenones bearing electron withdrawing groups, such as nitro gave good to excellent yield (52-92%) of corresponding imidazo[1,2-*a*]pyridines (entries 23-28, Table 2.2). It is worth to mention that the synthesis of these 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridines (entries 27 and 28, Table 2.2) is exceptional in the reported oxidative coupling methods.[47, 50] 2-(Imidazo[1,2-*a*]pyridin-2-yl)phenol, which displayed ESIPT could be successfully achieved in 61% yield using the optimized reaction conditions (entry 29, Table 2.2). The optimized condition was smoothly extended towards heterocyclic compound like 2-acetylthiophene and the corresponding tandem product, 2-(thiophen-2-yl) imidazo[1,2-*a*]pyridine was isolated in 56% yield (entry 30, Table 2.2).

Table 2.2 CuI catalyzed tandem synthesis of substituted imidazo[1,2-*a*]pyridines[a]

Entry	Ar	R	Product		% Yield[b]
1	Ph	H		**30aa**	71
2	Ph	4-Me		**30ab**	79
3	$C_{10}H_7$	H		**30ac**	68
4	$C_{10}H_7$	3-Me		**30ad**	60
5	3-MeC_6H_4	H		**30ae**	79
6	3-MeC_6H_4	5-Me		**30af**	73

Entry	Ar	R	Product		% Yield[b]
7	4-MeC$_6$H$_4$	H		**30ag**	72
8	4-MeC$_6$H$_4$	5-Me		**30ah**	76
9	3-OMeC$_6$H$_4$	5-Me		**30ai**	49
10	4-OMeC$_6$H$_4$	H		**30aj**[c]	48
11	4-OMeC$_6$H$_4$	5-Me		**30ak**	62
12	3,4-(OMe)$_2$C$_6$H$_3$	H		**30al**	74
13	3,4-(OMe)$_2$C$_6$H$_3$	3-Me		**30am**	68
14	3,4-(OMe)$_2$C$_6$H$_4$	4-Me		**30an**	71
15	4-FC$_6$H$_4$	H		**30ao**	63
16	4-FC$_6$H$_4$	3-Me		**30ap**	58
17	4-ClC$_6$H$_4$	H		**30aq**	62
18	4-ClC$_6$H$_4$	5-Me		**30ar**	56
19	2-BrC$_6$H$_4$	H		**30as**	60
20	2-BrC$_6$H$_4$	4-Me		**30at**	87
21	4-BrC$_6$H$_4$	H		**30au**	58
22	4-BrC$_6$H$_4$	4-Me		**30av**	76
23	3-NO$_2$C$_6$H$_4$	H		**30aw**	52

Entry	Ar	R	Product		% Yield[b]
24	3-NO$_2$C$_6$H$_4$	3-Me		**30ax**	69
25	3-NO$_2$C$_6$H$_4$	5-Me		**30ay**	60
26	4-NO$_2$C$_6$H$_4$	H		**30az**	86
27	4-NO$_2$C$_6$H$_4$	4-Me		**30ba**	92
28	4-NO$_2$C$_6$H$_4$	5-Me		**30bb**	91
29	2-OHC$_6$H$_4$	H		**30bc**	61
30	2-thienyl	H		**30bd**	56

[a]Reaction conditions; **28** (1.0 mmol), **29** (1.2 mmol), CuI (0.2 mmol), 1,4-dioxane, 100 °C, 14 h.
[b]Isolated yields. [c]Ethanol was used as solvent with reaction time 22 h.

Finally, scope of the methodology was validated by synthesizing zolimidine, drug used for peptic ulcers, in single step (**Scheme 2.13**). When 1-(4-(methylsulfonyl)phenyl)ethanone (**28b**) (1.0 mmol) was treated with **29a** (1.2 mmol) in the presence of CuI (0.2 mmol) in 1,4-dioxane at 100 °C for 14 h, zolimidine (**30be**) was isolated in 61% yield.
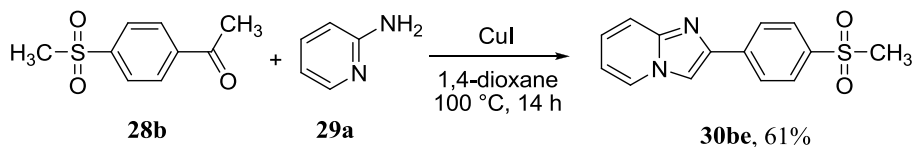
Scheme 2.13 One-step synthesis of zolimidine (**30be**)

The mechanism of the reported reaction is uncertain at this stage. Based on literature precedent,[54, 57-58] it was proposed that reaction initiates with imine formation (**31**) from the reaction of ketone (**28**) and 2-aminopyridine (**29**) which can equilibrate to enamine **32**. Reaction of **32** with CuI generates the adduct **33** that undergoes intramolecular aerobic oxidative cyclization through the intermediate **34** affords the desired fused imidazoles **30** (**Scheme 2.14**).
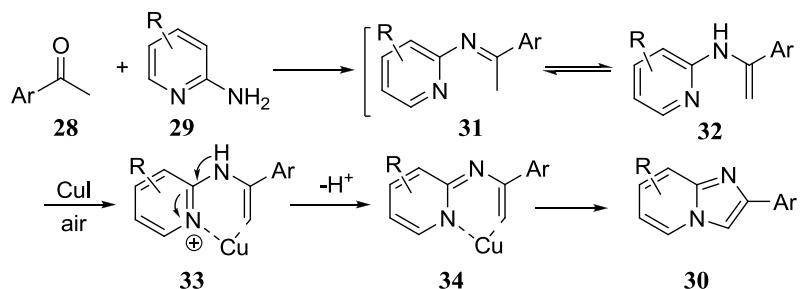
Scheme 2.14 Plausible mechanism for the synthesis of **30aa**

2.3 Conclusions

In summary, we have successfully developed a novel and efficient method for the synthesis of imidazo[1,2-*a*]pyridines, a key structural motif of several important pharmacological drug molecules, from commercially available acetophenones and 2-aminopyridines using CuI as catalyst without the use of any additional Lewis acid or external ligand. Since, the depicted methodology tolerates several reactive functionalities such as fluoro, chloro, bromo, hydroxyl, nitro, methoxy etc, these tandem products will allow access to complex molecules by post functionalization. The present methodology is smoothly extended to synthesize anti-ulcer drug, Zolimidine in single step.

2.4 Experimental

General: Melting points were determined in open capillary tubes on a EZ-Melt automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates (Merck). The chemical structures of final products were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) determined on a Bruker AV 300 spectrometer. ^{13}C NMR spectra were fully decoupled. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (internal) as the standard. All chemicals were obtained from commercial suppliers and used without further purification.

General procedure for the synthesis of 2-phenylimidazo[1,2-*a*]pyridines (30a) *via* tandem oxidative amination and cyclizations: A clean oven-dried 10 mL RB flask was charged with **28** (94 mg, 1.0 mmol), **29** (145 mg, 1.2 mmol), CuI (38 mg, 0.2 mmol) and 1,4-dioxane (3.0 mL).

The resulting solution was stirred at 100 °C for 14 h under ambient air. On completion, the reaction mass was evaporated to dryness. The crude residue was purified by column chromatography (EtOAc: hexanes, 1:2) to obtain 2-phenylimidazo[1,2-*a*]pyridine (**30a**).

2-Phenylimidazo[1,2-*a*]pyridine (30aa)
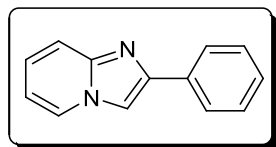
Yield 71%; off-white solid; mp 134-136 °C (Lit.[59] 136-137 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.11 (d, *J* = 6.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.85 (s, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.78 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.74, 137.95, 133.65, 128.69, 127.99, 126.11, 125.59, 124.76, 117.55, 112.51, 108.19.

7-Methyl-2-phenylimidazo[1,2-*a*]pyridine (30ab)
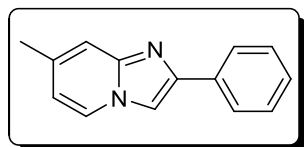
Yield 79%; off-white solid; mp 162-164 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00 – 7.84 (m, 3H), 7.71 (s, 1H), 7.43 – 7.37 (m, 3H), 7.33 – 7.23 (m, 1H), 6.55 (dd, *J* = 6.9, 1.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.14, 145.50, 135.54, 133.97, 128.65, 127.76, 125.97, 124.77, 115.88, 115.00, 107.54, 21.37. HRMS calcd for $C_{14}H_{13}N_2$ 209.1073 found 209.1069 [M + H]$^+$.

2-(Naphthalen-1-yl)imidazo[1,2-*a*]pyridine (30ac)
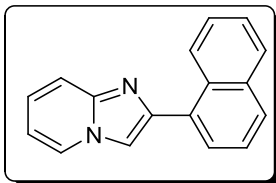
Yield 68%; yellow syrup; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.65 – 8.57 (m, 1H), 8.09 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.92 – 7.79 (m, 3H), 7.78 (s, 1H), 7.68 (dd, *J* = 9.1, 0.7 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.20 – 7.11 (m, 1H), 6.75 (td, *J* = 6.8, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.38, 145.23, 133.99, 131.81, 131.52, 128.47, 128.37, 127.71, 126.46, 125.98, 125.80, 125.57, 125.42, 124.58, 117.70, 112.40, 111.23. HRMS calcd for $C_{17}H_{13}N_2$ 245.1073 found 245.10078 [M + H]$^+$.

8-Methyl-2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridine (30ad)
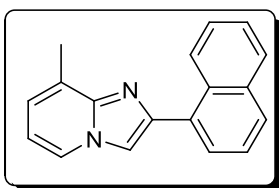
Yield 60%; brown syrup; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.63 – 8.55 (m, 1H), 8.00 (d, *J* = 6.4 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.80 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.77 (s, 1H), 7.56 – 7.45 (m, 3H), 6.99 – 6.95 (m, 1H), 6.69 (t, *J* = 6.8 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$)

δ 145.75, 144.72, 134.00, 132.08, 131.76, 128.35, 128.30, 127.76, 127.72, 126.33, 126.15, 125.75, 125.43, 123.40, 123.26, 112.39, 111.67, 17.27. HRMS calcd for $C_{18}H_{15}N_2$ 259.1230 found 259.1235 $[M + H]^+$.

2-(m-Tolyl)imidazo[1,2-a]pyridine (30ae)
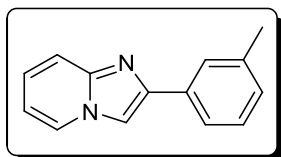
Yield 79%; colourless solid; mp 97-99 °C; ^{1}H NMR (300 MHz, CDCl_3) δ 8.06 (dt, J = 6.8, 1.1 Hz, 1H), 7.83 (s, 1H), 7.81 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.62 (dd, J = 9.1, 0.7 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.18 – 7.08 (m, 2H), 6.73 (td, J = 6.8, 1.1 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.89, 145.63, 138.39, 133.63, 128.75, 128.59, 126.74, 125.56, 124.57, 123.11, 117.48, 112.34, 108.12, 21.45. HRMS calcd for $C_{14}H_{13}N_2$ 209.1073 found 209.10079 $[M + H]^+$.

6-Methyl-2-(m-tolyl)imidazo[1,2-a]pyridine (30af)
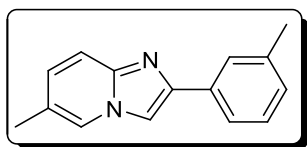
Yield 73%; colorless solid; mp 126-128 °C; ^{1}H NMR (300 MHz, CDCl_3) δ 7.82 (s, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.98 (dd, J = 9.2, 1.4 Hz, 1H), 2.40 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.46, 144.63, 138.33, 133.69, 128.59, 128.54, 127.84, 126.62, 123.31, 123.00, 122.00, 116.70, 107.87, 21.44, 18.07. HRMS calcd for $C_{15}H_{15}N_2$ 223.1230 found 223.1225 $[M + H]^+$.

2-(p-Tolyl)imidazo[1,2-a]pyridine (30ag)
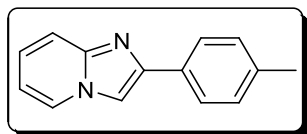
Yield 72%; colorless solid; mp 144-146 °C (Lit.[52] 144-145 °C); ^{1}H NMR (300 MHz, CDCl_3) δ 8.01 (dt, J = 6.8, 1.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.75 (s, 1H), 7.59 (dd, J = 9.1, 0.6 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.14 – 7.06 (m, 1H), 6.69 (td, J = 6.8, 1.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.89, 145.61, 137.76, 130.98, 129.43, 125.93, 125.52, 124.45, 117.38, 112.23, 107.78, 21.30.

6-Methyl-2-(p-tolyl)imidazo[1,2-a]pyridine (30ah)
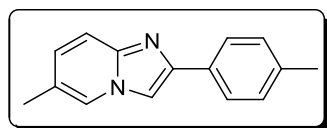
Yield 76%; colorless solid; mp 204-205 °C; ^{1}H NMR (300 MHz, CDCl_3) δ 7.84 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.67 (s, 1H), 7.46

(d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.02 (dd, *J* = 9.2, 1.5 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.10, 144.49, 137.74, 130.56, 129.37, 128.23, 125.73, 123.35, 122.27, 115.92, 107.70, 21.10, 17.85. HRMS calcd for C$_{15}$H$_{15}$N$_2$ 223.1230 found 223.1228 [M + H]$^+$.

2-(3-Methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridine (30ai)
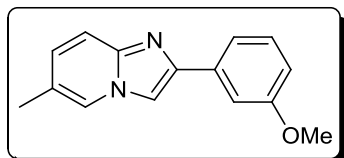
Yield 49%; pale-yellow solid; mp 126-128 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.84 (s, 1H), 7.73 (s, 1H), 7.56 – 7.52 (m, 1H), 7.51 – 7.48 (m, 1H), 7.48 – 7.45 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.87 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.88 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.04, 145.35, 144.67, 135.39, 129.65, 127.84, 123.31, 122.04, 118.40, 116.79, 114.02, 110.85, 108.12, 55.37, 18.08. HRMS calcd for C$_{15}$H$_{15}$N$_2$O 239.1179 found 239.1186 [M + H]$^+$.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (30aj)
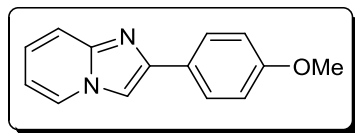
Yield 48%; colorless solid; mp 136-138 °C (Lit.[52] 137-138 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.05 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.73 (s, 1H), 7.59 (dd, *J* = 9.1, 0.7 Hz, 1H), 7.16 – 7.08 (m, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.71 (td, *J* = 6.8, 1.1 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.58, 145.71, 145.61, 127.29, 126.50, 125.46, 124.42, 117.25, 114.14, 112.21, 107.24, 55.30.

2-(4-Methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridine (30ak)
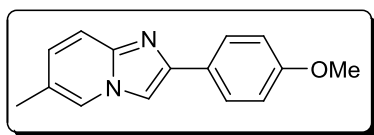
Yield 62%; pale-yellow solid; mp 179-180 °C (Lit.[59] 179-181 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.86 – 7.82 (m, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.63 (s, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.01 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.46, 144.94, 144.49, 128.13, 127.11, 126.18, 123.31, 122.18, 115.83, 114.10, 107.19, 55.20, 17.86.

2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridine (30al)
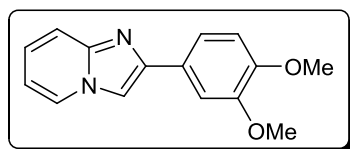
Yield 74%; yellow solid; mp 104-106 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.06 (d, J = 6.8 Hz, 1H), 7.76 (s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 8.3, 2.0 Hz, 1H), 7.17 – 7.09 (m, 1H), 6.93 – 6.88 (m, 1H), 6.72 (td, J = 6.8, 0.9 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 149.23, 149.01, 145.77, 145.56, 126.90, 125.45, 124.46, 118.47, 117.24, 112.27, 111.31, 109.25, 107.49, 56.01, 55.92. HRMS calcd for C$_{15}$H$_{15}$N$_2$O$_2$ 225.1128 found 225.1121 [M + H]$^+$.

2-(3,4-Dimethoxyphenyl)-8-methylimidazo[1,2-*a*]pyridine (30am)
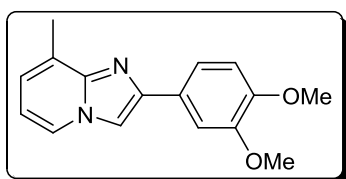
Yield 68%; off-white solid; mp 124-126 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.93 (d, J = 6.7 Hz, 1H), 7.74 (s, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.45 (dd, J = 8.3, 2.0 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.63 (t, J = 6.8 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 149.17, 148.88, 146.09, 145.19, 127.31, 127.26, 123.29, 123.18, 118.58, 112.22, 111.30, 109.48, 107.96, 55.96, 55.92, 17.10. HRMS calcd for C$_{16}$H$_{17}$N$_2$O$_2$ 269.1285 found 269.1278 [M + H]$^+$.

2-(3,4-Dimethoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (30an)
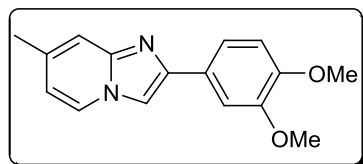
Yield 71%; yellow solid; mp 135-137 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.84 (s, 1H), 7.68 (s, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 8.3, 1.8 Hz, 1H), 6.98 (dd, J = 9.2, 1.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 149.22, 148.88, 145.45, 144.62, 127.63, 127.09, 123.23, 121.87, 118.31, 116.52, 111.29, 109.15, 107.25, 56.01, 55.92, 18.07. HRMS calcd for C$_{16}$H$_{17}$N$_2$O$_2$ 269.1285 found 269.1289 [M + H]$^+$.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine (30ao)
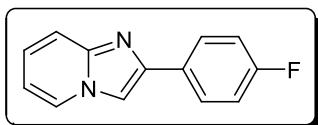
Yield 63%; colorless solid; mp 161-163 °C (Lit.[60] 164-165 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.05 (dt, J = 6.8, 1.1 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.75 (s, 1H), 7.60 (dd, J = 9.1, 0.6 Hz, 1H), 7.19

– 7.05 (m, 3H), 6.73 (td, *J* = 6.8, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.68 (d, *J* = 246.8 Hz), 145.67, 144.90, 130.03 (d, *J* = 3.2 Hz), 127.68 (d, *J* = 8.1 Hz), 125.57, 124.75, 117.43, 115.62 (d, *J* = 21.6 Hz), 112.44, 107.79.

2-(4-Fluorophenyl)-7-methylimidazo[1,2-*a*]pyridine (30ap)
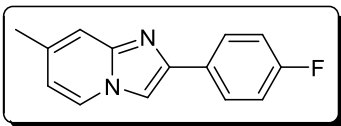
Yield 58%; off-white solid; mp 138-139 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.94 (d, *J* = 6.9 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.68 (s, 1H), 7.35 (d, *J* = 0.6 Hz, 1H), 7.15 – 7.04 (m, 2H), 6.58 (dd, *J* = 6.9, 1.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.59 (d, *J* = 246.5 Hz), 146.16, 144.64, 135.71, 130.20 (d, *J* = 3.2 Hz), 127.58 (d, *J* = 8.1 Hz), 124.75, 115.81, 115.70, 115.24 (d, *J* = 25.6 Hz), 107.18, 21.36. HRMS calcd for C$_{14}$H$_{12}$FN$_2$ 227.0979 found 227.0985 [M + H]$^+$.

2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (30aq)
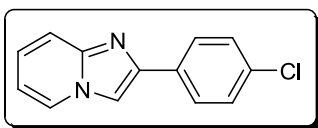
Yield 62%; colorless solid; mp 201-202 °C (Lit.[60] 201-202 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.09 (d, *J* = 6.8 Hz, 1H), 7.86 – 7.78 (m, 3H), 7.58 (d, *J* = 9.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.26 – 7.15 (m, 1H), 6.79 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.58, 144.20, 133.74, 131.87, 128.87, 127.18, 125.72, 125.43, 116.89, 112.83, 108.44. HRMS calcd for C$_{13}$H$_{10}$ClN$_2$ 229.0527 found 229.0524 [M + H]$^+$ 231.0779 [M + H + 2]$^+$.

2-(4-Chlorophenyl)-6-methylimidazo[1,2-*a*]pyridine (30ar)
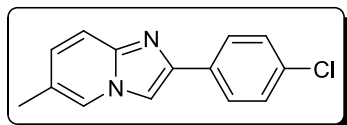
Yield 56%; colorless solid; mp 210-212 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.82 – 7.74 (m, 2H), 7.71 (s, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.05 (dd, *J* = 9.2, 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.59, 143.83, 133.55, 131.96, 128.81, 128.66, 127.04, 123.41, 122.62, 116.08, 108.17, 17.90. HRMS calcd for C$_{14}$H$_{12}$ClN$_2$ 243.0684 found 243.0689 [M + H]$^+$ 245.0221 [M + H + 2]$^+$.

2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine (30as)
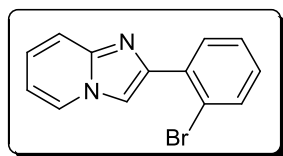
Yield 60%; pale yellow solid; mp 80-81 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.28 (s, 1H), 8.17 – 8.13 (m, 2H), 7.68 – 7.62 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 6.78 (t, *J* = 6.7

Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.53, 143.27, 134.48, 133.64, 131.68, 128.85, 127.50, 125.73, 124.72, 121.50, 117.67, 112.43, 111.97. HRMS calcd for C$_{13}$H$_{10}$BrN$_2$ 273.0022 found 273.0016 [M + H]$^+$ 275.0215 [M + H + 2]$^+$.

2-(2-Bromophenyl)-7-methylimidazo[1,2-*a*]pyridine (30at)
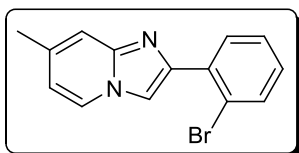
Yield 87%; colorless solid; mp 98-99 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.21 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 6.9 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.36 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 6.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.28, 143.27, 136.09, 134.92, 133.96, 132.01, 129.02, 127.77, 125.25, 121.82, 116.27, 115.47, 111.73, 21.58. HRMS calcd for C$_{14}$H$_{12}$BrN$_2$ 287.0178 found 287.0171 [M + H]$^+$ 289.0189 [M + H + 2]$^+$.

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (30au)
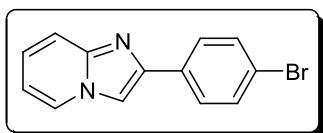
Yield 58%; off-white solid; mp 201-203 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.09 (d, *J* = 6.8 Hz, 1H), 7.87 – 7.75 (m, 3H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.21 – 7.12 (m, 1H), 6.77 (td, *J* = 6.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.73, 144.68, 132.76, 131.83, 127.55, 125.62, 124.95, 121.87, 117.56, 112.62, 108.22. HRMS calcd for C$_{13}$H$_{10}$BrN$_2$ 273.0022 found 273.0026 [M + H]$^+$ 275.0123 [M + H + 2]$^+$.

2-(4-Bromophenyl)-7-methylimidazo[1,2-*a*]pyridine (30av)
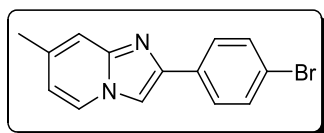
Yield 76%; pale yellow solid; mp 210-212 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.94 (d, *J* = 6.9 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.71 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 1H), 6.59 (dd, *J* = 6.9, 1.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.20, 144.40, 135.88, 132.98, 131.75, 127.46, 124.78, 121.61, 115.89, 115.22, 107.63, 21.40. HRMS calcd for C$_{14}$H$_{12}$BrN$_2$ 287.0178 found 287.0175 [M + H]$^+$ 289.0192 [M + H + 2]$^+$.

2-(3-Nitrophenyl)imidazo[1,2-*a*]pyridine (30aw)
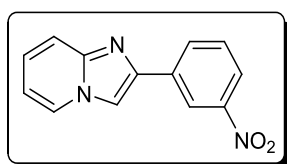
Yield 52%; yellow solid; mp 201-203 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.80 – 8.76 (m, 1H), 8.64 (d, *J* = 0.4 Hz, 1H), 8.56 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.43 – 8.36 (m, 1H), 8.21 – 8.14 (m, 1H), 7.75

(t, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 9.1, 0.7 Hz, 1H), 7.35 – 7.27 (m, 1H), 6.95 (td, *J* = 6.8, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 148.86, 145.49, 142.44, 136.20, 132.17, 130.83, 127.63, 126.17, 122.64, 120.18, 117.34, 113.24, 111.05. HRMS calcd for $C_{13}H_{10}N_3O_2$ 240.0768 found 240.0766 [M + H]$^+$.

8-Methyl-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine (30ax):
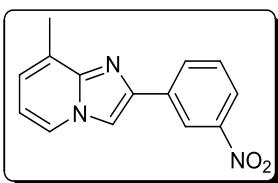
Yield 69%; yellow solid; mp 167-169 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.79 – 8.74 (m, 1H), 8.59 (s, 1H), 8.42 – 8.35 (m, 2H), 8.19 – 8.12 (m, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.16 – 7.06 (m, 1H), 6.84 (t, *J* = 6.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 148.78, 145.97, 141.81, 136.31, 132.12, 130.70, 126.87, 125.28, 124.45, 122.45, 120.07, 113.14, 111.46, 17.10. HRMS calcd for $C_{14}H_{12}N_3O_2$ 254.0924 found 254.0922 [M + H]$^+$.

6-Methyl-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine (30ay)
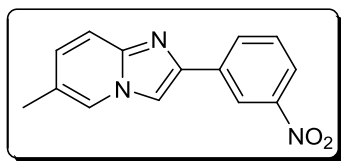
Yield 60%; yellow solid; mp 159-161 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.72 (t, *J* = 1.9 Hz, 1H), 8.32 – 8.26 (m, 1H), 8.17 – 8.10 (m, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.64 – 7.46 (m, 2H), 7.06 (dd, *J* = 9.2, 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.69, 144.97, 143.08, 135.89, 131.65, 129.60, 128.65, 123.47, 122.70, 122.24, 120.57, 117.00, 108.77, 18.11. HRMS calcd for $C_{14}H_{12}N_3O_2$ 254.0924 found 254.0927 [M + H]$^+$.

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine (30az)
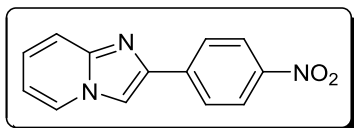
Yield 86%; yellow solid; mp 267-269 °C (Lit.[61] 268-270 °C); ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.65 (s, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 8.31 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.37 – 7.27 (m, 1H), 6.96 (td, *J* = 6.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 146.94, 145.72, 142.45, 140.97, 127.72, 126.76, 126.40, 124.65, 117.45, 113.39, 112.15. HRMS calcd for $C_{13}H_{10}N_3O_2$ 240.0768 found 240.0761 [M + H]$^+$.

7-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (30ba)
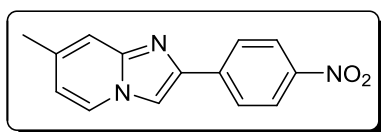
Yield 92%; yellow solid; mp 214-216 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.55 (s, 1H), 8.45 (d, *J* = 7.0 Hz, 1H), 8.29 (d, *J* = 9.1 Hz, 2H), 8.20 (d, *J* = 9.1 Hz, 2H), 7.39 (s, 1H), 6.80 (dd, *J*

= 6.9, 1.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.79, 146.14, 142.22, 141.17, 136.90, 126.86, 126.62, 124.59, 115.89, 115.58, 111.62, 21.33. HRMS calcd for $C_{14}H_{12}N_3O_2$ 254.0924 found 254.0926 [M + H]$^+$.

6-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (30bb)
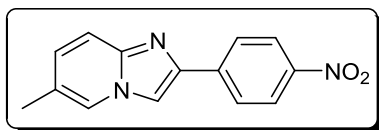
Yield 91%; yellow solid; mp 239-241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.36 (s, 1H), 8.29 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.18 (dd, *J* = 9.3, 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.80, 144.81, 142.27, 141.14, 129.39, 126.61, 124.96, 124.60, 122.67, 116.86, 111.83, 17.98. HRMS calcd for $C_{14}H_{12}N_3O_2$ 254.0924 found 254.0929 [M + H]$^+$.

2-(Imidazo[1,2-*a*]pyridin-2-yl)phenol (3bc)
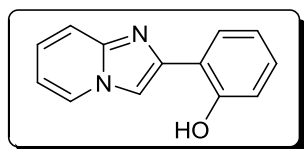
Yield 61%; colorless solid; mp 140-141 °C (Lit.[38] 142-143 °C); ^{1}H NMR (500 MHz, CDCl$_3$) δ 12.76 (s, 1H), 8.16 (d, *J* = 6.7 Hz, 1H), 7.87 (s, 1H), 7.64 – 7.56 (m, 2H), 7.31 – 7.21 (m, 2H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.34, 145.30, 143.44, 129.67, 125.75, 125.41, 125.18, 118.99, 117.70, 116.76, 116.21, 113.16, 106.73.

2-(Thiophen-2-yl)imidazo[1,2-*a*]pyridine (3bd)
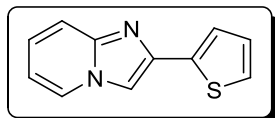
Yield 56%; colorless solid; mp 137-139 °C (Lit.[52] 137-138 °C); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03 (d, *J* = 6.8 Hz, 1H), 7.73 (s, 1H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.29 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.10 – 7.05 (m, 1H), 6.73 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.43, 140.85, 137.54, 127.74, 125.43, 125.03, 124.81, 123.68, 117.30, 112.53, 107.44.

2-(4-(Methylsulfonyl)phenyl)imidazo[1,2-*a*]pyridine (zolimidine, 30be)
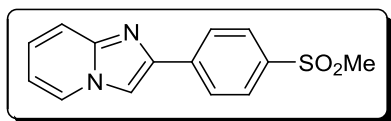
Yield 61%; white-crystalline solid; mp 241-242 °C (Lit.[61] 240-241 °C); ; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.23 – 8.09 (m, 3H), 8.06 – 7.92 (m, 3H), 7.66 (d, *J* = 9.1 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.84 (t, *J* = 6.8 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.95, 143.54, 139.22, 139.20, 127.89, 126.57, 125.81, 125.54, 117.84, 113.08, 109.64, 44.59.

Chapter II

PART-B

Synthesis of 5,7-Diarylpyrazolo[1,5-*a*]-pyrimidines *via* KOH Mediated Tandem Reaction of 1*H*-pyrazol-3-amines and Chalcones

2.5 Introduction

Synthesis of aza-heterocyclic molecules, particularly *N*-fused structures have found augmented interest in recent years due to their plethora of applications in a various domains such as medicinal chemistry, organometallics, and material chemistry. Among them, pyrazolo[1,5-*a*]pyrimidine motifs have received substantial attention because of their ubiquity in several commercial drugs such as zaleplon, indiplon (hypnotic), ocinaplon, lorediplon (anxiolytic) and insecticides such as pyrazophos (**Figure 2.2**).[62-63] Analogues of pyrazolo[1,5-*a*]pyrimidines were found to have a range of biological activities such as antifungal,[64] antibacterial,[65] antitumor,[66] analgesics,[67] anti-inflammatory,[68] anti-trichomonal,[69] KDR kinase inhibition,[70] CRF-1 receptor antagonists,[71-72] estrogen receptor ligands,[73] and COX-2 selective inhibition.[74] Pyrazolo[1,5-*a*]pyrimidines are also key scaffolds for the synthesis of industrial dyes which are used as semiconductors, organic light emitting diodes (OLEDs) and organic field effect transistors (OFETs).[75]
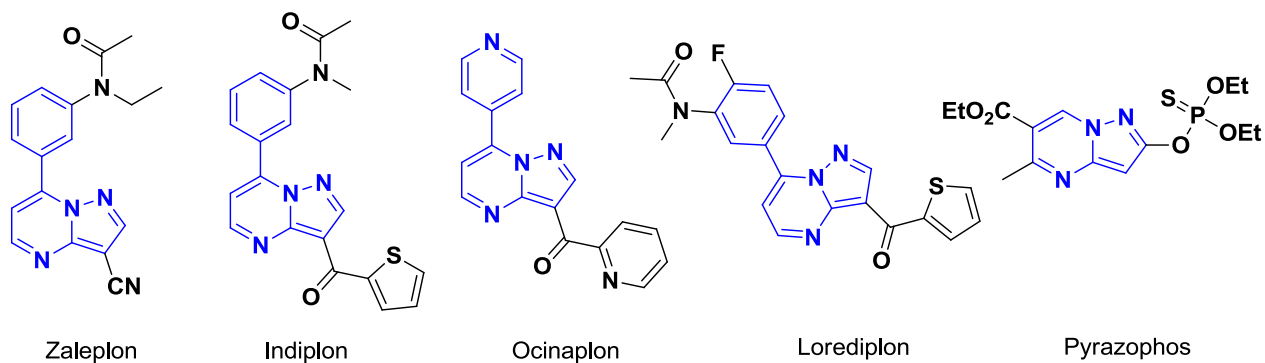
Figure 2.2 Structures of drugs containing pyrazolo[1,5-*a*]pyrimidine scaffold

Due to their extensive applications in various fields, diverse methods have been developed for the synthesis of pyrazolo[1,5-*a*]pyrimidines.[76-81] However, harsh reaction conditions, longer reaction times, low yields, regioselectivity concerns, commercially and economically unattractive bidentate electrophiles and reagents restricted their use in regular processes. Therefore, a straightforward and more efficient approaches which enable to access these structures in a more efficient manner by means of readily available and highly economical precursors and reagents are highly desirable.

On the other hand, simple and highly inexpensive inorganic bases like K_2CO_3, $NaHCO_3$, $NaOH$ and KOH have efficiently mediated the tandem sequences to access bioactive heterocyclic molecules in a single step starting from readily available raw materials. For example, Kawase and colleagues synthesized 2,2-dimethyl-2*H*-chromenes (**37**) through a K_2CO_3 mediated tandem reaction of salicylaldehydes (**35**) and *α,β*-unsaturated esters (**36**) (**Scheme 2.15**).[82] The tandem process proceeded through Michael addition, dehydration and subsequent decarboxylation to deliver good yields of dimethylchromenes.
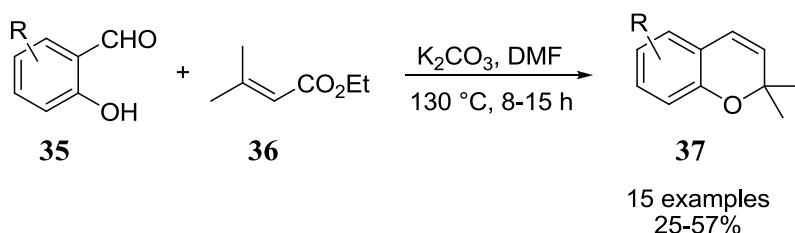
Scheme 2.15 K_2CO_3 mediated synthesis of 2,2-dimethyl-2*H*-chromenes

Rong and colleagues shown that NaOH is an optimum catalyst for the synthesis of densly substituted indanes as well as naphthalene derivatives (**40**) by the tandem protocol involving reaction among arylaldehydes (**5**), malononitrile (**38**) and cyclic ketones (**39**) under solvent-free conditions using a grinding method (**Scheme 2.16**). [83] Surprisingly, the reaction failed to proceed with a stoichiometric amounts of Lewis and Bronsted acids such as $ZnCl_2$, H_2SO_4 respectively and other inorganic salts like Na_2CO_3 and K_2CO_3. Whereas in presence of catalytic amount of strong base like NaOH or KOH, reaction proceeded smoothly and offered good yields of tandem products (**40**).
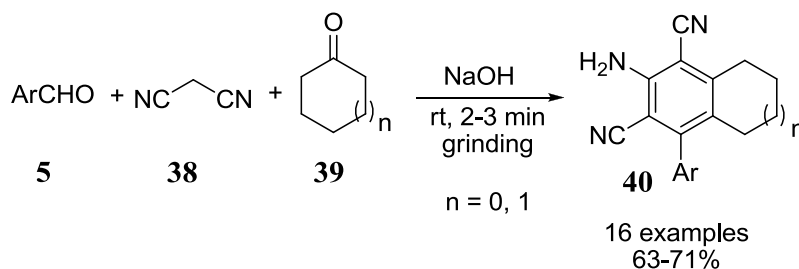
Scheme 2.16 NaOH mediated synthesis of indanes and naphthalenes

Chalcones [1,3-diarylprop-2-en-1-ones] (**41**) are an effective bidentate electrophiles and have been employed for the synthesis of various bioactive heterocycles.[84-87] They are efficient

Michael acceptors and offer a wide variety of heterocycles when reacted with a range of bi-nucleophiles. For example, dihydropyrimidinones (**42**), isooxazolines (**43**) and pyrazolines (**44**) could be prepared when chalcones are treated with urea, hydroxylamine and hydrazine respectively (**Scheme 2.17**).[88]
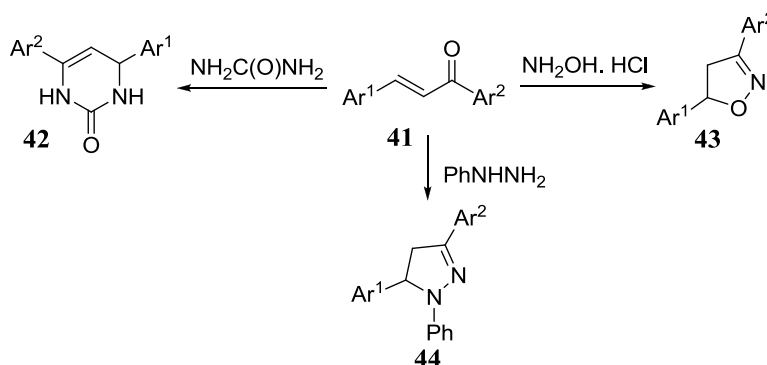
Scheme 2.17 Synthesis of various heterocyclic motifs from chalcones

Tu and collaborators prepared *N*-substituted 2-aminopyridines (**46**) starting from chalcones (**41**) through a microwave assisted tandem multicomponent approach (**Scheme 2.18**).[89] Here, chalcones (**41**) were treated with malononitrile (**38**) and a wide variety of primary amines (**45**) to afford good yields of highly substituted aminopyridines (**46**). This tandem protocol follows Michael addition, intramolecular condensation and subsequent aromatization to deliver desired aminopyridines.
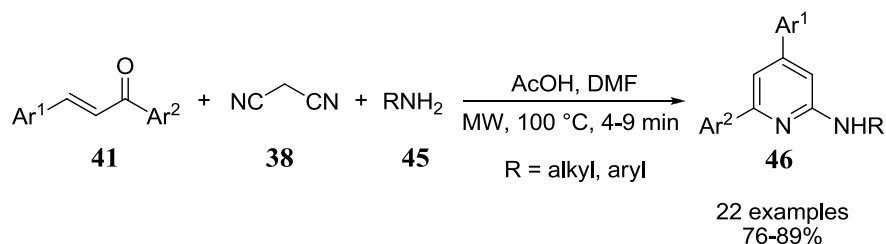
Scheme 2.18 Synthesis of 2-aminopyridines from chalcones

van Leusen *et al.* reported a tandem protocol for the synthesis of pyrroles (**48**) through the reaction of chalcones (**41**) and TosMIC (**47**) in the presence of KO*t*Bu or NaH (**Scheme 2.19**).[90] Michael addition followed by *5-endo-dig* cyclization and finally tosylate ion elimination sequence offered the desired 3,4-disubstituted pyrroles (**48**) in good yields.
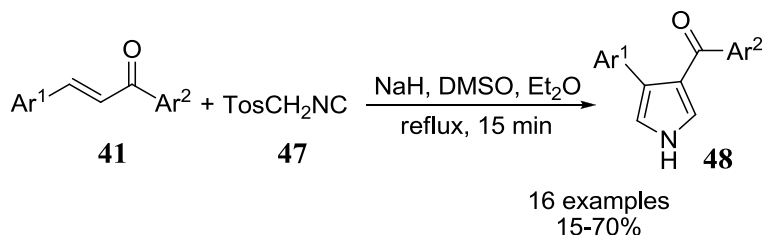
Scheme 2.19 Synthesis of pyrroles from chalcones

Very few reports were found where chalcones (**41**) were used as substrates for the synthesis of pyrazolo[1,5-*a*]pyrimidines (**51**). Lipson and co-workers reported that dihydropyrazolo[1,5-*a*]pyrimidines (**50**) could be obtained as imine-enamine tautomeric mixtures when chalcones were treated with 3-aminopyrazoles (**49**) under argon atmosphere (**Scheme 2.20**).[91] Formation of pyrazolo[1,5-*a*]pyrimidines (**51**) was also observed along with dihydro tautomers (**50**) under aerobic conditions.
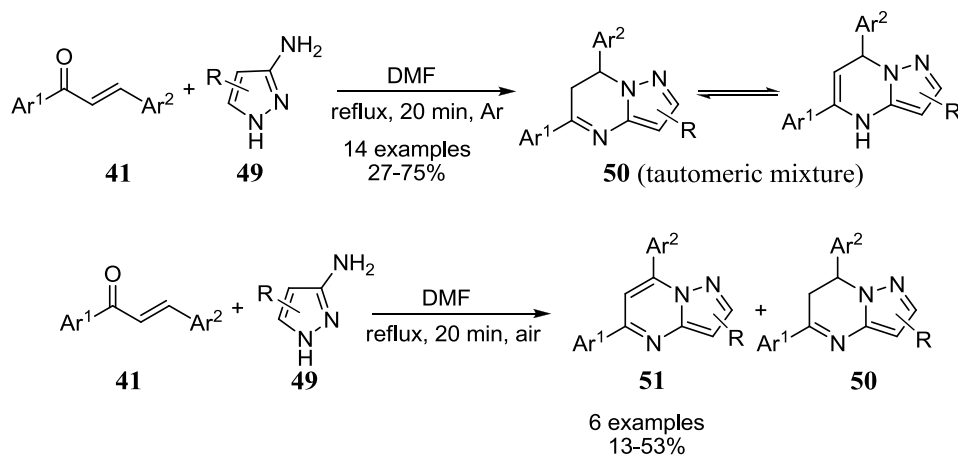
Scheme 2.20 Synthesis of dihydropyrazolo[1,5-*a*]pyrimidines from chalcones

Elnagdi and Erian prepared a couple of 2,3,5,7-tetrasubstituted pyrazolo[1,5-*a*]pyrimidines (**51**) with chalcones (**41**) as precursors in the presence of $NH_4OAc/AcOH$ (**Scheme 2.21**).[92] This report mainly focussed on reactions of 1*H*-pyrazol-3-amines (**49**) with various electrophiles such as 3-dimethylaminopropiophenone, cinnamaldehyde, tetracyanoethylene together with chalcones for the construction of pyrazolo[1,5-*a*]pyrimidines (**51**).

Scheme 2.21 Synthesis of pyrazolo[1,5-*a*]pyrimidines from chalcones

With our interest in the synthesis of aza-fused heterocycles, we have developed a facile method for the synthesis of 5,7-diarylpyrazolo[1,5-*a*]pyrimidines (**51**) by cyclocondensation of chalcones (**41**) and 3-aminopyrazoles (**49**) in the presence of catalytic amount of KOH.[93]

2.6 Results and Discussion

We began our investigation with the reaction of chalcone (**41a**) and 1*H*-pyrazol-3-amine (**49a**) in presence of 2 equiv. of K_2CO_3 in toluene at 110 °C (**Scheme 2.22**). To our surprise, dihydro pyrazolo[1,5-*a*]pyrimidine (**50a**) was not detected in the reaction, and the expected 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**51a**) was isolated in 52% yield.

Scheme 2.22 K_2CO_3 mediated synthesis of pyrazolo[1,5-*a*]pyrimidines from chalcones

The structure of **51a** was characterized by NMR data and compared with previous reports. Characteristic two doublets at δ 8.20 and 6.83 ppm (with *J* = 2.2 Hz) corresponding to C-2 and C-3 protons of pyrazole ring, and a singlet at δ 7.36 ppm for C-6 proton of pyrimidine ring appeared in the ¹H NMR of **51a**. All other protons were located at their respective positions. Additionally, ¹³C NMR and melting point were in agreement with literature reports.[94] A representative ¹H and ¹³C NMR of **51a** is shown in **Figure 2.3**.

Figure 2.3 ^{1}H and ^{13}C NMR spectra (in CDCl$_3$; recorded on a Bruker AV 300 spectrometer) of 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**51a**)

With this result, further optimization was carried out by varying the solvent, base, temperature and reaction times to improve the yields of **51a** (Table 2.3). When various solvents were screened, it was realized that the best yield of **51a** was obtained in DMF (entry 5, Table 2.3). Moderate yield of **51a** was obtained in 1,4-dioxane and toluene whereas reaction did not proceed in acetonitrile and water (entries 1-4, Table 2.3). Increasing the reaction temperatures did not let to improvement in the yield of **51a** but decreasing the temperature had negative effect on the yield of **51a** (entries 6-7, Table 2.3). Excellent improvement in the yield (from 78% to 95%) of **51a** was observed by replacing K_2CO_3 with KOH (entry 8, Table 2.3). With KOH as a optimum base for this transformation, further efforts were made to reduce the equivalents of base and it was found that catalytic amount of KOH can efficiently promote the tandem cyclocondensation and rapid aromatization in short reaction time (entries 8-10, Table 2.3). When the tandem reaction was performed in the absence of base poor yield of **51a** was observed (entry 12, Table 2.3). Under microwave irradiation, cyclocondensation proceeded smoothly to afford **51a** in good yields (entry 13, Table 2.3). With the aforesaid investigations, 10 mol % of KOH in DMF for 20 min was found to be most favourable condition for the targeted tandem process (entry 10, Table 2.3).

With the standardized conditions in hand, we turned our focus to unearth the generality of the method to access substituted pyrazolo[1,5-*a*]pyrimidines (**51**) and the results are summarized in Table 2.4. It was observed that 3-aminopyrazole with C-5 substitutions such as methyl, aryl and heteroaryl groups smoothly participated to afford corresponding fused pyrazoles **51b**, **51d-f** in good to high yields (entries 2, 4-6, Table 2.4). However, 3-aminopyrazole with C_4-cyano substitution gave moderate yields of fused products (entry 3, Table 2.4). Similarly, chalcones with substitutions like methyl, methoxy, cyano, nitro on both the aryl groups underwent smooth cyclization to afford the tandem products in moderate to good yields (entries 7-15, Table 2.4). Reactive hydroxyl group at *ortho*-position on Ar[1] was well tolerated under the present conditions and produced corresponding fused azoles **51p** in moderate yields (entry 16, Table 2.4). To our delight chalcone, (*E*)-3-phenyl-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one bearing pyrrole functionality also participated in tandem cyclization and resulted 55% yield of novel pyrazolo[1,5-*a*]pyrimidine **51q** (entry 17, Table 2.4).

Table 2.3 Optimization of reaction conditions for the synthesis of **51a**[a]
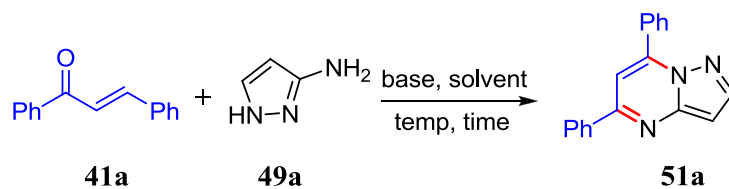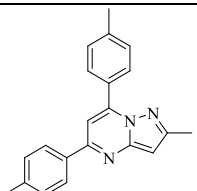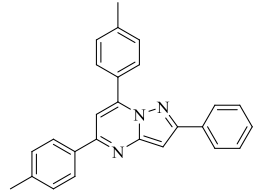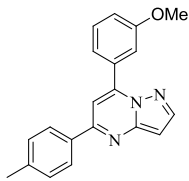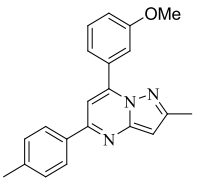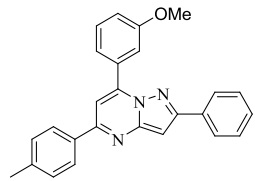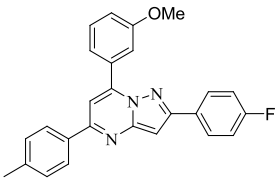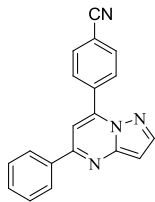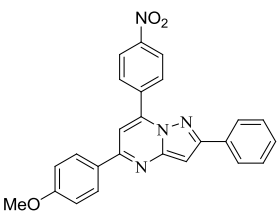
Entry	Base (equiv)	Solvent	Time	Temp (°C)	% Yield[b]
1	K_2CO_3 (2)	toluene	6 h	110	52
2	K_2CO_3 (2)	1,4-dioxan	6 h	110	57
3	K_2CO_3 (2)	CH_3CN	6 h	80	NR[c]
4	K_2CO_3 (2)	H_2O	6 h	100	NR[c]
5	K_2CO_3 (2)	DMF	6 h	110	78
6	K_2CO_3 (2)	DMF	6 h	150	80
7	K_2CO_3 (2)	DMF	6 h	50	47
8	KOH (2)	DMF	20 min	110	95
9	KOH (1.5)	DMF	20 min	110	92
10	**KOH (0.1)**	**DMF**	**20 min**	**110**	**89**
11	KOH (0.1)	DMF	20 min	80	75
12	–	DMF	6 h	110	32
13	KOH (0.1)	DMF	5 min	110	76[d]

[a]Reaction conditions: **41a** (1 mmol), **49a** (1.2 mmol), base, solvent (5 mL), temp, time. [b]Isolated yields. [c]No product formation was observed. [d]Under microwave irradiation.

Table 2.4 Substrate scope for the tandem synthesis of 5,7-diaryl pyrazolo[1,5-a]pyrimidines[a]
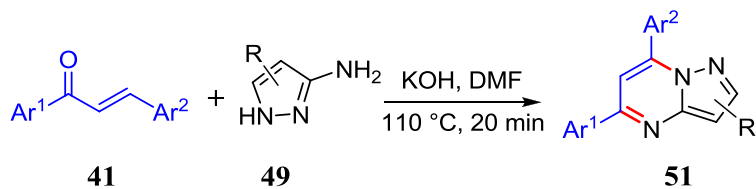
Entry	Ar^1	Ar^2	R	Product		% Yield[b]
1	C_6H_5	C_6H_5	H		**51a**	89
2	C_6H_5	C_6H_5	5-Me		**51b**	82
3	C_6H_5	C_6H_5	4-CN		**51c**	58
4	C_6H_5	C_6H_5	5-C_6H_5		**51d**	83
5	C_6H_5	C_6H_5	5-(4-FC_6H_4)		**51e**	82
6	C_6H_5	C_6H_5	5-(2-thienyl)		**51f**	86
7	4-MeC_6H_4	4-MeC_6H_4	H		**51g**	71

Entry	Ar[1]	Ar[2]	R	Product		% Yield[b]
8	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	5-Me		**51h**	70
9	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	5-C$_6$H$_5$		**51i**	67
10	4-MeC$_6$H$_4$	3-OMeC$_6$H$_4$	H		**51j**	66
11	4-MeC$_6$H$_4$	3-OMeC$_6$H$_4$	5-Me		**51k**	69
12	4-MeC$_6$H$_4$	3-OMeC$_6$H$_4$	5-C$_6$H$_5$		**51l**	95
13	4-MeC$_6$H$_4$	3-OMeC$_6$H$_4$	5-(4-FC$_6$H$_4$)		**51m**	78
14	C$_6$H$_5$	4-CNC$_6$H$_4$	H		**51n**	75
15	4-OMeC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	5-C$_6$H$_5$		**51o**	45

Entry	Ar[1]	Ar[2]	R	Product	% Yield[b]
16	2-OHC$_6$H$_4$	C$_6$H$_5$	H	**51p**	41[c]
17	2-C$_4$H$_4$N	3-ClC$_6$H$_4$	5-C$_6$H$_5$	**51q**	55

[a]Reaction conditions: **41** (1.0 mmol), **49** (1.2 mmol), KOH (0.1 mmol), DMF (5 mL), 110 °C, 20 min.
[b]Isolated yields. [c]Reaction time was 2 h.

With the success over generality of the protocol, the reaction of chalcone (**41a**), and 1*H*-pyrazol-3-amine (**49a**) was performed in gram-scale which afforded 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**51a**) in 81% isolated yield which further showed the potency of optimized condition for the bulk processes (**Scheme 2.23**).

41a, 1.0 g   **49a**   KOH, DMF, 110 °C, 20 min   **51a** 1.04 g (81%)
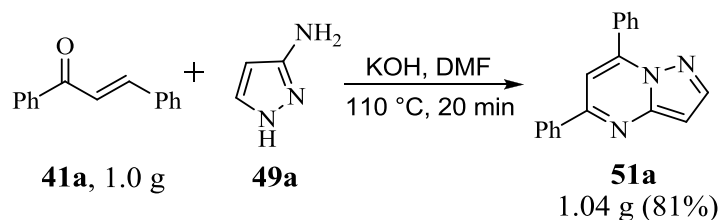
Scheme 2.23 Gram-scale synthesis of 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**51a**)

Based on our experimental observations and previous reports,[93] two paths (path I and path II) are possible for this transformation as shown in **Scheme 2.24**. The most preferred path seems to be path I, where Michael addition of 1*H*-pyrazol-3-amine (**49**) on chalcone (4**1**) through its tautomer gives Michael adduct **52**. Intramolecular imine formation from **52** gives dihydropyrazolo[1,5-*a*]pyrimidines **50** (path I, **Scheme 2.24**). In path II, initial condensation of amine with carbonyl group of chalcone results in the formation of intermediate **53** which on intramolecular Michael addition gives **50**. Arial oxidation of **50** leads to the formation of **51**.
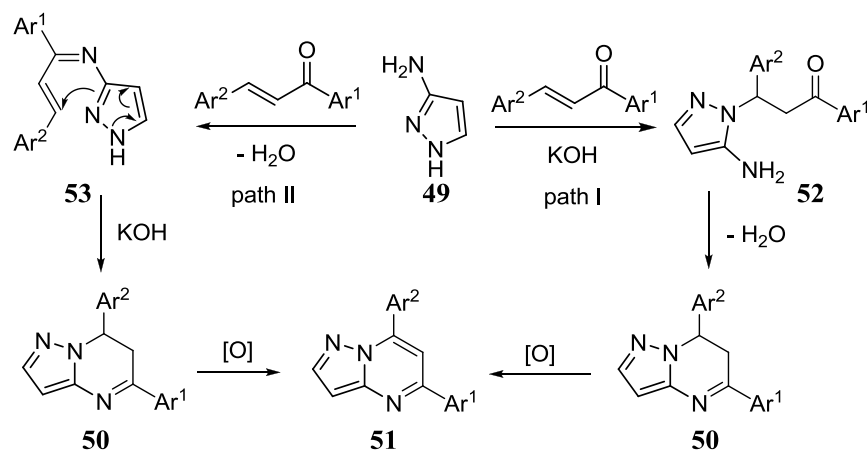
Scheme 2.24 Plausible mechanism for the formation of pyrazolo[1,5-*a*] pyrimidines (**51**)

2.7 Conclusions

In conclusion, we have demonstrated a simple and effective protocol for the synthesis of substituted pyrazolo[1,5-*a*]pyrimidines through tandem reaction of chalcones and 1*H*-pyrazol-3-amines in the presence of catalytic amount of KOH. Mild reaction conditions, shorter reaction times, high yields, good functional group tolerance, simplified isolation procedures are some of the salient features of the reported method. A gram-scale reaction has been attempted to illustrate the potency of reported procedure towards the bulk synthesis.

2.8 Experimental

General: Chalcones were synthesized by reacting acetophenones and arylaldehydes employing the procedure reported previously.[95] All other chemicals were obtained from commercial suppliers and were used without further purification. Silica gel 60-120 mesh was used for column chromatography.

Representative procedure for the synthesis of 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (51a)

An oven dried 25 mL RB flask was charged with chalcone (**41a**, 208 mg, 1.0 mmol), 3-aminopyrazole (**49a**, 100 mg, 1.2 mmol), KOH (6 mg, 0.1 mmol) and DMF (5 mL). The resulting solution was stirred at 110 °C for 20 min. On completion, the reaction mass was allowed to cool to ambient temperature, diluted with water (20 mL) and extracted into ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and

organic solvent was evaporated on a rotatory evaporator. The crude residue was purified by column chromatography (silica gel 60-120 mesh, eluent 20% EtOAc/hexanes).

5,7-Diphenylpyrazolo[1,5-*a*]pyrimidine (51a)
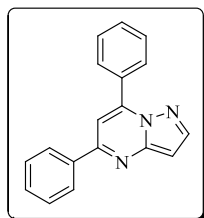
Yield 89%; off-white solid; mp 83-85 °C (Lit.[94] 85-86 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.20 (d, J = 2.2 Hz, 1H), 8.18 – 8.13 (m, 2H), 8.09 (dd, J = 6.5, 2.6 Hz, 2H), 7.64 – 7.58 (m, 3H), 7.57 – 7.50 (m, 3H), 7.36 (s, 1H), 6.83 (d, J = 2.2 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.20, 149.89, 146.84, 145.20, 137.54, 131.54, 130.96, 130.31, 129.27, 128.95, 128.73, 127.29, 105.20, 97.20.

2-Methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (51b)
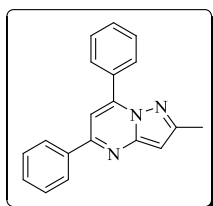
Yield 82%; yellow solid; mp 115-117 °C (Lit.[94] 110-112 °C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.21 – 8.02 (m, 4H), 7.63 – 7.57 (m, 3H), 7.57 – 7.49 (m, 3H), 7.27 (s, 1H), 6.61 (s, 1H), 2.57 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.85, 155.46, 150.69, 146.19, 137.77, 131.71, 130.89, 130.11, 129.30, 128.89, 128.69, 127.23, 104.43, 96.50, 14.93.

5,7-Diphenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (51c)
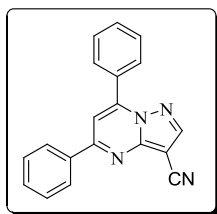
Yield 58%; off−white solid; mp 188-191 °C (Lit.[91] 194-195); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.43 (s, 1H), 8.32 – 8.26 (m, 2H), 8.08 – 8.04 (m, 2H), 7.68 – 7.63 (m, 3H), 7.62 (s, 1H), 7.61 – 7.58 (m, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.60, 151.42, 148.32, 147.41, 135.84, 131.84, 131.65, 130.07, 129.45, 129.16, 128.96, 127.78, 113.35, 107.22, 83.04.

2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine (51d)
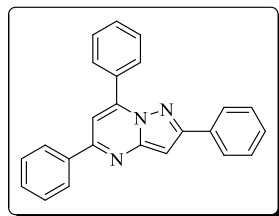
Yield 83%; off-white solid; mp 155-157 °C (Lit.[94] 154-155 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.31 – 8.22 (m, 2H), 8.21 – 8.15 (m, 2H), 8.08 – 8.01 (m, 2H), 7.68 – 7.60 (m, 3H), 7.60 – 7.53 (m, 3H), 7.52 – 7.46 (m, 2H), 7.42 – 7.41 (m, 1H), 7.39 (s, 1H), 7.13 (s, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 156.25, 156.07, 151.09, 146.34, 137.60, 133.05, 131.45, 130.94, 130.21, 129.57, 128.90, 128.66, 127.28, 127.12, 126.68, 126.50, 105.04, 93.72.

2-(4-Fluorophenyl)-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (51e)
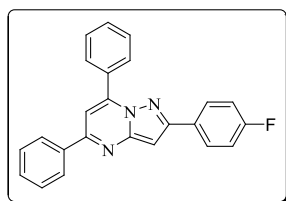
Yield 82%; ash colored solid; mp 157-158 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.26 – 8.21 (m, 2H), 8.19 – 8.17 (m, 1H), 8.17 – 8.15 (m, 1H), 8.06 – 7.99 (m, 2H), 7.66 – 7.61 (m, 3H), 7.59 – 7.51 (m, 3H), 7.39 (s, 1H), 7.20 – 7.13 (m, 2H), 7.06 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.34 (d, J = 248.01 Hz), 156.24, 155.34, 151.19, 146.39, 137.57, 131.44, 131.04, 130.32, 129.52, 129.31 (d, J = 3.12 Hz), 128.97, 128.62, 128.39 (d, J = 8.26 Hz), 127.26, 115.68 (d, J = 21.65 Hz), 105.13, 93.54. HRMS calcd for C$_{24}$H$_{17}$FN$_3$ 366.1401 found 366.1408 [M + H]$^+$.

5,7-Diphenyl-2-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (51f)
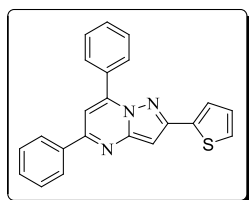
Yield 86%; off-white solid; mp 153-155 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.26 – 8.21 (m, 2H), 8.19 – 8.14 (m, 2H), 7.65 – 7.61 (m, 4H), 7.59 – 7.50 (m, 3H), 7.41 – 7.35 (m, 2H), 7.17 – 7.11 (m, 1H), 7.00 (s, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.33, 151.57, 151.04, 146.23, 137.54, 136.44, 131.32, 131.03, 130.30, 129.52, 128.94, 128.58, 127.74, 127.25, 126.29, 125.78, 105.05, 93.56. HRMS calcd for C$_{22}$H$_{16}$N$_3$S 354.1059 found 354.1056 [M + H]$^+$.

5,7-Di(*p*-tolyl)pyrazolo[1,5-*a*]pyrimidine (51g)
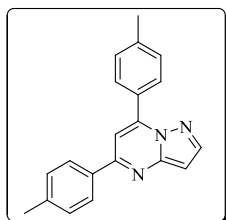
Yield 71%; yellow solid; mp 109-110 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.16 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 8.01 – 7.96 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 7.34 (s, 2H), 6.79 (d, J = 2.3 Hz, 1H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.16, 149.92, 146.84, 145.02, 141.32, 140.56, 134.81, 129.66, 129.39, 129.19, 128.70, 127.19, 104.70, 96.86, 21.58, 21.42. HRMS calcd for C$_{20}$H$_{18}$N$_3$ 300.1495 found 300.1494 [M + H]$^+$.

2-Methyl-5,7-di(p-tolyl)pyrazolo[1,5-*a*]pyrimidine (51h)
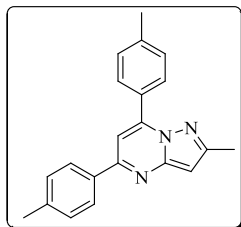
Yield 70%; yellow solid; mp 155-157 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.02 – 7.92 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 6.57 (s, 1H), 2.56 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.79, 155.22, 150.73, 146.18, 141.19, 140.30, 135.04, 129.59, 129.34, 129.22, 128.88, 127.12, 103.91, 96.18, 21.57, 21.39, 14.93. HRMS calcd for C$_{21}$H$_{20}$N$_3$ 314.1652 found 314.1655 [M + H]$^+$.

2-Phenyl-5,7-di(*p*-tolyl)pyrazolo[1,5-*a*]pyrimidine (51i)
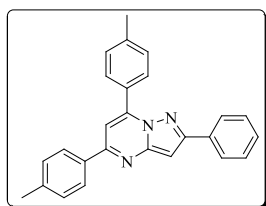
Yield 67%; off-white solid; mp 170-172 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 8.09 – 8.02 (m, 4H), 7.55 – 7.40 (m, 5H), 7.38 – 7.32 (m, 3H), 7.09 (s, 1H), 2.52 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.06, 151.18, 146.34, 141.34, 140.48, 134.91, 133.25, 129.65, 129.47, 129.25, 128.92, 128.80, 128.67, 127.85, 127.14, 126.62, 104.53, 93.47, 21.62, 21.43. HRMS calcd for C$_{26}$H$_{22}$N$_3$ 376.1808 found 376.1805 [M + H]$^+$.

7-(3-Methoxyphenyl)-5-p-tolylpyrazolo[1,5-*a*]pyrimidine (51j)
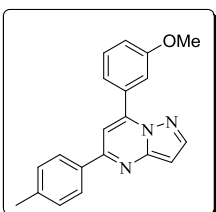
Yield 66%; off-white solid; mp 93-95 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (d, J = 2.3 Hz, 1H), 8.08 – 8.03 (m, 2H), 7.65 – 7.61 (m, 2H), 7.56 – 7.49 (m, 1H), 7.37 (d, J = 5.3 Hz, 1H), 7.36 (s, 1H), 7.35 (s, 1H), 7.17 – 7.09 (m, 1H), 6.80 (d, J = 2.3 Hz, 1H), 3.92 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.65, 156.16, 149.92, 146.58, 145.13, 140.66, 134.72, 132.82, 129.83, 129.69, 127.20, 121.57, 116.54, 114.89, 105.10, 96.98, 55.50, 21.42. HRMS calcd for C$_{20}$H$_{18}$N$_3$O 316.1444 found 316.1448 [M + H]$^+$.

7-(3-Methoxyphenyl)-2-methyl-5-p-tolylpyrazolo[1,5-*a*]pyrimidine (51k)
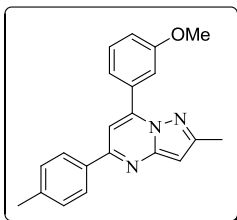
Yield 69%; white solid; mp 113-115 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.25 (s, 1H), 7.12 (d, J = 6.7 Hz, 1H), 6.58 (s, 1H), 3.92 (s, 3H), 2.55 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.59, 155.83, 155.34, 150.71, 145.91, 140.41, 134.92, 132.97, 129.77, 129.62, 127.12, 121.62, 116.54, 114.91, 104.31, 96.29, 55.49, 21.39, 14.91. HRMS calcd for C$_{21}$H$_{20}$N$_3$O 330.1601 found 330.1605 [M + H]$^+$.

7-(3-Methoxyphenyl)-2-phenyl-5-p-tolylpyrazolo[1,5-*a*]pyrimidine (51l)
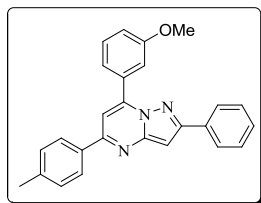
Yield 95%; ash colour solid; mp 135-137 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.10 – 8.03 (m, 4H), 7.91 – 7.86 (m, 1H), 7.78 – 7.72 (m, 1H), 7.53 – 7.40 (m, 4H), 7.39 – 7.32 (m, 3H), 7.19 – 7.13 (m, 1H), 7.10 (s, 1H), 3.95 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.51, 156.13, 153.06, 151.19, 146.03, 140.58, 134.78, 133.18, 132.74, 129.67, 129.63,

128.85, 128.70, 127.15, 126.58, 121.84, 116.87, 115.00, 104.91, 93.59, 55.54, 21.43. HRMS calcd for $C_{26}H_{22}N_3O$ 392.1757 found 392.1758 $[M + H]^+$.

2-(4-Fluorophenyl)-7-(3-methoxyphenyl)-5-p-tolylpyrazolo[1,5-*a*]pyrimidine (51m)
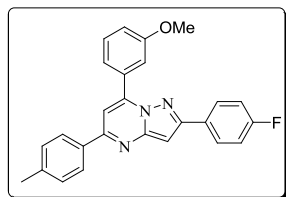
Yield 78%; ash colour solid; mp 152-153 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 8.04 − 7.98 (m, 2H), 7.84 (dd, J = 2.4, 1.7 Hz, 1H), 7.77 − 7.71 (m, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.40 − 7.34 (m, 3H), 7.20 − 7.13 (m, 3H), 7.04 (s, 1H), 3.95 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.29 (d, J = 247.98 Hz), 159.52, 156.19, 155.19, 151.23, 146.05, 140.65, 134.71, 132.67, 129.68, 129.33 (d, J = 8.23 Hz), 128.39 (d, J = 21.64 Hz), 127.14, 121.80, 116.78, 115.76, 115.54, 115.05, 104.98, 93.33, 55.54, 21.43. HRMS calcd for $C_{26}H_{21}FN_3O$ 410.1663 found 410.1669 $[M + H]^+$.

4-(5-Phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)benzonitrile (51n)
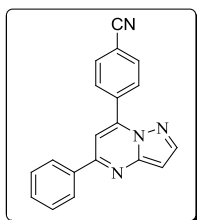
Yield 75%; yellow solid; mp 150-153 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.23 (d, J = 8.3 Hz, 2H), 8.18 (d, J = 2.2 Hz, 1H), 8.17 − 8.12 (m, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.63 − 7.51 (m, 3H), 7.38 (s, 1H), 6.85 (d, J = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.17, 149.80, 145.43, 144.56, 137.08, 135.73, 132.42, 130.64, 130.02, 129.07, 127.27, 118.12, 114.50, 105.58, 97.77. HRMS calcd for $C_{19}H_{13}N_4$ 297.1135 found 297.1129 $[M + H]^+$.

5-(4-Methoxyphenyl)-7-(4-nitrophenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (51o)
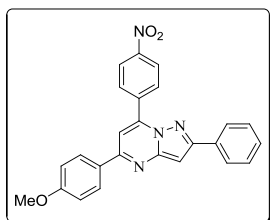
Yield 45%; yellow solid; mp 199-201 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.50 − 8.33 (m, 4H), 8.12 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 7.2 Hz, 2H), 7.54 − 7.40 (m, 3H), 7.33 (s, 1H), 7.09 − 7.01 (m, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.52, 155.66, 151.02, 148.94, 143.63, 137.61, 132.71, 130.59, 129.56, 129.15, 128.80, 128.76, 127.47, 126.55, 123.69, 114.42, 105.12, 93.90, 55.48. HRMS calcd for $C_{25}H_{19}N_4O_3$ 423.1452 found 423.1456 $[M + H]^+$.

2-(7-Phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)phenol (51p)
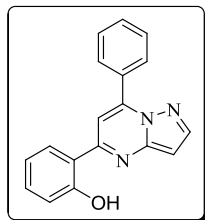
Yield 41%; yellow solid; mp 174-176 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 13.63 (s, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 8.11 − 8.02 (m, 2H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.68 − 7.52 (m, 3H), 7.45 − 7.35 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.64, 157.24, 147.87, 146.71, 145.37, 132.95, 131.30, 131.15, 129.34, 128.80, 127.34, 119.17, 118.86, 117.70, 103.48, 96.29. HRMS calcd for C$_{18}$H$_{14}$N$_3$O 288.1131 found 288.1126 [M + H]$^+$.

7-(3-Chlorophenyl)-2-phenyl-5-(1*H*-pyrrol-2-yl)pyrazolo[1,5-*a*]pyrimidine (51q)
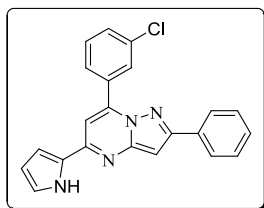
Yield 55%; yellow solid; mp 216-218 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.91 (s, 1H), 8.18 (t, *J* = 1.7 Hz, 1H), 8.08 (dt, *J* = 7.1, 1.6 Hz, 1H), 8.02 − 7.97 (m, 2H), 7.61 − 7.53 (m, 2H), 7.52 − 7.36 (m, 3H), 7.11 (s, 1H), 7.06 − 7.02 (m, 1H), 6.94 − 6.89 (m, 1H), 6.88 (s, 1H), 6.38 (dd, *J* = 6.1, 2.6 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.05, 150.72, 148.92, 144.68, 134.57, 133.19, 133.09, 130.76, 130.16, 129.68, 129.54, 128.80, 128.64, 128.15, 127.64, 126.52, 122.15, 110.93, 103.72, 92.62. HRMS calcd for C$_{22}$H$_{16}$ClN$_4$ 371.1058 found 371.1059 [M + H]$^+$.

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Chapter III

Functionalization of Fused Azaheterocycles by Multi-component Reactions

3.1. Introduction

Multi-component reactions (MCRs), where three or more easily accessible compounds react together in a single step to form a product displaying features of all inputs without isolating the intermediate have become an important tool for generating organic compounds with high degree of molecular diversity (**Figure 3.1**).[1-4] MCRs play an important role in modern synthetic chemistry and offer significant advantages over conventional multi-step syntheses.[5-8] These reactions have broad substrate scope and capability to tolerate diverse functionalities. They allow construction of novel libraries of small sized drug-like molecules with structural diversity, that are of pharmaceutical interest. 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 processes.
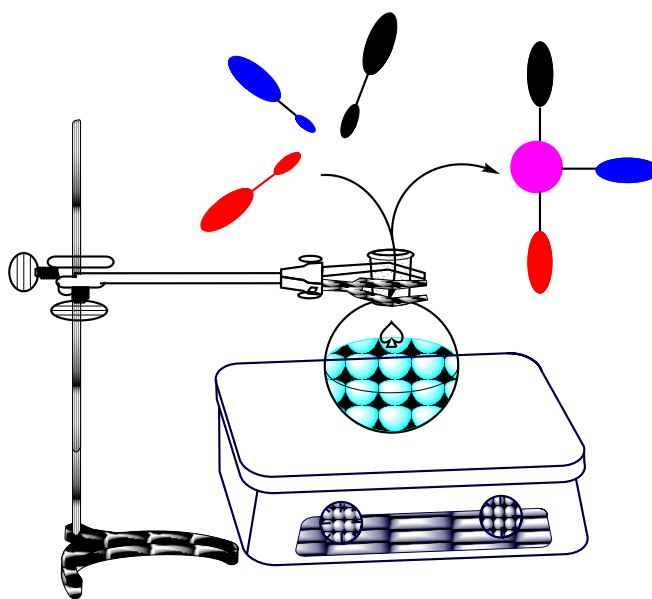
Figure 3.1 General representation of a multi-component reaction

Literature is flooded with the articles of MCRs which show their potency in the synthetic field. Some of the classical MCRs are briefly reviewed.

In 1850, Strecker developed three component reaction (TCR) of aldehydes (**1**), prussic acid (**2**) and ammonia (**3**) for the synthesis of α-aminonitriles (**4**). Subsequent hydrolysis of these products led to the valuable α-aminoacids (**5**) (**Scheme 3.1**).[9] Initially, aldehyde and ammonia

reacts to form iminium ion with the elimination of H_2O, then nucleophilic attack of cyanide ion on iminium carbon yields the three-component product aminonitriles.

$$R^1CHO + HCN + NH_3 \longrightarrow$$
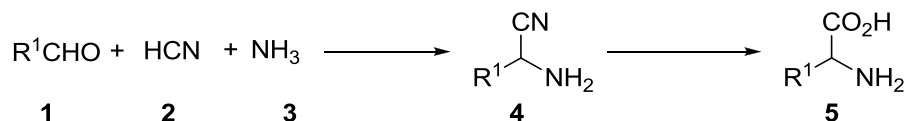
Scheme 3.1 Strecker synthesis of α-amino acids

In 1881, Hantzsch reported the synthesis of dihydropyridines (**7**) by the condensation of aldehydes (**1**), β-ketoesters (**6**) and ammonia (**3**) (**Scheme 3.2**).[10] These three-component products undergoes subsequent aromatization in presence of $KMnO_4$ or HNO_3 to afford the corresponding pyridine analogues.
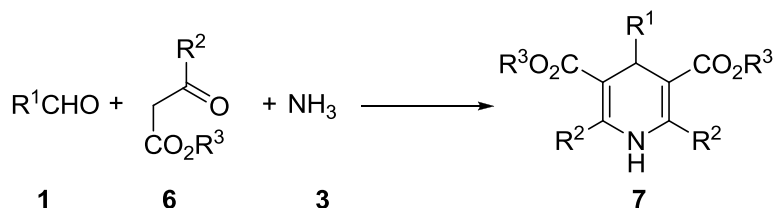
Scheme 3.2 Hantzsch dihydropyridines synthesis

Another important contribution in this area by Biginelli for the synthesis of dihydropyrimidines (**9**) through the acid catalyzed condensation of arylaldehydes (**1**), β-ketoesters (**6**) and urea (**8**) (**Scheme 3.3**).[11] This method has gained great interest due to the outcome of this reaction, pyrimidines are found to have great medicinal values. This procedure is initiated by an aldol condensation among aldehyde and active methylene compound. Then, nucleophilic addition of urea on aldol adduct with the subsequent elimination of H_2O affords the desired product (**9**).
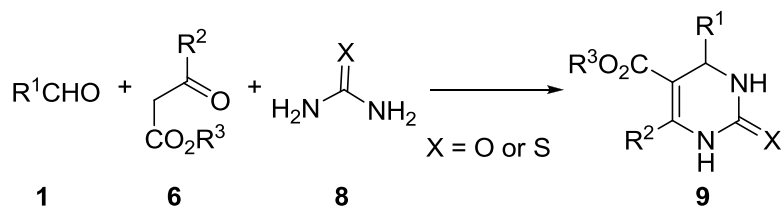
Scheme 3.3 Biginelli three-component synthesis of dihydropyrimidines

In 1912, Mannich disclosed the three component reaction of carbonyl compounds (**10**), primary or secondary amines (**11**) and formaldehyde (**12**) for the synthesis of β-amino carbonyl compounds (**13**) (**Scheme 3.4**).[12] These products are termed as Mannich bases and are produced

through initial formation of imine by reacting amine and formaldehyde with simultaneous attack of carbonyl compound *via* its enol form.
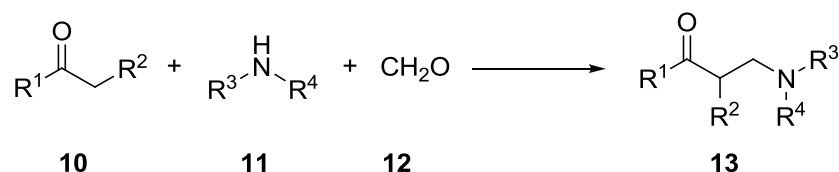
Scheme 3.4 Mannich reaction for the synthesis of *β*-amino carbonyl compounds

Robinson was the foremost scientist who employed the concept of multicomponent reactions for the synthesis of natural products in 1917. This method allowed an easy access to alkaloid, tropinone (**17**) from succinaldehyde (**14**), methylamine (**15**) and calcium salt of acetone dicarboxylic acid (**16**) (**Scheme 3.5**).[13]
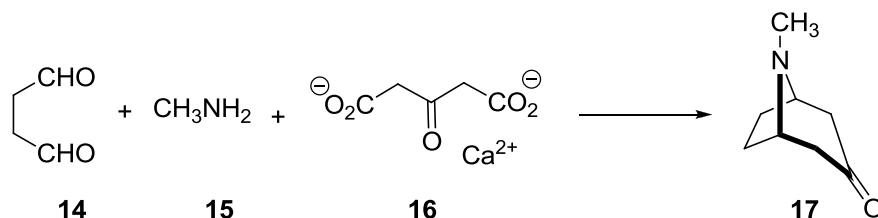
Scheme 3.5 Robinson three-component synthesis of tropinone

Another important foremost isocyanide based multicomponent procedure was discovered by Passerini in 1921 which involved the reaction of carboxylic acids (**18**), carbonyl compounds (**19**) and isonitriles (**20**) for the synthesis of *α*-acyloxy carboxamides (**21**) in a single step (**Scheme 3.6**).[14] Based on reaction media (polar/non-polar solvent) two different reaction pathways were hypothesized for the formation Passerini products.
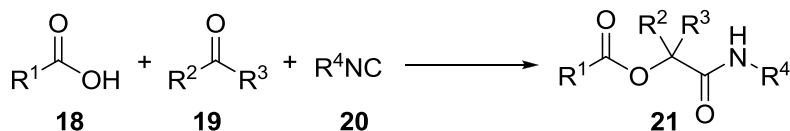
Scheme 3.6 Passerini three-component synthesis of *α*-acyloxy carboxamides

In 1959, Ugi group made a significant breakthrough in this field which portrays the synthesis of *α*-acylamino amides (**23**) through a four-component reaction. Ugi reaction is one of the widely employed method and offers diamides (**23**) by the reaction among aldehydes (**1**), primary amines (**22**), carboxylic acids (**18**) and isonitriles (**20**) (**Scheme 3.7**).[15] It was expected that 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 (**23**).
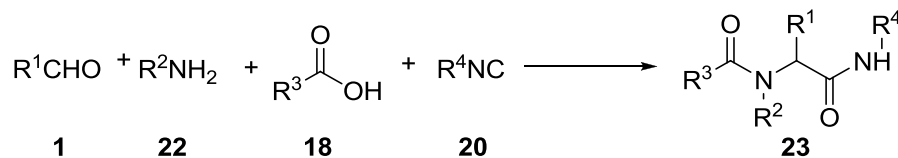
Scheme 3.7 Ugi four-component reaction for the synthesis of α-acylamino amides

In this fashion, unprecedented blossom of reports have been published on MCRs which delivered either potential bioactive motifs in a reduced number of synthetic steps or a new libraries for biological screenings.[16-18] In addition, there are several articles where these multicomponent reactions are amalgamated with other valuable C−C as well as C−heteroatom bond forming reactions in a domino sequence to access complex structures in a single step.[19-21]

The amidoalkyl naphthols (**26**) are important scaffolds for the synthesis of 1,3-amino oxygenated compounds.[22-23] In addition, they are potent biological building blocks in medicinal chemistry.[24] The most recognized method to achieve these motifs is acid catalyzed three component reaction (3CR) of aldehydes (**1**), β-naphthol (**24**) and acetamide (**25**) (**Scheme 3.8**).[25-26] A plethora of reports are available in the literature with diverse Lewis as well as Bronsted acids as a catalysts and variable reaction conditions. Recently, our group has synthesized these motifs by employing environmental benign lanthanide triflate Yb(OTf)$_3$ as a catalyst in eco-friendly ionic liquid, [bmim]BF$_4$ media.[27]
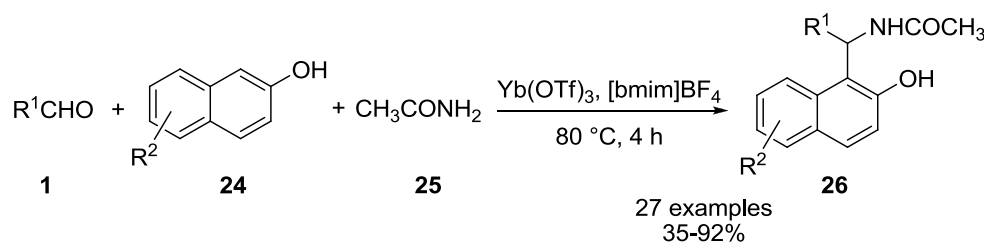
Scheme 3.8 Yb(OTf)$_3$ catalyzed synthesis of amidoalkyl naphthols

Aza-fused heterocyclic moieties such as imidazo[1,2-*a*]pyridine and pyrazolo[1,5-*a*]pyrimidine are core structures of nonbenzodiazepine drugs that are mainly used for treating sleep disorders.[28] For example, imidazo[1,2-*a*]pyridine nucleus is present in zolpidem, alpidem,

necopidem, and saripidem and pyrazolo[1,5-*a*]pyrimidine nucleus is present in ocinaplon and lorediplon drugs. These skeletons are also present in other drugs like zolimidine used for peptic ulcers and zaleplon and indiplon used for hypnotic disorders. Analogues of these two significant motifs have also been studied for various activities such as antifungal,[29] antiviral,[30] CDK inhibition,[31] CRF-1 receptor antagonist,[32] KDR kinase inhibition,[33] phosphodiesterase inhibition,[34] specific serotonin 5-HT6 receptor antagonists,[35] antitumor activity,[36] orally active inhibition of Lck[37] and anxiolytes.[38-39]

Pyrazolo[1,5-*a*]pyrimidine acetamides have been found as high affinity ligands for the translocator proteins.[40] There are very few reports utilized multi-step protocols for the synthesis of pyrazolo[1,5-*a*]pyrimidine acetamides.[41] Owing to the important biological properties of imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines synthesis of novel analogues containing these motifs has attracted interest of several research groups.[42-46]

Recently, Chaubet *et al.* has reported synthesis of polysubstituted 2-amino-1,3-thiazoles *via* tandem aza-Friedel–Crafts reaction/Hantzsch cyclization.[47] They have achieved *N*-[(aryl)(2-alkyl/arylimidazo[1,2-*a*]pyridin-3-yl)-methyl]thiourea (**28**) *via* three-component reaction of imidazo[1,2-*a*]pyridine (**27**), aldehydes (**1**) and thiourea (**8**) using TiCl$_4$ or thiamine.HCl as a catalyst (**Scheme 3.9**).
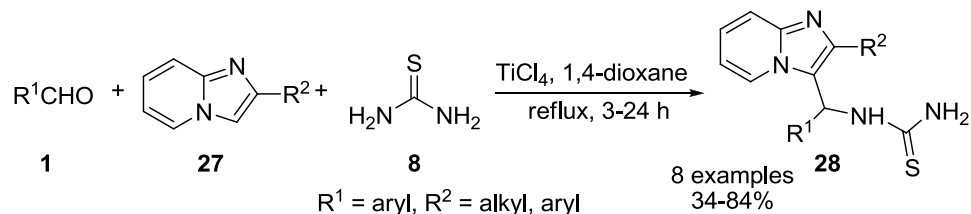
Scheme 3.9 3CR of imidazo[1,2-*a*]pyridines, aldehydes and thiourea

Over the past decades, rare earth metals have been used in various organic transformations as catalysts, especially lanthanide triflates function as efficient Lewis acid catalysts.[48-49] Moisture insensitiveness, stability, high catalytic activity, and reusability without much loss of activity are distinctive features of metal triflates. From environmental and efficiency point of view lanthanide triflates have become highly attractive Lewis acid catalysts for various chemical reactions.

By careful investigation of the three component reaction of *β*-naphthol, aldehydes and amides (**Scheme 3.8**) as well as Chaubet protocol (**Scheme 3.9**), we envisioned that three-component reaction of 2-arylimidazo[1,2-*a*]pyridines, aldehydes and amides enables the construction of 1-amidomethylimidazo[1,2-*a*]pyridines and these are structurally relevant to the imidazo[1,2-*a*]pyridine based anxiolytic drugs saripidem and necopidem as shown in **Scheme 3.10**.
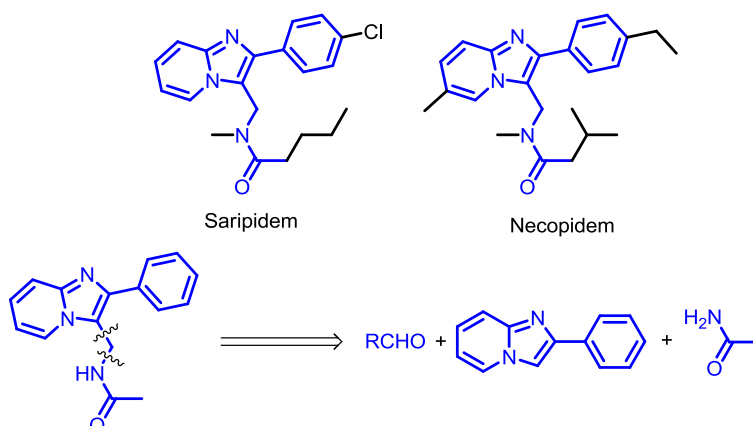
Scheme 3.10 Access to imidazo[1,2-*a*]pyridine based drug-like molecules

We investigated one-pot reaction of imidazo[1,2-*a*]pyridine (**27**) with aldehydes (**1**) and acetamide (**25**) in the presence of Yb(OTf)$_3$. The reaction was efficient and offered good yields of 1-amidomethyl-imidazo[1,2-*a*]pyridines (**29**) (**Scheme 3.11**).
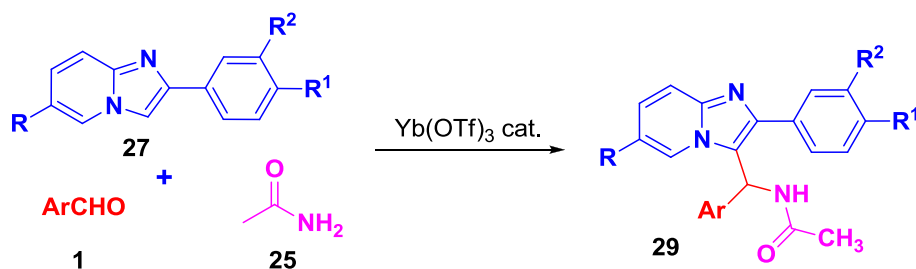
Scheme 3.11 Three-component reaction of imidazo[1,2-*a*]pyridines, aldehydes and amides

3.2 Results and discussion

The key precursors, imidazo[1,2-*a*]pyridines (**27**) were synthesized by reacting appropriately substituted *α*-bromoacetophenone with 2-aminopyridines.[50] To optimize the reaction conditions for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines (**29**), initially we attempted condensation of 2-*p*-tolyl-1*H*-imidazo[1,2-*a*]pyridine (**27a**), 4-chlorobenzaldehyde (**1a'**) and

acetamide (**25**) using 20 mol % of Yb(OTf)$_3$ in toluene at reflux for 12 h (**Scheme 3.12**). Surprisingly, two new spots were identified by TLC with the complete consumption of raw materials (**Figure 3.2**). These two compounds were isolated by column chromatography and their structures were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass data.
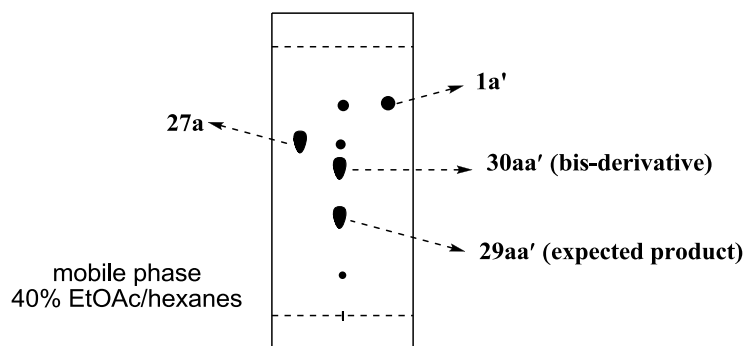
Figure 3.2 TLC analysis for the reaction of **27**, **1a'** and **25**

The ESI-MS spectrum of **29aa'** displayed a peak at *m/z* 389.9 for [M + H]$^+$ ion and a peak at 1682 cm^{-1} was observed for amidic C=O stretching in the IR spectrum. The ^{1}H NMR spectrum contained a characteristic doublet at δ ~ 9.17 (d, *J* = 7.8 Hz, 1H) for amide −NH and a doublet at δ ~ 6.79 (d, *J* = 7.8 Hz, 1H) for −CH attached to amide. A peak appeared at δ 170.11 ppm in ^{13}C NMR for C=O of acetamide group along with other carbons of **29aa'**. A representative ^{1}H and ^{13}C NMR of **29aa'** is shown in **Figure 3.3**. These spectral data are consistent with the expected 3CR product, *N*-((4-chlorophenyl)(2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)methyl)-acetamide (**29aa', Scheme 3.12**). ^{1}H NMR of compound **30aa'** contained a characteristic singlet at δ ~ 6.65 ppm and displayed a ion at *m/z* 539.2 for [M + H]$^+$ ion in ESI-MS. A representative ^{1}H and ^{13}C NMR of **30aa'** is shown in **Figure 3.4**. These spectral data are consistent with the structure, 3,3'-((4-chlorophenyl)methylene)bis(2-*p*-tolylimidazo[1,2-*a*]pyridine) (**30aa', Scheme 3.12**).
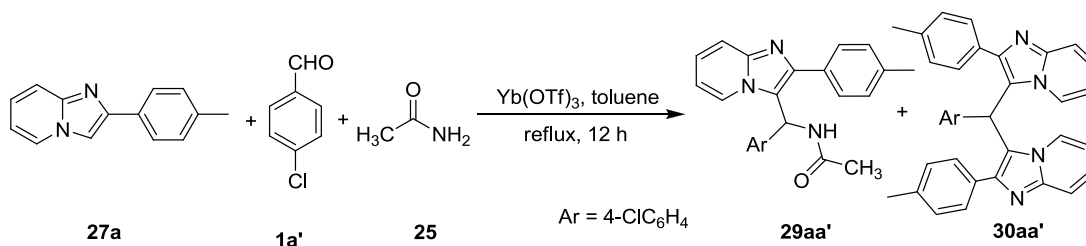
Scheme 3.12 Three-component reaction of imidazo[1,2-*a*]pyridine (**27**), aldehyde (**1a'**) and acetamide (**25**)
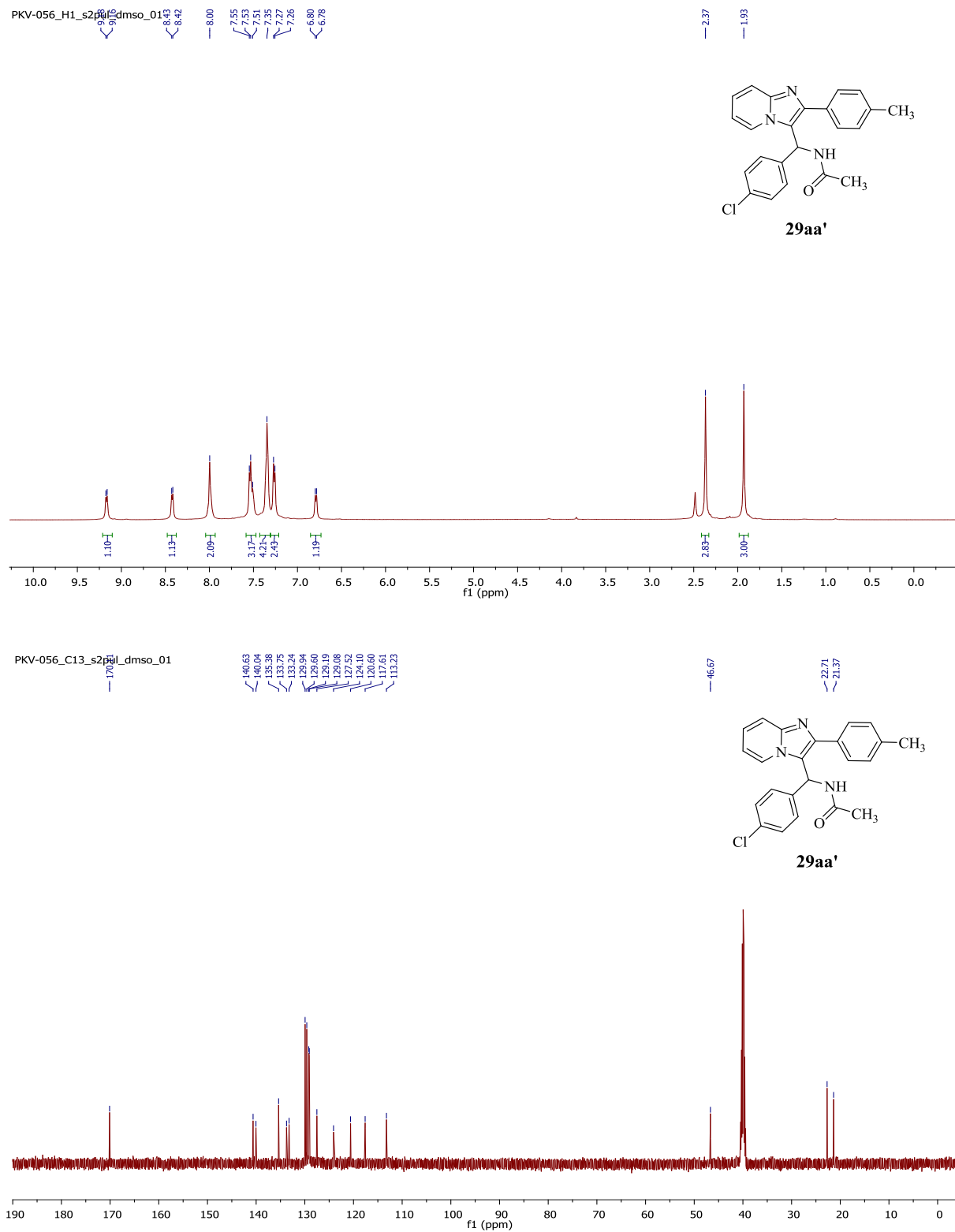
Figure 3.3 ^{1}H and ^{13}C NMR spectra (in DMSO-d_6; recorded on a Bruker AV 300 spectrometer) of 1-amidomethyl-imidazo[1,2-a]pyridines (**29aa'**)
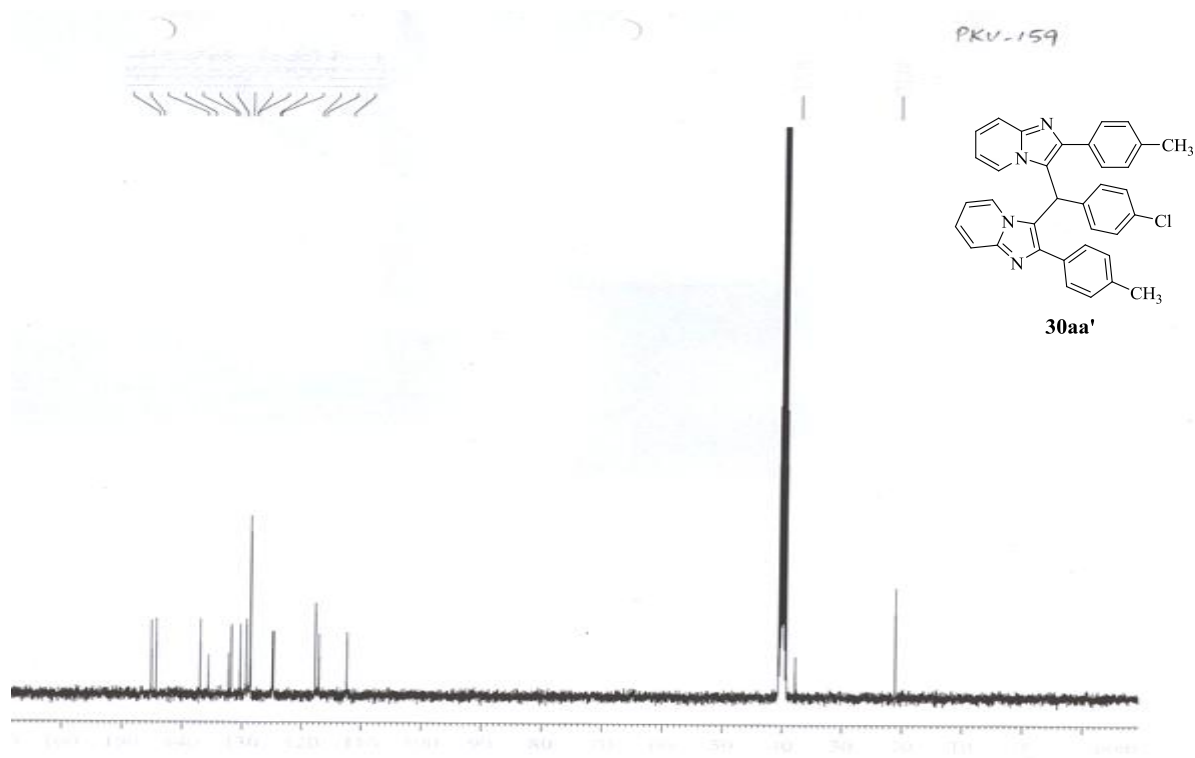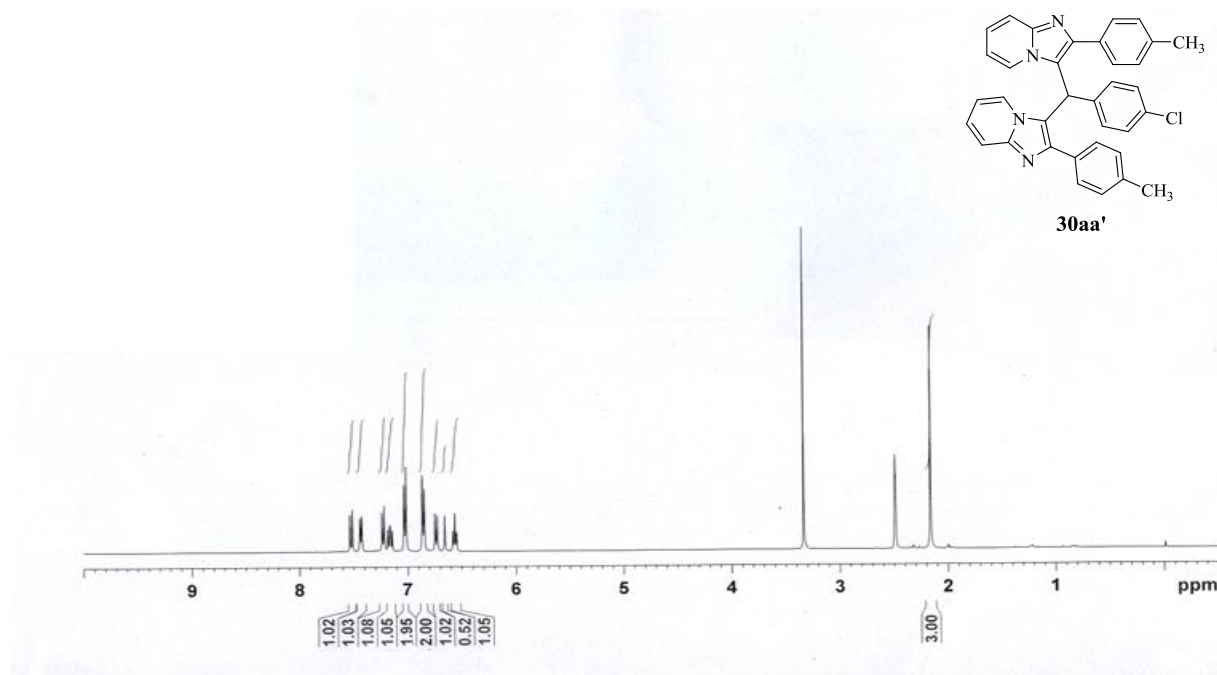
Figure 3.4 ^{1}H and ^{13}C NMR spectra (in DMSO-d_6; recorded on a Bruker AV 300 spectrometer) of bis(imidazo[1,2-*a*]pyridyl)methane (**30aa'**)

To study the effect of solvent on the outcome of the three-component process, we performed the model reaction in different solvents such as 1,4-dioxane, DMF, toluene, water, [bmim][BF$_4$], [bmim][PF$_6$] and [bmim][Br] (**Figure 3.5a**). Among all solvents, [bmim][PF$_6$] gave the best yield of **29aa'** (75%). The product was poorly soluble in non-polar solvents such as diethyl ether and thus we were not able to extract it from [bmim][PF$_6$]. We tried regular water/ethyl acetate workup, but [bmim][PF$_6$] is soluble in ethyl acetate and not in water. Lastly, we performed column chromatography of the reaction mass, but in this case also we could not remove ionic liquid completely from the product. Recrystallization using dichloromethane was found to be good method for the removal of ionic liquid but recovery of product was low. Thus, we selected 1,4-dioxane as a solvent of choice for this reaction although it gave relatively lower yield of **29aa'** (72%) than that of [bmim][PF$_6$] (**Figure 3.5a**).

To find the best catalyst, we screened the model reaction with 1,4-dioxane as a optimum solvent by varying diverse acidic catalysts (**Figure 3.5b**). While there was no conversion observed when the reaction was performed without any catalyst, other metal triflates such as AgOTf, Cu(OTf)$_2$, Sc(OTf)$_3$, Er(OTf)$_3$ and Zn(OTf)$_2$ gave poor yield of **29aa'**. It is worthy to mention that in all the cases the reaction was incomplete with starting materials remaining in the reaction mixture. Among all metal triflates Yb(OTf)$_3$ gave highest yield of **29aa'** (72%) whereas *p*-TSA resulted in 65% of **29aa'**. The high catalytic activity of Yb(OTf)$_3$ could be explained by the fact that Yb^{+3} is the hardest cation and therefore the most oxophilic, due to its smaller ionic radius, so it can coordinate with oxygen atom of C=O group in aldehyde to make it more electrophilic, leading to the enhancement of rate of reaction. The variation in the loading of the catalyst also affected the yield of **29aa'**. When 5, 10 and 20 mol % of Yb(OTf)$_3$ was used for model reaction under standardized reaction condition it resulted in 45%, 54% and 72% yield of **29aa'**, respectively. Further increase in the catalyst loading did not improve the yield of **29aa'**.
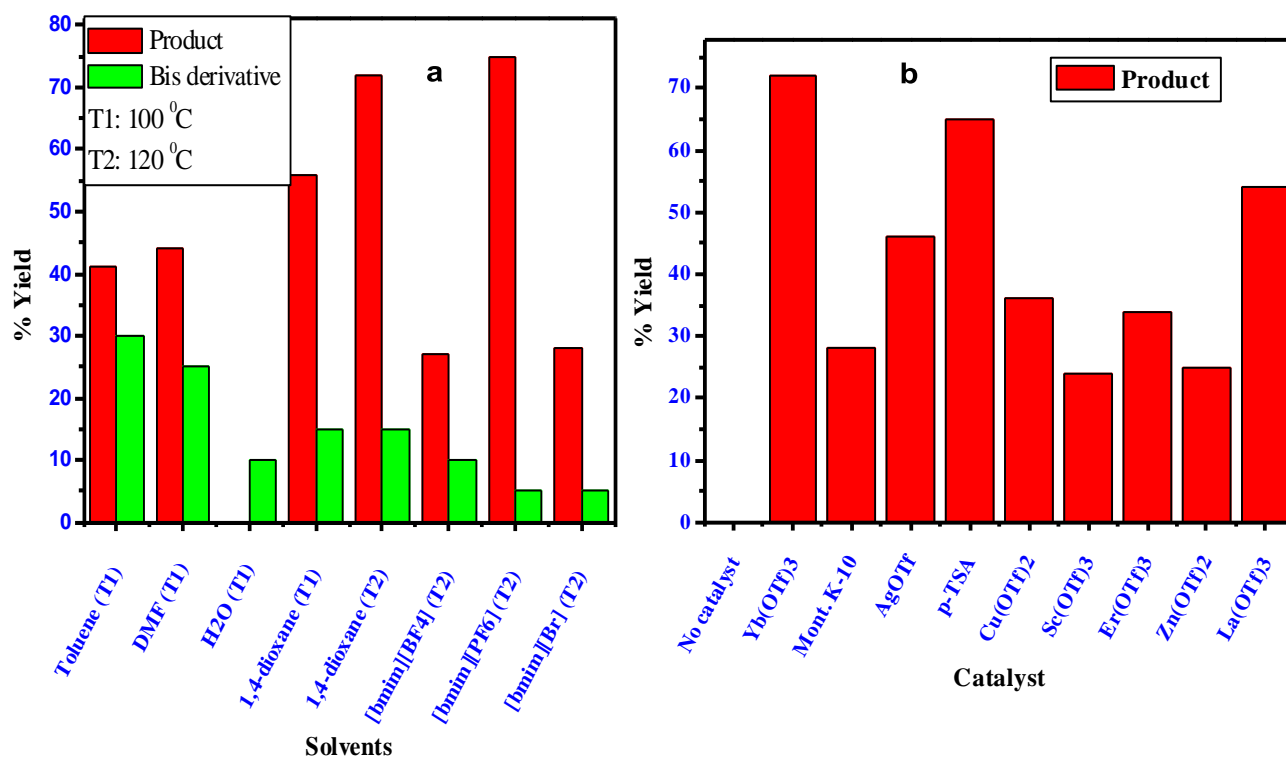
Figure 3.5 Optimizing suitable solvent and catalyst for the three-component synthesis of **29**

In order to investigate the generality of the reaction, we applied this strategy to various substrates having both electron donating and electron withdrawing groups. The results are summarized in Table 3.1. The substituent on C-2 phenyl ring of imidazo[1,2-*a*]pyridine (**27**) has predominant effect on the yield of TCR product. If the substituent is an electron releasing group it decreases the yield of **29** and enhances the yield of **30**. It may be due to the fact that presence of electron rich aryl group at C-2 position increases electron density on the imidazo[1,2-*a*]pyridine nucleus and makes it more nucleophilic to attack on intermediate of **27** and **1.** In contrary, when the substituent is an electron withdrawing group such as nitro, it gives better yield of **29**. This may be due to the decreased nucleophilicity of imidazo[1,2-*a*]pyridine. Similarly, it was found that aldehydes with electron donating groups resulted in lower yields of **29** as compared to the aldehydes having electron withdrawing groups (Table 3.1).

It is also noteworthy to mention that when 6-bromoimidazo[1,2-*a*]pyridine was used, low yield of corresponding imidazo[1,2-*a*]pyridylamide (**29**) was obtained (entries 18-20, Table 3.1). However, there was no corresponding *bis*(imidazo[1,2-*a*]pyridines) derivatives (**30**) detected in

this case. This might be due to decreased nucleophilicity of imidazo[1,2-*a*]pyridine nucleus in presence of bromo group.

To our delight, heterocyclic aldehydes such as indole-3-carboxaldehyde (entries 15 and 22, Table 3.1) and thiophene-2-carboxaldehyde (entry 16, Table 3.1) as well as aliphatic aldehydes such as 1-butanal (entries 21 and 26, Table 3.1) smoothly reacted under these conditions to give the corresponding amides in good yields. When acetamide was replaced with benzamide and formamide, miscellaneous results were observed. When formamide reacted, the corresponding condensation product **29cf** was isolated in moderate yield (entry 28, Table 3.1), whereas benzamide failed to give the corresponding product and this may be due to poor nucleophilicity of benzamide compared to acetamide.

Table 3.1 Yb(OTf)$_3$ synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines (**29**)[a]
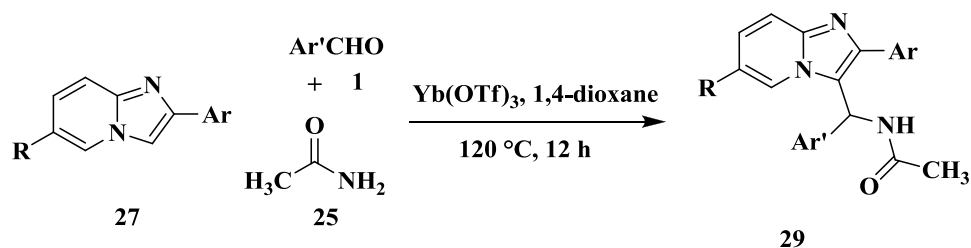
27a: Ar = 4-CH$_3$C$_6$H$_4$, R = H
27b: Ar = 4-OCH$_3$C$_6$H$_4$, R = H
27c: Ar = 3-NO$_2$C$_6$H$_4$, R = H
27d: Ar = 4-ClC$_6$H$_4$, R = H
27e: Ar = 4-ClC$_6$H$_4$, R = Br
27f: Ar = 4-BrC$_6$H$_4$, R = H
27g: Ar = 4-FC$_6$H$_4$, R = H
27h: Ar = 2-thienyl, R = H

1a′: Ar′ = 4-ClC$_6$H$_4$
1b′: Ar′ = 4-OCH3C$_6$H$_4$
1c′: Ar′ = 3-OCH3C$_6$H$_4$
1d′: Ar′ = 3,4-(OCH$_3$)$_2$C$_6$H$_3$
1e′: Ar′ = C$_6$H$_5$
1f′: Ar′ = 3-NO$_2$C$_6$H$_4$

1g′: Ar′ = 4-NO$_2$C$_6$H$_4$
1h′: Ar′ = 3-indolyl
1i′: Ar′ = 2-thienyl
1j′: Ar′ = n-propyl
1k′: Ar′ = 4-CNC$_6$H$_4$

Sr. No.	Ar	R	Ar′	Product	% Yield [b]
1	4-CH$_3$C$_6$H$_4$	H	4-ClC$_6$H$_4$	**29aa'**	72
2	4-CH$_3$C$_6$H$_4$	H	4-OCH$_3$C$_6$H$_4$	**29ab'**	36
3	4-CH$_3$C$_6$H$_4$	H	3-OCH$_3$C$_6$H$_4$	**29ac'**	33
4	4-CH$_3$C$_6$H$_4$	H	3-NO$_2$C$_6$H$_4$	**29af'**	28
5	4-OCH$_3$C$_6$H$_4$	H	4-ClC$_6$H$_4$	**29ba'**	62
6	4-OCH$_3$C$_6$H$_4$	H	4-OCH$_3$C$_6$H$_4$	**29bb'**	49
7	4-OCH$_3$C$_6$H$_4$	H	3,4-(OCH$_3$)$_2$C$_6$H$_3$	**29bd'**	39
8	4-OCH$_3$C$_6$H$_4$	H	C$_6$H$_5$	**29be'**	52
9	4-OCH$_3$C$_6$H$_4$	H	3-NO$_2$C$_6$H$_4$	**29bf'**	44
10	3-NO$_2$C$_6$H$_4$	H	4-ClC$_6$H$_4$	**29ca'**	62

11	3-NO$_2$C$_6$H$_4$	H	4-OCH$_3$C$_6$H$_4$	**29cb'**	59
12	3-NO$_2$C$_6$H$_4$	H	C$_6$H$_5$	**29ce'**	55
13	3-NO$_2$C$_6$H$_4$	H	3-NO$_2$C$_6$H$_4$	**29cf'**	74
14	3-NO$_2$C$_6$H$_4$	H	4-NO$_2$C$_6$H$_4$	**29cg'**	65
15	3-NO$_2$C$_6$H$_4$	H	3-Indolyl	**29ch'**	39
16	3-NO$_2$C$_6$H$_4$	H	2-Thienyl	**29ci'**	29
17	4-ClC$_6$H$_4$	H	3-NO$_2$C$_6$H$_4$	**29df'**	40
18	4-ClC$_6$H$_4$	Br	4-ClC$_6$H$_4$	**29ea'**	46
19	4-ClC$_6$H$_4$	Br	3-NO$_2$C$_6$H$_4$	**29ef'**	30
20	4-ClC$_6$H$_4$	Br	4-NO$_2$C$_6$H$_4$	**29eg'**	32
21	4-BrC$_6$H$_4$	H	*n*-propyl	**29fj'**	38
22	4-FC$_6$H$_4$	H	3-indolyl	**29gh'**	41
23	2-thienyl	H	4-OCH$_3$C$_6$H$_4$	**29hb'**	32
24	2-thienyl	H	3-OCH$_3$C$_6$H$_4$	**29hc'**	35
25	2-thienyl	H	3-NO$_2$C$_6$H$_4$	**29hf'**	52
26	2-thienyl	H	*n*-propyl	**29hj'**	33
27	2-thienyl	H	4-CNC$_6$H$_4$	**29hk'**	49
28	3-NO$_2$C$_6$H$_4$	H	3-NO$_2$C$_6$H$_4$	**29cf**	36[c]

[a]Reaction conditions: Compound **27** (1.0 equiv), **1** (1.0 equiv), **25** (1.5 equiv), 1,4-dioxane, 120 °C, 12 h. [b]Isolated yield. [c]HCONH$_2$ was used.

To further explore the scope of the methodology, we studied one-pot, TCR reaction of 2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**31**) with 4-chlorobenzaldehyde (**1a'**) and acetamide (**25**) under these conditions (**Scheme 3.13**). The reaction resulted in major formation of expected *N*-((4-chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl) acetamide (**32a'**) along with two other minor products (**Figure 3.6**).
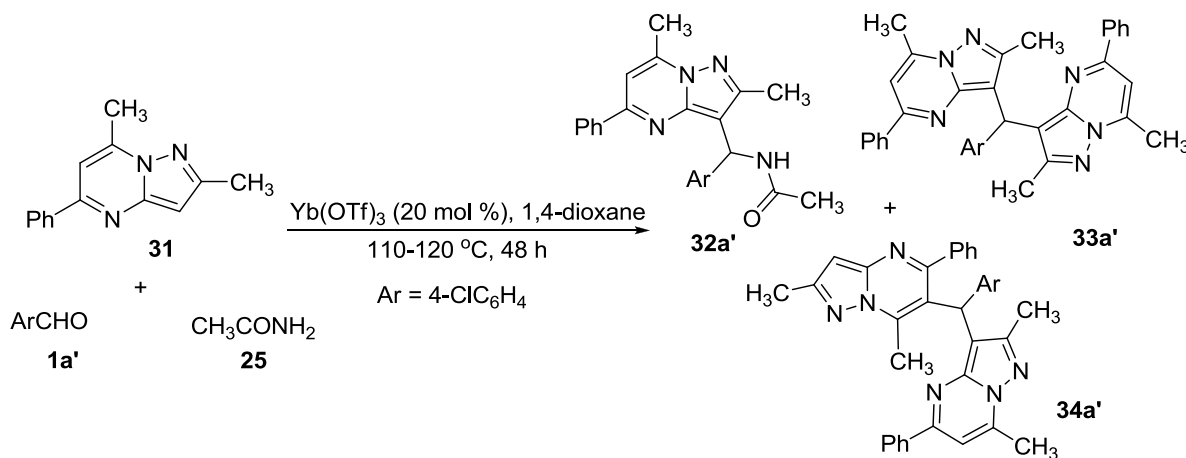
Scheme 3.13 Yb(OTf)$_3$ catalyzed TCR of pyrazolo[1,5-*a*]pyrimidine, aldehyde and acetamide
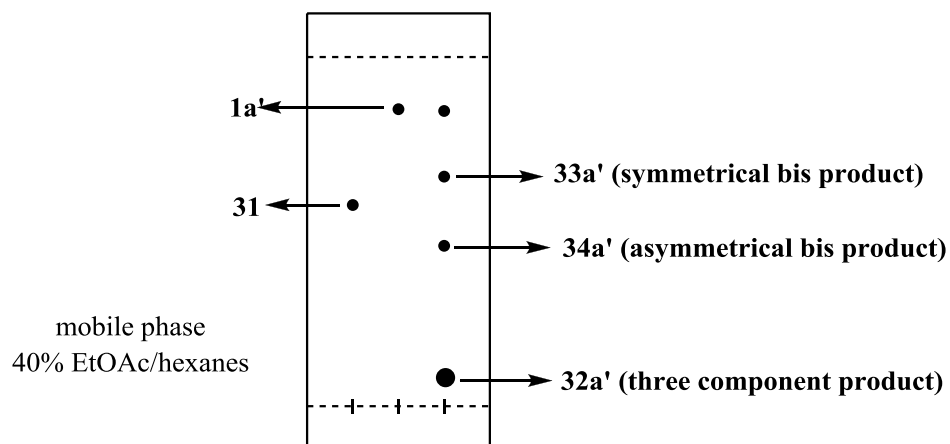
Figure 3.6 TLC analysis for the reaction of **31**, **1a'** and **25**

The structure of **32a'** was established by ^{1}H & ^{13}C NMR as well as high resolution mass spectrometry data. A doublet was observed at δ 8.70 for NH protons along with doublet at δ 6.39 for CH protons in the ^{1}H NMR of **32a'**. The total integration was for 21 protons in the ^{1}H NMR out of which 10 were in the range of δ 2.07–6.72 and they were assigned to three methyl groups and one CH proton. The other 11 protons were assigned as five for phenyl protons at C_5, four for 4-chlorophenyl protons, one for C_6–proton and one for NH of acetamide group. The ^{13}C NMR spectrum also showed signal for 21 carbons out of which four were in aliphatic region corresponding to 3 × CH_3 group carbons and one for methylene carbon. In ESI-MS spectra a peak was observed at *m/z* 405.1474 that corresponds to $C_{23}H_{22}ClN_4O^+$ [M + H]$^+$ ion and thus confirms the structure of **32a'**. A representative ^{1}H and ^{13}C NMR of **32a'** is shown in **Figure 3.7**. The other two products were characterized as *bis*-derivatives (**33a'** & **34a'**). In the ^{1}H NMR spectrum of first non-polar spot a singlet was observed at δ 6.33 for one proton and two singlets were observed at δ 2.42 and 2.50 each for six protons indicating the presence of CH and 4 × CH_3 groups that are of two different type. In the ^{13}C NMR spectrum signals for 18 carbon were present out of which three were in the range of δ 34.49–14.46. A peak was observed at *m/z* 569.2227 in the ESI-MS spectrum that corresponds to $C_{35}H_{30}ClN_6^+$ [M + H]$^+$ ion. Thus, based on NMR and mass analysis the structure of the compound was characterized to be 3-((4-chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)-2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**33a'**). A representative ^{1}H and ^{13}C NMR of **33a'** is shown in **Figure 3.8**. Similarly for **34a',** there was a singlet for CH proton at δ 6.37 but peak for NH proton was absent in the ^{1}H NMR spectrum of the compound. The interesting part of the ^{1}H

NMR spectrum for this compound was the presence of four peaks in the range δ 2.32–2.78 each for three proton indicating presence of 4 × CH$_3$ groups. Also in the ^{13}C NMR spectrum there were five carbons in the range of δ 34.75–14.19 indicating presence of CH group along with four different CH$_3$ groups. A peak was observed at *m/z* 569.2231 in ESI-MS spectrum that corresponds to C$_{35}$H$_{30}$ClN$_6$$^+$ [M + H]$^+$ ion. Thus based, on spectral analysis this product was identified to be 6-((4-chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl) methyl)-2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**34a'**). A representative ^{1}H and ^{13}C NMR of **34a'** is shown in **Figure 3.9**.

In order to understand the generality of the reaction we reacted **31** with different aldehydes (**1**) having electron withdrawing as well as electron donating groups, and acetamide (**25**) and the results are summarized in Table 3.2. It is evident from table 3.2 that aldehydes with electron withdrawing groups (entry 1-6, Table 3.2) gave better yields of the product (**32**) as compared to those having electron donating groups (entry 8-12, Table 3.2).

Table 3.2 Yb(OTf)$_3$ synthesis of 1-amidomethyl-pyrazolo[1,5-a]pyrimidines (**32**)[a]
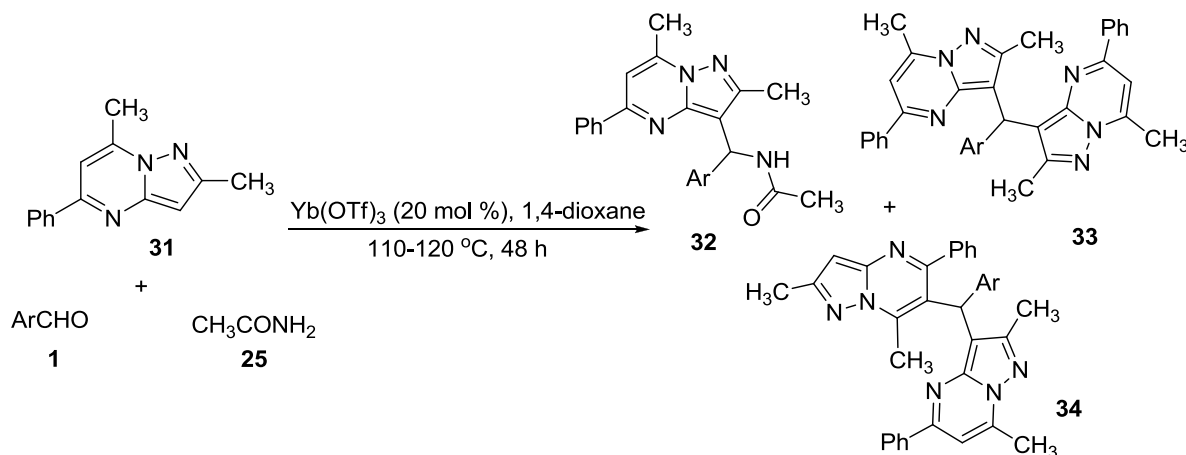
Entry	Ar'	Time (h)	% Yield[b]		
			32	**33**	**34**
1	4-ClC$_6$H$_4$	48	74 (**32a'**)	8 (**33a'**)	4 (**34a'**)
2	4-BrC$_6$H$_4$	48	71 (**32b'**)	15 (**33b'**)	-[c]
3	3-ClC$_6$H$_4$	48	56 (**32c'**)	14 (**33c'**)	6 (**34c'**)
4	2-FC$_6$H$_4$	48	42 (**32d'**)	19 (**33d'**)	21 (**34d'**)
5	4-NO$_2$C$_6$H$_4$	48	69 (**32e'**)	13 (**33e'**)	7 (**34e'**)
6	3-NO$_2$C$_6$H$_4$	48	56 (**32f'**)	9 (**33f'**)	5 (**34f'**)
7	C$_6$H$_5$	24	58 (**32g'**)	18 (**33g'**)	-[c]
8	4-CH$_3$C$_6$H$_4$	48	58 (**32h'**)	17 (**33h'**)	8 (**34g'**)
9	3,4-(OCH$_3$)$_2$C$_6$H$_3$	24	47 (**32i'**)	19 (**33i'**)	17 (**34h'**)
10	2-OCH$_3$C$_6$H$_4$	24	59 (**32j'**)	13 (**33j'**)	-[c]
11	3,4,5-(OCH$_3$)$_3$C$_6$H$_2$	48	39 (**32k'**)	26 (**33k'**)	-[c]
12	4-OCH$_2$C$_6$H$_5$C$_6$H$_4$	24	56 (**32l'**)	-[c]	-[c]

[a]Reaction conditions: Compound **31** (1.0 equiv), **1** (1.0 equiv), **25** (1.5 equiv), Yb(OTf)$_3$ (20 mol %), 1,4-dioxane, 120 °C. [b]Isolated yield. [c]Not isolated.
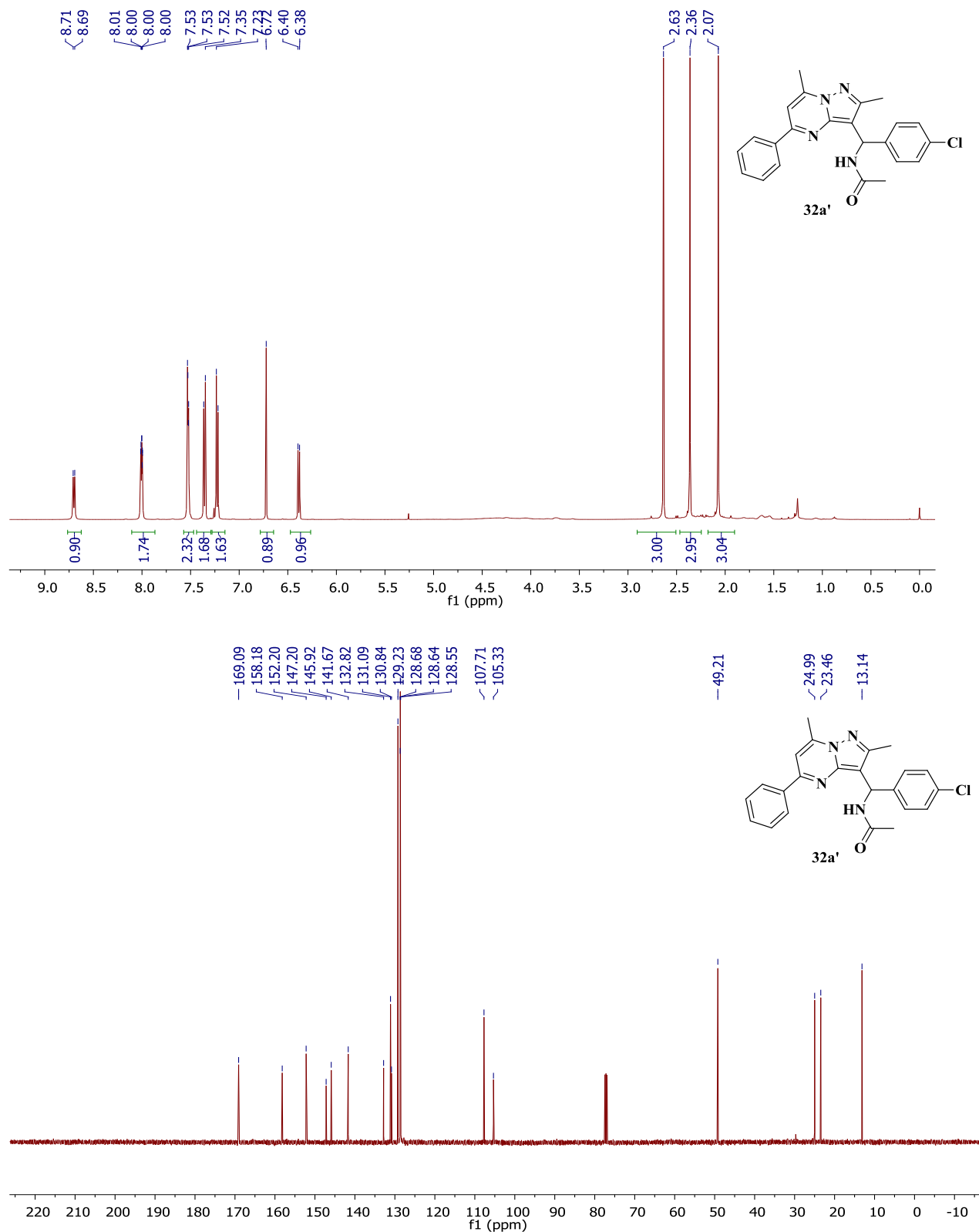
Figure 3.7 ^{1}H and ^{13}C NMR spectra (in DMSO-d_6; recorded on a Bruker AV 500 spectrometer) of 1-amidomethyl pyrazolo[1,5-*a*]pyrimidine (**32a'**)
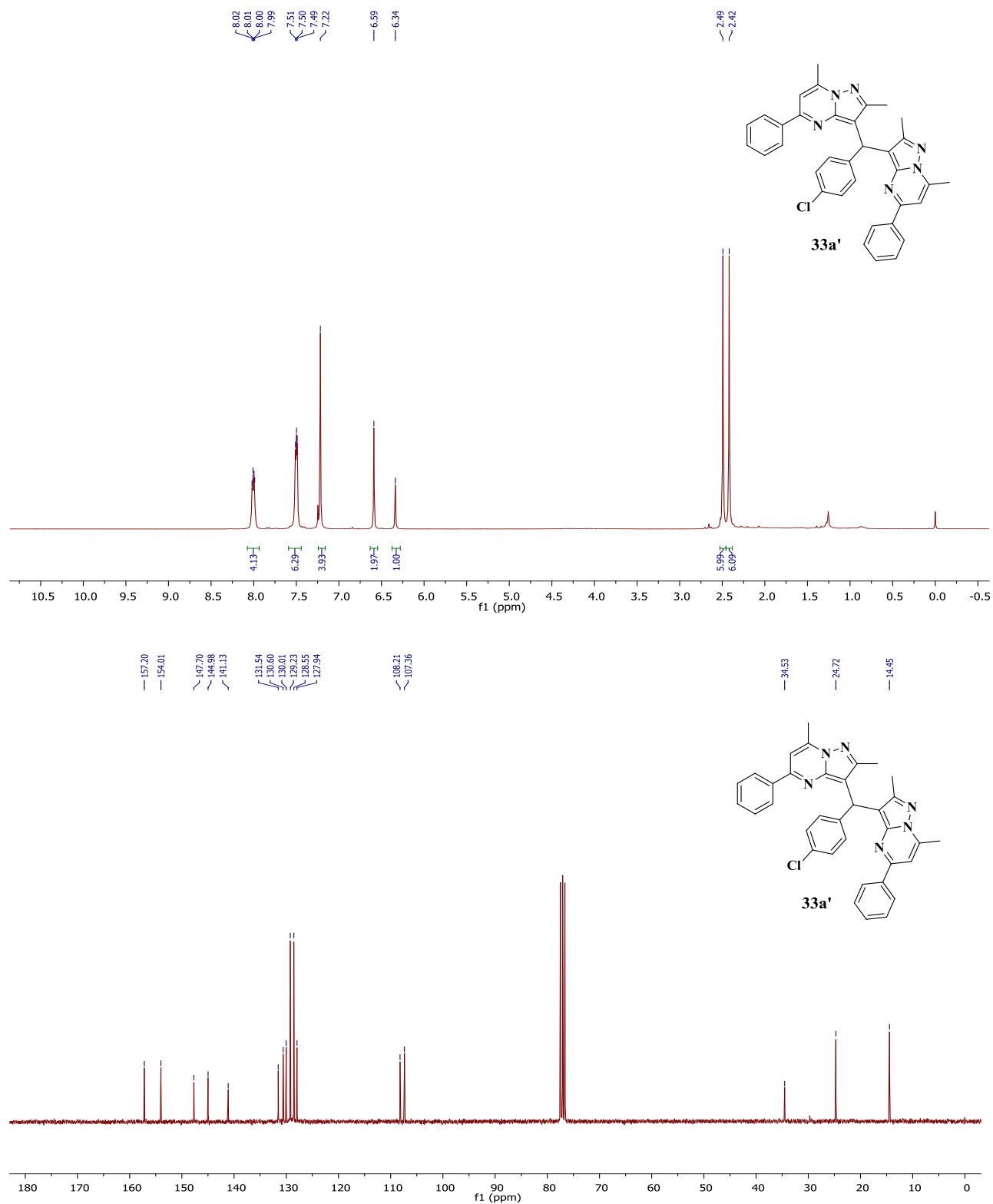
Figure 3.8 ^{1}H and ^{13}C NMR spectra (in DMSO-d_6; recorded on a Bruker AV 400 spectrometer) of symmetrical bis(pyrazolo[1,5-a]pyrimidine) (**33a'**)
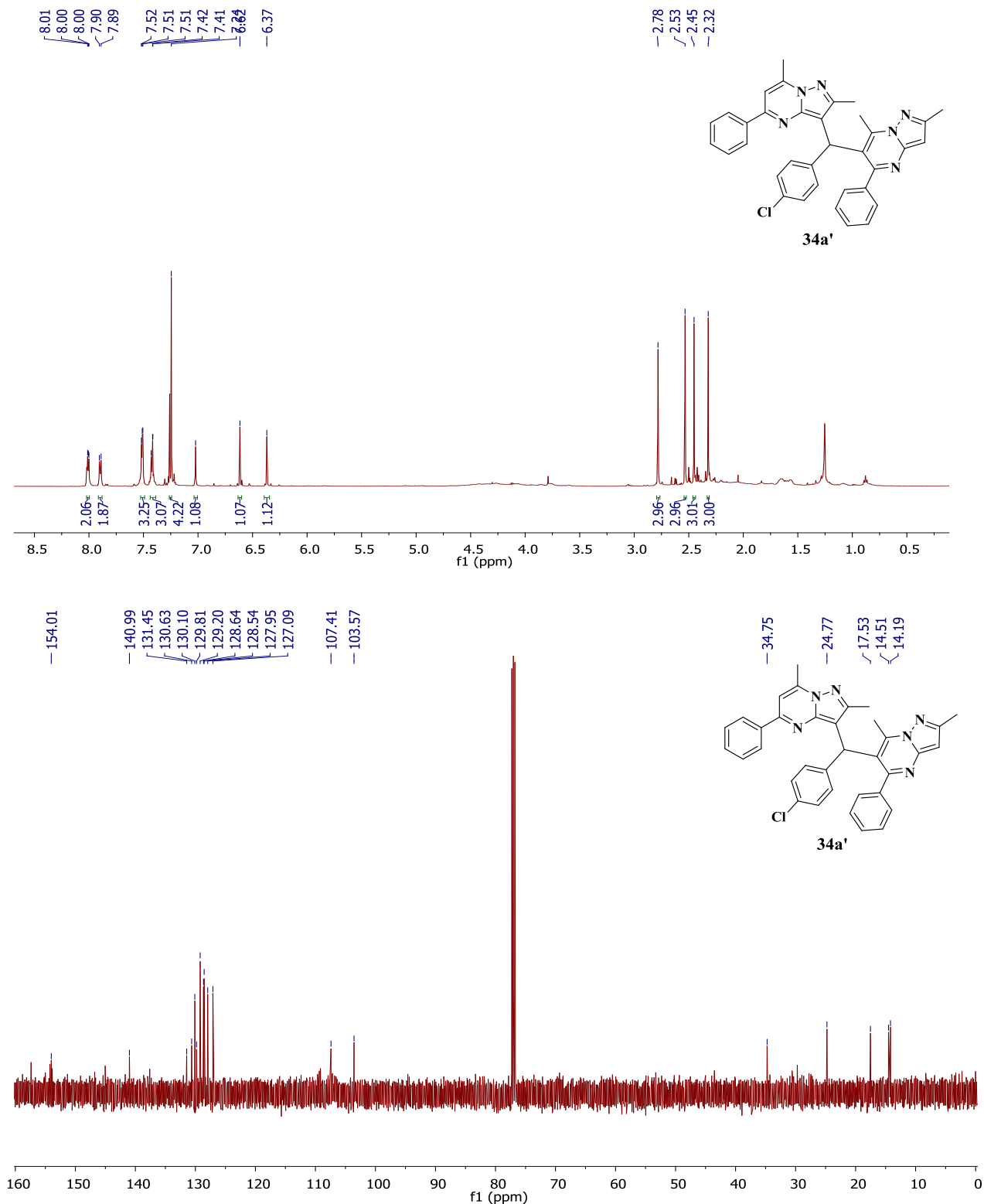
Figure 3.9 ^{1}H and ^{13}C NMR spectra (in DMSO-d_6; recorded on a Bruker AV 500 spectrometer) of asymmetrical bis(pyrazolo[1,5-a]pyrimidine) (**34a'**)

Based on the product distribution and data obtained from ^{1}H & ^{13}C NMR spectra, a plausible mechanism is proposed for the three-component products as shown in **Scheme 3.14**. In the presence of Lewis acid carbonyl group of aldehyde gets activated and acquires a partial positive charge making it electron deficient. Apparently, the C_3–carbon of the imidazole ring in imidazo[1,2-*a*]pyridine (**27**) and pyrazole ring in pyrazolo[1,5-*a*]pyrimidine (**31**) is electron rich position. Thus, this carbon attacks activated carbonyl group to give carbomethanol intermediate **35**. This intermediate then generates intermediate **36** on loss of hydroxyl group assisted by Yb(OTf)$_3$, that on reaction with acetamide gives the desired product **29** or **32**. However, if the intermediate **36** is attacked by another molecule of imidazo[1,2-*a*]pyridine/2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine *bis*-derivatives are formed (**30**, **33** and **34**). In case of 2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**31**) there are two different sites (C_3–carbon and C_6–carbon) were available for attack. If **36** is attacked by **31** from the C_3–carbon symmetrical *bis*-product (**33**) is formed and if it is attacked by **36** from C_6–carbon unsymmetrical *bis*-product (**34**) is formed.
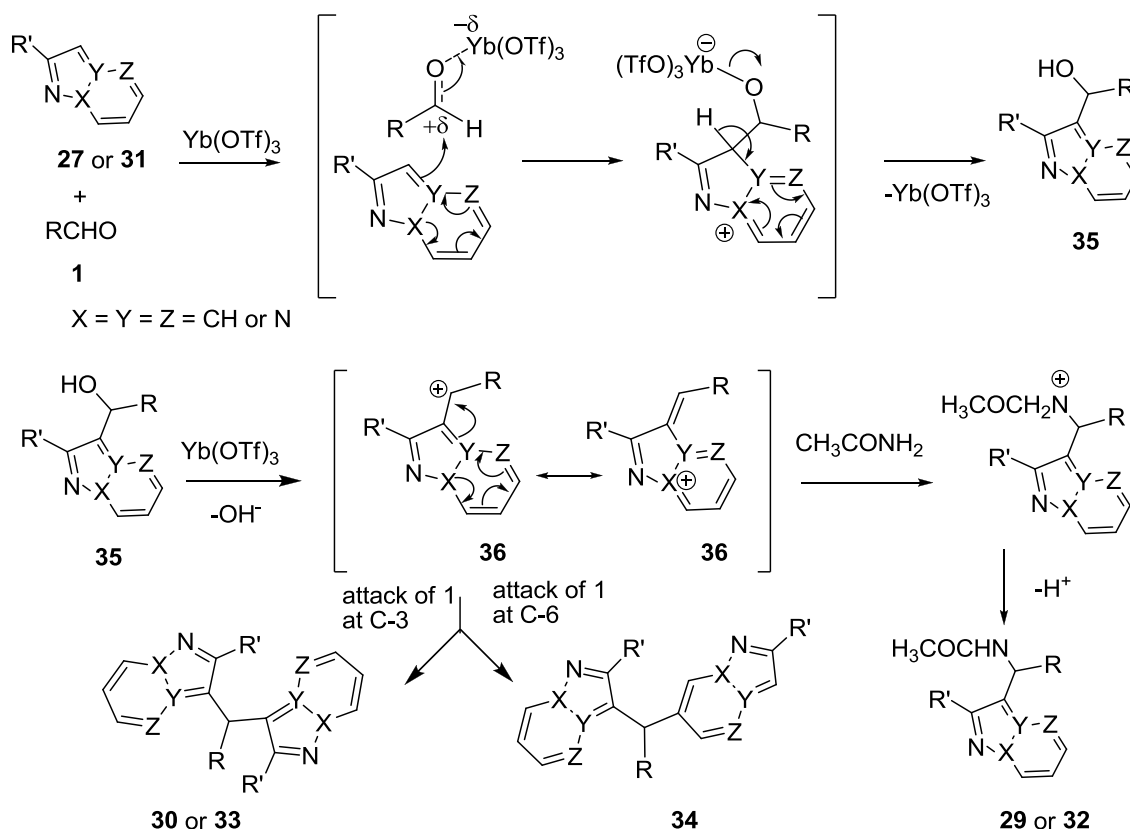
Scheme 3.14 Plausible mechanism for formation of compounds **29**, **30**, **32, 33** and **34**

Formation of larger amount of *bis*-products in the case of aldehydes with electron releasing groups may be explained by the fact that the electron donating group in aryl ring stabilizes the intermediate **36** and allows nucleophilic imidazo[1,2-*a*]pyridine/pyrazolo[1,5-*a*]pyrimidine to compete with acetamide in the second step. To clarify these observations, 2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine (**27c**) was treated with 3,4,5-trimethoxybenzaldehyde (**1l'**) and acetamide (**25**) under the optimized conditions. As expected *bis*-product 3,3'-((3,4,5-trimethoxyphenyl)methylene)-bis(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine) (**30cl′**) was obtained as major product in 42% yield and *N*-((2-(3-nitrophenyl)-imidazo[1,2-*a*]pyridin-3-yl)(3,4,5-trimethoxyphenyl)methyl)acetamide was not formed (**Scheme 3.15**).
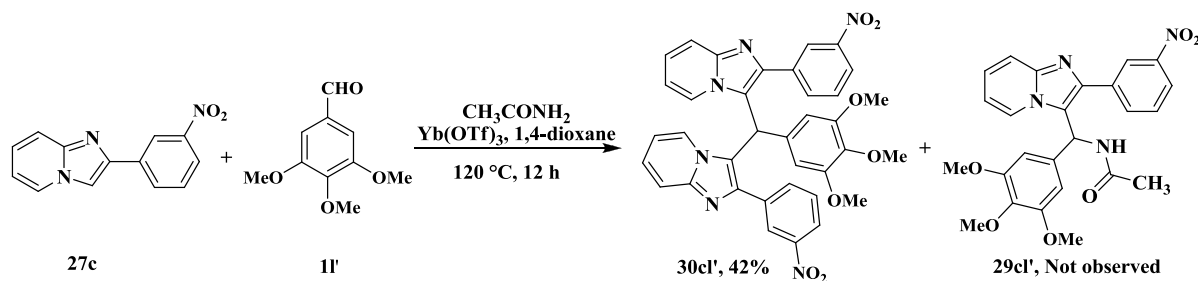
Scheme 3.15 TCR of imidazo[1,2-*a*]pyridine (**27c**) with trimethoxy benzaldehyde (**1l'**)

3.3 Conclusion

The one-pot, 3CR reaction of imidazo[1,2-*a*]pyridine or pyrazolo[1,5-*a*]pyrimidine with aldehydes and acetamide in presence of Yb(OTf)$_3$ gave good yields of new class of drug like structures, 1-amidomethyl imidazo[1,2-*a*]pyridines/pyrazolo[1,5-*a*]pyrimidines. The reaction of pyrazolo[1,5-*a*]pyrimidine with aldehydes resulted in formation of two new symmetrical and unsymmetrical aryl methylene-*bis*-pyrazolo[1,5-*a*]pyrimidines and imidazo[1,2-*a*]pyridine gave symmetrical aryl methylene-*bis*(imidazo[1,2-*a*]pyridine) together with expected three-component products. The structure of all the compounds was established by NMR and mass analysis. A plausible mechanism has been represented based on the product distribution.

3.4 Experimental

General: Reactions were performed in 1.0 mmol scale. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F$_{254}$ plates (Merck). The chemical structures of final products were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR)

determined on a Bruker NMR spectrometer (300 & 400 MHz) or a Varian NMR spectrometer (500 MHz). HRMS were obtained from Biosystems QStar Elite time-of-flight electrospray mass spectrometer. Yb(OTf)$_3$ was procured from Sigma-Aldrich, India and all other chemicals were obtained from commercial suppliers and used without further purification. Synthesis of 2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**31**) was achieved by the reaction of 3-amino-5-methylpyrazole with 1-phenyl-1,3-butandione following the literature procedure.[51] Although most of the compounds were isolated as a solids, sharp melting range of these compounds could not be measured because they shrink then decomposes in the melting tube

Representative procedure for the three-component reaction of imidazo[1,2-*a*]pyridine (27)/ pyrazolo[1,5-*a*] pyrimidines (31), aldehyde (1) and acetamide (25)

To an oven-dried 10 mL round-bottom flask containing a magnetic stir bar was imidazo[1,2-*a*]pyridine/ pyrazolo[1,5-*a*]pyrimidines (1.0 mmol), aldehyde (**1**) (1.0 mmol), acetamide (**25**) (88.5 mg, 1.5 mmol), Yb(OTf)$_3$ (142.6 mg, 0.2 mmol) and 1,4-dioxane (3 mL). The reaction mixture was stirred at 120 °C for the appropriate time. On completion, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness and the crude product thus obtained, was purified by silica gel column chromatography. The pure products were characterized based upon their spectroscopic data.

***N*-((4-Chlorophenyl)(2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29aa')**
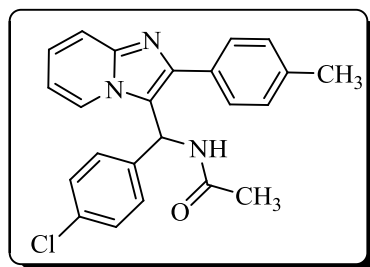
Yield 72%; colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.17 (d, *J* = 7.8 Hz, 1H), 8.42 (d, *J* = 7.0 Hz, 1H), 8.04 – 7.94 (m, 2H), 7.55 – 7.49 (m, 3H), 7.38 – 7.32 (m, 4H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.11, 140.63, 140.04, 135.38, 133.75, 133.24, 129.94, 129.60, 129.19, 129.08, 127.52, 124.10, 120.60, 117.61, 113.23, 46.67, 22.71, 21.37. ESI-MS: *m/z* 389.92 [M + H]$^+$.

N-((4-Methoxyphenyl)(2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29ab')
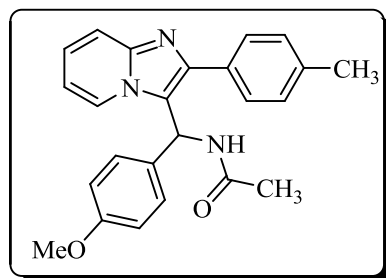
Yield 36%; off-white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.28 – 7.23 (m, 3H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.81 – 6.78 (m, 2H), 3.68 (s, 3H), 2.33 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.70, 158.93, 144.70, 144.27, 137.44, 131.96, 130.22, 129.47, 128.87, 127.70, 126.01, 125.11, 119.14, 117.42, 114.65, 112.20, 55.54, 47.28, 22.80, 21.27. ESI-MS: *m/z* 386.12 [M + H]$^+$, 771.38 [2M + H]$^+$.

N-((3-Methoxyphenyl)(2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29ac')
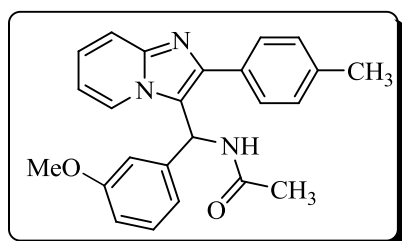
Yield 36%; pink solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.08 (d, *J* = 7.8 Hz, 1H), 7.99 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.62 (dd, *J* = 9.1, 0.8 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.84 – 6.81 (m, 3H), 6.61 (s, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 3.66 (s, 3H), 2.33 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.79, 160.05, 144.70, 144.43, 140.23, 137.49, 131.89, 130.45, 129.48, 128.87, 125.92, 125.21, 118.89, 118.61, 117.42, 112.73, 112.63, 112.28, 55.46, 47.62, 22.78, 21.27. ESI-MS: *m/z* 386.17 [M + H]$^+$, 771.34 [2M + H]$^+$.

N-((3-Nitrophenyl)(2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (**29af'**)
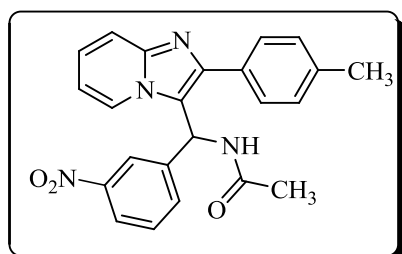
Yield 28%; off-white solid; ^{1}H NMR (500 MHz, DMSO-d_6):δ 9.23 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 6.6 Hz, 1H), 7.89 (s, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.54 – 7.42 (m, 4H), 7.34 – 7.27 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 6.8 Hz, 1H), 2.28 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.20, 148.31, 144.93, 144.74, 140.89, 137.47, 133.40, 131.65, 130.58, 129.15, 129.13, 125.65, 125.52, 122.70, 121.49, 118.25, 117.47, 112.77, 47.34, 22.79, 21.21. ESI-MS: *m/z* 401.15 [M + H]$^+$.

N-((4-Chlorophenyl)(2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29ba')
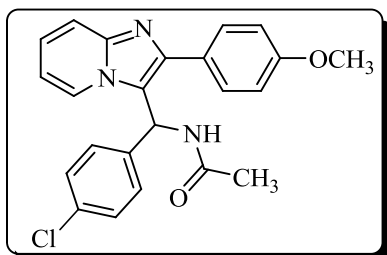
Yield 62%; purple solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.66 − 7.61 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 − 7.24 (m, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.84 − 6.79 (m, 2H), 3.78 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.92, 159.46, 144.75, 144.37, 137.57, 132.28, 130.22, 129.14, 128.47, 126.93, 125.72, 125.29, 118.05, 117.37, 114.35, 112.36, 55.59, 47.33, 22.79. ESI-MS: *m/z* 406.12 [M + H]${}^{+}$.

N-((4-Methoxyphenyl)(2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)-acetamide (29bb')
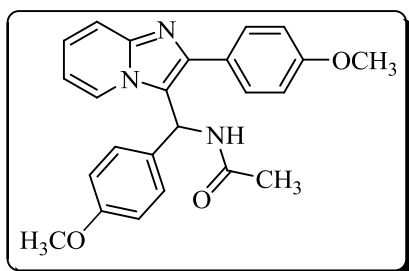
Yield 49%; brown solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 6.9 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.28 − 7.22 (m, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.96 − 6.83 (m, 4H), 6.80 (d, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.23, 158.92, 158.43, 144.19, 143.63, 129.2, 129.70, 127.23, 126.69, 125.43, 124.53, 118.23, 116.82, 114.19, 113.82, 111.63, 55.09, 55.05, 46.82, 22.32. ESI-MS: *m/z* 402.1 [M + H]${}^{+}$.

N-((3,4-Dimethoxyphenyl)(2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)-acetamide (29bd')
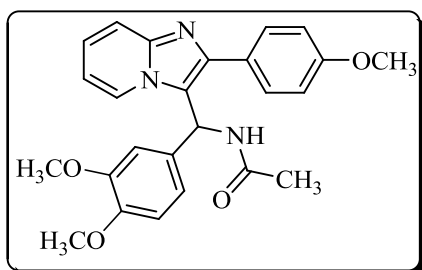
Yield 39%; brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 6.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.84 − 6.76 (m, 3H), 6.69 (s, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ

169.72, 159.36, 149.40, 148.59, 144.57, 144.11, 130.68, 130.23, 127.26, 125.95, 125.01, 118.81, 118.58, 117.30, 114.28, 112.29, 112.17, 110.59, 55.94, 55.89, 55.57, 47.58, 22.83. ESI-MS: *m/z* 432.1 [M + H]$^+$.

N-((2-(4-Methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)acetamide (29be')
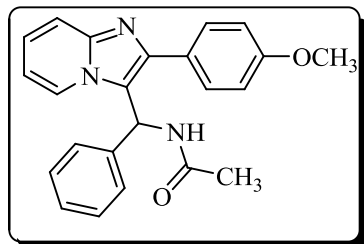
Yield 52%; purple solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.10 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.30 − 7.23 (m, 4H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.83, 159.43, 144.70, 144.31, 138.53, 130.18, 129.26, 127.80, 127.11, 126.47, 125.87, 125.11, 118.47, 117.33, 114.38, 112.14, 55.58, 47.75, 22.79. ESI-MS: *m/z* 372.15 [M + H]$^+$, 743.32 [2M + H]$^+$.

N-((2-(4-Methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(3-nitrophenyl)methyl)acetamide (29bf')
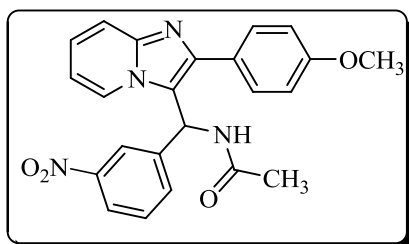
Yield 44%; off-white solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 6.9 Hz, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.55 − 7.44 (m, 4H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.94 − 6.84 (m, 4H), 3.75 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.19, 159.34, 148.31, 144.77, 144.67, 140.92, 133.43, 130.59, 130.45, 126.87, 125.54, 125.46, 122.73, 121.48, 117.89, 117.39, 114.05, 112.68, 55.56, 47.35, 22.80. ESI-MS: *m/z* 417.15 [M + H]$^+$.

### *N*-((4-Chlorophenyl)(2-(3-nitrophenyl)*H*-imidazo[1,2-*a*]-pyridin-3-yl)methyl)acetamide (29ca')
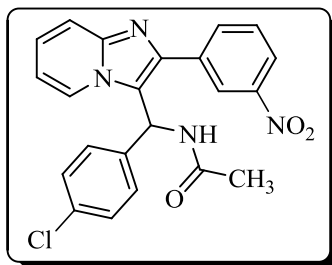
Yield 62%; pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H), 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.10 (d , *J* = 8.4 Hz, 2H), 6.96 (t, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz,

DMSO-d_6): δ 170.03, 148.15, 144.90, 142.02, 136.92, 136.48, 135.34, 132.51, 130.21, 128.92, 128.81, 126.17, 125.78, 123.73, 122.68, 120.01, 117.71, 113.18, 47.15, 22.76. ESI-MS: *m/z* 421.2 [M + H]$^+$.

N-((4-Methoxyphenyl)(2-(3-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29cb')

Yield 59%; yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (d, *J* = 8.0 Hz, 1H), 8.50 (s, 1H), 8.18 − 8.09 (m, 3H), 7.71 − 7.66 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 6.8 Hz, 1H), 6.82 − 6.78 (m, 3H), 3.66 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.86, 159.04, 148.22, 144.84, 141.79, 136.59, 135.25, 130.26, 129.57, 128.04, 125.98, 125.92, 123.70, 122.65, 120.68, 117.76, 114.51, 112.98, 55.53, 47.24, 22.74. ESI-MS: *m/z* 417.1 [M + H]$^+$.

N-((2-(3-Nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)-(phenyl)methyl)acetamide (29ce')
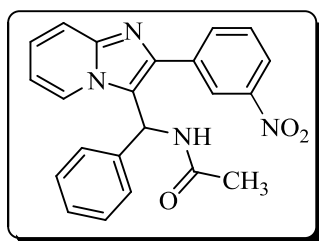
Yield 55%; off-white solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (d, *J* = 7.8 Hz, 1H), 8.54 (t, *J* = 2.1 Hz, 1H), 8.20 − 8.16 (m, 2H), 8.09 (d, *J* = 6.9 Hz, 1H), 7.74 − 7.66 (m, 2H), 7.39 − 7.35 (m, 1H), 7.34 − 7.21 (m, 3H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.96 − 6.88 (m, 2H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.50, 147.73, 144.46, 141.40, 137.38, 136.02, 134.72, 129.78, 128.62, 127.42, 126.29, 125.52, 125.43, 123.21, 122.22, 119.92, 117.28, 112.52, 47.12, 22.25. ESI-MS: *m/z* 387.1 [M + H]$^+$.

N-((3-Nitrophenyl)(2-(3-nitrophenyl)*H*-imidazo[1,2-*a*]-pyridin-3-yl)methyl)acetamide (29cf')
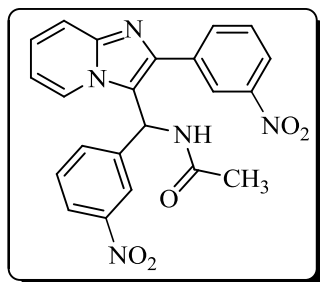
Yield 74%; yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.32 (d, *J* = 8.1 Hz, 1H), 8.23 − 8.22 (m, 1H), 8.13 (d, *J* = 6.9 Hz, 1H), 8.09 − 8.05 (m, 1H), 8.01 (s, 1H), 7.95 (t, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.44 − 7.39 (m, 2H), 7.07 − 7.02 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.74, 147.57, 147.14, 144.28, 141.75, 139.99, 135.92, 135.21,

133.36, 129.79, 129.36, 125.87, 125.04, 123.51, 122.17, 122.09, 121.44, 119.52, 117.23, 112.96, 46.54, 22.33. ESI-MS: *m/z* 432.0 [M + H]$^+$.

N-((4-Nitrophenyl)(2-(3-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29cg')
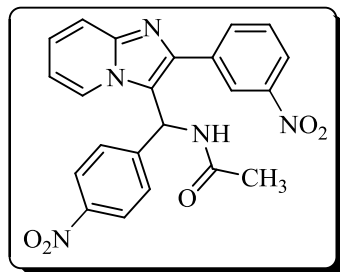
Yield 65%; brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (d, *J* = 7.6 Hz, 1H), 8.36 – 8.35 (m, 1H), 8.12 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.05 – 8.01 (m, 4H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.37 (m, 3H), 7.00 – 6.96 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.21, 148.09, 147.13, 145.86, 144.95, 142.28, 136.29, 135.42, 130.18, 128.42, 126.30, 125.65, 123.92, 123.82, 122.72, 119.69, 117.86, 113.38, 47.43, 22.78. ESI-MS: *m/z* 432.1 [M + H]$^+$.

N-((1*H*-Indol-3-yl)(2-(3-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29ch')
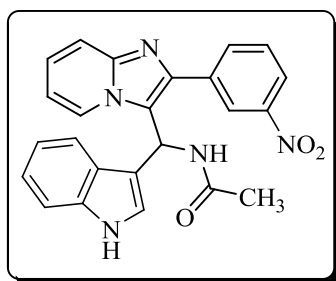
Yield 39%; yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 9.18 (d, *J* = 7.2 Hz, 1H), 8.69 (s, 1H), 8.45 (d, *J* = 6.8 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.33 – 7.29 (m, 2H), 7.05 – 6.99 (m, 3H), 6.99 – 6.88 (m, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.70, 148.25, 144.78, 140.78, 137.24, 136.81, 135.15, 130.20, 126.39, 125.63, 123.90, 123.46, 122.59, 121.98, 121.26, 119.53, 118.50, 117.72, 112.72, 112.22, 111.36, 42.70, 22.73. ESI-MS: *m/z* 426.1 [M + H]$^+$.

N-((2-(3-Nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)-(thiophen-2-yl)methyl)acetamide (29ci')
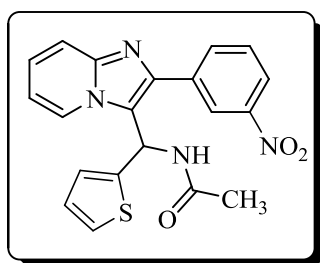
Yield 29%; red solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.62 (s, 1H), 8.42 – 8.04 (m, 3H), 7.88 – 7.61 (m, 2H), 7.58 – 7.18 (m, 2H), 7.21 – 6.89 (m, 3H), 6.83 (s, 1H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.78, 148.37, 145.01, 142.08, 141.49, 136.37, 135.16, 130.45, 127.75, 126.56, 126.20, 125.85, 123.51, 122.87, 120.15, 117.78, 113.10, 44.80, 22.65. ESI-MS: *m/z* 393.09 [M + H]$^+$, 785.17 [2M + H]$^+$.
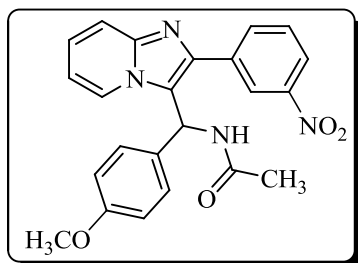
(*N*-((2-(4-Chlorophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(3-nitrophenyl)methyl)acetamide (29df')
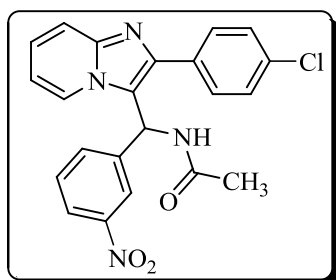
Yield 40%; pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (d, *J* = 8.0 Hz, 1H), 8.06 – 8.04 (m, 2H), 7.93 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.36 – 7.32 (m, 3H), 6.95 – 6.92 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.22, 148.25, 144.78, 143.57, 140.66, 133.60, 133.50, 132.94, 131.03, 130.54, 128.44, 125.97, 125.56, 122.74, 121.73, 118.99, 117.60, 113.07, 47.16, 22.80. ESI-MS: *m/z* 421.1 [M + H]+.

N-((6-Bromo-2-(4-chlorophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(4-chlorophenyl)methyl)-acetamide (29ea')
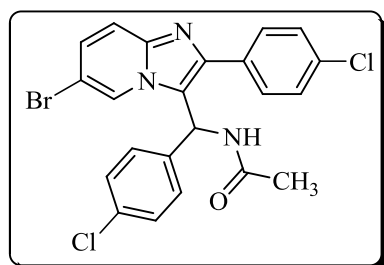
Yield 46%; off-white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.27 (d, *J* = 7.7 Hz, 1H), 8.33 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 9.5 Hz, 1H), 7.50 – 7.47(m, 3H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.96, 144.06, 143.40, 136.76, 133.28, 133.04, 132.75, 130.78, 129.21, 128.87, 128.71, 128.66, 125.61, 119.82, 118.74, 106.80, 47.02, 22.80. ESI-MS: *m/z* 489.97 [M + H + 2]+.

N-((6-Bromo-2-(4-chlorophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(3-nitrophenyl)methyl)-acetamide (29ef')
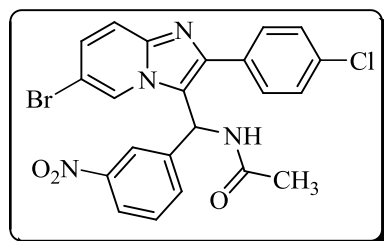
Yield 30%; pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.26 (d, *J* = 7.6 Hz, 1H), 8.34 (s, 1H), 8.11 – 8.00 (m, 1H), 7.94 (d, *J* = 12.7 Hz, 1H), 7.66 (dd, *J* = 13.3, 9.5 Hz, 1H), 7.61 – 7.41 (m, 5H), 7.39 – 7.26 (m, 2H), 7.04 – 6.92 (m, 1H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.20, 148.21, 144.28, 143.26, 140.20, 133.60, 133.13, 132.99, 131.03, 130.54, 128.86, 128.41, 125.46, 122.84, 121.88, 119.87, 118.69, 106.97, 46.90, 22.82. ESI-MS: *m/z* 501 [M + H + 2]+.

N-((6-Bromo-2-(4-chlorophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)(4-nitrophenyl)methyl)-acetamide (29eg')
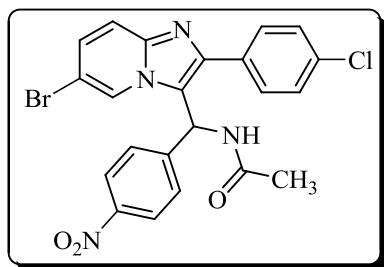
Yield 32%; brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (d, *J* = 8.0 Hz, 1H), 8.27 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 7.69 – 7.63 (m, 3H), 7.48 – 7.35 (m, 5H), 6.96 (d, *J* = 8.0 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.16, 147.31, 145.58, 144.28, 143.44, 133.31, 132.92, 130.90, 128.91, 128.76, 128.37, 125.48, 124.20, 119.45, 118.79, 107.00, 47.27, 22.82. ESI-MS: *m/z* 499 [M + H]$^+$ and 501 [M + H +2]$^+$.

N-(1-(2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)-butyl)acetamide (29fj')
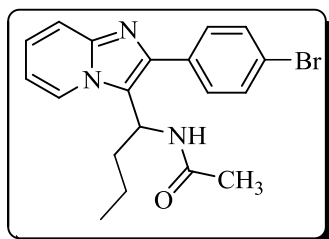
Yield 38%; colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.96 (t, *J* = 6.8 Hz, 1H), 5.40 (q, *J* = 7.8 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.85 (s, 3H), 1.81 – 1.69 (m, 1H), 1.14 – 1.03 (m, 1H), 1.03 – 0.91 (m, 1H), 0.66 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.76, 144.41, 141.91, 134.79, 131.66, 131.46, 125.96, 124.93, 121.36, 121.08, 117.69, 112.64, 45.33, 33.57, 22.84, 19.60, 13.60.

N-((2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(1*H*-indol-3-yl)methyl)acetamide (29gh')
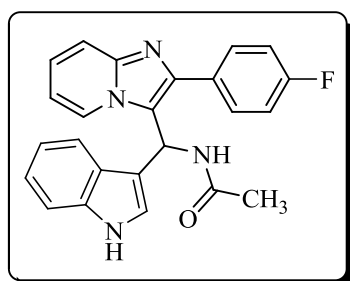
Yield 41%; pink solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.07 (s, 1H), 9.14 (d, *J* = 7.4 Hz, 1H), 8.43 (d, *J* = 6.8 Hz, 1H), 7.93 – 7.91 (m, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.24 (m, 3H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.84 – 6.82 (m, 1H), 1.94 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.59, 144.57, 142.07, 137.27, 131.03, 130.97, 126.38, 125.67, 125.04, 123.75, 121.97, 120.04, 119.47, 118.48, 117.48, 117.48, 115.84, 115.67, 112.28, 111.68, 42.71, 22.81.

N-((4-Methoxyphenyl)(2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)methyl)acetamide (29hb')
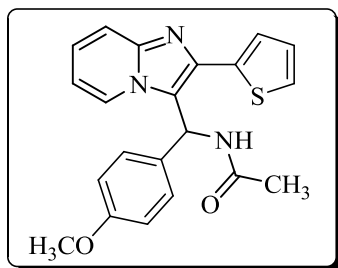
Yield 35%; off-white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.0 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.53 (d, J = 3.6, 1H), 7.28 – 7.25 (m, 1H), 7.15 – 7.12 (m, 1H), 7.01 – 6.97 (m, 3H), 6.90 (s, 1H), 6.89 (s, 1H), 6.82 (td, J = 6.9, 1.1 Hz, 1H), 3.70 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.86, 159.00, 144.65, 138.37, 137.78, 129.80, 128.46, 127.67, 127.14, 126.02, 125.65, 125.57, 118.70, 117.23, 114.74, 112.50, 55.55, 46.99, 22.79.

N-((3-Methoxyphenyl)(2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)methyl)acetamide (29hc')
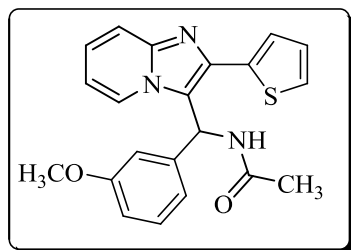
Yield 32%; off-white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.61 – 7.59 (m, 2H), 7.54 (d, J = 3.6, 1H), 7.31 – 7.26 (m, 1H), 7.24 (dd, J = 10.6, 4.0 Hz, 1H), 7.14 (dd, J = 5.1, 3.6 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.68 (s, 1H), 6.60 (d, J = 7.8 Hz, 1H), 3.68 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.95, 160.13, 144.66, 139.84, 138.52, 137.70, 130.61, 128.49, 127.21, 125.94, 125.75, 125.61, 118.56, 118.44, 117.23, 112.76, 112.64, 112.57, 55.49, 47.32, 22.77.

N-((3-Nitrophenyl)(2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)methyl)acetamide (29hf')
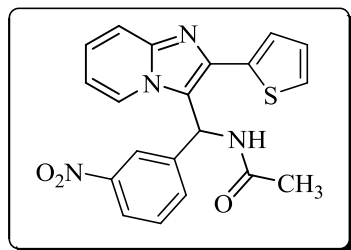
Yield 52%; pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.99 (s, 1H), 7.95 (d, J = 6.8 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.59 (t, J = 5.4 Hz, 2H), 7.49 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.09 (dd, J = 5.6, 2.4 Hz, 1H), 6.86 (t, J = 6.6 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.30, 148.53, 144.82, 140.56, 138.84, 137.22, 133.36, 130.92, 128.36, 127.45, 126.19, 126.14, 125.71, 123.03, 121.26, 117.68, 117.34, 113.00, 47.08, 22.79.

N-(1-(2-(Thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)-butyl)acetamide (29hj')
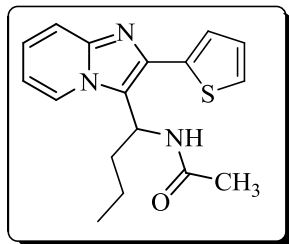
Yield 33%; colorless solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 6.8 Hz, 1H), 8.64 (d, *J* = 7.0 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.29 – 7.22 (m, 1H), 7.15 – 7.06 (m, 1H), 6.93 (t, *J* = 6.8 Hz, 1H), 5.64 – 5.59 (m, 1H), 2.04 – 1.93 (m, 1H), 1.84 (s, 3H), 1.84 – 1.75 (m, 1H), 1.27 – 1.16 (m, 1H), 1.14 – 1.01 (m, 1H), 0.75 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 169.60, 144.21, 138.28, 137.23, 128.25, 126.75, 126.00, 125.91, 125.05, 120.40, 117.35, 112.60, 45.05, 33.47, 22.85, 19.69, 13.73.

**N-((4-Cyanophenyl)(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)acetamide (29hk')**
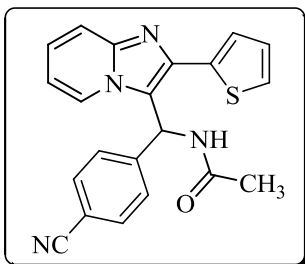
Yield 49%; off-white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.26 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 6.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 5.0 Hz, 1H), 7.46 (d, *J* = 3.3 Hz, 1H), 7.37 – 7.24 (m, 3H), 7.18 – 7.03 (m, 2H), 6.85 (t, *J* = 6.8 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 170.25, 144.84, 143.97, 138.87, 137.32, 133.27, 128.46, 127.64, 127.44, 126.08, 125.88, 125.69, 119.04, 117.49, 117.35, 112.89, 110.76, 47.43, 22.77.

N-((3-Nitrophenyl)(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)formamide (29cf)
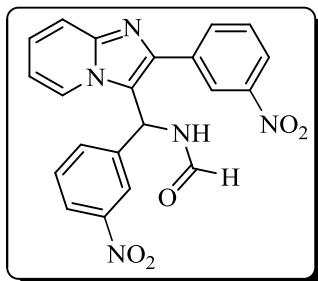
Yield 36%; off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (d, *J* = 8.0 Hz, 1H), 8.43 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 6.8 Hz, 1H), 8.07 – 7.04 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.44 – 7.38 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 6.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.94, 148.06, 147.62, 144.81, 142.37, 139.90, 136.31, 135.65, 133.84, 130.35, 129.90, 126.46, 125.50, 124.02, 122.79, 122.63, 121.89, 119.65, 117.75, 113.49, 45.53. ESI-MS: *m/z* 418.10 [M + H]⁺.

3,3'-((4-Chlorophenyl)methylene)bis(2-*p*-tolylimidazo[1,2-*a*]pyridine) (30aa')
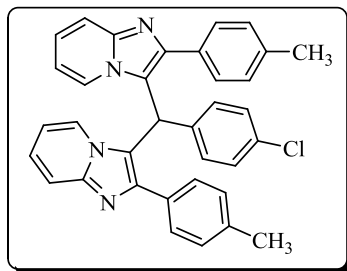
Yield 15%;Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 6.8 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 7.02 (d, J = 8.0 Hz, 4H), 6.85 (d, J = 8.0 Hz, 4H), 6.73 (d, J = 8.4 Hz, 2H), 6.65 (s, 1H), 6.56 (t, J = 6.8 Hz, 2H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.13, 144.32, 137.09, 136.63, 132.20, 131.85, 130.31, 129.35, 128.68, 128.62, 124.93, 124.75, 117.72, 117.18, 112.41, 37.79, 21.08; ESI-MS: *m/z* 539.20 [M + H]$^+$.

3,3'-((3,4,5-Trimethoxyphenyl)methylene)bis(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine) (30cl′)
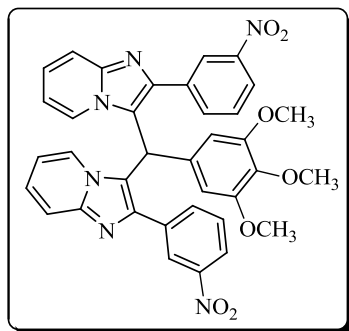
Yield 42%; red solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 6.8 Hz, 2H), 7.54 – 7.51 (m, 4H), 7.41 – 7.28 (m, 6H), 6.91 (t, J = 6.8 Hz, 2H), 6.64 (s, 1H), 6.26 (s, 2H), 3.44 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.40, 146.62, 144.36, 142.62, 136.74, 135.15, 131.29, 129.02, 125.75, 125.24, 123.39, 122.37, 118.35, 117.36, 113.36, 106.36, 59.85, 55.88, 38.62; ESI-MS: *m/z* 657.30 [M + H]$^+$.

N-((4-Chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)-acetamide (32a')
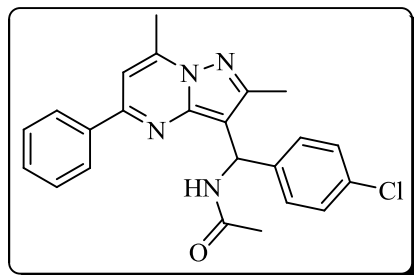
Yield 74%; colorless solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.70 (d, J = 8.1 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.54 – 7.48 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 6.39 (d, J = 8.1 Hz, 1H), 2.63 (s, 3H), 2.36 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.09, 158.18, 152.20, 147.20, 145.92, 141.67, 132.82, 131.09, 130.84, 129.23, 128.68, 128.64, 128.55, 107.71, 105.33, 49.21, 24.99, 23.46, 13.14; ESI-MS *m/z* calcd for C$_{23}$H$_{22}$ClN$_4$O$^+$ 405.1477, found 405.1474 [M + H]$^+$.

N-((4-Bromophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)-acetamide (32b')
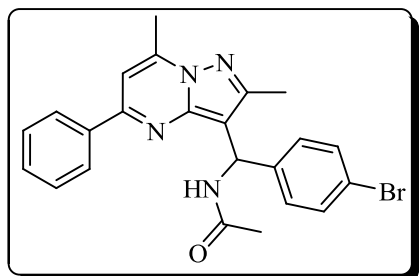
Yield 71%; viscous liquid; ^{1}H NMR (300 MHz, CDCl₃) δ 8.68 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 3.8 Hz, 2H), 7.58 – 7.51 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 6.36 (d, *J* = 8.1 Hz, 1H), 2.64 (s, 3H), 2.42 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, CDCl₃) δ 169.19, 158.18, 152.28, 147.20, 145.99, 142.12, 131.53, 131.11, 130.86, 129.24, 129.01, 128.69, 121.05, 107.70, 105.26, 49.28, 24.96, 23.41, 13.10.

N-((3-Chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)-acetamide (32c')
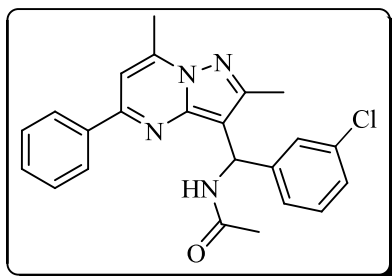
Yield 56%; viscous liquid; ^{1}H NMR (300 MHz, CDCl₃) δ 8.68 (d, *J* = 8.2 Hz, 1H), 8.07 – 7.96 (m, 2H), 7.59 – 7.48 (m, 3H), 7.38 (s, 1H), 7.35 – 7.30 (m, 1H), 7.25 – 7.13 (m, 2H), 6.72 (s, 1H), 6.39 (d, *J* = 8.2 Hz, 1H), 2.63 (s, 3H), 2.37 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, CDCl₃) δ 169.19, 158.26, 152.26, 147.21, 145.96, 145.11, 134.25, 131.09, 130.86, 129.74, 129.26, 128.67, 127.35, 127.23, 125.54, 107.77, 105.18, 49.37, 24.95, 23.41, 13.15.

N-((2,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)-(2-fluorophenyl)methyl)-acetamide (32d')
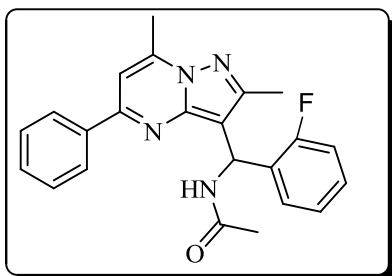
Yield 42%; sticky pale yellow solid; ^{1}H NMR (300 MHz, CDCl₃) δ 8.66 (d, *J* = 8.0 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.63 – 7.47 (m, 4H), 7.24 – 7.12 (m, 1H), 7.11 – 6.92 (m, 2H), 6.69 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 2.65 (s, 3H), 2.40 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, CDCl₃) δ 168.94, 161.65, 158.37, 157.85, 152.27, 147.09, 145.84, 130.99, 130.03, 129.85, 129.20, 129.03, 128.97, 128.77, 128.65, 124.06, 124.02, 115.75, 115.46, 107.56, 105.34, 44.46, 44.41, 24.99, 23.32, 13.03, 13.00.

N-((2,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)-(4-nitrophenyl)methyl)acetamide (32e')
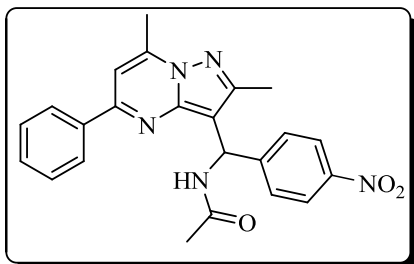
Yield 69%; yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.75 (d, *J* = 8.2 Hz, 1H), 8.16 – 8.05 (m, 2H), 8.02 (d, *J* = 6.8 Hz, 2H), 7.61 – 7.55 (m, 5H), 6.78 (s, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 2.67 (s, 3H), 2.39 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.45, 158.67, 152.13, 150.23, 147.19, 146.92, 146.10, 131.20, 130.65, 129.24, 128.70, 128.04, 123.78, 107.99, 104.44, 49.46, 24.98, 23.31, 13.13.

N-((2,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)(3-nitrophenyl)methyl)acetamide (32f')
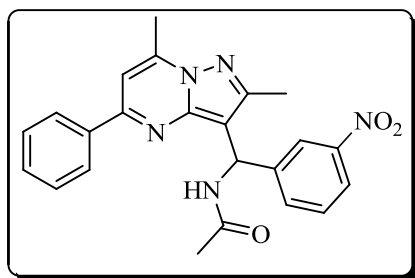
Yield 56%; yellow solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.71 (d, *J* = 7.8 Hz, 1H), 8.29 (t, *J* = 1.9 Hz, 1H), 8.09 – 8.04 (m, 1H), 8.03 – 7.98 (m, 2H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.46 (t, *J* = 7.9 Hz, 1H), 6.76 (s, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 2.67 (s, 3H), 2.39 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.35, 158.64, 152.15, 148.48, 147.23, 146.14, 145.30, 133.63, 131.18, 130.73, 129.35, 129.27, 128.71, 122.21, 122.09, 107.99, 104.63, 49.45, 24.97, 23.35, 13.16.

N-((2,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)(3,4,5-trimethoxyphenyl)methyl)-acetamide (32k')
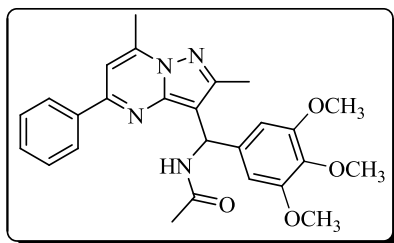
Yield 39%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.01 – 7.89 (m, 2H), 7.51 – 7.42 (m, 3H), 6.68 (s, 2H), 6.66 (s, 1H), 6.27 (d, *J* = 8.4 Hz, 1H), 3.72 (s, 9H), 2.57 (s, 3H), 2.35 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.15, 157.97, 153.17, 152.34, 147.18, 145.97, 138.85, 137.13, 131.10, 130.89, 129.23, 128.69, 107.59, 105.94, 104.36, 60.76, 56.12, 49.92, 24.92, 23.47, 13.18.

3,3'-((4-Chlorophenyl)methylene)bis(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine) (33a')
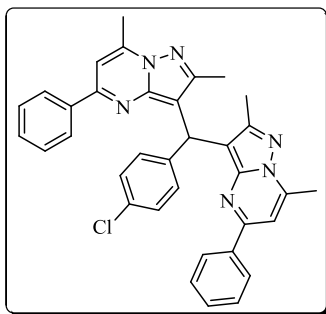
Yield 8%; colorless liquid; ^{1}H NMR (400 MHz, CDCl$_3$) δ ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01 (dd, *J* = 6.5, 2.8 Hz, 4H), 7.53 − 7.49 (m, 6H), 7.27 − 7.08 (m, 4H), 6.60 (s, 2H), 6.33 (s, 1H), 2.50 (s, 6H), 2.42 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 157.19, 153.98, 147.67, 144.95, 141.08, 131.51, 131.38, 130.60, 129.99, 129.21, 128.55, 127.93, 108.18, 107.37, 34.49, 24.74, 14.46; ESI-MS *m/z* calcd for C$_{35}$H$_{30}$ClN$_6^+$ 569.2215, found 569.2227 [M + H]$^+$.

3,3'-((3-Chlorophenyl)methylene)bis(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine) (33c')
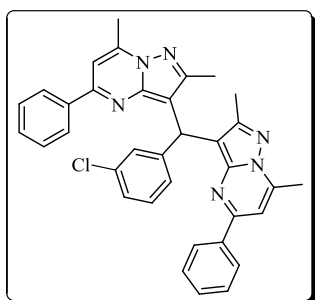
Yield 14%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.06 − 7.96 (m, 4H), 7.57 − 7.45 (m, 8H), 7.17 (d, *J* = 1.3 Hz, 2H), 6.59 (s, 2H), 6.35 (s, 1H), 2.49 (s, 6H), 2.42 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.26, 154.02, 147.71, 145.00, 144.86, 133.88, 131.53, 130.60, 129.25, 129.09, 128.73, 128.55, 126.86, 125.95, 107.95, 107.41, 34.84, 24.72, 14.45.

3,3'-((4-Nitrophenyl)methylene)bis(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine) (33e')
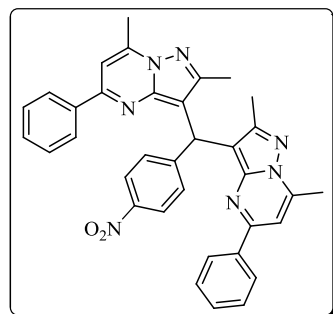
Yield 13%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.12 (d, *J* = 7.6 Hz, 2H), 8.05 − 8.01 (m, 4H), 7.54 − 7.49 (m, 6H), 7.46 (d, *J* = 7.6 Hz, 2H), 6.63 (s, 2H), 6.42 (s, 1H), 2.50 (s, 6H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.54, 153.81, 150.72, 147.65, 146.21, 145.12, 131.33, 130.72, 129.42, 129.23, 128.59, 123.14, 107.58, 107.32, 35.27, 24.75, 14.38.

3,3'-(Phenylmethylene)bis(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine) (33g')
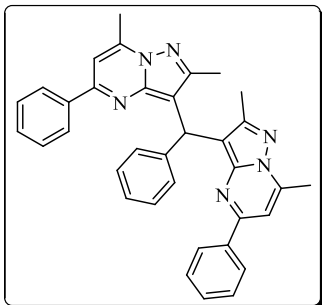
Yield 18%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.08 – 7.96 (m, 4H), 7.62 – 7.43 (m, 5H), 7.33 – 7.20 (m, 5H), 6.58 (s, 2H), 6.40 (s, 1H), 2.50 (s, 6H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.04, 154.19, 147.74, 144.92, 142.50, 131.65, 130.53, 129.23, 128.61, 128.53, 127.88, 125.71, 108.64, 107.28, 34.95, 24.71, 14.42.

3,3'-((3,4,5-Trimethoxyphenyl)methylene)bis(2,7-di-methyl-5-phenylpyrazolo[1,5-*a*]-pyrimidine) (33k')
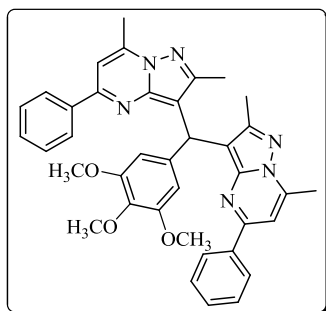
Yield 26%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.07 – 7.94 (m, 4H), 7.55 – 7.45 (m, 6H), 6.62 (s, 2H), 6.60 (s, 2H), 6.33 (s, 1H), 3.85 (s, 3H), 3.70 (s, 6H), 2.52 (s, 6H), 2.47 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.05, 153.96, 152.83, 147.68, 144.92, 138.12, 136.26, 131.51, 130.62, 129.24, 128.55, 108.78, 107.28, 106.22, 60.96, 56.18, 35.33, 24.73, 14.47.

6-((4-Chlorophenyl)(2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)methyl)-2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (34a')
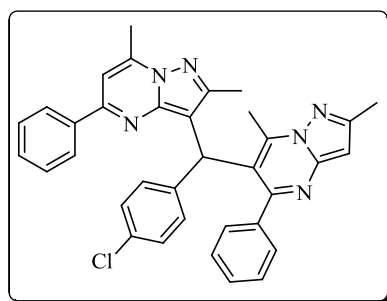
Yield 4%; colorless liquid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.89 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.53 – 7.50 (m, 3H), 7.43 – 7.41 (m, 2H), 7.26 – 7.24 (s, 5H), 7.02 (s, 1H), 6.62 (s, 1H), 6.37 (s, 1H), 2.78 (s, 3H), 2.53 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.01, 140.99, 131.45, 130.63, 130.10, 129.81, 129.20, 128.64, 128.54, 127.95, 127.09, 107.41, 103.57, 34.75, 24.77, 17.53, 14.51, 14.19; ESI-MS *m/z* calcd for C$_{35}$H$_{30}$ClN$_6^+$ 569.2215, found 569.2231 [M + H]$^+$.

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Chapter IV

Synthesis of Novel Azole fused Fused Polyheterocycles by Transition Metal Catalyzed C−H Activation

For a long time, many synthetic groups have continuously focused on the development of efficient methods for aryl-aryl bond formation, because many bioactive motifs are found to have these biaryl linkages.[1] As a result of extensive efforts toward this end, several innovative methods have been achieved and they are updated with the time to make these processes more viable in terms of economy as well as synthetic simplicity. Among them, transition metal catalyzed cross-coupling reactions are worth mentioning because they enable C−C and C−heteroatom bond formations with high efficiencies and high functional group tolerance under mild conditions.[2] Although earlier methods such as Ullmann reaction used stoichiometric amounts of copper salts and harsh reaction conditions for these couplings, the advancements like employing organic ligands and transition metal complexes make these procedures milder, more efficient and highly selective to afford high yields of the corresponding coupled products.[3-4] Moreover, these strategies have successfully been utilized for the synthesis of several natural products.[5] The catalytic construction of biaryls can be broadly classified into three major types.

i) Traditional cross-coupling reaction

This class of reactions are well examined and successfully used in several industrial procedures. They involve coupling of an organometallic partner with an aryl halide or a pseudoarylhalide or coupling of two aryl halides (**Scheme 4.1**). These couplings generally necessitates pre-activation of both the precursors prior to the reaction. The well established reactions which comes under this category includes Suzuki reaction, Stille reaction, Kumada and Negishi couplings.[6-8]

X = halo, OTf; M = B, Sn, Si, Mg

Scheme 4.1 General representation of traditional cross coupling reaction

ii) Direct arylation or C−H activation

In recent years, the concept of direct arylation is more familiar in the literature. This method enables aryl-aryl coupling among aryl compound containing unactivated C−H bond with pre-activated aryl partner (**Scheme 4.2**). This approach has several advantages over traditional reaction because it avoids the necessity of stoichiometric amount of organometallic reagent for the coupling reaction.[9]

X = halo, OTf
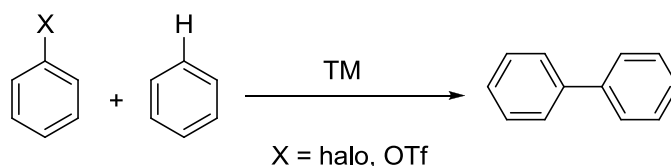
Scheme 4.2 General representation of direct arylation

iii) Cross Dehydrogenative Coupling (CDC) or double C−H activation

Cross dehydrogenative couplings are in general comprehended as coupling between two unactivated C−H bonds in presence of transition metal catalysts (**Scheme 4.3**). In recent years, this technique is in high demand because it does not rely on the pre-activated precursors such as aryl halides and organometallic agents thereby eliminates the waste generation in the coupling process. Some of the challenges like site selectivity of the molecules with diverse C−H bonds have been addressed by incorporating the directing group which binds with the transitional metal and allows the activation of C−H bond of interest. Since the formation of C−C bonds with the loss of H_2 molecule is thermodynamically not favoured, external oxidant is commonly employed in CDC processes.[10-12]
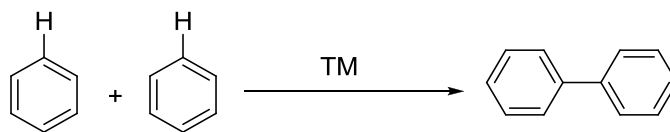
Scheme 4.3 General representation of cross dehydrogenative coupling (CDC)

With our interest in synthesis of novel fused azaheterocycles using transition metal catalyzed C−H functionalizations, in this chapter, we have discussed our efforts for the development of a novel methodology to synthesize azole fused imidazo[1,2-*a*]pyridines.

Chapter IV

PART-A

One-pot Sequential C−N and Cross Dehydrogenative Couplings: Synthesis of Novel Azole Fused Imidazo[1,2-*a*]pyridines

4.1 Introduction

Fused heterocyclic molecular frameworks are found in large number of biologically active natural and synthetic compounds.[13] Imidazo[1,2-*a*]pyridine, a bicyclic *N*-fused imidazole is a privileged structural motif present in several natural products and pharmacologically relevant structures, with a wide range of activities such as anti-bacterial, anti-viral, anti-ulcer, anthelmintic, anti-inflammatory, anti-convulsant, hypnotic, gastrointestinal, and immune modulatory activities.[14-15] Owing to their broad range of biological importance, considerable efforts have been directed towards the synthesis and functionalization of imidazo[1,2-*a*]pyridine derivatives.[16-17]

The cross dehydrogenative coupling (CDC) has emerged as an efficient and straightforward methods for the construction of C−C and C−N bonds in organic synthesis from the viewpoint of synthetic simplicity and efficiency, atom economy, and environmental benefits.[12, 18-20] It avoids pre-functionalization of substrates and minimizes by-product formation. Particularly, C−H functionalization involved in multi bond approaches such as multicomponent reactions, cascade reactions and one-pot synthetic sequences is a useful tool for the synthesis of complex molecules in a single step. A number of novel methodologies have been established to generate diverse poly heterocycles *via* cross dehydrogenative coupling.[10, 21-28]

For example, Bao and co-workers attempted palladium catalyzed intramolecular double sp^2 C−H activation for the synthesis of azole fused isoquinoline frameworks (**2**) (**Scheme 4.4**).[29] Here, 2-position of imidazole ring and unreactive benzene C−H bond were activated using catalytic amount of PdCl$_2$ with the stoichiometric amount of Cu(OAc)$_2$ as an oxidant for the intramolecular C−C bond formation. Good yields of polyheterocyclic motifs have been achieved using the developed methodology.
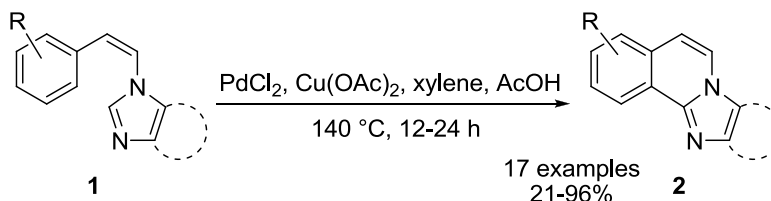
Scheme 4.4 Double sp^2 C−H activation for the synthesis of azole fused isoquinoline frameworks

Guo and colleagues synthesized *N*-fused heterocycles (**4**) through intramolecular double C−H activation *viz*. CDC of *N*-benzylated purines (**3**) (**Scheme 4.5**).[30] Pd(OAc)$_2$ proved as an effective catalyst in conjunction with the oxidant AgOAc under ligand and base-free conditions. This protocol was smoothly extended to benzimidazoles which offered good yields of corresponding fused azoles.
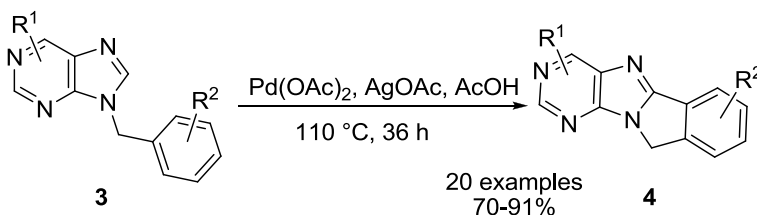
Scheme 4.5 Synthesis of fused *N*-heterocycles *via* tandem C−H activation

In other case, indole based tetracyclic fused azoles (**6**) have been synthesized using CDC strategy (**Scheme 4.6**).[31] Here catalytic amount of Pd(OAc)$_2$, with the assistance from Cu(OAc)$_2$ and K$_2$CO$_3$ was successful in promoting the envisioned C−H activation/functionalization and delivered good to excellent yields of fused azoles.
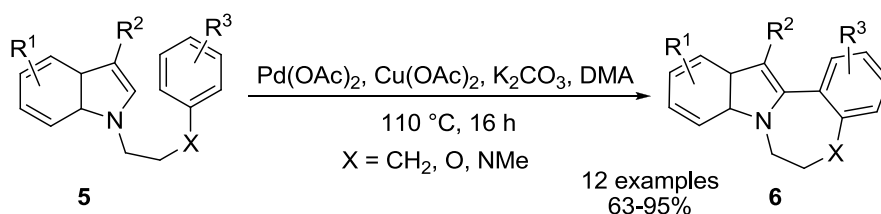
Scheme 4.6 Intramolecular oxidative C−H coupling for medium-ring synthesis

Ackermann group accessed triazole fused heterocyclic motifs (**8**) by employing palladium catalyzed CDC reaction (**Scheme 4.7**).[32] A library of fused tri/tetracyclic azoles have been achieved using the developed methodology. Interestingly, these dehydrogenative couplings proceeded smoothly under aerobic conditions.
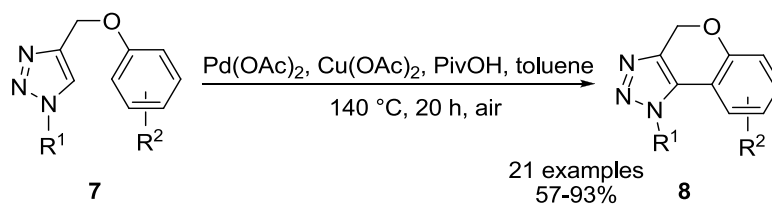
Scheme 4.7 Palladium catalyzed dehydrogenative direct arylations of 1,2,3-triazoles

152

Although a variety of classical methods have been developed to synthesize imidazo[1,2-*a*]pyridine derivatives, there is still a need to develop novel fused imidazo[1,2-*a*]pyridines because of their significance in the pharmaceutical industry. As a part of our continued interest in synthesis of novel heterocycles containing imidazo[1,2-*a*]pyridines, we have developed an efficient protocol for the synthesis of novel azole-fused imidazo[1,2-*a*]pyridines by one-pot Ullmann type coupling followed by intramolecular C−C bond formation *via* cross dehydrogenative coupling.

4.2 Results and Discussion

The investigation was commenced with the Ullmann coupling between 2-(2-bromophenyl)-imidazo[1,2-*a*]pyridine (**9a**) and 1*H*-imidazole (**10a**) in the presence of 5 mol % CuI in DMF at 150 °C using K_2CO_3 as base, and the C−N coupled product, 2-(2-(1*H*-imidazol-1-yl)phenyl)-imidazo[1,2-*a*]pyridine (**11a**) was obtained in 80% yield (**Scheme 4.8**). When the catalyst loading was increased to 10 mol %, the yield of **11a** increased to 92%.
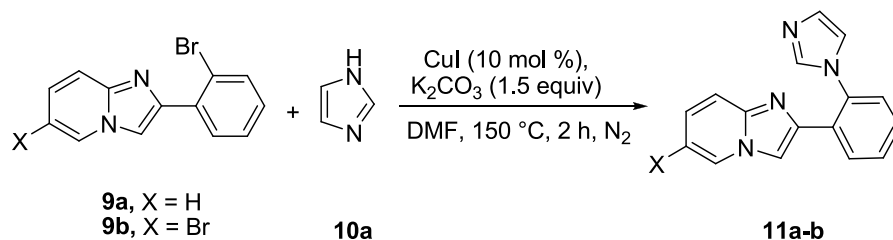
Scheme 4.8 C−N coupling of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine(**9**)

Notably the Ullmann type C−N coupling efficiently proceeded without any external ligands. The compound **11a** was characterized by its NMR and HRMS data. All the protons and carbons were located at their respective positions in ^{1}H and ^{13}C NMR. Additionally, HRMS peak at 261.1139 for [M+H]$^+$ confirmed the structure of **11a**. A representative ^{1}H and ^{13}C NMR of **11a** is shown in **Figure 4.1**. Moreover, when 6-bromo-2-(2-bromophenyl)-imidazo[1,2-*a*]pyridine (**9b**) was reacted with *1H*-imidazole (**10a**) under the optimized reaction conditions, excellent regioselectivity was observed for C−N coupling and monosubstituted compound, 2-(2-(1*H*-imidazol-1-yl)phenyl)-6-bromoimidazo[1,2-*a*]pyridine (**11b**) was obtained in 85% yield (**Scheme 4.8**). Formation of a disubstituted compound by double C−N coupling was not observed and we anticipated that this was due to the *ortho*-directing effect of the nitrogen in the

153

imidazole moiety of imidazo[1,2-*a*]pyridine. The directed *ortho*-cross coupling strategy has been studied for the direct amination of *ortho*-functionalized haloarenes.[33-34]

After optimizing the reaction conditions for C−N coupling, we performed palladium-catalyzed coupling reaction of **11a** using 5 mol % of Pd(PPh$_3$)$_2$Cl$_2$, 2 equiv. of Cu(OAc)$_2$ and 1.5 equiv. of K$_2$CO$_3$ in DMA at 150 °C (**Scheme 4.9**). To our delight the reaction was completed in 1 h to give cyclized product imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (**12a)** in 55% yield.

11a **12a**
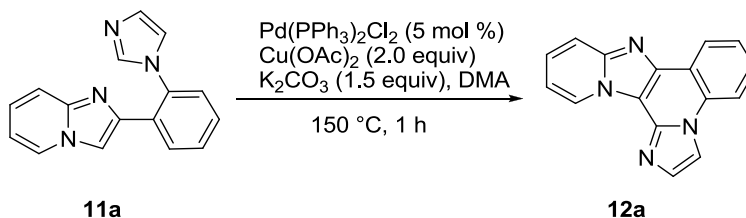
Scheme 4.9 Double C−H activation of 2-(2-(imidazolyl)phenyl)imidazo[1,2-*a*]pyridine (**11a**)

The structure of **12a** was characterized by NMR and HRMS data. The characteristic singlets of C-3 position of imidazo[1,2-*a*]pyridine and C-2 position of imidazole disappeared in **12a**. All protons and carbons were located at their respective positions in ^{1}H and ^{13}C NMR of **12a**. Additionally, HRMS peak at 259.0956 for [M+H]$^+$ confirmed the structure of **12a**. A representative ^{1}H and ^{13}C NMR of **12a** are shown in **Figure 4.2**.
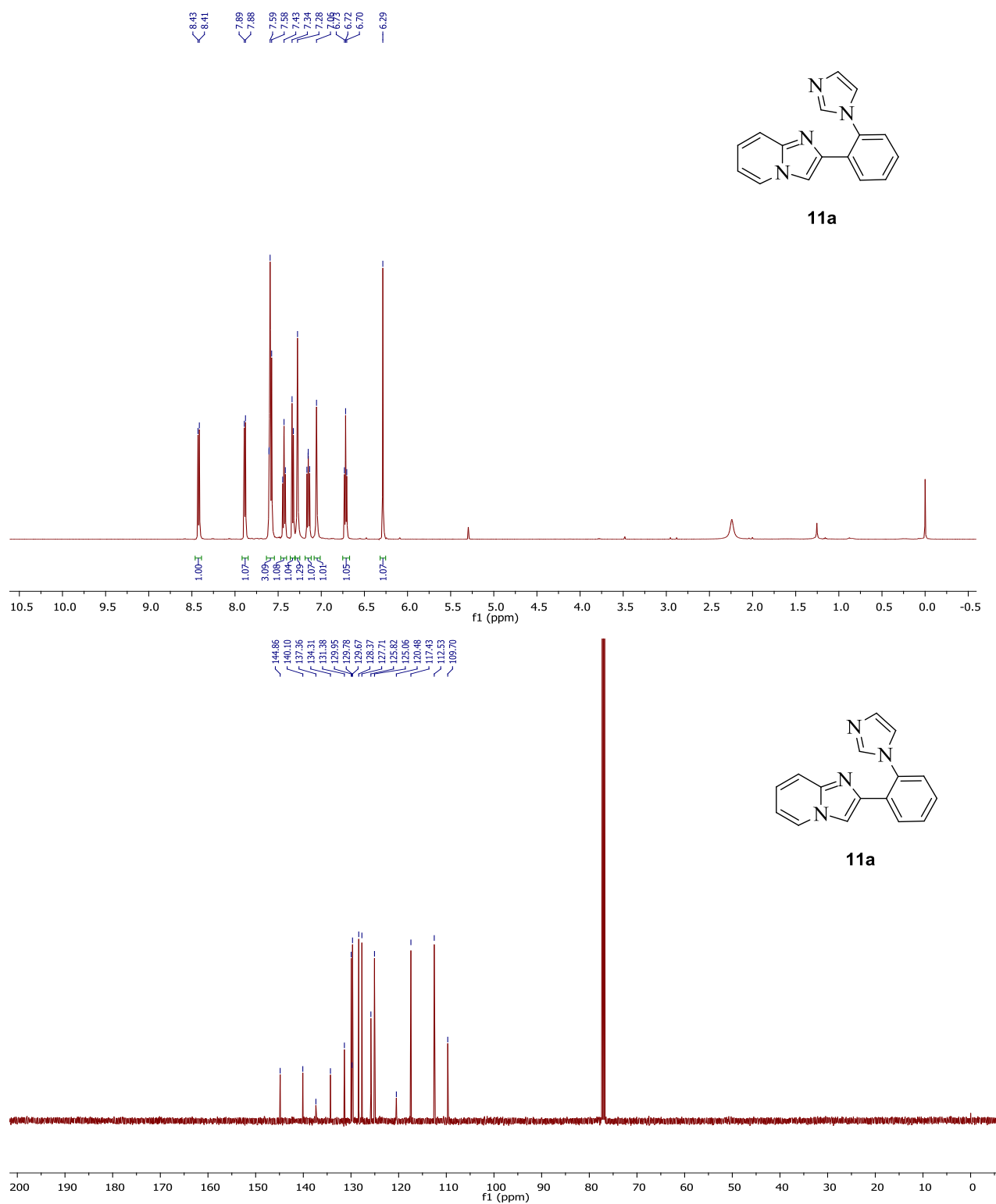
Figure 4.1 ^{1}H and ^{13}C NMR spectra (in CDCl$_3$; recorded on a Bruker AV 500 spectrometer) of 2-(2-(1*H*-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**11a**)
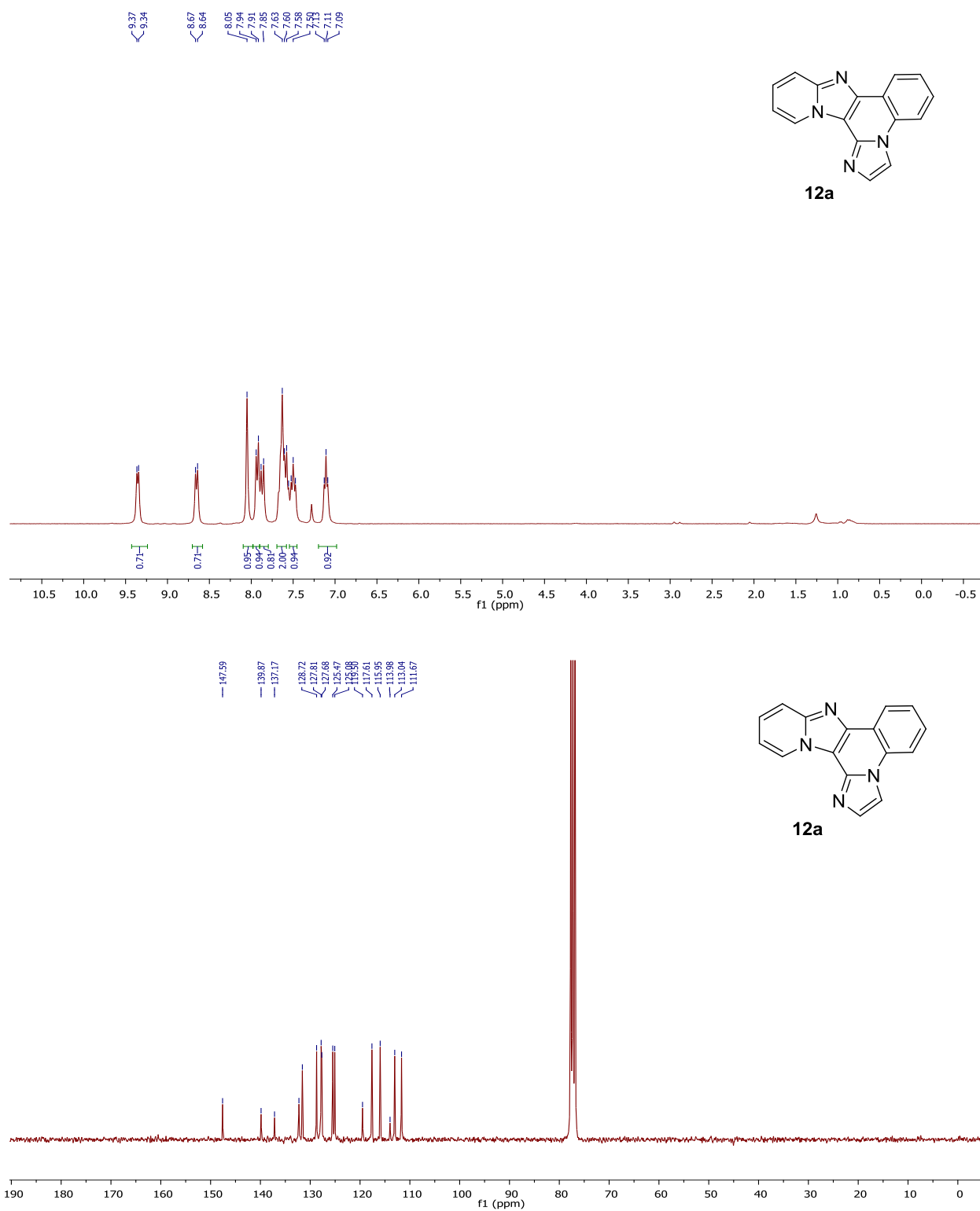
Figure 4.2 ^{1}H and ^{13}C NMR spectra (in CDCl$_3$; recorded on a Bruker AV 500 spectrometer) of imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (**12a**)

With the encouraging results in hand, we decided to perform the C−N coupling and cross dehydrogenative coupling reaction in a one-pot manner. Thus we chose to add palladium catalyst to the reaction mixture containing C−N coupling product without isolation. A reaction of **9a** with **10a** in the presence 10 mol % of CuI, 1.5 equiv. of K_2CO_3 in DMF at 150 °C, followed by addition of 5 mol % of $Pd(PPh_3)_2Cl_2$, 2 equiv. of $Cu(OAc)_2$ resulted **12a** in 61% isolated yield (entry 1, Table 4.1). To optimize the reaction conditions for the one-pot procedure, a series of experiments were conducted and the results are summarized in Table 4.1.

Table 4.1 Optimization of reaction conditions for the one-pot synthesis of **12a**[a]
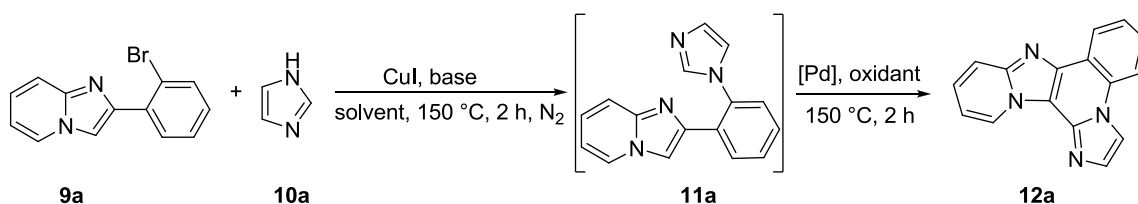
Entry	Catalyst	Oxidant	Base	Solvent	% Yield[b]
1	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	K_2CO_3	DMF	61
2	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	K_2CO_3	DMF	41
3	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**K_2CO_3**	**DMF**	**75[c]**
4	$Pd(PPh_3)_4$	$Cu(OAc)_2$	K_2CO_3	DMF	60
5	$Pd(dba)_2$	$Cu(OAc)_2$	K_2CO_3	DMF	25
6	$Pd(OAc)_2$	$CuCl_2$	K_2CO_3	DMF	55
7	$Pd(OAc)_2$	CuI	K_2CO_3	DMF	-[d]
8	$Pd(OAc)_2$	t-BuOOH	K_2CO_3	DMF	28
9	$Pd(OAc)_2$	$Cu(OTf)_2$	K_2CO_3	DMF	42
10	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	DMF	62
11	$Pd(OAc)_2$	$Cu(OAc)_2$	Cs_2CO_3	DMF	22
12	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	DMF	53
13	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	DMA	40
14	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	1,4-dioxane	22
15	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	toluene	15
16	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	DMSO	68
17	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	EDC	12
18	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	xylene	25

[a]Reaction condition: **9a** (1.00 mmol), **10a** (1.20 mmol), CuI (0.10 mmol), base (1.5 mmol), solvent (3.0 mL), 150 °C, 2h, then [Pd] (0.05 mmol), oxidant (1.2 mmol), 150 °C, 2 h. [b]Isolated yields.
[c]Yield of **12a** was 23% when 2-(2-chlorophenyl)imidazo[1,2-a]pyridine was used instead of **9a**.
[d]Only **11a** was formed.

Although the palladium catalysts Pd(dppf)Cl$_2$, Pd(OAc)$_2$, Pd(PPh$_3$)$_4$, and Pd(dba)$_2$ all gave the desired product, Pd(OAc)$_2$ proved to be an ideal catalyst among the investigated (entry 3, Table 4.1). It is also worth mentioning that no designed ligand was required for the dehydrogenative coupling with the palladium catalyst under these conditions. Among different oxidants and bases screened, combination of Cu(OAc)$_2$ and K$_2$CO$_3$ was found to be best choice for this reaction. Finally, the effect of different solvents was studied and it was observed that better yields of **12a** was obtained in polar aprotic solvents (e.g., DMSO, DMA and DMF) compared to apolar solvents (1,4-dioxane, toluene, xylene and EDC). DMF proved to be best solvent for this transformation (entry 3, Table 4.1). The cross dehydrogenative coupling failed completely when the reaction was carried out in the presence of Pd(OAc)$_2$ but without Cu(OAc)$_2$ (entry 7, Table 4.1) and only C−N coupled product **11a** was observed.

By using the optimized reaction conditions as indicated in entry 3 of Table 4.1, we evaluated the scope of the one-pot C−N coupling and cross dehydrogenative coupling. Representative products are illustrated in **Scheme 4.10**. In addition to the simple imidazole (**10a**), other azoles such as, benzimidazole (**10b**), 1,2,4-triazole (**10c**), 4-methylimidazole (**10d**) and 1*H*-imidazo[4,5-*b*]pyridine (**10e**) coupled with **9a** to give the corresponding azole fused imidazo[1,2-*a*]pyridines (**12b–d** and **12o**) in good yields. Different imidazo[1,2-*a*]pyridine derivatives such as 2-(2-bromophenyl)-6-methyl-imidazo[1,2-*a*]pyridine (**9c**), 2-(2-bromophenyl)-7-methyl-imidazo[1,2-*a*]pyridine (**9d**), 2-(2-bromophenyl)-6-fluoroimidazo[1,2-*a*]pyridine (**9e**), and 2-(2-bromophenyl)-6-chloroimidazo[1,2-*a*]pyridine (**9f**) could also be participated to afford the corresponding azole fused imidazo[1,2-*a*]pyridines (**12e–n** and **12p**) in good yields (62–78%). The reaction with 2-(2-chlorophenyl)imidazo[1,2-*a*]pyridine was slow and only 23% of **12a** was isolated when **10a** was reacted with 2-(2-chlorophenyl)imidazo[1,2-*a*]pyridine under these reaction conditions (Table 4.1, footnote c).
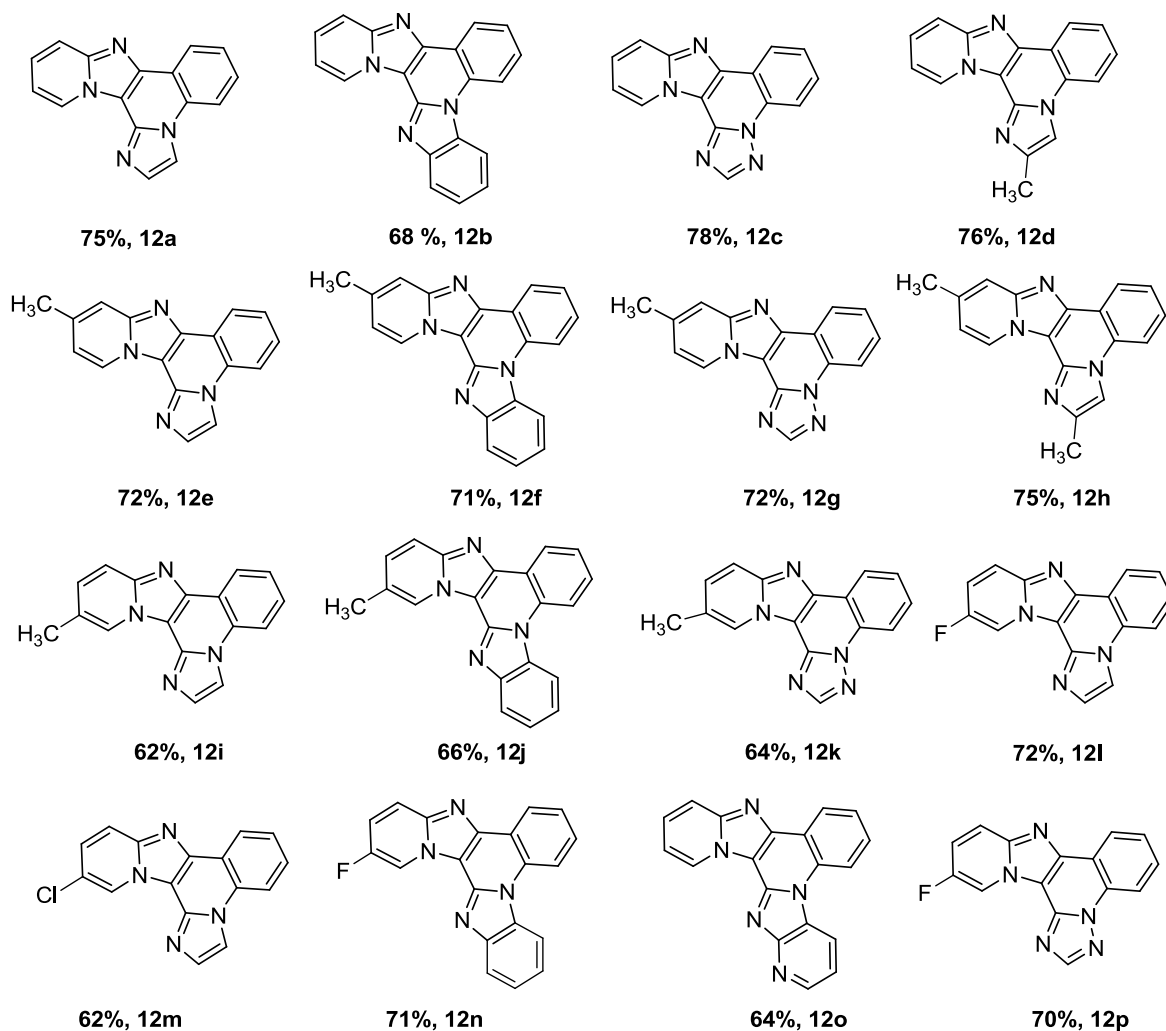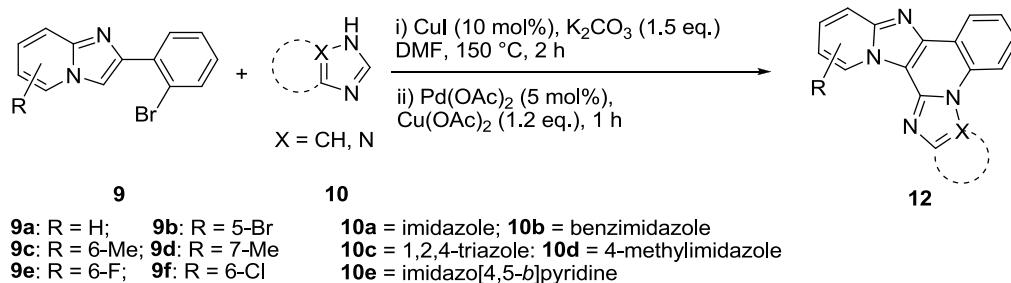
Scheme 4.10 Substrate scope for the one-pot C−N coupling and CDC reaction

Based on the results obtained and literature precedent, it is proposed that the fused azoles (**12**) could be produced through Pd(II)-Pd(0) catalytic cycle as shown in **Scheme 4.11**. Initially, C$_2$−H bond cleavage of the azole (**11**) leads to the formation of the intermediate **13** *via* concerted

metallation-deprotonation,[35] which undergoes intramolecular deprotonation-metallation to give palladium(II) complex **14** as a key intermediate. Reductive elimination from **14** affords the azole fused imidazo[1,2-*a*]pyridines (**12**) and a Pd(0) which is then oxidized to Pd(II) by Cu(II). The better catalytic activity of Pd(OAc)$_2$ over other palladium catalysts may be explained by the fact that the palladium bound acetate in **13** helps in deprotonation during the second C−H activation. Ofial *et al.* have reported that palladium bound acetate plays an important role as a proton acceptor during the second C−H bond cleavage in cross dehydrogenative coupling reactions.[16]
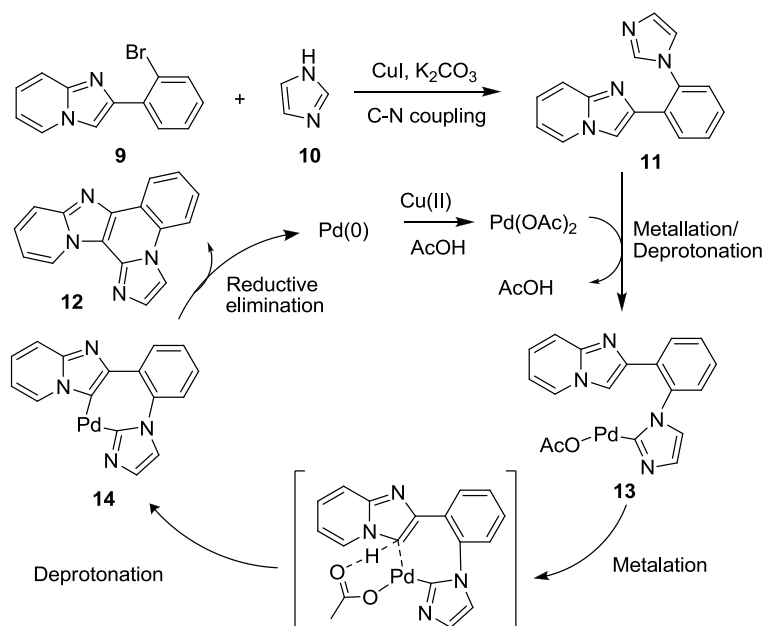
Scheme 4.11 Proposed mechanism for the formation of imidazo[1,2-*a*]pyrido[2',1':2,3]-imidazo[4,5-*c*]quinoline (**12a**) (For clarity, ligands for Pd are omitted)

4.3 Conclusion

In summary, we have successfully developed an efficient and simple one-pot protocol for the synthesis of structurally complex and novel azole fused imidazo[1,2-*a*]pyridines by sequential Ullman-type C−N coupling and oxidative intramolecular C−C bond formation *via* double C−H activation or CDC coupling without the requirement of designed ligands.

4.4 Experimental

General: All chemicals were obtained from the commercial suppliers and used without further purification. Melting points were determined in open capillary tubes on a MPA120-Automated

melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates (Merck). The chemical structures of final products were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) determined on a Bruker NMR spectrometer (300 MHz) or a Varian NMR spectrometer (500 MHz). ^{13}C NMR spectra are fully decoupled. Chemical shifts were reported in parts per millions (ppm) using deuterated solvent peak or Tetramethylsilane (internal) as the standard. The chemical structures of final products were confirmed by a high-resolution Biosystems QStar Elite time-of-flight electrospray mass spectrometer.

Preparation of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (9a)

A solution of 2'-bromoacetophenone (5.0 g, 25 mmol), *N*-bromosuccinimide (NBS) (4.5 g, 25 mmol) and *p*-toluenesulphonic acid (7.1 g, 37.5 mmol) in acetonitrile (40 mL) was stirred for 4 h at reflux temperature. After completion of the reaction as indicated by TLC the reaction mass was allowed to cool to ambient temperature and evaporated the volatiles. The residue was diluted with water and the product was extracted into ethyl acetate. Organic layer was dried over anhydrous sodium sulfate and evaporated the volatiles. The crude 2-bromo-1-(2-bromophenyl)ethanone (6.6 gr, 95%, light brown liquid) was subjected to next step without further purifications.

To a solution of 2-bromo-1-(2-bromophenyl)ethanone (6.5 g, 23.38 mmol) and sodium bicarbonate (2.9 g, 35.07 mmol) in ethanol (65 mL) was added 2-aminopyridine (2.2 g, 23.38 mmol) and reaction mixture was stirred at reflux for 2 h. On completion, the reaction mass was allowed to cool to ambient temperature and evaporated the volatiles. The residue was diluted with water and extracted into ethyl acetate. Organic layer was dried over anhydrous sodium sulfate and evaporated the volatiles. The crude compound was purified by column chromatography to get 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**9a**) as a yellow solid.
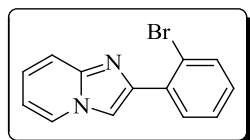
Yield: 4.15 g, (65%); mp 80-81 °C; ^{1}H NMR (500 MHz, CDCl₃): δ 8.28 (s, 1H), 8.17 − 8.13 (m, 2H), 7.68 − 7.62 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 6.78 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz,

CDCl$_3$) δ 144.52, 143.35, 134.53, 133.61, 131.72, 128.97, 127.51, 125.73, 124.78, 121.51, 117.72, 112.44, 112.04. HRMS calcd for 273.0022, found 272.9788 [M + H]$^+$ and 274.9784 [M + H + 2]$^+$.

Preparation of 2-(2-(1*H*-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (11a)

To a solution of **9a** (0.27 g, 1.0 mmol), **10a** (0.068 g, 1.0 mmol) in DMF (3 mL) was added CuI (0.019 g, 0.1 mmol), K$_2$CO$_3$ (0.2 g, 1.5 mmol) and purged the solution with N$_2$ then stirred for 2 h at 150 °C. The reaction mass was cooled to room temperature, diluted with water and extracted into ethyl acetate. Organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated the volatiles. The crude compound was purified by column chromatography (EtOAc/hexanes) to get 2-(2-(1H-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**11a**) as off-white solid.
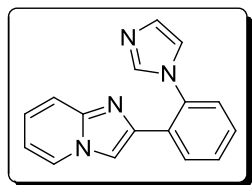
Yield: 240 mg, (92%); mp 149-151 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.89 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.65 − 7.55 (m, 3H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.29 (s, 1H), 7.18 − 7.14 (m, 1H), 7.06 (s, 1H), 6.73 (td, *J* = 6.8, 1.1 Hz, 1H), 6.29 (s, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.86, 140.10, 137.36, 134.31, 131.38, 129.95, 129.78, 129.67, 128.37, 127.71, 125.82, 125.06, 120.48, 117.43, 112.53, 109.70; HRMS calcd for 261.1135, found 261.1139 [M + H]$^+$.

General procedure for the synthesis of compound 12a

To a solution of **9a** (273 mg, 1.0 mmol) and **10a** (68 mg, 1.0 mmol) in DMF (3 mL) was added CuI (19 mg, 10 mol %), K$_2$CO$_3$ (207 mg, 1.5 mmol) and purged the solution with N$_2$ and then stirred for 2 h at 150 °C. After 2 h, Pd(OAc)$_2$ (11 mg, 5 mol %) and Cu(OAc)$_2$ (272 mg, 1.2 mmol) were added to the reaction mass at same temperature and continued the stirring for additional 2 h. On completion, the reaction mass was allowed to cool to ambient temperature, diluted with water and extracted into ethyl acetate (2 × 10 mL). Organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated the volatiles. The crude compound was purified by column chromatography (EtOAc/hexanes/Et$_3$N).

Imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12a)
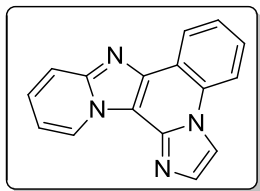
Yield 75%; mp 217-218 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.34 (d, *J* = 6.7 Hz, 1H), 8.66 (d, *J* = 7.9 Hz, 1H), 8.04 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.08 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.18, 139.42, 136.80, 131.83, 131.29, 128.37, 127.37, 127.36, 125.13, 124.59, 119.04, 117.24, 115.65, 113.61, 112.71, 111.37; HRMS (ESI) calcd for C$_{16}$H$_{11}$N$_4^+$ 259.0978, found 259.0956 [M + H]$^+$.

Benzo[4,5]imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12b)
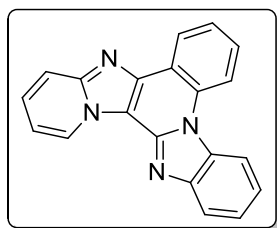
Yield 68%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.62 (d, *J* = 6.6 Hz, 1H), 8.76 (d, *J* = 7.7 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H), 8.41 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (m, 3H), 7.18 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.54, 145.34, 142.45, 141.69, 135.04, 131.34, 129.14, 128.31, 128.16, 124.89, 124.56, 124.12, 122.56, 120.00, 119.23, 117.30, 115.94, 113.62, 113.21; HRMS (ESI) calcd for C$_{20}$H$_{13}$N$_4^+$ 309.1135, found 309.1126 [M + H]$^+$.

Pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,4]triazolo[4,3-*a*]quinoline (12c)
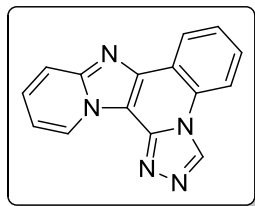
Yield 78%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.23 (d, *J* = 6.7 Hz, 1H), 8.72 (d, *J* = 7.9 Hz, 1H), 8.59 (d, *J* = 8.3 Hz, 1H), 8.42 (s, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.16 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 152.34, 148.32, 142.02, 141.80, 132.57, 129.38, 128.55, 127.29, 126.12, 124.15, 118.37, 117.63, 116.68, 113.31; HRMS (ESI) calcd for C$_{15}$H$_{10}$N$_5^+$ 260.0931, found 260.0938 [M + H]$^+$.

2-Methylimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12d)
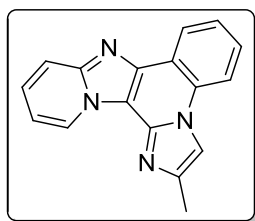
Yield 76%; mp 197-198 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.26 (d, *J* = 6.5 Hz, 1H), 8.58 (d, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 8.8 Hz, 2H), 7.68 (s, 1H), 7.62 – 7.36 (m, 3H), 7.03 (t, *J* = 6.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.95, 140.92, 139.09, 136.03, 131.49, 130.59, 128.24, 127.47, 127.33, 124.63, 124.40, 118.50, 117.05, 115.46, 112.58, 108.09, 14.38; HRMS (ESI) calcd for C$_{17}$H$_{13}$N$_4^+$ 273.1135, found 273.1129 [M + H]$^+$.

11-Methylimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12e)
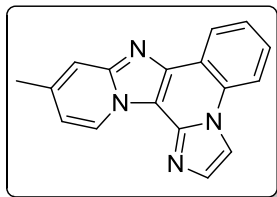
Yield 72%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.16 (d, J = 6.9 Hz, 1H), 8.63 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.59 (m, 4H), 6.90 (d, J = 6.8 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.67, 139.40, 138.85, 136.85, 131.67, 131.18, 128.17, 126.35, 125.04, 124.49, 119.06, 115.63, 115.61, 115.39, 113.28, 111.25, 21.90; HRMS (ESI) calcd for C$_{17}$H$_{13}$N$_4$$^+$ 273.1135, found 273.1118 [M + H]$^+$.

3-Methylbenzo[4,5]imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12f)

Yield 71%; mp 242-244 °C, ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.24 (d, J = 6.7 Hz, 1H), 8.54 (d, J = 7.7 Hz, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 6.7 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.70, 145.06, 142.15, 141.33, 139.63, 134.57, 130.98, 128.67, 126.91, 124.49, 124.19, 123.79, 122.14, 119.61, 118.92, 115.62, 115.56, 115.53, 113.39, 112.08, 21.94; HRMS (ESI) calcd for C$_{21}$H$_{15}$N$_4$$^+$ 323.1291, found 323.1303 [M + H]$^+$.
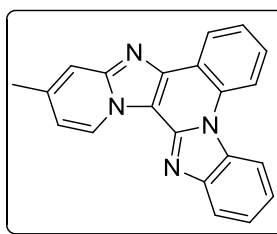
11-Methylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,4]triazolo[1,5-*a*]quinoline (12g)
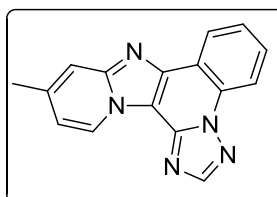
Yield 72%; mp 221-222 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.96 (d, J = 6.9 Hz, 1H), 8.61 (d, J = 7.9 Hz, 1H), 8.51 (d, J = 8.3 Hz, 1H), 8.36 (s, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.56 (s, 1H), 6.92 (d, J = 6.9 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.21, 148.67, 141.95, 141.60, 140.10, 132.30, 129.12, 126.15, 125.94, 124.01, 118.26, 116.53, 115.87, 111.46, 21.94; HRMS (ESI) calcd for C$_{16}$H$_{12}$N$_5$$^+$ 274.1087, found 274.1106 [M + H]$^+$.

2,11-Dimethylimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12h)

Yield 75%; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.14 (d, J = 6.9 Hz, 1H), 8.61 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.65 − 7.47 (m, 3H), 6.87 (d, J = 6.9 Hz, 1H), 2.52 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 147.54, 140.88, 139.23, 138.72, 136.27, 131.48, 128.07, 126.53, 124.57, 124.41, 118.71, 115.49, 115.19, 113.05, 107.98,

21.89, 14.43; HRMS (ESI) calcd for $C_{18}H_{15}N_4^+$ 287.1291, found 287.1288 $[M + H]^+$.

12-Methylimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12i)

Yield 62%; mp 190-191 °C; ^1H NMR (300 MHz, CDCl$_3$) δ 9.04 (s, 1H), 8.59 (d, J = 7.2 Hz, 1H), 8.00 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.33 – 7.24 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.20, 139.17, 136.76, 131.58, 131.08, 130.68, 128.19, 125.08, 124.84, 124.43, 122.81, 118.97, 116.38, 115.59, 113.20, 111.33, 18.19; HRMS (ESI) calcd for $C_{17}H_{13}N_4^+$ 273.1135, found 273.1145 $[M + H]^+$.

2-Methylbenzo[4,5]imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12j)

Yield 66%; mp 234-235 °C; ^1H NMR (300 MHz, CDCl$_3$) δ 9.35 (s, 1H), 8.70 (d, J = 7.7 Hz, 1H), 8.62 (d, J = 8.5 Hz, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.83 – 7.69 (m, 2H), 7.62 – 7.32 (m, 4H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 147.53, 145.21, 142.21, 134.79, 131.52, 131.22, 128.91, 125.69, 124.65, 124.47, 124.00, 123.27, 122.42, 119.80, 119.20, 116.47, 115.85, 113.57, 18.33; HRMS (ESI) calcd for $C_{21}H_{15}N_4^+$ 323.1291, found 323.1278 $[M + H]^+$.

12-Methylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,4]triazolo[1,5-*a*]quinoline (12k)

Yield 64%; mp 196-198 °C; ^1H NMR (300 MHz, CDCl$_3$) δ 9.02 (s, 1H), 8.72 (dd, J = 7.9, 1.1 Hz, 1H), 8.60 (d, J = 8.2 Hz, 1H), 8.44 (s, 1H), 7.87 – 7.76 (m, 2H), 7.74 – 7.66 (m, 1H), 7.43 (dd, J = 9.3, 1.6 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.28, 147.46, 141.94, 132.46, 131.91, 129.29, 129.16, 126.17, 124.90, 124.08, 123.56, 118.50, 116.90, 116.71, 18.25; HRMS (ESI) calcd for $C_{16}H_{12}N_5^+$ 274.1087, found 274.1104 $[M + H]^+$.

12-Fluoroimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12l)

Yield 72%; mp 212-214 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.67 (s, 1H), 8.43 (d, J = 7.7 Hz, 1H), 8.37 (d, J = 8.3 Hz, 1H), 7.94 (dd, J = 9.3, 4.5 Hz, 1H), 7.78 – 7.52 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.61 (d, J = 236.0 Hz), 145.18, 140.42, 136.08, 132.39, 131.69, 129.72, 126.23, 124.55, 120.41 (d, J = 25.8 Hz), 119.10, 118.77 (d, J = 8.8 Hz), 117.59,

114.71, 114.44, 114.05, 113.89. HRMS (ESI) calcd for $C_{16}H_{10}FN_4^+$ 277.0884, found 277.0872 $[M + H]^+$.

12-Chloroimidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12m)

Yield 62%; mp 228-229 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.44 (d, J = 7.7 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.66 – 7.48 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.60, 139.88, 136.16, 132.49, 132.10, 129.74, 129.19, 126.16, 125.04, 124.63, 120.74, 118.93, 118.73, 117.57, 114.01. HRMS (ESI) calcd for $C_{16}H_{10}ClN_4^+$ 293.0589, found 293.0591 $[M + H]^+$.

2-Fluorobenzo[4,5]imidazo[1,2-*a*]pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (12n)

Yield 71%; mp 264-266 °C; ^1H NMR (300 MHz, CDCl$_3$) δ 9.60 (s, 1H), 8.73 (d, J = 7.2 Hz, 1H), 8.65 (d, J = 8.5 Hz, 1H), 8.40 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.3 Hz, 1H), 7.92 (dd, J = 9.6, 4.7 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.66 – 7.46 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.08, 135.18, 131.39, 129.69, 125.17, 124.98, 124.58, 123.20, 120.86, 120.52, 120.35, 119.05, 117.75, 117.64, 116.19, 115.69, 115.14, 113.82. HRMS (ESI) calcd for $C_{20}H_{12}FN_4^+$ 327.1041, found 327.1065 $[M + H]^+$.

Pyrido[2',1':2,3]imidazo[4,5-*c*]pyrido[2',3':4,5]imidazo[1,2-*a*]quinoline (12o)

Yield 64%; mp > 270 °C; ^1H NMR (300 MHz, CDCl$_3$) δ 10.04 (d, J = 8.5 Hz, 1H), 9.52 (d, J = 6.7 Hz, 1H), 8.68 (d, J = 7.8 Hz, 1H), 8.56 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.45 (dd, J = 8.0, 4.8 Hz, 1H), 7.20 (t, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.68, 146.68, 143.24, 142.73, 141.79, 137.37, 134.82, 130.09, 129.21, 128.50, 126.66, 125.55, 124.55, 119.97, 118.82, 118.50, 117.49, 114.00, 112.38. HRMS (ESI) calcd for $C_{19}H_{12}N_5^+$ 310.1087, found 310.1095 $[M + H]^+$.

12-Fluoropyrido[2',1':2,3]imidazo[4,5-*c*][1,2,4]triazolo[1,5-*a*]quinoline (12p)

Yield 70%; mp 238-240 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.16 (s, 1H), 8.68 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 8.1 Hz, 1H), 8.45 (s, 1H), 7.99 – 7.87 (m, 1H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.1 Hz, 1H), 7.52 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.79 (d, *J* = 240.5 Hz), 152.80, 152.19, 146.09, 142.90, 141.87, 133.07, 129.94, 126.59, 124.52, 120.99 (d, *J* = 25.6 Hz), 118.61, 118.36 (d, *J* = 8.4 Hz), 117.13, 114.82, 114.27, 113.37; HRMS (ESI) calcd for C$_{15}$H$_9$FN$_5$$^+$ 278.0836, found 278.0841 [M + H]$^+$.
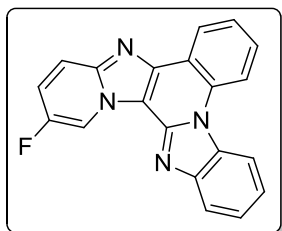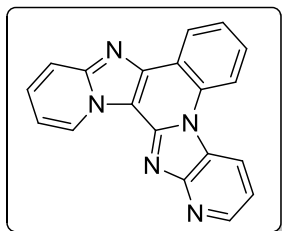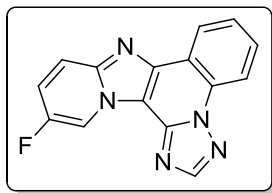
Chapter IV

PART-B

Copper Catalyzed Tandem Synthesis of 1,2,3-Triazole Fused Imidazo[1,2-*a*]pyridines

4.5 Introduction

Transition metal-catalyzed coupling reactions plays a vital role in organic as well as medicinal chemistry allowing construction of novel and biologically relevant molecules.[36] In particular, significant attention has been focussed on copper catalysts over other expensive transition metals such as palladium, ruthenium and rhodium for the formation of C−C and C−heteroatom bonds mainly because of their efficiency, good functional group tolerance and economical attractiveness.[3] Tandem or cascade reactions catalyzed by copper salts serves as an efficient tool for the assembly of complex biologically active heterocyclic molecules from simple substrates.[4] 1,2,3-Triazoles are found to have broad range of applications in the field of synthetic, medicinal as well as material chemistry.[37-38] Since the pioneering work by Sharpless[39] and Meldel[40] groups, copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become the finest way to generate 1,4-substituted-1,2,3-triazoles. Other important copper-catalyzed reaction is Ullmann coupling.[41] The scope of Ullmann-type reaction was actively developed after the discovery of organic ligands and applied in various fields to synthesize potentially important molecules *via* C−C as well as C−heteroatom bond formation.[42-44] Transition metal catalyzed direct C−H functionalization has become an alternative to traditional cross coupling reactions that result in fabrication of complex molecular skeleton where pre-functionalization of precursors can be obviated.[12, 45] Moreover, inexpensive copper salts have also proved to be efficient catalysts in the area of C−H activation and functionalization to assemble vital organic frameworks.[46-47] In recent years, several novel methodologies have been reported for the synthesis fused 1,2,3-triazoles.[48-49]

Recently, Ackermann group demonstrated the synthesis of fully decorated 1,2,3-triazoles (**18**) *via* Cu/Pd catalyzed click reaction, direct arylation sequence in one-pot (**Scheme 4.12**).[50] Initially terminal alkyne (**15**), sodium azide (**16**) and aryl iodide (**17**) was reacted in presence of CuI/DMEDA system at ambient temperature for 2 h. Then added aryl halide and LiO*t*-Bu and stirred for 20 h at 140 °C to achieve 1,4,5-trisubstituted triazoles in good yields.

Scheme 4.12 Copper catalyzed modular syntheses of fully decorated 1,2,3-triazoles

Choudhary *et al.* reported the synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines (**20**) through Pd/Cu catalyzed tandem reactions of 1-azido-2-(prop-2-ynyloxy)benzenes (**19**) with aryl iodides (**17**) (**Scheme 4.13**). [51] It was envisaged that initially C–C bond formation occurs at terminal alkyne in Sonogashira fashion which follows the intramolecular 1,3-dipolar cycloaddition to achieve the targeted fused azoles.

Scheme 4.13 Pd/Cu catalyzed synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines

Kumara Swamy and Nagarjuna Reddy synthesized fused pentacyclic 1,2,3-triazoles (**26**) from *ortho*-halo substituted *O*-propargylated phenols (**21**) and azides (**22** and **24**) (**Scheme 4.14**). This one-pot protocol proceeds *via* CuAAC followed by intramolecular direct arylation.[52] Diverse [6,6]-, [6,7]-, [6,8]-, and [6,9] ring-fused triazole frameworks have been achieved using the developed protocol.

Scheme 4.14 Copper catalyzed one-pot synthesis of fused triazole frameworks

Lautens and collaborators have described the synthesis of novel fused 1,2,3-triazoles (**28**) through [3+2] cycloaddition of alkynyl halides (**27**) and alkyl azides (**22**) followed by intramolecular direct arylations using Cu/Pd dual catalytic system (**Scheme 4.15**).[53] They have also reported palladium catalyzed direct arylation of 5-iodotriazole precursors to construct fused-1,2,3-triazoles.[49]
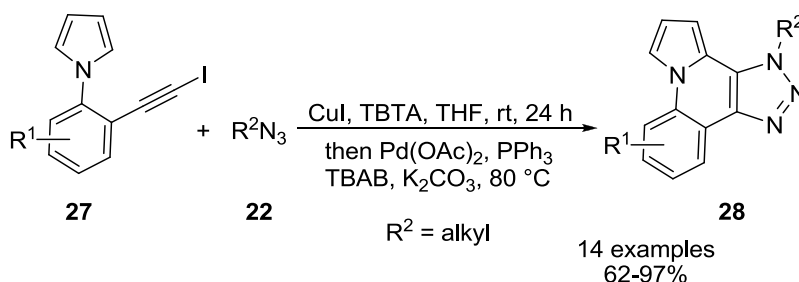
Scheme 4.15 Synthesis of fused 1,2,3-triazoles from alkynyl halide precursors

An efficient tandem synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines (**30**) has been achieved *via* copper catalyzed tandem reaction starting from ethyl 2-azido-3-(2-iodoaryl)acrylates (**29**) and arylalkynes (**15**) (**Scheme 4.16**).[54] This protocol afforded good yields of fused triazoles through C−C bonding in a Sonogashira coupling fashion followed by 1,3-dipolar [3+2] cycloaddition in presence of catalytic amount of copper. When refluxed in AcOH, these fused azoles expelled N_2 and produced 1,3-disubstituted isoquinolines in good yields.
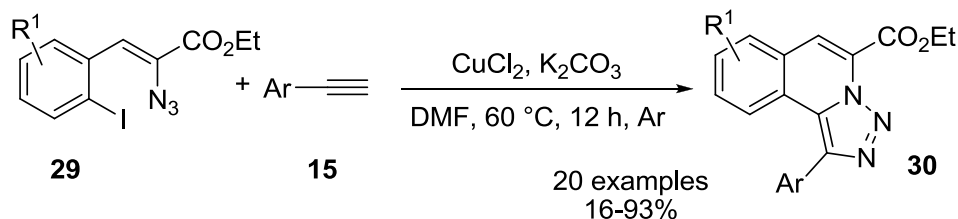
Scheme 4.16 Copper catalyzed tandem synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines

Cai and colleagues trapped C−Cu produced in CuAAC for the intramolecular Ullmann coupling to synthesize novel fused-1,2,3-triazoles (**32**) from *N*-(2-iodoaryl)-propiolamides (**31**) and azides (**22**) (**Scheme 4.17**).[55] A detailed investigations have suggested that the reported domino transformation proceeds through initial copper catalyzed azide alkyne cycloaddition (CuAAC) to afford reactive triazole intermediate with C_5−Cu bond which was then inserted into aryl halide bond and led to the formation of fused triazoles.
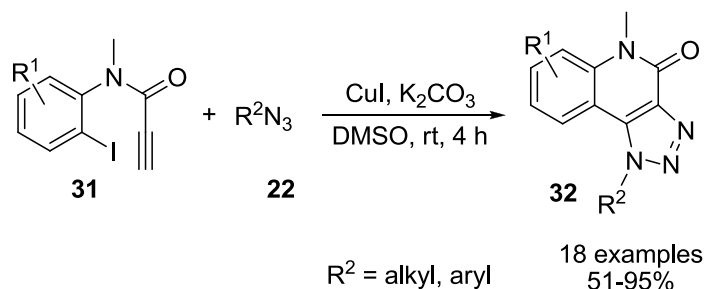
Scheme 4.17 Copper catalyzed synthesis of fused triazoles through CuAAC and C−Cu trapping

However, the combination of copper catalyzed CuAAC, Ullmann-type coupling and C−H functionalization are limited in the literature. Based on the importance of imidazo[1,2-*a*]pyridine nucleus, we believe that further functionalization leading to fused novel heterocycles will have a new and interesting properties. As a part of our continuous efforts for the synthesis of novel heterocycles containing imidazo[1,2-*a*]pyridines, we have developed a ligand-free inexpensive copper-catalyzed tandem CuAAC, Ullmann type C−N coupling and intramolecular direct arylation for the regioselective synthesis of novel 1,2,3-triazole fused-imidazo[1,2-*a*]pyridines.

4.6 Results and Discussion

3-Bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**33a**), phenylacetylene (**15a**) and sodium azide (**16**) were chosen as model substrates for the initial investigation and the results are summarized in Table 4.2. In a typical experiment, compound **33a** (1 mmol) was treated with **15a** (1.2 mmol) and **16** (1.2 mmol) in the presence of $CuCl_2 \cdot 2H_2O$ (20 mol %) and K_2CO_3 (2.5 mmol) in DMF at 80 °C for 24 h. 3-Bromo-2-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)phenyl)-imidazo[1,2-*a*]pyridine (**34a**) (entry 1, Table 4.2) was obtained in 66% yield (**Scheme 4.18**). It was realized that direct Cu-catalyzed arylation product of **34a** can be achieved in one-pot at higher temperature, thus the reaction temperature was increased to 150 °C with other conditions keeping similar to entry 1 (Table 4.2). To our delight, target compound (**35a**) was obtained in 65% yield (entry 2, Table 4.2). In the absence of copper catalyst, reaction failed to furnish tandem product, starting materials were recovered (entry 3, Table 4.2) whereas inseparable mixture of compounds was observed in the absence of base (entry 4, Table 4.2).
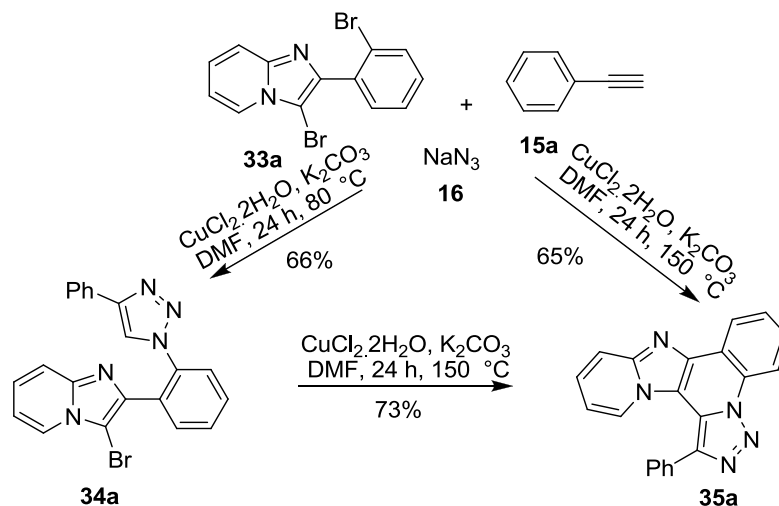
Scheme 4.18 Tandem reaction of **33a**, **15a** and **16** in the presence of copper catalyst

The structure of **35a** was characterized by NMR and HRMS data. All protons and carbons were located at their respective positions in ^{1}H and ^{13}C NMR. Additionally, HRMS peak at 358.1050 for [M+Na]$^+$ confirmed the structure of **35a**. A representative ^{1}H and ^{13}C NMR of **35a** is shown in **Figure 4.3**. To improve the yield of desired pentacyclic product **35a,** various copper salts, bases and solvents were screened (Table 4.2). Use of CuI and CuO resulted in poor yields, Cu(OAc)$_2$ gave relatively better yield of desired product (entries 5-7, Table 4.2). At the same time CuBr$_2$, Cu(OTf)$_2$, and Cu$_2$O gave moderate yields of desired product **35a** (entries 9-11, Table 4.2) whereas CuSO$_4$ resulted in formation of **34a** (entry 8, Table 4.2). Among all the screened catalysts, CuCl$_2$.2H$_2$O was found to give the best yield of **35a**. Next, we screened various bases such as *t*-BuOK, Cs$_2$CO$_3$, K$_2$CO$_3$, Na$_2$CO$_3$ and NaOAc (entries 12-15, Table 4.2) with CuCl$_2$.2H$_2$O as the catalyst. Among these, K$_2$CO$_3$ turned out to be the most effective base to give **35a** (entry 2, Table 4.2) whereas use of NaOAc resulted in formation of **34a** (entry 15, Table 4.2). Finally, the effect of solvents was also investigated for this tandem process yielding **35a**. Polar aprotic solvents such as DMF and DMSO were found to be effective (entries 2 and 16, Table 4.2) for this conversion. 1,4-Dioxane and toluene (entries 17-18, Table 4.2) did not give any reaction. Use of acetonitrile resulted in formation of **34a** (entry 19, Table 4.2). Moreover, use of external ligands like *N,N'*-dimethylethylenediamine, 1,10-phenanthroline and L-proline (40 mol %) failed to improve the yield of **35a** (entries 20-22, Table 4.2).
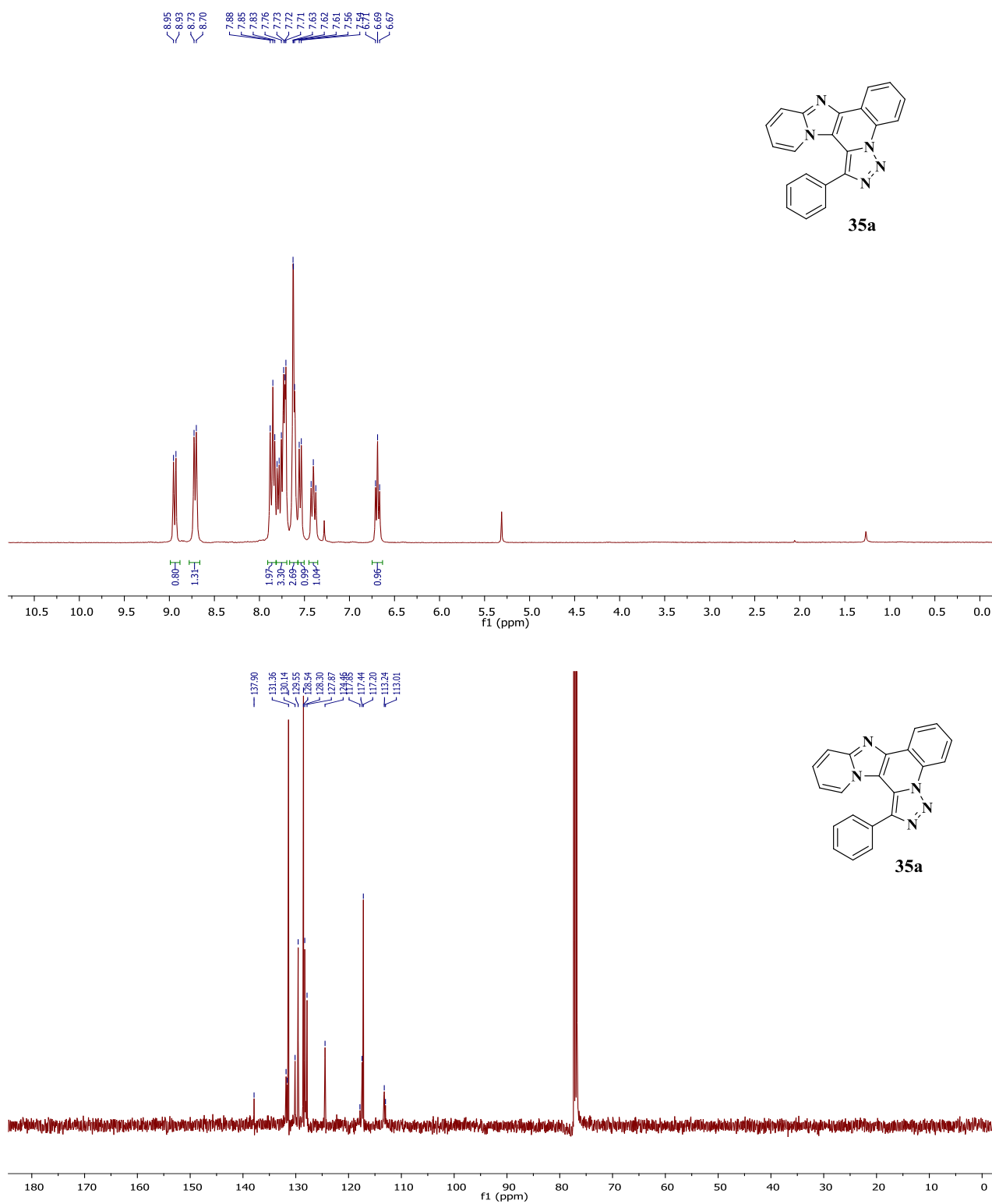
Figure 4.3 ^{1}H and ^{13}C NMR spectra (in CDCl$_3$; recorded on a Bruker AV 300 spectrometer) of 1,2,3-triazole fused imidazo[1,2-*a*]pyridine (**35a**)

Table 4.2 Optimization of reaction conditions for the synthesis of **35a** *via* tandem reaction[a]

Entry	Catalyst	Base	Solvent	Temp (°C)	% Yield[b]
1	CuCl$_2$.2H$_2$O	K$_2$CO$_3$	DMF	80	-[c]
2	**CuCl$_2$.2H$_2$O**	**K$_2$CO$_3$**	**DMF**	**150**	**65**
3	-[d]	K$_2$CO$_3$	DMF	150	NR[e]
4	CuCl$_2$.2H$_2$O	-[f]	DMF	150	-[g]
5	CuI	K$_2$CO$_3$	DMF	150	18[h]
6	CuO	K$_2$CO$_3$	DMF	150	22
7	Cu(OAc)$_2$	K$_2$CO$_3$	DMF	150	38
8	CuSO$_4$	K$_2$CO$_3$	DMF	150	-[h]
9	CuBr$_2$	K$_2$CO$_3$	DMF	150	48
10	Cu(OTf)$_2$	K$_2$CO$_3$	DMF	150	54
11	Cu$_2$O	K$_2$CO$_3$	DMF	150	45
12	CuCl$_2$.2H$_2$O	Na$_2$CO$_3$	DMF	150	22
13	CuCl$_2$.2H$_2$O	KO*t*Bu	DMF	150	50
14	CuCl$_2$.2H$_2$O	Cs$_2$CO$_3$	DMF	150	46
15	CuCl$_2$.2H$_2$O	NaOAc	DMF	150	-[h]
16	CuCl$_2$.2H$_2$O	K$_2$CO$_3$	DMSO	150	51
17	CuCl$_2$.2H$_2$O	K$_2$CO$_3$	1,4-dioxane	150	NR[e]
18	CuCl$_2$.2H$_2$O	K$_2$CO$_3$	toluene	150	NR[e]
19	CuCl$_2$.2H$_2$O	K$_2$CO$_3$	MeCN	150	-[h]
20	CuCl$_2$.2H$_2$O [i]	K$_2$CO$_3$	DMF	150	56
21	CuCl$_2$.2H$_2$O [j]	K$_2$CO$_3$	DMF	150	62
22	CuCl$_2$.2H$_2$O [k]	K$_2$CO$_3$	DMF	150	traces[g]

[a]Reaction conditions: **33a** (1.0 mmol), **15a** (1.2 mmol), NaN$_3$ (1.2 mmol), Catalyst (0.2 mmol), base (2.5 mmol), solvent (4 mL), 24 h. [b]Isolated yields. [c]**34a** was isolated in 66% yield. [d]No copper catalyst. [e]No conversion. [f]No base was used. [g]A mixture of products was observed. [h]The major product was **34a**. [i]*N,N'*-dimethylethylenediamine was used (40 mol %). [j]1,10-phen was used (40 mol %). [k]L-proline was used (40 mol %).

Having optimized the reaction conditions (entry 2, Table 4.2), we investigated the scope of this tandem reaction and the results are summarized in **Scheme 4.19**. Various substituted phenylacetylenes smoothly reacted under the optimized conditions to give desired 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines (**35a-o**) in moderate to good yields. For example, phenylacetylenes with electron donating substituents such as 4-methoxy, 4-butyl, 4-pentyl, 4-*tert*-butyl and 3-methyl produced the corresponding 1,2,3-triazole-fused imidazo[1,2-*a*]-pyridines (**35b-e** and **35n**) in good yields (59-68%) and 4-fluorophenylacetylene with electron withdrawing fluoro group underwent smooth conversion to afford 62% of 1,2,3-triazole-fused

imidazo[1,2-*a*]pyridines (**35f**). Aliphatic alkynes also efficiently participated in tandem reaction to give the corresponding 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines in comparatively better yields (72%, **35g** and 76%, **35h**). Similarly, different substituted imidazo[1,2-*a*]pyridines also produced 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines in good yields (74%, **35i**; 68%, **35j**; 78%, **35k**; 76%, **35l**; 71%, **35m;** 73%, **35o**). Unfortunately, reaction of 3-bromo-2-(2-bromophenyl)-5-methyl imidazo[1,2-*a*]pyridine (**33d**) with **15a** and **16** failed to give the corresponding 1,2,3-triazole-fused imidazo[1,2-*a*]pyridine (**35p**). This may be due to the steric hindrance caused by 5-methyl in imidazo[1,2-*a*] pyridine nucleus.

Since two bromo groups are present in the starting material (**33),** two regioisomers can be visualized for the compounds **35a-o** from the tandem process (explained for compound **35i** in **Figure 4.4**). To understand the reactivity of each of the bromo groups, two individual experiments were performed using the optimized reaction conditions. In the first experiment, 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**9a**) was treated with **15a** and **16**, the anticipated product, 2-(2-(4-phenyl-1H-1,2,3-triazol-1-yl) phenyl)imidazo[1,2-*a*]pyridine (**36**) was obtained *via* CuAAC followed by Ullmann-type coupling reaction in good yield (78%, **Scheme 4.20**). In the second experiment, 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**37**) was treated with **15a** and **16**. A mixture of products was observed in this reaction from which two major products isolated were found to be dehalogenated starting material i.e. 2-phenylimidazo[1,2-*a*]pyridine (**38**) and Sonagashira-type coupling product i.e 2-phenyl-3-(phenylethynyl)imidazo[1,2-*a*]pyridine (**39**) (**Scheme 4.20**). In addition to these two products, formation of azide-alkyne condensation (AAC) product between **15a** and **16** were also observed in the reaction mixture. The outcome from these experiments indicates that the bromo substituent at the 2-aryl ring undergoes Ullmann-type coupling. This is due to the *ortho*-directing effect of the nitrogen atom in the imidazole moiety of imidazo[1,2-*a*]pyridine that chelates with copper and favours the C−N coupling.[56] On the other hand, the bromo on compound **37** appears to be more prone towards C−C bond formation.
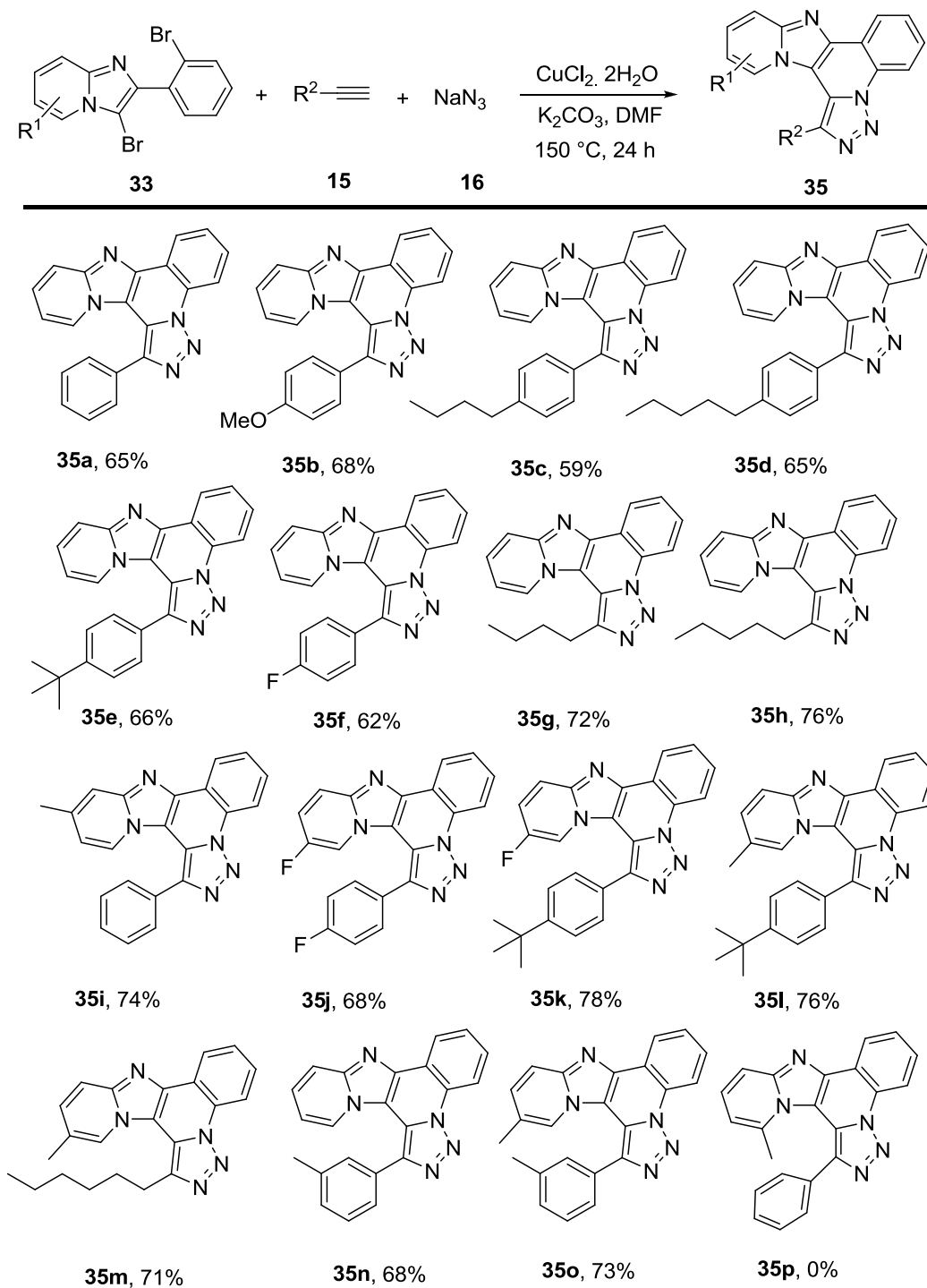
Scheme 4.19 Substrate scope for the synthesis of 1,2,3-triazoloimidazo[1,2-*a*]pyridines (**35**)
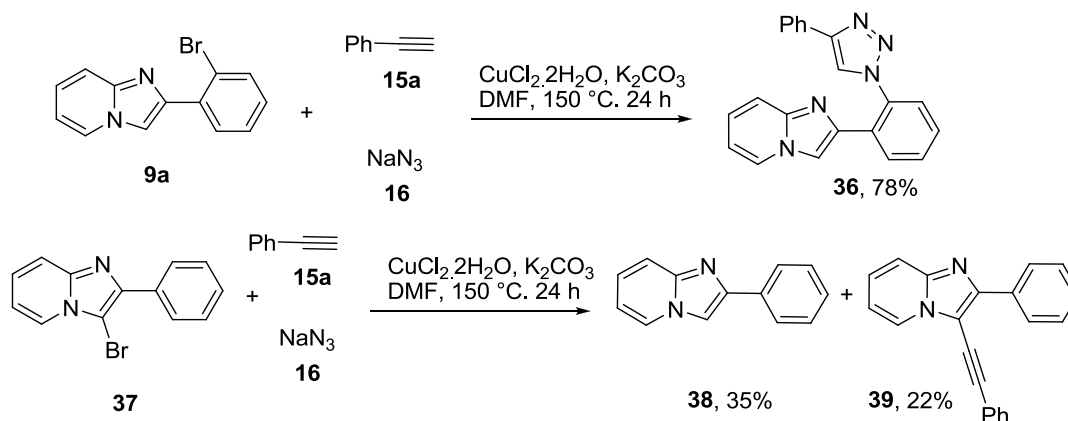
Scheme 4.20 Reactivity of bromo group on imidazo[1,2-*a*]pyridine

Based on these two independent experimental results, regioisomer **A** appears to be a more logical product than the regioisomer **B** (**Figure 4.4**). But to conclusively ascertain the correct structure of the product, compound **35i** was selected for NOE studies. Compound **35i** was strategically chosen as the CH$_3$ group on the pyridine ring would enable assignment of aromatic proton resonances indicated by blue and red dots in **Figure 4.4** required to verify any NOE enhancement on the phenyl substituent on triazole ring of regioisomer **A**. For the regioisomer **B**, with phenyl group on the other side, no NOE would be expected. Focussing on the methyl group in the HMBC, the proton indicated by the blue dot was assigned to the resonance at 6.5 ppm (^{13}C shift 115 ppm from HSQC). Subsequently, from the COSY, the proton indicated by the red dot was assigned to the resonance at 7.4 ppm (^{13}C shift 127.2 ppm from HSQC). The ^{13}C NMR spectrum of **35i** helped in identifying symmetrical phenyl ring carbons (128.4 ppm and 131.3 ppm) which in turn helped to (through HSQC experiment) identify the chemical shifts of proton they harboured (7.6 and 7.7 ppm; shown in black dots in **Figure 4.4**). After having identified the chemical shifts of the protons of interest, 1D NOESY experiment was run. Irradiation at frequency of the signal at δ 7.4 ppm (proton shown in red dot in **Figure 4.4**) enhanced the signal at δ 6.5 ppm (proton shown in blue dot in Figure 1), which was expected. However, there is also a significant response at a resonance involving δ 7.7 ppm, which is assigned for two of the 4 protons (shown in black dot in **Figure 4.4**) on the benzene ring substituent. If the benzene ring is on the other side (isomer **B**) then no enhancement would be expected on benzene ring substituent. Thus, based on the two experiments with **9a** and **37** and the NOE results, the structure of 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines were conclusively established as corresponding to regioisomer **A** (**Figure 4.4**).
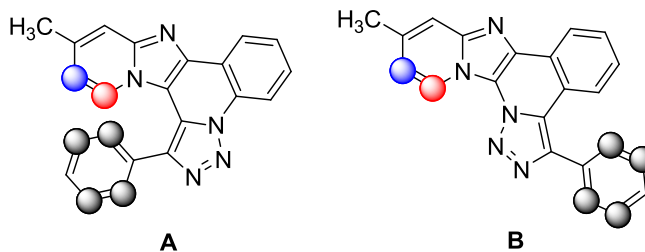
Figure 4.4 Possible regioisomers of compound **35i**

Although, mechanistic details are not clear at this point, based on experimental observations, intermediates isolated and the literature precedent it has been proposed that Cu(II) can initially oxidize alkynes to result in reactive Cu(I) along with diyne.[54] Subsequently, Cu(I)-catalyzed CuAAC reaction followed by *ortho*-directed Ullman-type C−N coupling with phenyl triazole leads to intermediate **34a** (**Scheme 4.18**). Intramolecular direct arylation of intermediate **34a** affords the desired 1,2,3-triazole-fused imidazo[1,2-*a*]pyridine (**35a**). There are two possible pathways for the transformation of intermediate **34a** into fused triazole **35a**: a) direct arylation of intermediate **34a**, as reported by Ackermann group,[50] and b) by C−Cu trapping as reported by Cai group.[55] To clarify mechanism of this step, isolated compound **34a** was subjected under the optimized reaction conditions (**Scheme 4.18**) which led to formation of **35a** in excellent yield (73%). This indicates that this step proceeds *via* direct arylation instead of C−Cu trapping.

4.7 Conclusion

In summary, we have successfully developed an efficient and simple tandem protocol for the synthesis of novel 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines *via* CuAAC, Ullmann-type C−N coupling followed by intramolecular C−C bond formation by C−H functionalization. The reaction shows high generality and functional group tolerance. It provides a straightforward means for the preparation of fused triazoles derivatives.

4.8 Experimental

General: Melting points were determined in open capillary tubes on a MPA120-Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates (Merck). The chemical structures of final products were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) determined on a Bruker AV NMR 300 MHz spectrometer. ^{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 chemical structures of all the products were confirmed by a Bruker microTOF Mass spectrometer. 1-Ethynyl-3-methylbenzene was prepared by Sonagashira coupling between 3-iodotoluene and trimethylsilylacetylene followed by TMS deprotection using tetrabutylammonium fluoride. All other chemicals were obtained from commercial suppliers and used without further purification.

Preparation of 3-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (33a)

9a   33a
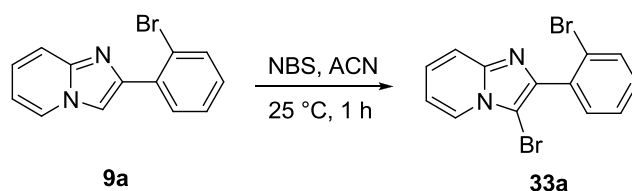
To a solution of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**9a**, 4.0 g, 14.76 mmol) in acetonitrile (40 mL) added *N*-bromosuccinimide (2.89 g, 16.23 mmol) and stirred at 25 °C for 1 h. On completion, the volatiles were evaporated. The residue was diluted with ethyl acetate and washed with saturated sodium thiosulfate solution and water. The ethyl acetate layer dried over anhydrous Na_2SO_4 and concentrated the solvent in *vacuo*. The crude residue was purified by column chromatography to yield 3-bromo-2-(2-bromophenyl)H-imidazo[1,2-*a*]pyridine (**33a**) (4.26 g, 82%) as yellow solid; mp 146-147 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.24 (d, J = 6.9 Hz, 1H), 7.81 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.49 – 7.30 (m, 3H), 7.07 (t, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.41, 144.17, 134.54, 133.37, 132.74, 130.46, 127.37, 125.38, 124.38, 124.13, 118.31, 113.62. 94.72. HRMS calcd for $C_{13}H_9Br_2N_2$ 350.9127 found 350.9116 [M + H]$^+$.

3-Bromo-2-(2-bromophenyl)-7-methylimidazo[1,2-*a*]pyridine (33b)
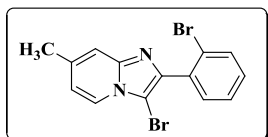
Yield 88%; off-white solid; mp 131-133 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00 (dd, J = 6.8, 1.9 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.24 (t, J = 7.7 Hz, 1H), 6.76 (d, J = 5.4 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.43, 143.52, 136.09, 134.36, 132.94, 132.33, 130.12, 126.95, 123.70, 123.16, 116.31, 116.00, 93.52, 21.16. HRMS calcd for $C_{14}H_{11}Br_2N_2$ 364.9283 found 364.9278 [M + H]$^+$.

3-Bromo-2-(2-bromophenyl)-6-fluoroimidazo[1,2-a]pyridine (33c)
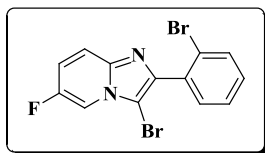
Yield 85%; off-white solid; mp 211-213 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 − 8.61 (m, 1H), 7.84 − 7.73 (m, 2H), 7.58 − 7.47 (m, 3H), 7.47 − 7.37 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.56, 152.40, 145.23, 142.71, 133.91, 133.02, 132.21, 130.19, 127.01, 123.67, 118.66, 118.54, 117.24, 116.90, 111.26, 110.70, 95.62. HRMS calcd for $C_{13}H_8Br_2FN_2$ 368.9033 found 368.9049 $[M + H]^+$.

3-Bromo-2-(2-bromophenyl)-5-methylimidazo[1,2-a]pyridine (33d)
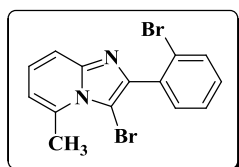
Yield 65%; pale yellow solid; mp 138-139 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.76 (d, J = 7.7 Hz, 1H), 7.57 − 7.34 (m, 4H), 7.24 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 6.5 Hz, 1H), 3.04 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.99, 145.94, 137.44, 135.70, 133.37, 133.24, 131.28, 128.22, 126.38, 124.28, 116.86, 115.43, 93.36, 21.27. HRMS calcd for $C_{14}H_{11}Br_2N_2$ 364.9283 found 364.9279 $[M + H]^+$.

3-Bromo-2-(2-bromophenyl)-6-methylimidazo[1,2-a]pyridine (33e)
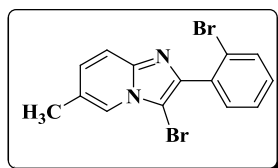
Yield 78%; off white solid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.93 (s, 1H), 7.69 (dd, J = 8.0, 1.1 Hz, 1H), 7.59 − 7.53 (m, 1H), 7.50 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (td, J = 7.5, 1.3 Hz, 1H), 7.32 − 7.23 (m, 1H), 7.12 (dd, J = 9.2, 1.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.18, 143.55, 134.36, 132.98, 132.40, 130.07, 128.22, 127.07, 123.76, 123.12, 121.72, 117.27, 93.88, 18.37.

Experimental procedure for the regioselective synthesis of 1,2,3-triazole fused imidazo[1,2-a]pyridines (35a-o)

1-Phenylpyrido[2',1':2,3]imidazo[4,5-c][1,2,3]triazolo[1,5-a]quinoline (35a)
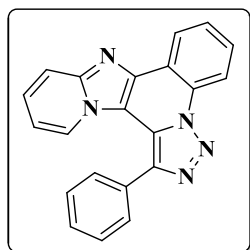
Mixture of compound **33a** (175 mg, 0.5 mmol), phenylacetylene (61 mg, 0.6 mmol), sodium azide (40 mg, 0.6 mmol), CuCl$_2$.2H$_2$O (17 mg, 0.1 mmol), K$_2$CO$_3$ (172 mg, 1.25 mmol) were vigorously stirred in DMF (3 mL) at 150 °C for 24 h. After cooling to room temperature, the reaction

mass was diluted with water and extracted into ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The crude compound was purified by flash chromatography on a short silica gel (ethyl acetate: hexanes) to afford 109 mg of compound **35a** (65%); yellow solid; mp 248-250 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.94 (d, J = 8.1 Hz, 1H), 8.71 (d, J = 7.6 Hz, 1H), 7.91 − 7.82 (m, 2H), 7.82 − 7.68 (m, 3H), 7.67 − 7.58 (m, 3H), 7.55 (d, J = 7.0 Hz, 1H), 7.45 − 7.35 (m, 1H), 6.69 (t, J = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.90, 131.84, 131.61, 131.36, 130.14, 129.55, 128.54, 128.30, 127.87, 124.46, 117.85, 117.44, 117.20, 113.24, 113.01; HRMS calcd for C$_{21}$H$_{13}$N$_5$Na 358.1063 found 358.1050 [M + Na]$^+$.

1-(4-Methoxyphenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35b)
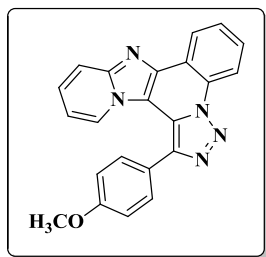
Yield 68%; white solid. mp 231-232 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.90 (d, J = 8.1 Hz, 1H), 8.69 (d, J = 7.6 Hz, 1H), 7.95 − 7.72 (m, 3H), 7.70 − 7.53 (m, 3H), 7.41 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 6.74 (t, J = 6.8 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.03, 148.12, 139.77, 137.80, 132.94, 132.00, 129.96, 128.54, 127.78, 127.54, 124.72, 124.55, 122.65, 119.08, 118.01, 117.38, 114.29, 113.51, 113.02, 55.84; HRMS calcd for C$_{22}$H$_{15}$N$_5$NaO 388.1169 found 388.1171 [M + Na]$^+$.

1-(4-Butylphenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35c)
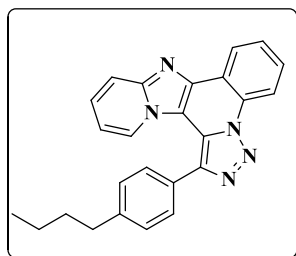
Yield 59%; off-white solid; mp 169-170 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.97 (d, J = 8.2 Hz, 1H), 8.76 (d, J = 7.8 Hz, 1H), 7.96 − 7.72 (m, 3H), 7.68 − 7.50 (m, 3H), 7.50 − 7.33 (m, 3H), 6.67 (t, J = 6.8 Hz, 1H), 2.82 (t, J = 7.5 Hz, 2H), 1.83 − 1.69 (m, 2H), 1.57 − 1.38 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.19, 144.73, 139.90, 138.11, 131.96, 131.66, 129.95, 129.65, 128.78, 128.63, 127.79, 127.51, 124.52, 122.79, 119.14, 117.99, 117.40, 113.51, 112.80, 35.84, 33.89, 22.54, 14.19; HRMS calcd for C$_{25}$H$_{22}$N$_5$ 392.1870 found 392.1879 [M + H]$^+$.

1-(4-Pentylphenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35d)
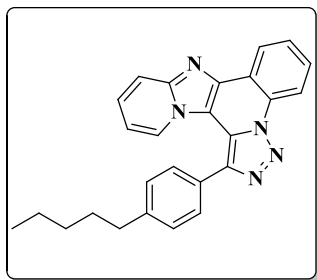
Yield 65%; pale yellow solid; mp 181-183 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.87 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (dd, *J* = 17.3, 9.3 Hz, 1H), 6.61 (t, *J* = 7.0 Hz, 1H), 2.79 (t, *J* = 7.5 Hz, 2H), 1.88 – 1.63 (m, 2H), 1.53 – 1.31 (m, 4H), 0.96 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.26, 144.69, 140.04, 138.04, 131.92, 131.64, 129.82, 129.70, 128.74, 128.59, 127.69, 127.29, 124.42, 122.78, 119.23, 118.03, 117.35, 113.46, 112.63, 36.11, 31.69, 31.36, 22.81, 14.27; HRMS calcd for C$_{26}$H$_{23}$N$_5$Na 428.1840 found 428.1856 [M + Na]$^+$.

1-(4-(*tert*-Butyl)phenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35e)
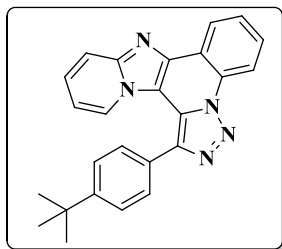
Yield 66%; colorless solid; mp 268-270 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.90 (d, *J* = 8.2 Hz, 1H), 8.65 (d, *J* = 7.7 Hz, 1H), 7.86 – 7.68 (m, 3H), 7.63 (s, 4H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.58 (t, *J* = 7.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.15, 148.22, 139.97, 137.99, 131.95, 131.55, 129.88, 129.45, 128.59, 127.74, 127.38, 125.58, 124.48, 122.90, 119.20, 118.01, 117.38, 113.49, 112.66, 35.25, 31.71; HRMS calcd for C$_{25}$H$_{22}$N$_5$ 392.1870 found 392.1869 [M + H]$^+$.

1-(4-Fluorophenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35f)
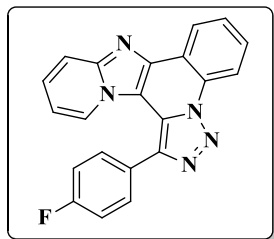
Yield 62%; colorless solid; mp 274-276 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.97 (d, *J* = 8.2 Hz, 1H), 8.76 (d, *J* = 8.0 Hz, 1H), 7.95 – 7.75 (m, 3H), 7.75 – 7.65 (m, 2H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.24 (m, 2H), 6.78 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 148.29, 136.91, 133.49, 133.38, 131.99, 130.13, 128.65, 128.20, 127.98, 127.71, 124.66, 122.79, 119.16, 118.29, 117.48, 116.01, 115.72, 113.16, 109.55; HRMS calcd for C$_{21}$H$_{13}$FN$_5$ 354.1150 found 354.1138 [M + H]$^+$.

1-Butylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35g)
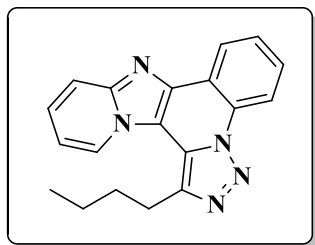
Yield 72%; colorless solid; mp 176-177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, *J* = 7.1 Hz, 1H), 8.69 (d, *J* = 8.2 Hz, 1H), 8.54 (t, *J* = 8.4 Hz, 1H), 7.97 – 7.71 (m, 3H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 7.0 Hz, 1H), 3.45 (t, *J* = 7.7 Hz, 2H), 1.93 – 1.75 (m, 2H), 1.59 – 1.40 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.55, 138.92, 137.02, 131.68, 129.40, 127.23, 126.98, 125.70, 123.98, 122.31, 118.65, 118.41, 116.93, 113.81, 113.23, 33.59, 28.07, 22.28, 13.72; HRMS calcd for $C_{19}H_{17}N_5Na$ 338.1371 found 338.1364 [M + Na]$^+$.

1-Pentylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35h)
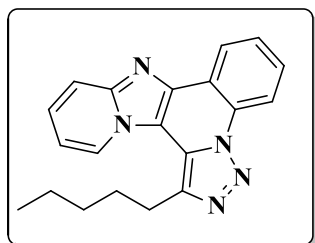
Yield 76%; colorless solid; mp 182-184 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.90 (d, *J* = 6.9 Hz, 1H), 8.88 (d, *J* = 8.3 Hz, 1H), 8.70 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.77 – 7.71 (m, 1H), 7.56 – 7.50 (m, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 3.53 – 3.49 (m, 2H), 2.06 – 1.96 (m, 2H), 1.64 – 1.54 (m, 2H), 1.47 (dd, *J* = 14.9, 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.23, 131.66, 131.60, 129.65, 127.48, 125.76, 124.06, 122.36, 118.40, 117.06, 113.93, 113.87, 113.60, 31.49, 28.46, 22.50, 14.10. HRMS calcd for $C_{20}H_{20}N_5$ 330.1713 found 330.1726 [M + H]$^+$.

11-Methyl-1-phenylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35i)
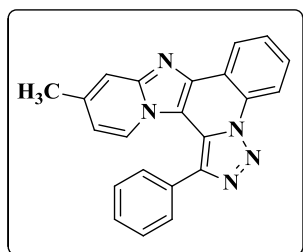
Yield 74%; colorless solid; mp 273-274 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.96 – 8.90 (m, 1H), 8.69 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.86 – 7.68 (m, 4H), 7.65 – 7.56 (m, 4H), 7.40 (d, *J* = 7.1 Hz, 1H), 6.52 (dd, *J* = 7.1, 1.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 148.94, 140.01, 139.77, 137.65, 132.65, 131.88, 131.48, 130.48, 130.07, 129.21, 128.47, 127.64, 124.61, 123.26, 119.52, 117.25, 116.56, 115.98, 113.13, 21.60; HRMS calcd for $C_{22}H_{16}N_5$ 350.1400 found 350.1398 [M + H]$^+$.

12-Fluoro-1-(4-fluorophenyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35j)
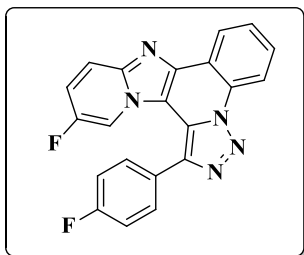
Yield 68%; pale yellow solid; mp 288-289 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.00 (d, *J* = 8.3 Hz, 1H), 8.76 (d, *J* = 7.8 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.91 – 7.86 (m, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.51 (dd, *J* = 4.4, 2.1 Hz, 1H), 7.44 – 7.34 (m, 3H); HRMS calcd for C$_{21}$H$_{11}$F$_2$N$_5$Na 394.0869 found 394.0880 [M + Na]$^+$.

1-(4-(*tert*-Butyl)phenyl)-12-fluoropyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]-quinoline (35k)
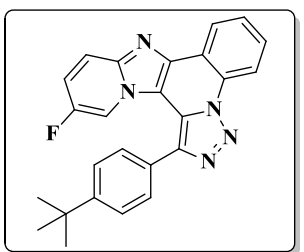
Yield 78%; off-white solid; mp 294-295 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.99 (d, *J* = 8.3 Hz, 1H), 8.73 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.70 – 7.62 (m, 4H), 7.35 – 7.31 (m, 1H), 7.26 (dd, *J* = 4.7, 2.3 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.55, 153.47, 151.65, 137.99, 131.60, 131.31, 130.36, 129.90, 128.56, 127.72, 125.47, 124.06, 119.41, 119.20, 117.93, 117.86, 117.20, 115.48, 115.13, 35.01, 31.36. HRMS calcd for C$_{25}$H$_{21}$FN$_5$ 410.1776 found 410.1770 [M + H]$^+$.

1-(4-(*tert*-Butyl)phenyl)-12-methylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]-quinoline (35l)
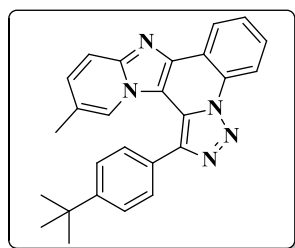
Yield 76%; colorless solid; mp 299-301 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.88 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.61 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.80 – 7.64 (m, 3H), 7.62 (s, 4H), 7.20 (s, 1H), 7.15 (dd, *J* = 9.2, 1.5 Hz, 1H), 1.96 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.68, 146.92, 139.45, 137.42, 131.37, 131.33, 130.12, 129.30, 129.13, 127.39, 126.16, 125.15, 123.87, 122.71, 122.07, 118.97, 117.01, 116.71, 112.74, 34.93, 31.47, 17.93. HRMS calcd for C$_{26}$H$_{24}$N$_5$ 406.2026 found 406.2035 [M + H]$^+$.

1-Hexyl-12-methylpyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35m)
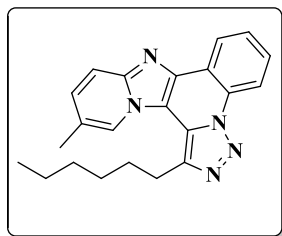
Yield 71%; colorless solid; mp 155-156 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.79 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.60 – 8.55 (m, 1H), 8.54 (s, 1H), 7.76 – 7.62 (m, 3H), 7.27 – 7.22 (m, 1H), 3.50 – 3.37 (m, 2H), 2.43 (s, 3H), 2.01 – 1.85 (m, 2H), 1.66 – 1.52 (m, 2H), 1.50 – 1.25 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.69, 138.80, 137.04, 131.44, 130.21, 129.22, 127.27, 123.78, 123.26, 123.13, 122.42, 118.79, 117.53, 116.94, 113.48, 32.23, 31.73, 29.22, 28.62, 22.63, 18.55, 14.06. HRMS calcd for C$_{22}$H$_{24}$N$_5$ 358.2026 found 358.2011 [M + H]$^+$.

1-(*m*-Tolyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35n)
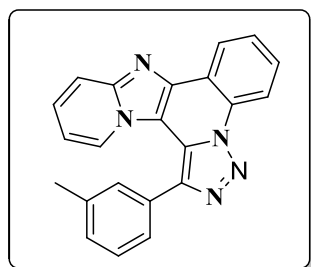
Yield 68%; pale yellow solid; mp 218-219 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.97 (dd, *J* = 8.3, 0.7 Hz, 1H), 8.73 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.80 – 7.74 (m, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.55 (s, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.38 (m, 2H), 6.71 (td, *J* = 6.9, 1.1 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.10, 139.90, 138.28, 137.86, 131.94, 131.80, 131.55, 130.08, 129.67, 128.41, 128.32, 128.30, 127.59, 127.26, 124.11, 122.42, 118.95, 117.79, 117.16, 113.09, 112.53, 21.50. HRMS calcd for C$_{23}$H$_{167}$N$_5$ 350.1400 found 350.1403 [M + H]$^+$.

12-Methyl-1-(*m*-tolyl)pyrido[2',1':2,3]imidazo[4,5-*c*][1,2,3]triazolo[1,5-*a*]quinoline (35o)
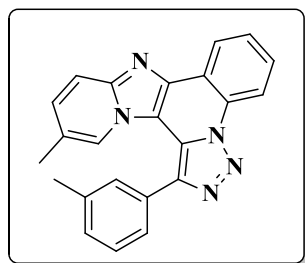
Yield 73%; pale yellow solid; mp 275-276 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 (d, *J* = 8.0 Hz, 1H), 8.67 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.77 – 7.69 (m, 2H), 7.54 (s, 1H), 7.53 – 7.50 (m, 2H), 7.49 – 7.45 (m, 1H), 7.26 (s, 1H), 7.23 (dd, *J* = 9.2, 1.5 Hz, 1H), 2.50 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.06, 139.65, 138.09, 137.61, 132.32, 132.03, 131.40, 130.22, 129.95, 129.39, 128.81, 128.15, 127.48, 126.26, 123.95, 122.76, 122.18, 119.07, 117.11, 116.84, 112.78, 21.46, 17.95. HRMS calcd for C$_{23}$H$_{18}$N$_5$ 364.1557 found 364.1548 [M + H]$^+$.

General procedure for the synthesis of compounds 36, 38 and 39

Mixture of compound **9a** or **37** (1 mmol), phenylacetylene (1.2 mmol), sodium azide (1.2 mmol), CuCl$_2$.2H$_2$O (0.2 mmol), K$_2$CO$_3$ (2.5 mmol) were vigorously stirred in DMF (4 mL) at 150 °C for 24 h. After cooling to room temperature, the reaction mass was diluted with water and extracted into ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The crude compound was purified by flash chromatography on a short silica gel (ethyl acetate: hexanes).

2-(2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (36)
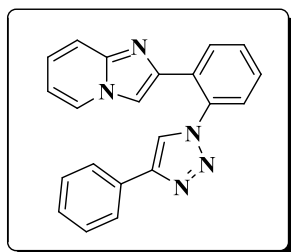
Yield 78%; off-white solid; mp 189-192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.43 (d, J = 6.8 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.79 – 7.69 (m, 1H), 7.59 (d, J = 3.1 Hz, 2H), 7.51 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.27 – 7.15 (m, 1H), 6.93 (s, 1H), 6.80 (t, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.98, 145.06, 140.34, 134.62, 131.26, 130.65, 130.56, 130.40, 128.86, 128.44, 128.29, 127.47, 126.15, 125.84, 125.00, 122.05, 117.55, 112.53, 110.39. HRMS calcd for 338.1400, found 338.1405 [M + H]$^+$.

2-phenylimidazo[1,2-*a*]pyridine (38)
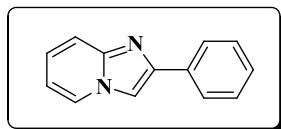
Yield 35%; off-white solid; mp 134-136 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.11 (d, J = 6.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.85 (s, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.78 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.74, 137.95, 133.65, 128.69, 127.99, 126.11, 125.59, 124.76, 117.55, 112.51, 108.19; ESI–MS(m/z): 195.1 (M+H)$^+$.

2-phenyl-3-(phenylethynyl)imidazo[1,2-*a*]pyridine (39)
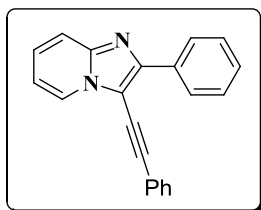
Yield 22%; viscous liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.66 (d, J = 6.8 Hz, 1H), 8.32 (d, J = 7.2 Hz, 2H), 7.76 – 7.73 (m, 2H), 7.56 – 7.44 (m, 8H), 7.15 (t, J = 6.8 Hz, 1H); ESI–MS(m/z): 295.1 (M+H)$^+$.

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Chapter V

Conclusions

Summary

5.1 General Conclusions

In recent years, the major concern in organic synthesis is to access the potent organic complex structures in a reduced number of synthetic steps from the simple and readily available precursors. In this context, development of multistep syntheses in a single step utilizing the multi-bond forming protocols such as tandem or domino sequences, multi-component reactions and one-pot sequential reactions are given high priority in synthetic organic chemistry. Moreover, modern upsurge in synthetic field, transition metal catalyzed C−H bond activation and functionalization is turned out as a most powerful tool for the construction of heterocyclic motifs without the necessity of pre-activation of substrates. These methods offer the C−C and C−heteroatom bond formations with high efficiencies, high functional group tolerance and excellent regioselectivities. Consequently, synthesis of potent heterocyclic motifs by employing atom-economical C−H functionalizations has become foremost priority of the majority of synthetic chemists.

The current thesis entitled "**Synthesis of Novel Fused Azaheterocycles by Tandem as well as Multicomponent Protocols**" deals with the syntheses of some selected *N*-fused heterocycles by employing the multi-bond forming reactions like multicomponent reactions, tandem sequences and also utilizing transition metal catalyzed C−H functionalizations. Mainly, the thesis is focused on synthesis and functionalization of nonbenzodiazepine drug skeletons, imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines. The thesis is divided into four chapters.

5.2 Specific Conclusions

The thesis entitled "**Synthesis of Novel Fused Azaheterocycles by Tandem as well as Multicomponent Protocols**" is divided in four chapters. A brief overview of these chapters is discussed below.

The first chapter of thesis describes a concise literature overview of chemistry of bicyclic *N*-fused imidazole, imidazo[1,2-*a*]pyridine. With the exclusion of very few synthetic approaches which involved the imidazole ring, majority of reports have exploited pyridine scaffolds as a key substrates for the synthesis of imidazo[1,2-*a*]pyridine nucleus. Diverse techniques such as multi-component reactions, tandem processes, rearrangement reactions, transition metal catalyzed C−H functionalizations, inter and intramolecular oxidative/reductive cyclizations has been employed for the construction of imidazo[1,2-*a*]pyridines. A detailed mechanisms have been discussed for the selected transformations. In conjunction with synthetic protocols, functionalization of imidazo[1,2-*a*]pyridines have also been discussed briefly in this chapter. Overall, this chapter provides a brief idea on synthetic protocols and functionalizations of imidazo[1,2-*a*]pyridine skeleton reported till October, 2014.

The second chapter of the thesis commences with significance of tandem reactions for the synthesis of diverse heterocyclic molecules. In this chapter, imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines have been synthesized using tandem reactions. The chapter is divided in two parts. In part-A, copper catalyzed oxidative C−H functionalization was successfully applied for the synthesis of imidazo[1,2-*a*]pyridines. The developed procedure involves CuI catalyzed tandem reaction among methyl ketones and 2-aminopyridines which offered high yields of imidazo[1,2-*a*]pyridines without the necessity of additional ligand or oxidant. The reaction was expected to proceeds *via* tandem imine formation and intramolecular aerobic oxidative C–H bond amination /cyclizations. An array of imidazo[1,2-*a*]pyridines have prepared by the reaction of readily available acetophenones and 2-aminopyridines in good to excellent yields. The optimized method was efficiently tolerated reactive functionalities such as hydroxy, bromo, fluoro and chloro. The scope of method was validated by a single step synthesis of zolimidine, drug used for peptic ulcers, in 61% yield. In part-B, a tandem reaction was developed for the regioselective synthesis of pyrazolo[1,5-*a*]pyrimidines. Here, 3-aminopyrazoles and chalcones are reacted in presence of catalytic amount of KOH and produced

high yields of pyrazolo[1,5-*a*]pyrimidines. Since 1,4-Michael addition of pyrazole endocyclic nitrogen on chalcones is expected to be more favoured in this protocol, regioselectivity issues are resolved successfully which were the main limitations in case of 1,3-diketones. A gram-scale reaction has been performed to demonstrate the potency of optimized procedure for the scale-up processes.

The third chapter of the thesis begins with brief history of multicomponent reactions along with some classical examples. This chapter is mainly focused on the functionalization of imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines by three-component reaction. An efficient one-pot condensation reaction of imidazo[1,2-*a*]pyridine/pyrazolo[1,5-*a*]pyrimidines, aldehydes and acetamide has been investigated using Yb(OTf)$_3$ as a catalyst in 1,4-dioxane. The reaction furnished good to excellent yields of nonbenzodiazepine drug like structures, 1-amidomethyl imidazo[1,2-*a*]pyridines/pyrazolo[1,5-*a*]pyrimidines. The outcome of the three-component reaction was found to be dependent on the nature of imidazo[1,2-*a*]pyridine/pyrazolo[1,5-*a*]pyrimidines and aldehydes. The reaction of pyrazolo[1,5-*a*]pyrimidine with aldehydes resulted in formation of two new symmetrical and unsymmetrical aryl methylene-*bis*-pyrazolo[1,5-*a*]pyrimidines and imidazo[1,2-*a*]pyridine gave symmetrical aryl methylene-*bis*(imidazo[1,2-*a*]pyridine) together with expected three-component products. A plausible mechanism has been proposed based on the product distribution.

The fourth chapter of the thesis describes importance of transition metal catalyzed C−H functioanlizatons for the synthesis complex structures in a single step. This chapter dealt with the synthesis of azole fused imidazo[1,2-*a*]pyridines by employing transition metal catalyzed C−H functionalizations. The chapter is divided in two parts. In part-A, an efficient one-pot protocol have been developed using sequential C−N coupling and intramolecular dehydrogenative cross-couplings for the synthesis of azole fused imidazo[1,2-*a*]pyridines. During the course of these investigations, it has been realized that nitrogen of imidazole ring in imidazo[1,2-*a*]pyridines has an ability to bind with transition metals and direct the coupling partner towards C-2 aryl ring. The directing ability was successfully adapted for the copper catalyzed Ullmann-type C−N coupling of imidazo[1,2-*a*]pyridines. In part-B, a ligand-free copper-catalyzed tandem azide-alkyne cycloaddition (CuAAC), Ullmann-type C−N coupling and intramolecular direct arylation has been described. The reaction shows high generality and functional group tolerance. It

provides a straightforward means for the preparation of fused triazoles derivatives. The designed strategy resulted in the construction of a novel triazole-fused azaheterocyclic frameworks in good yields. Since there are two equally reactive bromo groups in the precursors, two regioisomers are expected from the developed tandem C−H functionalization process. The exact structure of synthesized fused polycyclic structures have been ascertained based on controlled experiments in conjugation with NOE studies.

5.3 Future Scope of the Research Work

Transition metal catalyzed C−H activation which delivers C−C and C−heteroatom bonds, without the necessity of pre-functionalization of substrates is undoubtedly a valuable tool for the construction of diverse molecular frameworks. Last decade has witnessed an unexpected bundle of publications with this concept and a high abundant of synthetic libraries have been achieved using C−H activation strategy. In addition, multi-bond forming approaches like tandem reactions, multi-component reactions and one-pot sequences amalgamated with C−H activation offer high complexity and diversity in a single step. As many natural products in addition to pharmacologically active molecules contains fused heterocyclic compounds as their central frameworks, synthesis of these molecules by means of aforementioned hybrid methodologies is an potential alternative to traditional linear syntheses.

The thesis mainly focused on chemistry of nonbenzodiazepine drug skeletons, imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines. These *N*-fused structures have been synthesized while utilizing tandem reactions, multicomponent protocols and transition metal catalyzed C−H functionalizations. As the synthesized molecules are the key structures of wide range of non-benzodiazepine drugs, the developed procedures can be tuned further to access the drugs in a reduced number of steps or probably in a single step. These procedures have wide scope and can be employed for the synthesis of a diverse range of either bioactive heterocyclic molecules or to access new heterocyclic libraries for biological screenings. The synthetic methodologies and novel aza-fused heterocyclic compounds provided in the thesis will be a fine and adoptable example for the systematic construction of fused heterocycles for biological screenings.

Appendices

Appendices

1. **Kasiviswanadharaju Pericherla,** Bharti Khungar and Anil Kumar, One-pot, three-component synthesis of 1-amidomethylimidazo[1,2-*a*]pyridines catalyzed by ytterbium triflate, *Tetrahedron Letters* **2012**, *53*, 1253-1257.

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One-pot, three-component synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines catalyzed by ytterbium triflate

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ABSTRACT

A straightforward method has been developed for the synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines by Yb(OTf)$_3$ catalyzed three-component reaction of aldehydes, acetamide, and imidazo[1,2-*a*]pyridines. A series of substituted 3-substituted imidazo[1,2-*a*]pyridines were synthesized in moderate to good yield (21–74%) under mild reaction condition and the catalyst was recycled for four cycles.

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Click chemistry inspired structural modification of azole antifungal agents to synthesize novel 'drug like' molecules

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ABSTRACT

A new class of 'drug like' 1,4-disubstituted-1,2,3-triazoles is synthesized using one-pot reaction of sodium azide, α-bromo ketones, and alkynes in PEG-400/water (1:1, v/v) under the click chemistry reaction condition followed by reduction of keto group and alkylation. The method is simple, efficient and gives good yield of novel 1,2,3-triazole derivatives.

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One-pot sequential C–N coupling and cross dehydrogenative couplings: synthesis of novel azole fused imidazo[1,2-*a*]pyridines†

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An efficient one-pot protocol has been developed using sequential C–N coupling and intramolecular dehydrogenative cross-couplings for the synthesis of azole fused imidazo[1,2-*a*]pyridine derivatives in good yields (62–78%).

of synthetic simplicity and efficiency, atom economy, and environmental benefits.[6–9] It avoids pre-functionalization of substrates and minimizes by-product formation.

A number of novel methodologies have been established to generate diverse poly heterocycles *via* cross dehydrogenative

Povarov-Reductive Amination Cascade to Access 6-Aminoquinolines and Anthrazolines

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ABSTRACT
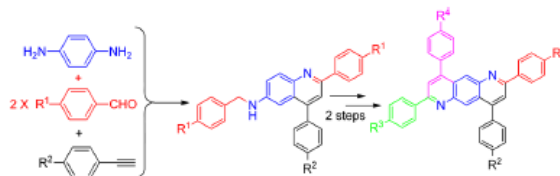
A new strategy is reported for the synthesis of 6-aminoquinoline derivatives *via* a tandem Povarov reaction, dihydroquinoline oxidation, and imine reduction. These products allow access to symmetrical as well as unsymmetrical tetraarylpyrido[2,3-*g*]quinolines, potentially useful organic electronics.

Copper-Catalyzed Tandem Azide—Alkyne Cycloaddition, Ullmann Type C—N Coupling, and Intramolecular Direct Arylation

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ABSTRACT

A ligand-free copper-catalyzed tandem azide—alkyne cycloaddition (CuAAC), Ullmann-type C—N coupling, and intramolecular direct arylation has been described. The designed strategy resulted in the synthesis of a novel trazole-fused azaheterocycle framework. The reaction gave good yields (59–77%) of 1,2,3-triazole-fused imidazo[1,2-a]pyridines in a single step.

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PAPER

Copper catalyzed tandem oxidative C–H amination/cyclizations: Direct access to imidazo[1,2-a]pyridines†

Kasiviswanadharaju Pericherla,[a] Pinku Kaswan,[a] Poonam Khedar,[a] Bharti Khungar,[a] Keykavous Parang[b] and Anil Kumar*[a]

A simple and convenient strategy is described for the synthesis of imidazo[1,2-a]pyridines *via* inexpensive copper-catalyzed tandem imine formation and intramolecular aerobic oxidative C–H bond amination/cyclizations. An array of imidazo[1,2-a]pyridines were prepared by the reaction of readily available acetophenones and 2-aminopyridines in good to excellent yields (48–92%). The scope of the method was validated by a single step synthesis of Zolimidine, a drug used for peptic ulcers, in 61% yield.

Synthesis and antiproliferative activities of quebecol and its analogs

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ARTICLE INFO

ABSTRACT

Simple and efficient synthesis of quebecol and a number of its analogs was accomplished in five steps. The synthesized compounds were evaluated for antiproliferative activities against human cervix adenocarcinoma (HeLa), human ovarian carcinoma (SK-OV-3), human colon carcinoma (HT-29), and human breast adenocarcinoma (MCF-7) cancer cell lines. Among all the compounds, 7c, 7d, 7f, and 8f exhibited antiproliferative activities against four tested cell lines with inhibition over 80% at 75 µM after 72 h, whereas, compound 7b and 7g were more selective towards MCF-7 cell line. The IC_{50} values for compounds 7c, 7d, and 7f were 85.1 µM, 78.7 µM, and 80.6 µM against MCF-7 cell line, respectively, showing slightly higher antiproliferative activtiy than the synthesized and isolated quebecol with an IC_{50} value of 104.2 µM against MCF-7.

Full paper/Mémoire

Synthesis, characterization and microbiocidal studies of novel ionic liquid tagged Schiff bases

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ABSTRACT

The synthesis of novel imidazolium ionic liquid, tagged Schiff, has been described. The synthesis was achieved in three steps from 2,4-dihydroxybenzaldehyde by selective alkylation with 1,3-dibromopropane, followed by reaction with 1-methylimidazole and Schiff base formation with aromatic amines. The compounds were evaluated for antibacterial and antifungal activities. The ionic liquid tagged Schiff base 4a showed the inhibition of both Gram positive and Gram negative bacteria. It also showed broad spectrum antifungal activity against all four tested fungi; however, 4f showed highest antifungal activity against A. niger.

Exploration of the CuAAC Reaction for the Synthesis of Novel 3-(Triazol-1-yl)-methyl-imidazo[1,2-*a*]pyridines

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Abstract: The archetypical CuAAC click chemistry is explored to assemble diverse 3-(triazol-1-yl)methyl-imidazo[1,2-*a*]pyridines. The approach is simple, general, and environmentally benign to generate a library of novel triazolo-imidazo[1,2-*a*]pyridine derivatives in good yield (30–90%).

Key words: azides, click chemistry, imidazo[1,2-*a*]pyrimidine 1,2,3-triazole, 3-(triazolyl)methyl-imidazo[1,2-*a*]pyridine

tuberculosis,[30,31] carbonic anhydrase,[32] c-Src kinase,[33] GSK-3,[34] and indoleamine 2,3-dioxygenase 1 inhibition.[35] They have been widely employed in the pharmaceutical, agrochemical, polymer, and materials field. Synthesis of triazolo-conjugated heterocycles through molecular-hybridization approach has attracted attention from many research groups because it may lead to molecules with improved pharmacophoric properties.[36,37] Therefore ex-

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Ligand-Free, Copper-Catalyzed Ullmann-Type C–N Coupling: Regioselective Synthesis of Azole-Substituted Imidazo[1,2-*a*]pyridines

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Abstract: A simple and highly efficient protocol for the regioselective synthesis of azole-substituted imidazo[1,2-*a*]pyridines has been developed using a ligand-free, copper-catalyzed Ullmann-type C–N coupling of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines with different azoles and in situ generated 1,2,3-triazoles. The reactions proceeded smoothly to furnish azolo-imidazo[1,2-*a*]pyridines in good to excellent yields (65–96%).

Key words: copper, ligand-free C–N coupling, imidazo[1,2-*a*]pyridines, 1,2,3-triazole, CuAAC, tandem reaction

ders), alpidem, necopidem and saripidem (anxiolytics), zolimidine (treatment of peptic ulcers), olprinone (cardiotonic agent), and miroprofen (analgesic).

Although some ligand-promoted C–N couplings have been reported on imidazo[1,2-*a*]pyridines, *ortho*-directed aminations of these privileged motifs are poorly studied.[5] In a continuation of our efforts towards designing novel heterocycles containing imidazo[1,2-*a*]pyridines,[16] we wish to report a regioselective, ligand-free, copper-catalyzed C–N coupling for the synthesis of azole-substituted

Copper Triflate: An Efficient Catalyst for Direct Conversion of Secondary Alcohols into Azides

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Abstract: A simple, practical, and efficient strategy has been demonstrated for the direct synthesis of organic azides from alcohols using azidotrimethylsilane (TMSN$_3$) as azide source in the presence of copper(II) triflate [Cu(OTf)$_2$]. A variety of alcohols was converted into the corresponding azides in good to excellent yields. The formation of an intermediate carbocation was confirmed by the synthesis of bis(diphenylmethyl) ether.

Key words: azides, azidotrimethylsilane, copper triflate, Lewis acid

and NaN$_3$/CCl$_4$–DMF.[28] Although the reported methods are effective, they suffer from limitations such as inaccessible and expensive reagents and long reaction times as well as cumbersome separation from the generated Ph$_3$P=O and unreacted Ph$_3$P.

Thus, in this communication we wish to report our preliminary results for the direct conversion of alcohols into azides using azidotrimethylsilane (TMSN$_3$) and copper(II) triflate [Cu(OTf)$_2$, Scheme 1].

Green Chemistry

PAPER

Imidazolium ionic liquid-tagged palladium complex: an efficient catalyst for the Heck and Suzuki reactions in aqueous media†

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An air stable, water soluble, and efficient ionic liquid-tagged Schiff base palladium complex was prepared. The synthesized complex was well characterized by NMR, mass spectrometry, FT-IR, UV-visible spectroscopy and powder X-ray diffraction. The complex was used as a catalyst for the Suzuki and Heck cross-coupling reactions in water. Good to excellent yields were achieved using a modest amount of the catalyst. In addition, the catalyst can be easily reused and recycled for six steps without much loss in activity, exhibiting an example of sustainable and green methodology.

Microwave assisted copper triflate-catalyzed rapid hydration of aryl acetylenes

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ABSTRACT

An efficient microwave-assisted copper triflate-catalyzed reaction for the hydration of terminal aryl acetylenes to prepare substituted acetophenones has been developed. Significantly shorter reaction time, low catalyst loading, and wide range of functional group tolerance are salient features of this methodology.

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Synthesis of Aza-Fused Isoquinolines through Domino Cross-Aldol Condensation and Palladium-Catalyzed Intramolecular Direct Arylation

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S Supporting Information

ABSTRACT: A straightforward method has been developed for the synthesis of aroyl-substituted imidazo-/benzimidazo-fused isoquinolines. The cascade reaction proceeds via a cross-aldol condensation of 2-(1H-imidazol-1-yl/benzimidazolyl-1-yl)-1-arylethanones and 2-bromobenzaldehyde followed by palladium-catalyzed intramolecular C—H functionalization. This approach offers a simple and efficient alternative one-pot protocol for the assembly of imidazo/benzimidazo[2,1-a]isoquinolines in moderate to good yields.

R[1] = H, 4-CH₃, 4-OCH₃, 4-Cl, 3-CH₃, 3-OCH₃, 2-CH₃, 3,4-(OCH₃)₂
azoles = imidazole, 4-methyl imidazole, benzimidazole

17 examples
18–70%

An Efficient and Facile Synthesis of Vinyl Sulfones via Microwave-Assisted Copper Triflate Catalyzed Hydrosulfonylation of Alkynes

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Abstract: An efficient method has been described for the synthesis of vinyl sulfones via hydrosulfonylation of alkynes using sodium arene sulfinates catalyzed by Cu(OTf)$_2$ under microwave irradiation. A variety of vinyl sulfones was obtained in good to excellent (71–89%) yields and with high regio- and stereoselectivity. Shortened reaction times, simple reaction conditions and low catalyst loading are the salient features of this protocol.

Key words: microwave, vinyl sulfones, copper triflate, alkynes, sodium arene sulfinates

or copper-catalyzed cross-coupling and addition reactions of sulfinate salts.[16] Despite this range of available methodologies, these methods suffer from one or more drawbacks in terms of sensitive functional group tolerance, formation of isomer mixtures and side products, or need for inaccessible starting materials, relatively harsh reaction conditions or tedious procedures. Therefore, there remains the need to develop facile, highly selective and resource-efficient protocols to construct vinyl sulfones.

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Synthesis of 3-aroylimidazo[1,2-a]pyridines via CuCl$_2$ catalyzed tandem dual carbon–nitrogen bonding

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ARTICLE INFO

ABSTRACT

A novel tandem approach has been demonstrated for the direct synthesis of bioactive 3-aroylimidazo[1,2-a]pyridines from chalcones and 2-aminopyridines. The reported tandem reaction is atom-economical and expected to proceed via 1,4-Michael addition followed by copper catalyzed oxidative C–N bonding. Catalytic amount of copper was found to be crucial for the success of tandem reaction and it altered the reaction pathway to furnish entirely new products. This protocol proved to be convenient as reaction proceeds smoothly without the necessity of any ligand in the presence of air as oxidant.

Oral presentations

1. **<u>Kasiviswanadharaju Pericherla</u>**, Bharti Khungar, Amitabh Jha and Anil Kumar, Copper catalyzed regioselective synthesis of 1,2,3-triazole fused imidazo[1,2-*a*]pyridines *via* tandem [3+2] azide-alkyne cycloaddition, Ullmann-type C–N coupling and intramolecular direct arylation, International Conference on Emerging Trends in Chemical Sciences (IETC-2013), Department of Chemistry, Vellore Institute of Technology, Vellore, Tamil Nadu (December 5-7, **2013**) (F*irst prize in oral presentation*).

Poster presentations

1. Anil Kumar, **<u>Kasiviswanadharaju Pericherla</u>** and Bharti Khungar, Synthesis and anti-microbial applications of ionic liquid supported schiff bases, International Conference on Green Chemistry (ICGC), Department of Chemistry, Central University of Rajasthan, Kishangarh (December 7-9, **2011**).

2. **<u>Kasiviswanadharaju Pericherla</u>**, Poonam Khedar, Bharti Khungar and Anil Kumar, One-pot three component synthesis of substituted imidazo[1,2-*a*]pyridines catalyzed by Yb(OTf)$_3$ and their anti cancer activities, National Symposium on Recent Trends in Chemical Science and Technology, Department of Chemistry, IIT Patna (March 3-4, **2012**).

3. **<u>Kasiviswandharaju Pericherla</u>**, Poonam Khedar, Bharti Khungar and Anil Kumar, Synthesis of substituted 1-amidomethyl imidazo[1,2-*a*]pyridines catalyzed by Yb(OTf)$_3$, National Symposium on Recent Trends in Chemical Sciences, Department of Chemistry, BITS Pilani, Pilani (March 25, **2012**).

4. Poonam Khedar, **<u>Kasiviswanadharaju Pericherla</u>**, Anil Kumar, Click chemistry inspired synthesis of 1,2,3 triazolylimidazo[1,2-a]pyridines, National Symposium on Recent Trends in Chemical Science and Technology, Department of Chemistry, IIT Patna (March 3-4, **2012**).

5. Poonam Khedar, **<u>Kasiviswanadharaju Pericherla</u>**, Anil Kumar, Click chemistry inspired synthesis of 1,2,3-triazolylimidazo[1,2-*a*]pyridines, National Symposium on Recent Trends in Chemical Sciences, Department of Chemistry, BITS Pilani, Pilani (March 25, **2012**).

6. Pinku Kaswan, **<u>Kasiviswanadharaju Pericherla</u>** and Anil Kumar, Ligand free CuI catalyzed amination of 2-(2-bromophenyl)*H*-imidazo[1,2-*a*]pyridines, 19th ISCB

International Conference (ISCBC-2013), Mohanlal Sukhadia University, Udaipur, Rajasthan (March 2-5, **2013**).

7. Poonam Khedar, **<u>Kasiviswanadharaju Pericherla</u>** and Anil Kumar, Synthesis of novel 1-((1-(2-aryloxy-2-arylethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-arylpiperazines, Recent Advances and Current Trends in Chemical and Biological Sciences, 19th ISCBC-2013, Mohanlal Sukhadia University, Udaipur (March, 2-5, **2013**).

8. Poonam Khedar, **<u>Kasiviswanadharaju Pericherla</u>** and Anil Kumar, Direct conversion of secondary alcohols into azide using $Cu(OTf)_2/TMSN_3$, NCRDCS 2014, Guru Jambheshwar University of Science and Technology, Hisar, Haryana (February 25-26, **2014**).

9. Hitesh Kumar Saini, **<u>Kasiviswanadharaju Pericherla</u>**, Shiv Dhiman and Anil Kumar, Direct approach towards the synthesis of imidazo[1,2-*f*]phenanthridines by palladium catalyzed intramolecular C–H functionalization, 20th ISCB International Conference (ISCBC-2014), University of Delhi, New Delhi, India (March 1-4, **2014**).

10. Pinku Kaswan, **<u>Kasiviswanadharaju Pericherla</u>**, Poonam Khedar and Anil Kumar, Copper catalyzed tandem oxidative C–H amination/oxidative cyclizations: direct access to imidazo[1,2-*a*]pyridines, 16th CRSI National Symposium in Chemistry, Department of Chemistry, IIT Bombay, Mumbai (February, 7-9, **2104**).

11. Nitesh Kumar Nandwana, Pinku Kaswan, **<u>Kasiviswanadharaju Pericherla</u>** and Anil Kumar, Synthesis of novel azole fused-quinazolines *via* one-pot sequential Ullmann type C−N bonding and intramolecular dehydrogenative C−N coupling, 20th ISCB International Conference (ISCBC-2014), University of Delhi, New Delhi, India (March 1-4, **2014**).

12. Shiv Dhiman, **<u>Kasiviswanadharaju Pericherla</u>**, Nitesh Nandwana and Anil Kumar, Palladium catalyzed cross-aldol/intramolecular direct arylation: an easy access to aza-fused isoquinolines, International Symposium on Recent Advances in Medicinal Chemistry (ISRAM), NIPER, S.A.S. Nagar, India (September 8-10, **2014**).

13. Pinku Kaswan, **<u>Kasiviswanadharaju Pericherla</u>**, Hitesh Kumar Saini and Anil Kumar, Tandem one-pot, three-component reaction of methyl ketones, aldehydes and 2-aminopyridines for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines, International Symposium on Recent Advances in Medicinal Chemistry (ISRAM), NIPER, S.A.S. Nagar, India (September 8-10, **2014**).

Kasiviswanadharaju Pericherla obtained his master degree in Organic Chemistry from DNR College, Andhra University, Vishakhapatnam, India during 2005-07. In 2007 August, he joined Albany Molecular Research, Hyderabad Research Centre (AMRHRC) as a Research Scientist Trainee and continued till December 2010. During this period, he involved in a variety of projects dealing with the synthesis of diverse organic molecules such as carbohydrates, complex heterocyclic as well as aliphatic molecules. In this period, he was promoted to Research Scientist and Research Scientist I designations and received best employee award for the year 2009. In January 2011, he joined Department of Chemistry, BITS Pilani for PhD program under the guidance of Dr. Bharti Khungar and Dr. Anil Kumar with the financial assistance from the institute. In June 2011, he cleared the Joint CSIR-UGC NET and was awarded Junior Research Fellowship (JRF) by UGC, New Delhi. He visited Prof. Amitabh Jha's lab, Acadia University, Canada with the support of a scholarship from the Canadian Bureau for International Education (CBIE) during September 2012 to March 2013. In Prof. Jha's group, he was involved in the synthesis of medicinally important quinoline libraries. He has published nineteen research articles in peer reviewed international journals and presented papers in three national/international conferences/symposiums.

His research interest lies in the development of new methods for the synthesis of bioactive aza-fused heterocyclic motifs and the construction of novel fused heterocyclic libraries using C−H activation/functionalizations.

Dr. Bharti Khungar is Assistant Professor at the Department of Chemistry, BITS Pilani, Pilani Campus, since July 2007. She carried out her doctoral research in Chemistry at University of Rajasthan, Jaipur under the supervision of Prof. U. D. Tripaathi and co-supervision of Dr. A. K. Varshney and obtained the Ph.D. degree in 2002. After this, she worked as a Lecturer in the Department of Chemistry, Laxmi Devi Institute of Engineering and Technology, Alwar, Rajasthan till 2005. Before Joining BITS she worked at the post of Senior Lecturer at Banasthali University, Rajasthan for two years.

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Dr. Anil Kumar is Associate Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. He obtained his PhD degree from Department of Chemistry, University of Delhi, Delhi, India under the guidance of Professor SMS Chauhan in 2004. During his doctoral studies Dr. Anil Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry. He was postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, USA in Prof. Keykavous Parang group during May 2004 to April 2006. In his postdoctoral studies he has worked on synthesis of novel Src kinase inhibitory agents and solid phase synthesis. He joined Department of Chemistry, Birla Institute of Technology and Science, Pilani, India as Assistant Professor in 2006 and was promoted to Associate Professor in February 2013. He was appointed as Associate Dean, Work Integrated Learning Programmes (WILP) in May 2014 and Head of Department of Chemistry in September 2014. He has visited University of Rhode Island, Kingston, USA as visiting scientist and Acadia University, Wolfville, Canada as Harrison McCain visiting professor.

Dr. Kumar is recipient of Harrison McCain Foundation award from Acadia University, Canada for 2012, ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2013 and Dr. Aravind Kumar memorial award from Indian Council of Chemist for 2014. He has 15 year of research experience and 8 year of teaching experience. He has published over 100 research papers in international journals of repute in the area of synthetic organic chemistry, green chemistry and medicinal chemistry and contributed a book chapter and one US patent He has participated in several national and international symposia/conferences and delivered more than 20 invited lectures. He has guided three PhD students and currently supervising 10 PhD students. He is editor for Canadian Chemical Transactions and member of editorial advisory board for The Open Catalysis Journal. He has completed three research projects as Principle Investigator and one as Co-PI sponsored by DST, CSIR and UGC. Currently, he has one major project from CSIR and one industry project from Ranbaxy in collaboration with Prof. Dalip Kumar. He has also served as a reviewer for several journals. He is life member of Chemical Research Society of India, Bangalore; Indian Society of Chemists and Biologists, Lucknow and Indian Council of Chemists, Agra.

His research interest lies in transition metal catalyzed C−H activation and tandem reactions, green chemistry, ionic liquids and medicinal chemistry.