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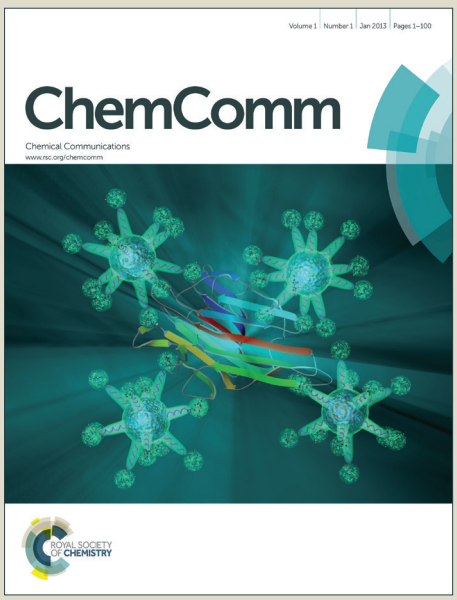

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Synthesis of Imidazo[1,2-*a*]pyridines: A Decade Update

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Imidazopyridine is one of the important fused bicyclic 5–6 heterocycles and it is recognized as "drug prejudice" scaffold due to its wide applications in medicinal chemistry. This moiety is also useful in material science because of its structural character. Synthesis of this moiety from the easily available chemicals is desirable due to its tremendous uses in the various branches of chemistry. Here we report a review on the synthesis of this scaffold employing different strategies such as condensation, multicomponent reaction, oxidative coupling, tandem reaction, aminooxygenation, hydroamination reaction etc.

Introduction

Imidazopyridine 'the imidazole moiety fused with the pyridine ring' is an important class of biologically active nitrogen containing heterocycle.[1] Among the various imidazopyridine derivatives, imidazo[1,2-*a*]pyridine moiety is the most important in the area of natural products and pharmaceuticals. These derivatives show a wide range of biological activities such as antifungal, antiinflammatory, antitumor, antiviral, antibacterial, antiprotozoal, antipyretic, analgesic, antiapoptotic, hypnoselective, and anxioselective activities.[2-12] They also act as *β*-amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotonic agents.[13-16] There are several drugs such as zolpidem (**1**, used in the treatment of insomnia),[17] alpidem (**2**, as an anxiolytic agent),[17] olprinone (**3**, for the treatment of acute heart failure),[18] zolimidine (**4**, used for the treatment of peptic ulcer),[19] necopidem and saripidem (**5** and **6**, both work as an anxiolytic agent)[20] available in the market which contain imidazo[1,2-*a*]pyridine moiety (Fig. 1). The optically active GSK812397 is a drug for the treatment of HIV infection.[21] The antibiotic drug Rifaximin also contains this fused heterocyclic moiety.[22] In addition, some abnormal *N*-heterocyclic carbenes are also prepared based on imidazo[1,2-*a*]pyridines.[23-24]

They are also important in the field of optoelectronics as the imidazo[1,2-*a*]pyridine moiety bearing 2-hydroxyphenyl substituent at 2-position (**11**) exhibits excited state intramolecular proton transfer (ESIPT) (Fig. 2).[25]

Accordingly, there is continuous effort towards the development of new methods for the synthesis of imidazo[1,2-*a*]pyridine derivatives with variety of substituents at the 2 and 3-positions of this moiety.

Efforts have been directed to develop different synthetic strategies for this privileged structure of imidazo[1,2-*a*]pyridines and various approaches have been adopted for this purpose. These are classified into some subcategories like condensation, multicomponent, oxidative coupling, tandem reaction, aminooxygenation, hydroamination reaction etc. A short review based on the synthetic strategies of imidazo[1,2-*a*]pyridines is presented here according to the reaction type (Fig. 3).

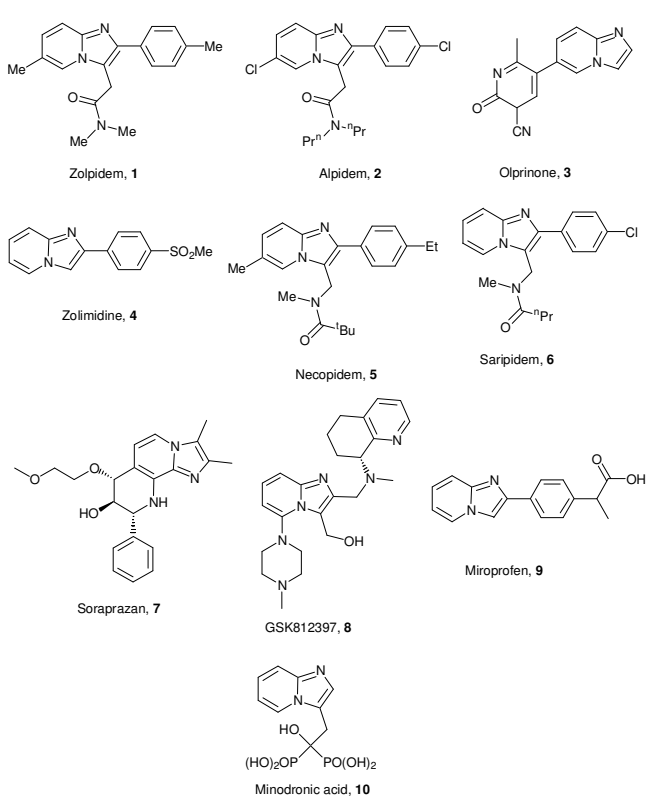


Fig. 1 Imidazo[1,2-*a*]pyridine-based drugs.

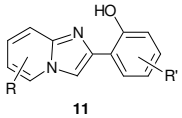


Fig. 2 Imidazo[1,2-*a*]pyridine scaffold as ESIPT.

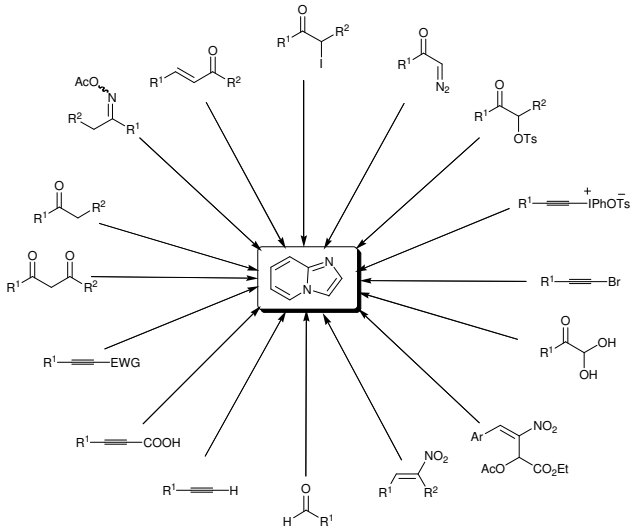
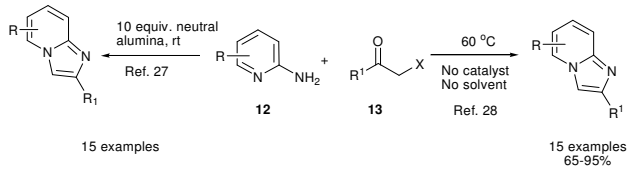


Fig. 3 Imidazo[1,2-*a*]pyridines from basic chemicals.

Condensation reaction:

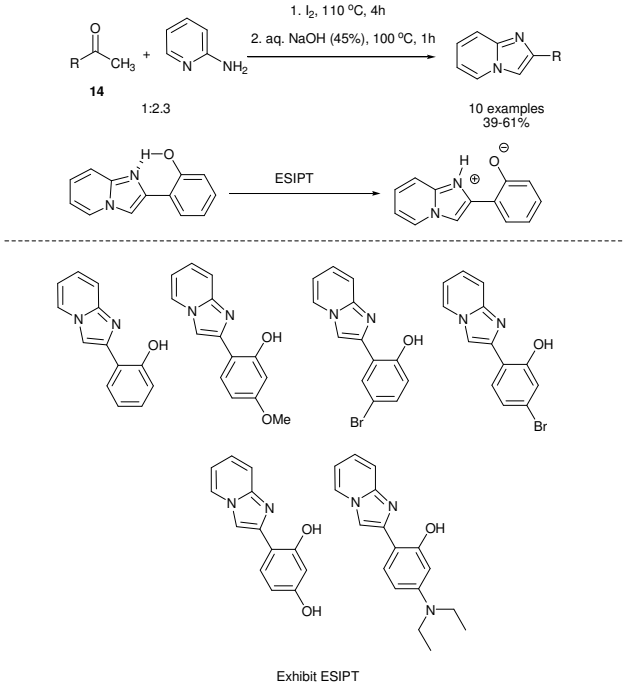
From *α*-haloketones:

A traditional approach for the synthesis of imidazo[1,2-*a*]pyridine derivatives is by the condensation reaction of *α*-haloketones with the 2-aminopyridines.[26] Over the years various catalytic and non-catalytic systems have been developed by the different groups. A few of them are described in this review. Sahu *et al* reported that the neutral alumina is an efficient medium for this transformation at room temperature (Scheme 1).[27] They synthesized various imidazopyridines employing this method. The Chen and Wu group[28] showed that the imidazo[1,2-*a*]pyridines could be synthesized from *α*-bromo/chloroketones and 2-aminopyridines under catalyst and solvent-free condition at 60 ºC. This methodology is also well applicable for the *α*-haloketones. The nucleophilic substitution of bromide by the pyridine-nitrogen in the 2-aminopyridine is the key step of these reactions.



Scheme 1 Synthesis of imidazopyridine derivatives from *α*-halo ketones.

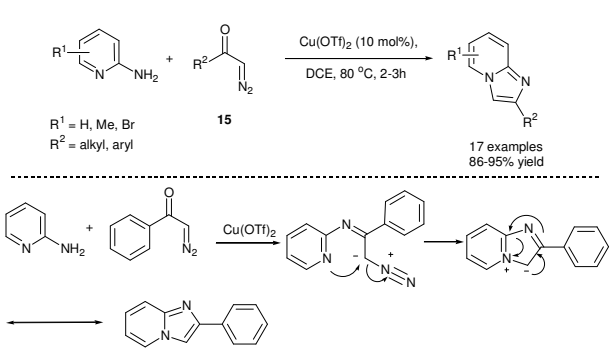
Cyrański and Gryko *et al* synthesized imidazo[1,2-*a*]pyridine derivatives from the ketones by the *in situ* generation of *α*-iodoketones (Scheme 2).[29] The reaction is dependent on the molar ratio of the amino pyridines and ketones and maximum yields was obtained with 2.3:1 ratio. They synthesized a library of imidazopyridines *via* an Ortoleva–King reaction followed by ring closure and studied their photophysical properties. Imidazo[1,2-*a*]pyridines possessing a 2-hydroxyphenyl substituent at 2-position exhibit excited-state intramolecular proton transfer (ESIPT). They also described that the imidazo[1,2-*a*]pyridines possessing aryl substituents at 2-position display strong emission bands in the blue region.



Scheme 2 Imidazo[1,2-*a*]pyridines from the ketones by the *in situ* generation of iodoketones.

From *α*-diazoketones:

α-Diazoketones are also useful like *α*-haloketones for the synthesis of imidazo[1,2-*a*]pyridines. The copper-catalyzed reaction between *α*-diazoketones (**15**) and 2-aminopyridines afforded these heterocycles with good selectivity and good yields (Scheme 3).[30] This $Cu(OTf)_2$ catalyzed reaction is equally efficient for both the aromatic and aliphatic diazoketones. Other Lewis acids like $In(OTf)_3$, $Bi(OTf)_3$, $InCl_3$, $InBr_3$, $Sc(OTf)_3$ and Brønsted acids like hetero polyacid, Amberlyst-15, PMA are not effective to afford the imidazopyridines by this reaction. This reaction undergoes *via* the imine formation followed by nitrogen insertion.

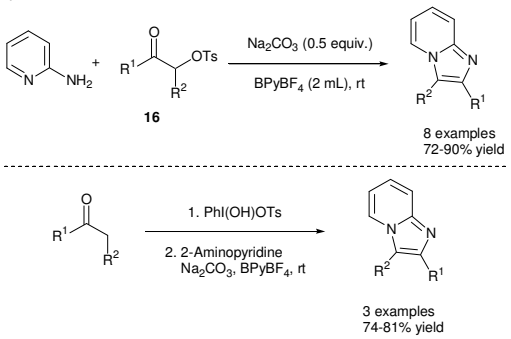


Scheme 3 Copper-catalyzed reaction between diazoketones and 2-aminopyridines.

From *α*-tosyloxyketones:

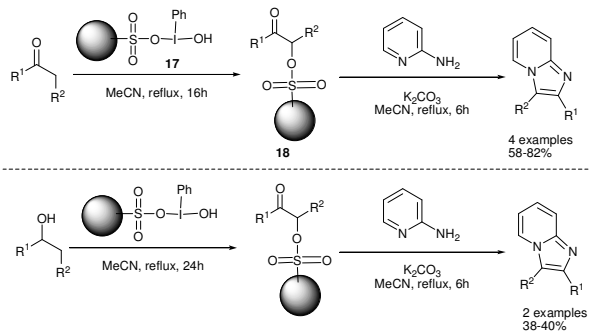
The reaction of *α*-tosyloxyketones (**16**) with 2-aminopyridine in ionic liquid $BPyBF_4$ at room temperature afforded the imidazopyridine derivatives within an hour.[31] The ionic liquid is preferable for this condensation reaction compared to common organic solvents. Longer reaction time and higher temperature are required in organic solvents. The imidazopyridines have been

synthesized directly from ketone by *in situ* generation of the *α*-tosyloxyketones (Scheme 4).

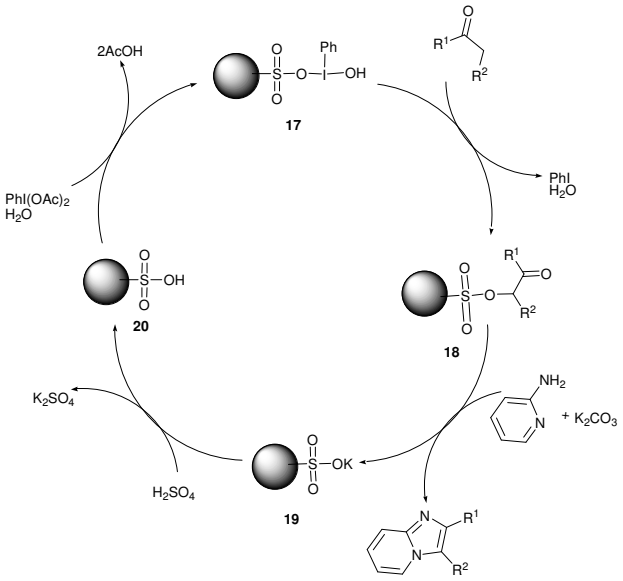


Scheme 4 Synthesis of imidazopyridines from *α*-tosyloxy ketones.

Togo and co-worker synthesized imidazo[1,2-*a*]pyridines starting from the ketone or alcohol (Scheme 5).[32] The methodology proceeds through the *in situ* generated *α*-sulfonyloxy ketones (**18**) by the macroporous polystyrenesulfonic acid and (diacetoxyiodo)benzene and followed by the reaction with 2-aminopyridine. Second step was carried out in presence of K_2CO_3 as base under acetonitrile medium. Macroporous polystyrenesulfonic acid (**17**) was regenerated by treatment with dilute sulfuric acid (Scheme 6). However this procedure was not applicable for the synthesis of imidazo[1,2-*a*]pyridines from aldehydes. The protocol was applied for the synthesis of these derivatives from the secondary alcohols *via* oxidative conversion of alcohols to the *α*-tosyloxy ketones. The yields of this direct method from alcohols was lower than that with the ketones.



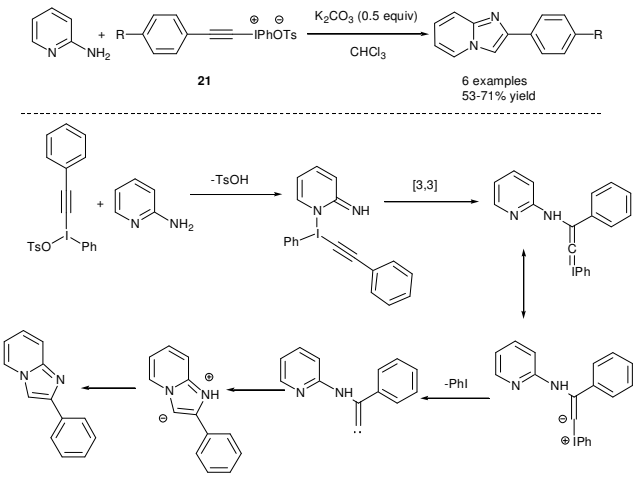
Scheme 5 Synthesis of imidazopyridines from ketones with polymer-supported [(hydroxy)(sulfonyloxy)iodo]benzene.



Scheme 6 Proposed reaction mechanism.

From alkynyl(phenyl)iodonium salts:

Chen *et al* developed a simple and facile method for the synthesis of 2-substituted imidazopyridines by the reaction of alkynyl(phenyl)iodonium salts (**21**) with 2-aminopyridine (Scheme 7).[33] Only K_2CO_3 in chloroform is effective to carry out the reaction. The reaction proceeds through the [3,3]-sigmatropic rearrangement followed intramolecular cyclization.

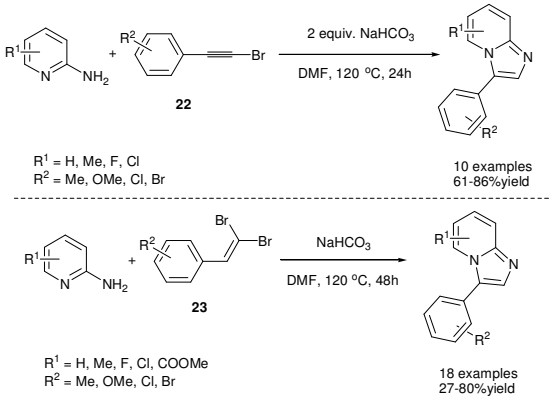


Scheme 7 Reaction of alkynyl(phenyl)iodonium salts with 2-aminopyridine.

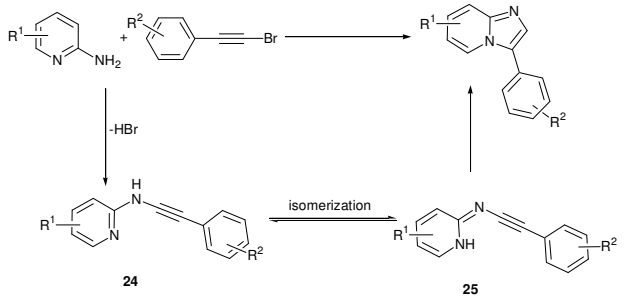
From 1-bromo-2-phenylacetylene / 1,1-dibromo-2-phenylethene:

Zhou *et al* synthesized 3-arylimidazo[1,2-*a*]pyridines by the catalyst-free cascade reaction between 2-aminopyridines and 1-bromo-2-phenylacetylenes (**22**) or 1,1-dibromo-2-phenylethenes (**23**) (Scheme 8).[34] Among the various additives like K_2CO_3, Cs_2CO_3, $NaHCO_3$, NaOAc, Et_3N, pyridine, AcOH; $NaHCO_3$ was the most efficient for the transformation. The bromoalkynes bearing electron-withdrawing groups on the aromatic ring afforded higher yields in comparison to those bearing electron donating groups. 2-Aminopyridine first coupled with the

haloalkynes to form an alkynylamine intermediate **24** which isomerized into the intermediate **25**. Finally **25** afforded the 3-arylimidazo[1,2-*a*]pyridine moiety through intramolecular cyclization reaction (Scheme 9).



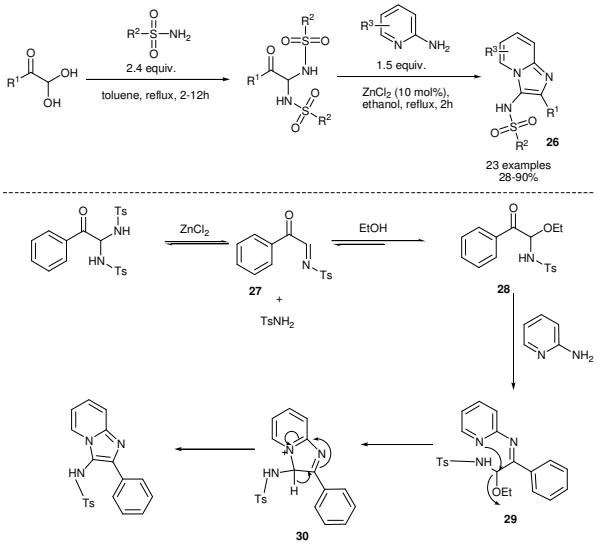
Scheme 8 Reaction of 2-aminopyridine with 1-bromo-2-phenylacetylene or 1,1-dibromo-2-phenylethene.



Scheme 9 Proposed reaction mechanism describing the formation of 3-arylimidazo[1,2-*a*]pyridines.

From arylglyoxal hydrates:

Yu *et al* developed a convenient one-pot two step methodology for the synthesis of *N*-(imidazo[1,2-*a*]pyridin-3-yl)sulfonamides (**27**) employing arylglyoxal hydrates, 2-aminopyridines, and sulfonamides as the reactants (Scheme 10).[35] This $ZnCl_2$-catalyzed reaction afforded the optimum yield in binary solvent toluene/EtOH with ratio 2:3. Various aryl/alkylglyoxal hydrates, 2-aminopyridines, and sulfonamides were used to establish the general applicability of the method. The electron rich aryl sulfonamides afforded better yields compared to the electron deficient ones. In presence of zinc chloride the *N*-tosyl-substituted aminal from the imine, reacts with the 2-aminopyridine to produce the intermediate **29**. The intermediate **29** leads to the intermediate **30** through intramolecular cyclization. Finally the *N*-(imidazo[1,2-*a*]pyridin-3-yl)sulfonamide was obtained from the **30** *via* deprotonation.

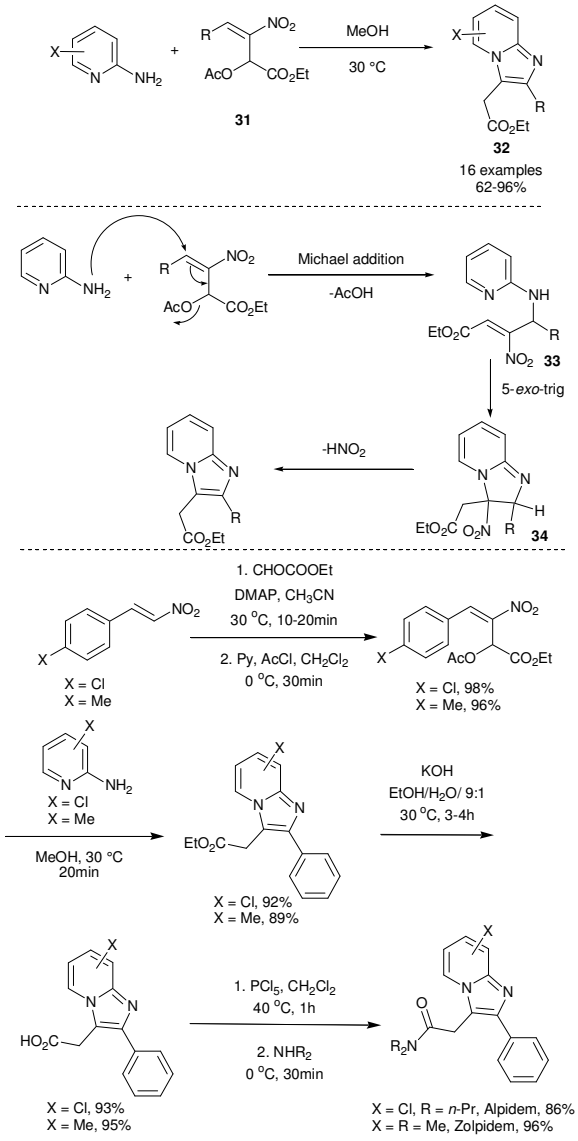


Scheme 10 One-pot two-step strategy for the synthesis of *N*-(imidazo[1,2-*a*]pyridin-3-yl)sulfonamides.

Tandem reaction:

Reaction between Morita-Baylis-Hillman (MBH) acetates of nitroalkenes and 2-aminopyridines:

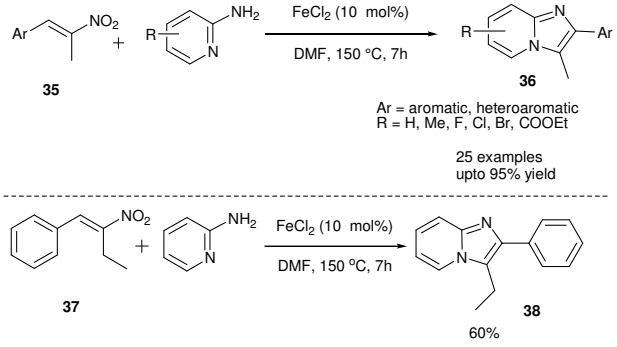
Namboothiri and his group synthesized functionalized imidazo[1,2-*a*]pyridines (**32**) by the reaction between Morita-Baylis-Hillman (MBH) acetates of nitroalkenes (**31**) and 2-aminopyridines under room temperature in MeOH (Scheme 11).[36] This reagent-free one-pot regioselective reaction proceeds through cascade inter-intramolecular double *aza*-Michael addition of 2-aminopyridines to MBH acetates. A library of imidazo[1,2-*a*]pyridine derivatives were synthesized employing different 2-aminopyridines and MBH acetates within short reaction time; however, this methodology was ineffective for the several aminoheterocycles like 2-aminopyrimidine, 2-aminopyrazine and 2-aminothiazole. The marketed drug alpidem and zolpidem have been prepared in six steps from the simple reagents employing this strategy with 72% and 78% overall yield respectively. The Michael addition of 2-aminopyridine to the MBH acetates through the exocyclic amino group and subsequent elimination of the acetate produced the intermediate **33**. The intermediate **33** was converted into the intermediate **34** through intramolecular Michael addition *via* pyridinium nitrogen. Finally **34** afforded the imidazopyridines by the elimination of HNO_2.



Scheme 11 Reaction and mechanism between MBH acetates of nitroalkenes and 2-aminopyridines.

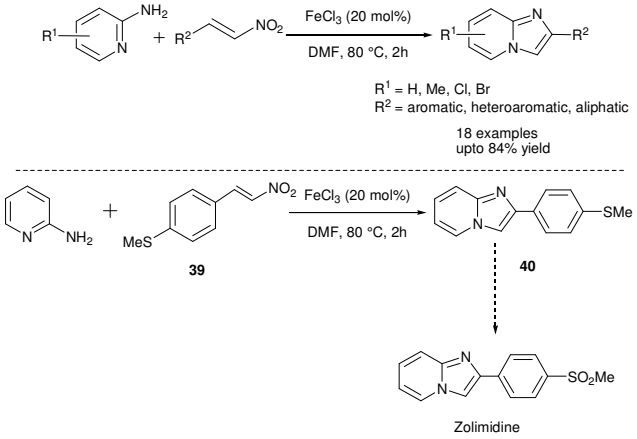
Tandem coupling between 2-aminopyridine and nitroolefin:

Yan and Huang *et al* reported a Fe(II)-catalyzed tandem coupling of 2-aminopyridines and 2-methylnitroolefins (**35**) for the synthesis of 3-methyl-2-arylimidazo[1,2-*a*]pyridine derivatives (**36**) (Scheme 12).[37] $FeCl_2$ was more suitable compared to the other iron salts for this transformation. A library of 3-methyl-2-arylimidazo[1,2-*a*]pyridines were synthesized to establish the general applicability of this method. This is also applicable for the synthesis of 3-ethyl-2-phenylimidazo[1,2-*a*]pyridine (**38**) with good yields. The reaction proceeds through tandem Michael addition/intramolecular cyclization.



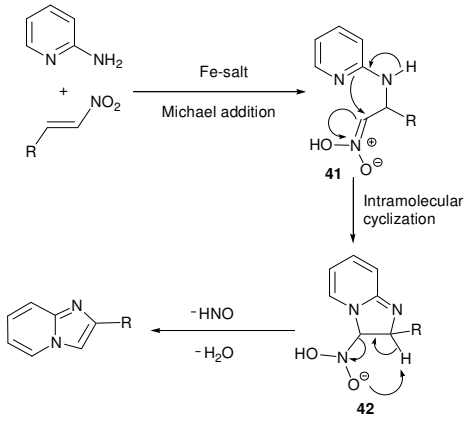
Scheme 12 Synthesis of 3-methyl-2-arylimidazo[1,2-*a*]pyridine derivatives from nitroolefin.

At the same time Hajra *et al* developed a simple and efficient methodology for the synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines by the cascade reaction between nitroolefins and 2-aminopyridines (Scheme 13).[38] The bielectrophilic nature of the nitroolefin was demonstrated by selecting the 2-aminopyridine as the suitable binucleophilic molecule. $FeCl_3$ was the most efficient catalyst among the Lewis acids such as $AlCl_3$, $ZnCl_2$, $LaCl_3$, $BF_3.OEt_2$, $In(OTf)_3$, $Cu(OTf)_2$ *etc* for this reaction. This $FeCl_3$-catalyzed reaction is applicable for both the aromatic as well as aliphatic nitroolefin and for various substituted 2-aminopyridines. They synthesized the key intermediate (**40**) for synthesizing the zolimidine drug employing this strategy. However this protocol is not applicable for the construction of 3-substituted imidazo[1,2-*a*]pyridine derivatives.



Scheme 13 Synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines from nitroolefins and 2-aminopyridines reported by Hajra *et al*.

The reaction proceeds through the initial formation of Michael adduct by the reaction of 2-aminopyridine with nitroolefin followed by intramolecular cyclization involving the pyridine nitrogen in a regioselective 5-*exo*-trig fashion to produce the intermediate **42**. Finally the product was obtained from the intermediate **42** *via* subsequent removal of water and nitroxyl (HNO) (Scheme 14).

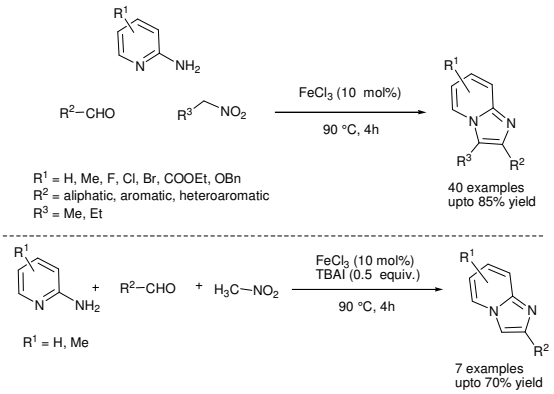


Scheme 14 Mechanism proposed to explain the imidazopyridine synthesis developed by Hajra and co-workers.

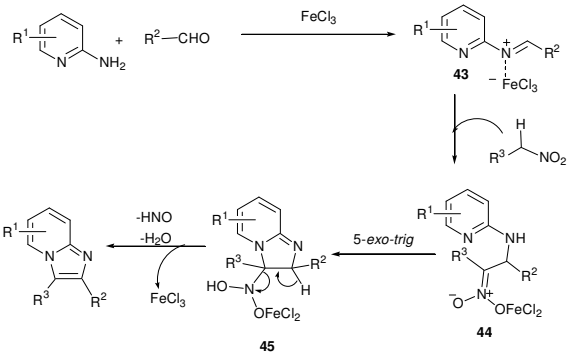
Employing multicomponent strategy:

Multicomponent reaction of 2-aminopyridine, aldehyde and nitroalkane:

Huang *et al* recently described a one-pot multicomponent approach for the synthesis of imidazopyridines (Scheme 15).[39a] The Fe(III)-catalyzed three-component cross-coupling reaction of 2-aminopyridine, aldehyde and nitroalkane offered a new strategy for the straight forward access to imidazo[1,2-*a*]pyridine rings. Aldehydes containing electron-withdrawing as well as electron-donating group well was tolerated. 2-Aminopyridine with electron-withdrawing substituents afforded higher yield compared to the electron-donating group containing 2-aminopyridines. Heteroaryl and aliphatic aldehydes also afforded the products. Nitropropane and nitromethane reacted under the optimized reaction conditions however TBAI (0.5 equiv.) was needed. First step of this three-component reaction is the imine (**43**) formation by the reaction of 2-aminopyridine with aldehyde (Scheme 16). In the next step Michael-addition followed by internal proton transfer and subsequent intramolecular Michael-addition afforded the intermediate **45**. Finally **45** afforded the product through the removal of HNO and H_2O. $FeCl_3$ acting as the Lewis acid facilitated the imine formation by increasing the electrophilicity of the aldehyde and also favored the Michael-addition steps. Subsequently, Hajra *et al* also reported a similar methodology in RNO_2-DMF as the binary solvent system.[39b]



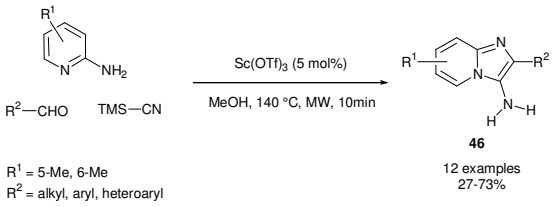
Scheme 15 Three-component approach.



Scheme 16 Plausible mechanism of the three-component reaction.

Multicomponent reaction of 2-aminopyridine, aldehyde and trimethylsilylcyanide:

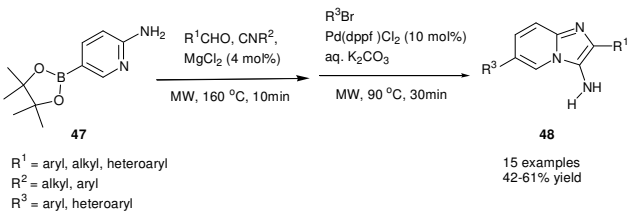
The Hulme group developed a multicomponent approach for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines (**46**) by the reaction of 2-aminopyridine, aldehyde and trimethylsilylcyanide (TMSCN) in methanol under microwave irradiation in presence of scandium triflate (Scheme 17).[40] The reaction is applicable for various aldehydes like aromatic, heteroaromatic and aliphatic aldehydes.



Scheme 17 Multi-component reaction accessing 3-aminoimidazo[1,2-*a*]pyridines.

Multicomponent reaction of 2-aminopyridine, aldehyde and isonitrile:

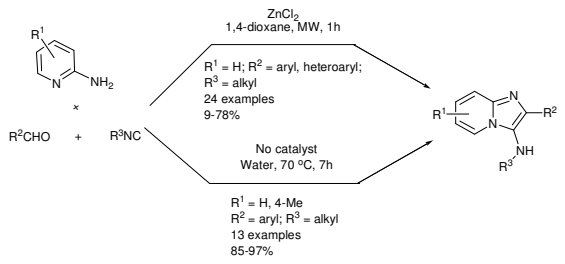
A rapid and efficient synthesis of various 2,6-disubstituted-3-amino-imidazopyridines (**48**) using a microwave-assisted one-pot cyclization/Suzuki coupling approach was described by DiMauro and co-workers (Scheme 18).[41] The reaction is applicable for various aldehydes, isonitriles and bromo derivatives. The utility of a 2-aminopyridine-5-boronic acid pinacol ester (**47**) as a robust and versatile building block for the synthesis of diverse compound library was emphasized. The boronate functional group was remarkably tolerant to the Lewis acid catalyzed cyclizations, and the subsequent Pd(0)-catalyzed Suzuki coupling reactions proceed cleanly in the presence of magnesium salts.



Scheme 18 Synthesis of 3-amino-imidazopyridines by a microwave-assisted four-component coupling in one pot.

In 2007, Rousseau *et al*[42] and Adib *et al*[43] independently reported the multicomponent synthesis of imidazo[1,2-*a*]pyridines using 2-aminopyridine, aldehyde and isonitrile

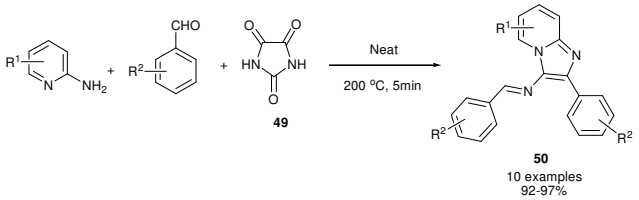
(Scheme 19). For both the cases 3-aminoimidazopyridine derivatives were obtained in high yields. The Adib group demonstrated that the reaction proceeded well in aquous media without any catalyst.



Scheme 19 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines by Rousseau and Adib group.

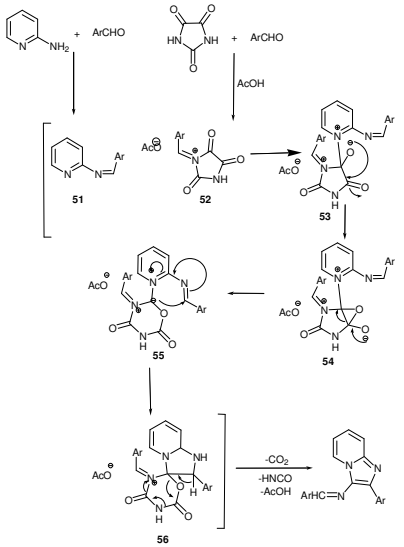
Multicomponent reaction of 2-aminopyridines, benzaldehydes and imidazoline-2,4,5-trione:

Subsequently, Adib *et al* described an efficient synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines (**50**) *via* a novel multicomponent reaction between 2-aminopyridines, benzaldehydes and imidazoline-2,4,5-trione (**49**) under solvent-free conditions at 200 ºC (Scheme 20).[44] The yield of the reaction was dependent on the the ratio of the reactant and best result was obtained by carrying out the reaction using aminopyridine, aldehyde and imidazoline-2,4,5-trione in the ratio of 1:2.5:1.5.



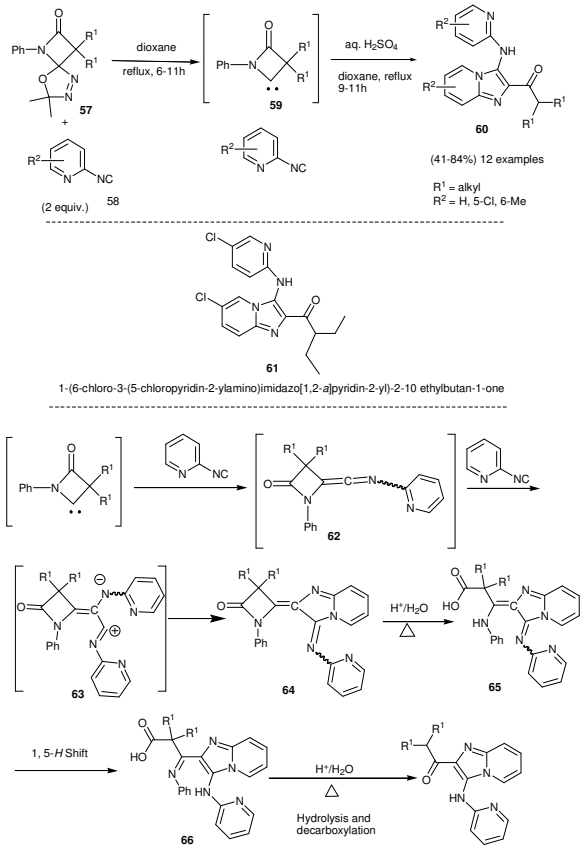
Scheme 20 Synthesis of imidazo[1,2-*a*]pyridines *via* a one-pot, three-component condensation reaction reported by Adib's group.

The plausible reaction mechanism of the reaction has been described in Scheme 21. Possibly, the reaction proceeds through the ring opening of imidazoline-2,4,5-trione.



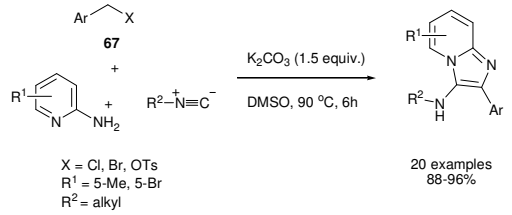
Scheme 21 Mechanism of the three-component reaction between 2-aminopyridine, aldehyde and imidazoline-2,4,5-trione.

The Cheng group reported that a one-pot reaction of *β*-lactam carbenes (**59**) with 2-pyridyl isonitriles (**58**) followed by acidic hydrolysis in 1,4-dioxane afforded 2-carbonyl-3-(pyridylamino)imidazo-[1,2-*a*]pyridines (**60**) (Scheme 22).[45] Aquous H_2SO_4 was the best acid for the hydrolysis and 1,4-dioxane was the best solvent for this reaction. The synthesized 1-(6-chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)-2-ethylbutan-1-one (**61**) was shown as an efficient fluorescent probe for mercury ion both in buffered aquous solution and acetonitrile.



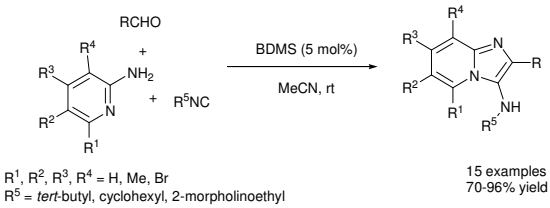
Scheme 22 Synthesis of 2-carbonyl-3-(pyridylamino)imidazo-[1,2-*a*]pyridines from *β*-lactam carbenes.

In 2011, the Adib group have developed a new and straightforward approach for the synthesis of imidazo[1,2-*a*]pyridines *via* a one-pot, three-component condensation reaction between 2-aminopyridines, benzyl halides or benzyl tosylates and isocyanides (Scheme 23).[46] Simple benzyl halides/tosylates were oxidized to the corresponding aldehydes under mild Kornblum oxidation conditions. The use of benzylic substrates in place of aldehydes is the main advantage of this reaction. Various benzylic substrates reacted well under the reaction conditions. Simple alkyl halides or alkyl tosylates were not suitable substrates for this reaction.



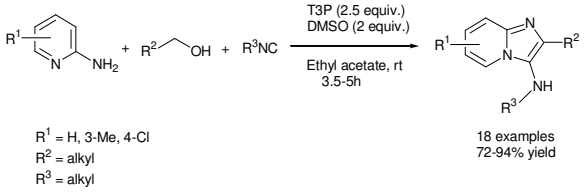
Scheme 23 Synthesis of imidazo[1,2-*a*]pyridines *via* a one-pot, three-component condensation reaction.

An efficient method for the synthesis of imidazo[1,2-*a*]pyridines has been developed by Khan's group using bromodimethylsulfonium bromide (BDMS) catalyzed three-component Ugi reaction by employing aromatic amidine, aromatic aldehyde, and isocyanide at room temperature (Scheme 24).[47] Electron-withdrawing group containing aldehydes reacted faster compared to the aromatic aldehydes having electron-donating group. The fluorescence properties of these imidazopyridine derivatives were also studied by them.



Scheme 24 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines by Khan *et al.*

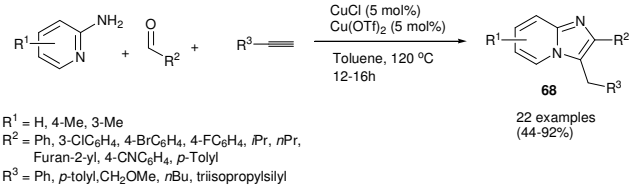
Mantelingu and co-workers reported that propylphosphonic anhydride (T3P) is an effective reagent for the synthesis of imidazo[1,2-*a*]pyridines from a variety of alcohols (Scheme 25).[48] The reaction proceeded through *in situ* oxidation/cyclocondensation from the alcohols. In this reaction T3P acts as an activator for both DMSO in oxidation reaction and the Schiff base in nucleophilic addition reaction with isocyanides.



Scheme 25 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines from alcohol.

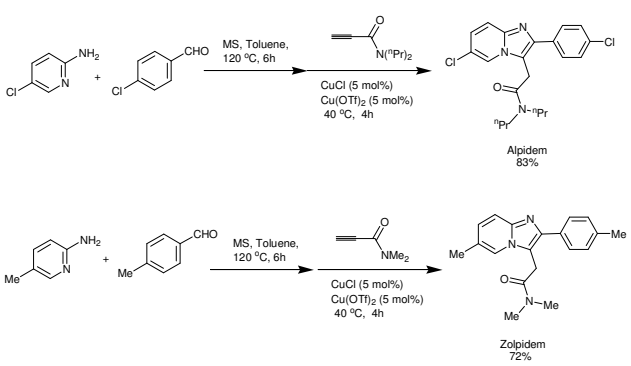
Multicomponent reaction of 2-aminopyridine, aldehyde and alkynes:

Gevorgyan and his co-worker have reported an elegant method for the synthesis of imidazo[1,2-*a*]pyridine derivatives (**68**) by the copper-catalyzed three-component coupling reaction of aldehydes, 2-aminopyridines and terminal alkynes (Scheme 26).[49]



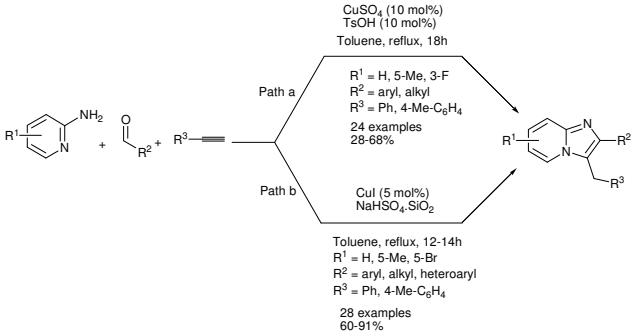
Scheme 26 Copper-catalyzed three-component coupling reaction towards imidazoheterocycles.

The employment of 2-aminoquinoline and 2-aminoisoquinoline as coupling partners in this transformation led to imidazoquinoline and imidazoisoquinoline frameworks in good yields. The synthetic utility of this three-component coupling reaction has been illustrated in a highly efficient one-pot synthesis of alpidem and zolpidem (Scheme 27).



Scheme 27 One-pot synthesis of alpidem and zolpidem by Gevorgyan and co-worker.

During the same time the Lei and Lin group utilised this approach for the synthesis of imidazopyridine derivatives using the $CuSO_4$/TsOH catalytic system (Scheme 28, path a).[50] Copper(II) salts were more efficient as the catalyst compared to the copper(I) and Ag(I) salts. Brønsted acid improved the yield of the reaction either by facilitating the alkyne addition through the protonation of the imine or by inhibiting the coordination of pyridine nitrogen to copper. Among the various Brønsted acids, TsOH was the most efficient co-catalyst. The methodology was applicable to various aminopyridines, alkynes and aldehydes having different sensitive functional groups (MOM, NO_2, Cl). Ghosh and co-worker have also developed an efficient one-pot method for the synthesis of diverse imidazo[1,2-*a*]pyridines through copper(I) iodide-$NaHSO_4{\cdot}SiO_2$ combined catalyst based reactions of aldehydes, 2-aminopyridines, and terminal alkynes in refluxing toluene, and also have established the corresponding mechanistic pathways (Scheme 28, path b).[51]



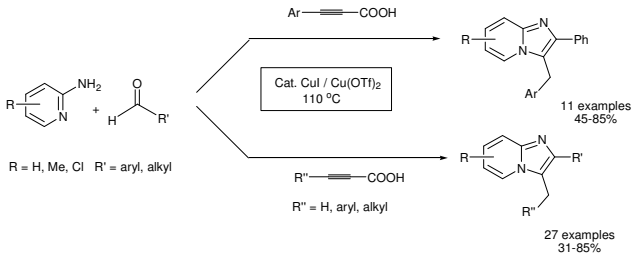
Scheme 28 Copper-catalyzed three-component coupling reaction by Lei and Ghosh group.

In 2011, Reddy *et al* have developed a one-pot strategy for the synthesis of imidazo[1,2-*a*]pyridines by means of coupling of 2-aminopyridine, aldehyde, and alkyne using indium(III) as catalyst in dry toluene under reflux conditions.[52] Among the indium(III)

salts indium bromide was the most effective in terms of selectivity.

Multicomponent reaction of 2-aminopyridine, aldehyde and alkynecarboxylic acid:

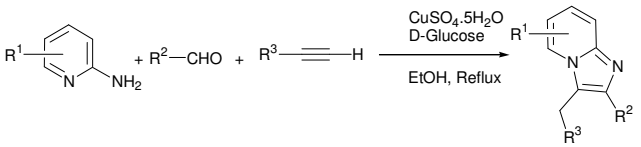
The Lee group used alkynecarboxylic acids and propiolic acids as alkyne sources in multicomponent-coupling reactions.[53] They have synthesized various imidazo[1,2-*a*]pyridine derivatives through multicomponent coupling reactions of 2-aminopyridines, aldehydes, and alkynecarboxylic acids in the presence of 10 mol% CuI/$Cu(OTf)_2$ (Scheme 29).



Scheme 29 Copper-catalyzed synthesis of imidazo[1,2-*a*]pyridines employing alkynecarboxylic acid.

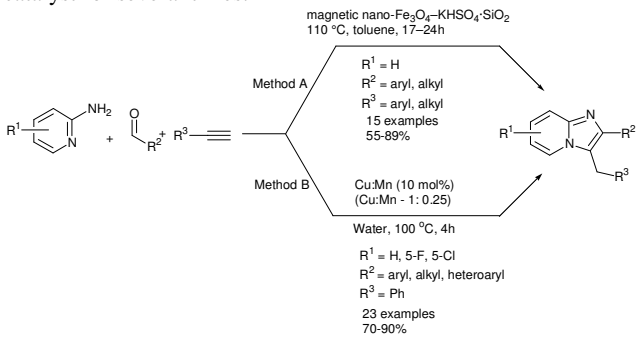
The Xamena and Corma group examined the catalytic activities of copper-containing MOFs.[54] These were found to be active, stable and reusable solid catalysts for three-component coupling of amines, aldehydes and alkynes to form the corresponding propargylamines which led to the effective production of indoles and imidazopyridines.

Guchhait *et al* explored the novel use of $CuSO_4$-glucose as surrogate to efficient Cu(I)–Cu(II) bicatalyst system in heterocycle synthesis (Scheme 30).[55] They demonstrated the catalytic efficiency of mixed Cu(I)–Cu(II) system, *in situ* generated by partial reduction of $CuSO_4$ with glucose in ethanol under open air, for the multicomponent reaction for the synthesis of *N*-fused imidazoles.



Scheme 30 Cu(I)-Cu(II) catalysis in A^3-coupling and cascade cycloisomerization: synthesis of versatile *N*-fused imidazoles.

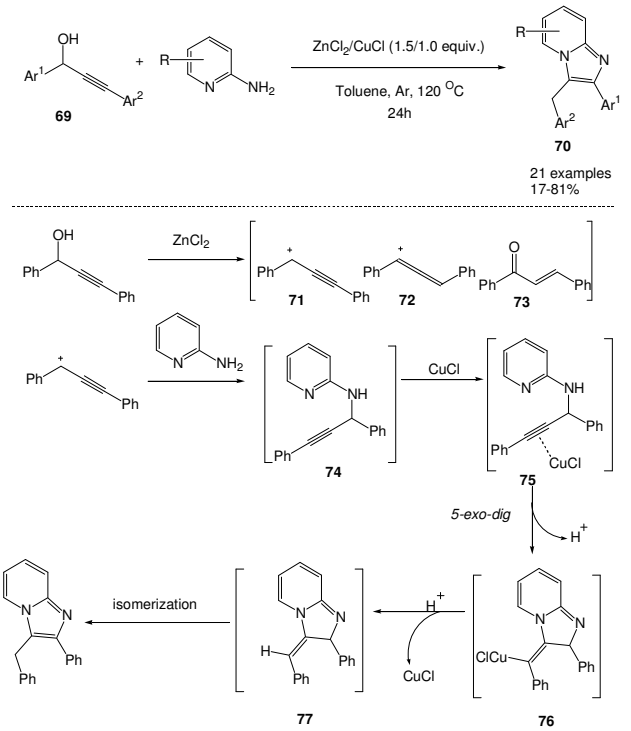
Singh and co-workers have demonstrated the catalytic use of magnetic nano-Fe_3O_4–$KHSO_4{\cdot}SiO_2$ for an efficient one-pot synthesis of imidazo[1,2-*a*]pyridines (Scheme 31, Method A).[56] The Bharate and Vishwakarma group also developed a method for the synthesis of imidazo[1,2-*a*]pyridines using the same approach of A^3-coupling reaction (Scheme 31, Method B).[57] The Cu–Mn catalyzed domino three-component coupling of 2-aminopyridines, aldehydes and alkynes followed by 5-*exo*-dig cycloisomerization produced imidazo[1,2-*a*]pyridines in good yields. Both the groups demonstrated the reusability of the catalyst for several times.



Scheme 31 Synthesis of imidazopyridines using nano-Fe_3O_4 and Cu–Mn bimetallic catalysts.

Reaction between propargylic alcohols and 2-aminopyridine:

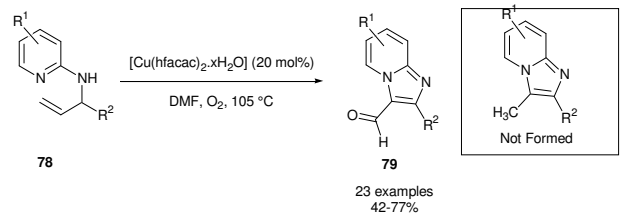
Lei and Lin *et al* synthesized imidazo[1,2-*a*]pyridines by the reaction of 2-aminopyridines and propargylic alcohols through tandem amination/cycloisomerization (Scheme 32).[58] This $ZnCl_2$/CuCl system promoted reaction was highly effective for the aryl substituted propargylic alcohols. The reaction proceeded through the formation of propargylic cation (**71**) followed by the amination by the exocyclic amino group of the 2-aminopyridine to form **74**. Through intramolecular cyclization **74** was converted into **76**. The intermediate **76** on protonation followed by isomerization afforded the products. Labeling experiment showed that partial [1,3] *H*-shift took place during copper promoted cycloisomerization. $ZnCl_2$ promoted the formation of propargylic cation and facilitated the favored amination step. On the other hand CuCl acted as accelerator for the cycloisomerization step.



Scheme 32 Tandem amination/cycloisomerization reaction between 2-aminopyridines and propargylic alcohol.

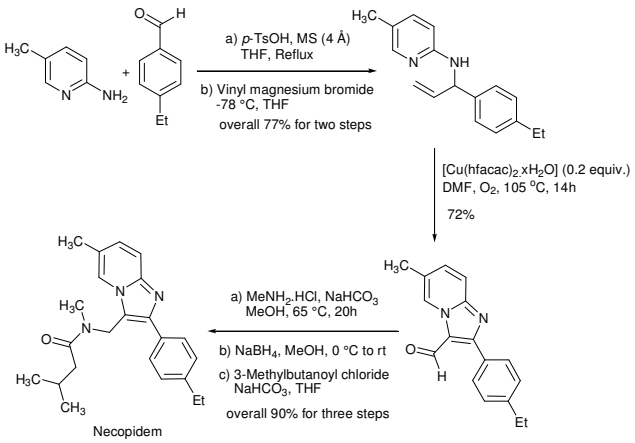
Aminooxygenation and hydroamination:

The Zhu group described an unexpected and novel intramolecular dehydrogenative aminooxygenation reaction for the construction of imidazopyridines containing a formyl group (Scheme 33).[59] This unprecedented copper-catalyzed (20 mol%) reaction in DMF or DMA was carried out under oxygen atmosphere employing simple acyclic precursors. Copper salt was essential for this transformation and other solvents like DMSO, NMP were not so effective like DMF or DMA. A library of imidazo[1,2-*a*]pyridine-3-carbaldehydes (**79**) with broad substrates scope was synthesized in moderate to good yields.



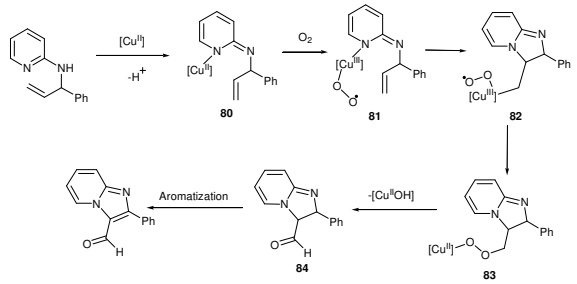
Scheme 33 Copper-catalyzed synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes and 1,2-disubstituted imidazole-4-carbaldehydes.

They prepared necopidem, an anxyolytic drug in about 50% overall yield through four step operations (Scheme 34).



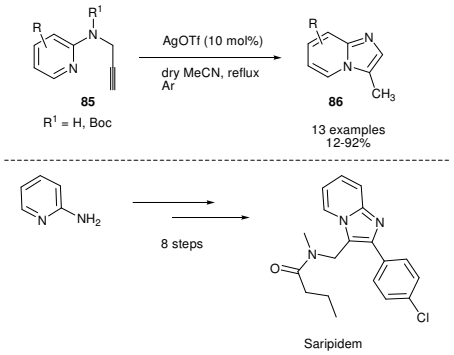
Scheme 34 Synthesis of the drug Necopidem.

Mechanistic studies in $^{18}O_2$ atmosphere proved that the carbonyl oxygen in the aldehyde product is derived from dioxygen rather than adventitious water in DMF. The reaction did not undergo in presence of copper salt (2 equiv.) under argon atmosphere. The reaction proceeds through the formation of peroxy-copper (III) intermediate **81** which undergoes insertion into the carbon–carbon double bond to form an alkyl copper(III) species **82**. The intermediate **83** formed through isomerisation by the copper (II) species and subsequent elimination of Cu(II)-OH afforded the aldehyde **84** which was readily transformed to the product due to spontaneous aromatization (Scheme 35).



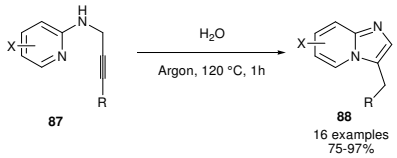
Scheme 35 Proposed reaction mechanism to explain the aminooxygenation reaction.

Chioua and his group showed that silver mediated cycloisomerization of the *N*-(prop-2-yn-1-yl)pyridine-2-amines (**85**) regioselectively afforded the 3-methylimidazo[1,2-*a*]pyridines (**86**) (Scheme 36).[60] Among the silver salts; AgOTf was the most effective for this cycloisomerization reaction in deoxygenated acetonitrile solvent. They also reported the DFT based mechanistic analysis which indicated that this method involves a kinetically favoured *exo*-dig rather than an *endo*-cyclization.

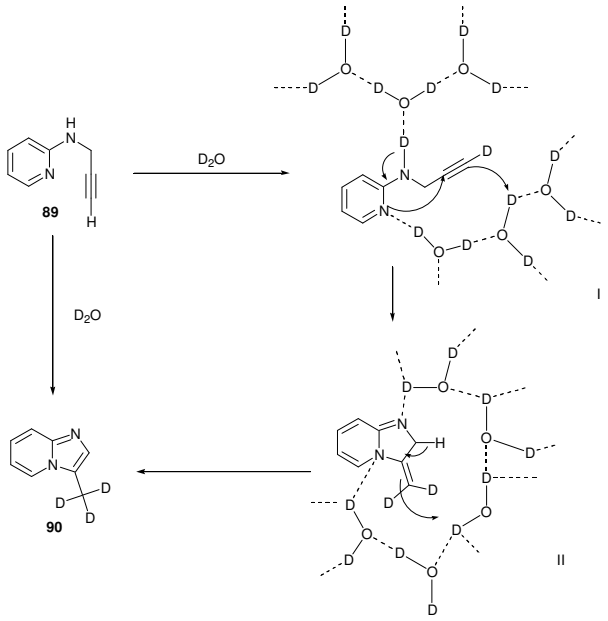


Scheme 36 Hydoamination by the silver salt.

Intramolecular hydroamination of *N*-(prop-2-yn-1-yl)pyridin-2-amines (**87**) in aqueous medium without any catalyst under argon atmosphere also afforded the methylimidazo[1,2-*a*]-pyridines (**88**) (Scheme 37).[61] In this reaction, water presumably plays a dual role as solvent and catalyst. Polar and non-polar organic solvents except ethanol were not able to produce the product in absence of any transition metal catalyst. Controlled experiments with deuterated water afforded the corresponding imidazo[1,2-*a*]-pyridines with mainly $-CD_3$ substituent (**90**). This observation was also rationalized by the reaction mechanism (Scheme 38).

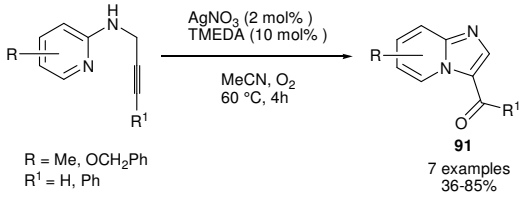


Scheme 37 Intramolecular hydroamination of N-(prop-2-yn-1-yl)pyridin-2-amines in water.



Scheme 38 Proposed mechanism.

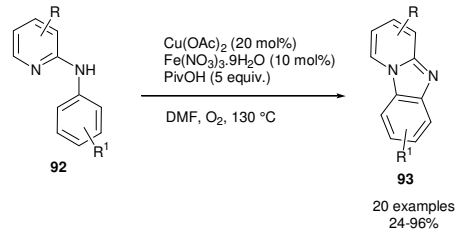
N-(Prop-2-yn-1-yl)pyridin-2-amines in presence 2 mol% of $AgNO_3$ and 10 mol% of TMEDA under oxygen atmosphere (balloon) in acetonitrile at 60 °C was converted into imidazo[1,2-*a*]pyridine-3-carbaldehydes (**91**) through intramolecular aminooxygenation (Scheme 39). This reaction proceeds smoothly in oxygen atmosphere, whereas the reaction produced lower amount of the desired product under aerobic conditions. Methylimidazo[1,2-*a*]-pyridine was generated as the major product along with the imidazo[1,2-*a*]pyridine-3-carbaldehyde under argon atmosphere also in presence of silver salts.



Scheme 39 Synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes through intramolecular aminooxygenation.

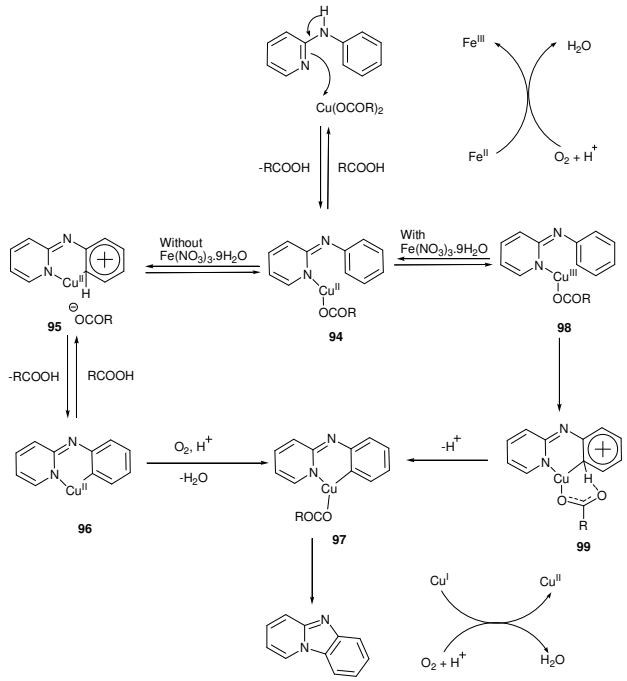
Intramolecular C-H amination:

Pyrido[1,2-*a*]benzimidazole (**93**) was synthesized by Zhu *et al* through the direct intramolecular aromatic C-H amination co-catalyzed by the copper and iron-salts in DMF medium under dioxygen atmosphere (Scheme 40).[62] Pivalic acid is required as an additive for this reaction to improve the yield. The iron salt did not promote the reaction itself but increased the yield of the reaction significantly by its ability to facilitate formation of the more electrophilic Cu(III) species required for the S_EAr (electrophilic aromatic substitution). In this process, the pyridinyl nitrogen in the substrates acts as both directing group as well as nucleophile.



Scheme 40 Synthesis of pyrido[1,2-*a*]benzimidazoles through the intramolecular aromatic C-H amination.

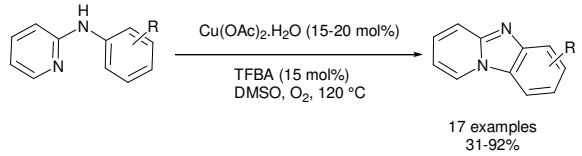
Mechanism proposed by them is represented in the Scheme 41. In absence of the iron salts the Cu(II) salts form the intermediate **96** from the initially formed adduct **94** through electrophilic aromatic substitution reaction followed by deprotonation. In presence of oxygen the intermediate **96** was converted into the reactive Cu(III) intermediate **97** through oxidation which on subsequent reductive elimination produced the product along with formation of Cu(I). In presence of the Fe(III)-salts, initially formed adduct **94** was oxidized into the Cu(III) intermediate **98** which readily undergoes electrophilic aromatic substitution to generate the intermediate **97** through the formation of six-member transition state **99**. Then reductive elimination takes place quickly before reversible protonation occurs. The formed Cu(I) is oxidized into the Cu(II) in presence of the oxygen to complete the catalytic cycle.



Scheme 41 Proposed reaction pathway to explain the copper/iron co-catalyzed intramolecular C-H amination.

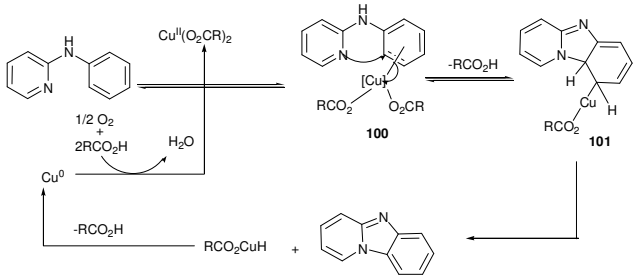
Maes *et al* investigated the role of acid additive in the synthesis of pyrido[1,2-*a*]benzimidazoles by direct copper-catalyzed amination (Scheme 42).[63] They studied the influence of the structure of the acid additive and the result showed that carboxylic acids like acetic acid, pivalic, butyric and benzoic acid produced the product with good efficiency. Non-carboxylic acids were also useful when used in catalytic amount. Among the various acid additives 3,4,5-trifluorobenzoic acid was clearly a

superior additive and this acid also provided a faster reaction and complete conversion of the starting material.



Scheme 42 Synthesis of pyrido[1,2-*a*]benzimidazoles by direct copper-catalyzed amination.

They proposed a mechanism in accordance their findings and controlled experiments and this is represented in the Scheme 43. First step is the coordination of the $(RCO_2)_2Cu^{II}$ with substrate and the intermediate **100** is formed. This intermediate **100** on subsequent intramolecular nucleophilic attack by the amidine on the activated arene (η^2 π complex) generates the σ-alkyl Cu^{II} species **101**. The intermediate **101** afforded the product *via* β-hydride elimination along with generation of RCO_2CuH which on reductive elimination forms the Cu^0 and RCO_2H. Cu^0 regenerates the $(RCO_2)_2Cu^{II}$ *via* oxidation in presence of oxygen and RCO_2H.

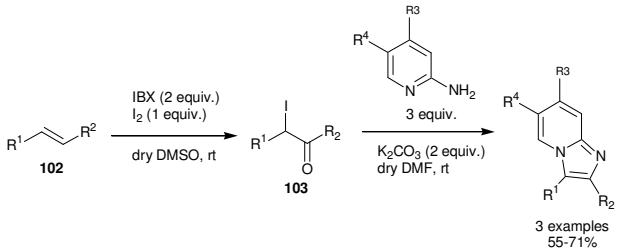


Scheme 43 Proposed reaction pathway.

Employing the strategy of oxidative coupling:

Oxidative coupling between 2-aminopyridine and alkene:

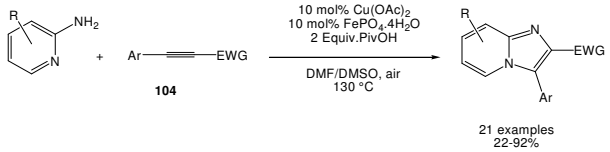
Donohoe *et al* synthesized imidazopyridines directly from the alkenes (**102**) through the *in situ* formation of α-iodo ketones **103** (Scheme 44).[64] This regioselective synthetic strategy offered a new way to synthesize these derivatives from the readily available alkenes under room temperature.



Scheme 44 Synthesis of imidazopyridines from alkenes.

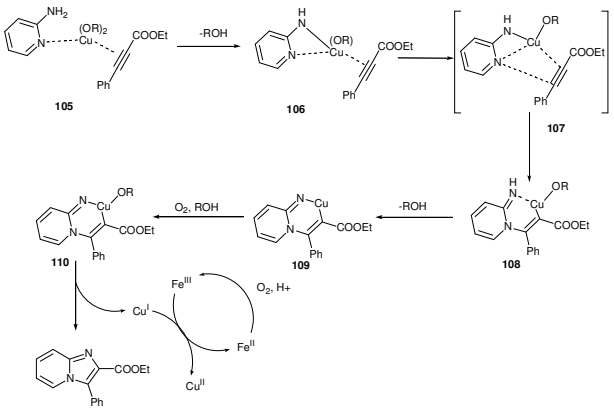
Oxidative coupling of alkyne with aminopyridine:

The Liu group developed a synthetic methodology for the imidazopyridines through the copper(II)/iron(III) co-catalyzed intermolecular diamination of alkynes (**104**) (Scheme 45).[65] This reaction involves two intermolecular oxidative C-N bond formations with high chemoselectivity and regioselectivity of the two nitrogens. Acidic additive, pivalic acid is essential and air is the terminal oxidant for this transformation. Copper halogenides like $CuCl_2$ and CuBr are totally ineffective to carry out this reaction. This methodology is suitable for the synthesis of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]isoquinolines with important pharmacological properties.



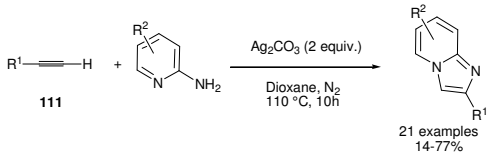
Scheme 45 Synthesis of imidazopyridines from alkynes.

The mechanism of this diamination reaction is represented in the Scheme 46. Copper at first coordinates with the endocyclic nitrogen atom to form adduct **105** which is readily converted into the intermediate **108** through the transition state **107**. The intermediate **108** generates the intermediate **109** *via* deprotonation and after that **109** is oxidized into the reactive Cu(III) species **110** in presence of aerial oxygen. Finally the product is obtained from the intermediate **110** through reductive elimination along with concurrent formation of Cu(I). This Cu(I) is oxidised into the Cu(II) by the Fe(III)-salt with the formation of Fe(II) which is readily converted into the Fe(III) in presence of aerial oxygen to complete the catalytic cycle.



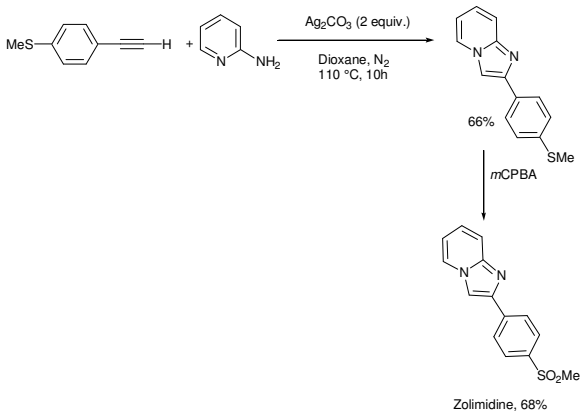
Scheme 46 Proposed reaction mechanism for the copper/iron co-catalyzed diamination of alkynes.

The direct coupling of terminal alkynes (**111**) with the 2-aminopyridines mediated by the silver salt afforded the imidazo[1,2-*a*]pyridines selectively in dioxane medium under nitrogen atmosphere (Scheme 47).[66] Among the silver salts Ag_2CO_3 was most efficient and two equivalents of the silver salt are essential for this transformation. This silver salt was recycled after the reaction by filtrating and treating with the nitric acid and Na_2CO_3. In this oxidative transformation, no terminal alkyne homocoupling byproduct was observed. No additional additive is required for this reaction and this synthetic protocol is applicable for a wide range of alkynes (aryl, heteroaryl and aliphatic), 2-aminopyridines, 1-aminoisoquinoline and 2-aminoquinoline. However this procedure is unsuccessful for the internal alkynes such as prop-1-ynylbenzene, 1,2-diphenylethyne and dimethyl but-2-ynedioate.



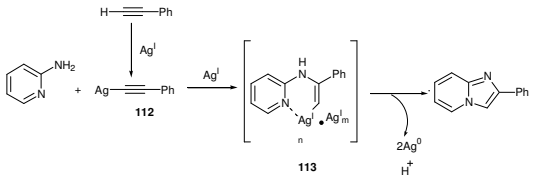
Scheme 47 Synthesis of imidazo[1,2-*a*]pyridines by the direct oxidative coupling of terminal alkynes with 2-aminopyridines.

Applying this simple methodology the antiulcer drug zolimidine was easily synthesized in two steps (Scheme 48).



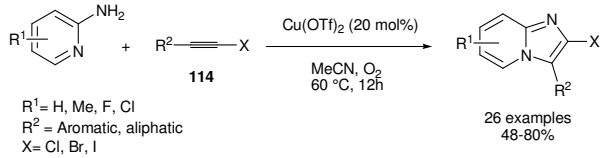
Scheme 48 Synthesis of the drug Zolimidine.

This Ag-mediated C–H/N–H oxidative cross-coupling/cyclization reaction proceeds *via* the formation of silver acetylide complex (**112**). The coupling of this silver acetylide (**112**) with the aminopyridine generates an intermediate (**113**) which affords the product *via* two single-electron oxidation (Scheme 49).



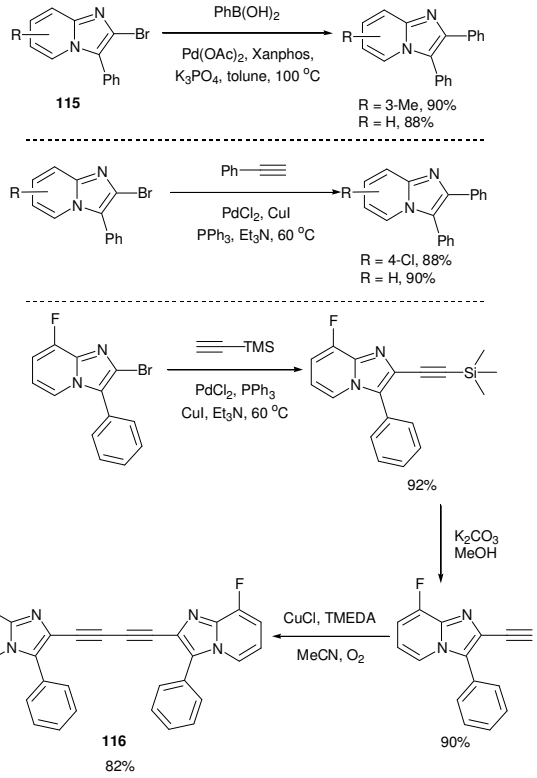
Scheme 49 Mechanism proposed to explain the synthesis imidazopyridines as reported by Lei *et al*.

Wu and Jiang *et al* developed a one-pot methodology for the construction of 2-haloimidazo[1,2-*a*]pyridines by the oxidative coupling between haloalkynes (**114**) and 2-aminopyridines (Scheme 50).[67] This copper triflate catalyzed intermolecular oxidative diamination of haloalkynes has been carried out employing molecular oxygen as the oxidant and it is applicable to both aromatic and aliphatic haloalkynes. Homocoupling of the haloalkynes took place in presence of basic additive. Solvent has a dramatic role in the reaction and among the common solvents; acetonitrile was the most effective solvent.



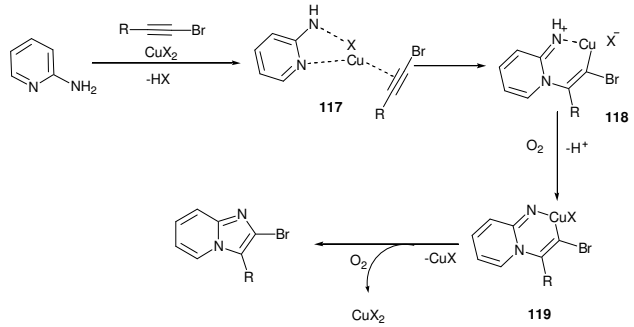
Scheme 50 Synthesis of 2-halo imidazo[1,2-*a*]pyridines from haloalkynes.

Highly substituted imidazopyridines were synthesized by the traditional cross-coupling reaction of 2-haloimidazopyridine moieties **115** (Scheme 51). They also synthesized highly conjugated molecules **116** which are of much potential in the area of optoelectronics employing this simple methodology.



Scheme 51 Functionalization of 2-halo imidazo[1,2-*a*]pyridines.

The first step of the reaction is co-ordination of the copper triflate with the 2-aminopyridine and bromoalkyne to form the intermediate **117** which was further transformed into the intermediate **118** (Scheme 52). The intermediate **118** was converted into the intermediate **119** through deprotonation followed by subsequent oxidation. Finally the intermediate **119** afforded the 2-haloimidazopyridine *via* reductive elimination. The Cu(I) gets transformed into Cu(II) in presence of molecular oxygen.

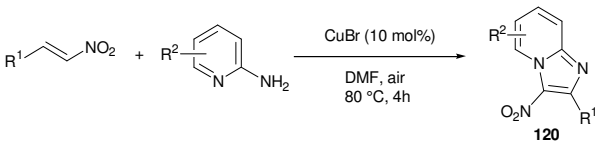


Scheme 52 Probable mechanism of the diamination of haloalkynes.

Oxidative coupling between nitroolefins and 2-

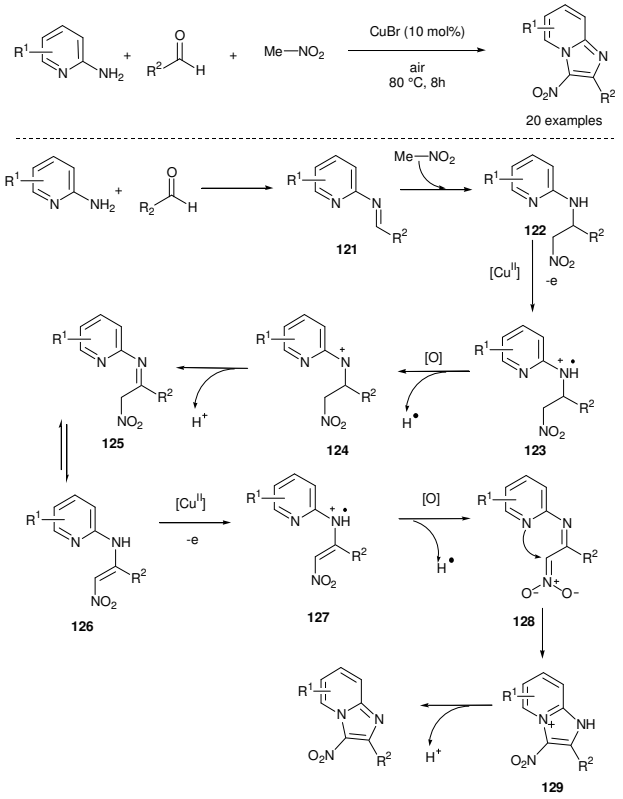
aminopyridine:

Nitroalkenes are good Michael acceptors and also bielectrophilic in nature. They are potentially useful for the synthesis of various heterocycles through annulation. Lewis acid catalyzed coupling between 2-aminopyridine and nitroalkene afforded 3-unsubstituted imidazopyrines via sequential Michael addition/cyclization/denitration.[37-39] Interestingly copper-catalyzed oxidative coupling of nitroolefins with the 2-aminopyridines produced 3-nitro imidazo[1,2-*a*]pyridines (**120**) (Scheme 53).[68] Oxygen balloon is not required during the course of the reaction as aerial oxygen is sufficient to act as the terminal oxidant. Copper bromide was the most efficient catalyst in DMF solvent at 80 ºC and various imidazopyridines were synthesized with up to 95% yield within 4 h. Better yields were obtained in case of electron rich aminopyridines and nitroolefins compared to the electron deficient one. This reaction proceeds through Michael addition followed by intramolecular cyclization involving formation of two nitrenium ion.



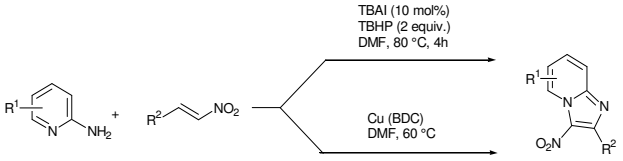
Scheme 53 Copper-catalyzed oxidative coupling of nitroolefins with 2-aminopyridines.

Subsequently, a copper bromide-catalyzed three-component approach of this methodology was undertaken to avoid the formation of the nitroolefins (Scheme 54).[69] This reaction was carried out employing 2-aminopyridines, aromatic aldehydes, and $MeNO_2$ to synthesize more diversified 3-nitro-2-arylimidazo[1,2-*a*]pyridine derivatives. This methodology is applicable for the aromatic aldehyde only and longer reaction time is required compared to the direct coupling of nitroolefins with the 2-aminopyridines.



Scheme 54 Three-component oxidative cyclization reaction of 2-aminopyridines, aromatic aldehydes, and $MeNO_2$.

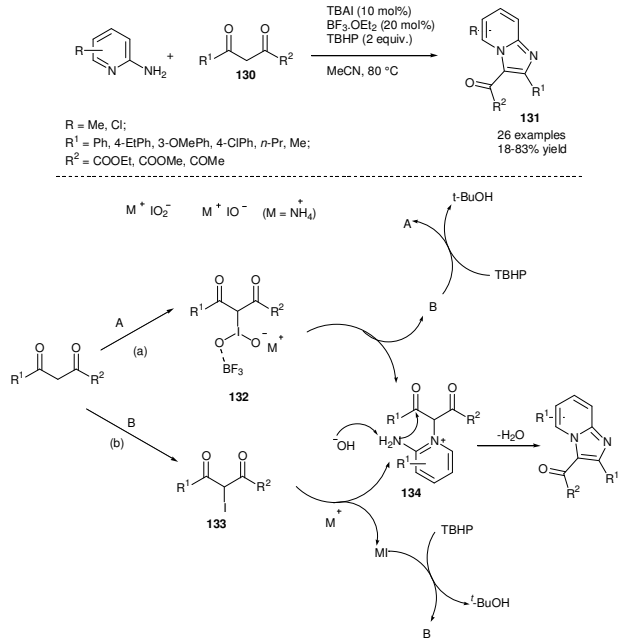
Xu and Li *et al* reported a modified metal-free approach of this strategy employing TBAI as the catalyst and TBHP as the oxidant in DMF medium (Scheme 55).[70] Very recently Pitchumani and his co-workers employed copper terephthalate metal–organic framework (Cu(BDC) MOF, BDC = 1,4-benzenedicarboxylate) as a heterogeneous catalyst for this reaction (Scheme 55).[71]



Scheme 55 Oxidative coupling between nitroolefines and 2-aminopyridines employing TBAI and Cu(BDC) catalytic system.

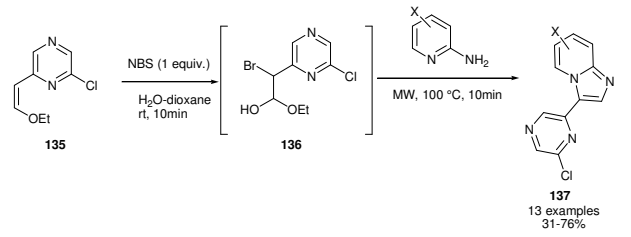
Oxidative coupling between 1,3-diones and 2-aminopyridine:

Imidazo[1,2-*a*]pyridines have been synthesized by the TBAI-catalyzed direct oxidative coupling of 2-aminopyridine and 1,3-diones (**130**) (Scheme 56).[72] $BF_3.OEt_2$ is required as additive and the TBHP as the terminal oxidant for this method and this protocol is applicable for the *β*-diketone and *β*-ketoester. The yield of the reaction is very sensitive on the ratio of 2-aminopyridines and 1,3-diones and 1.5:1 is the optimum ratio for this transformation. The reaction proceeds through the *in situ* formation of quaternary ammonium (hypo)iodite salts from the oxidation of quaternary ammonium iodides by TBHP and $BF_3.OEt_2$ facilitates the reaction by increasing the electrophilicity of the quaternary ammonium (hypo)iodite salts.



Scheme 56 Oxidative coupling between 2-aminopyridine and 1,3-diones for the synthesis of imidazopyridines.

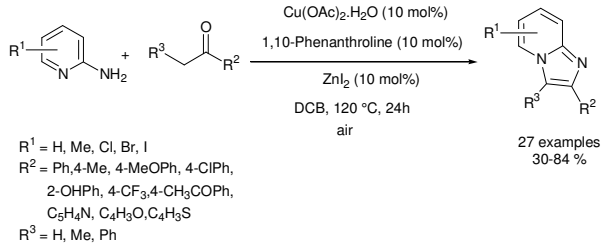
Collins *et al* reported a new methodology for the synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines (**137**) by the reaction between 2-chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine (**135**) and 2-aminopyridines (Scheme 57).[73] 2-Chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine was initially treated with the *N*-bromosuccinimide (NBS) in dioxane–water to generate the 2-bromo-2-(6-chloropyrazin-2-yl)-1-ethoxyethanol intermediate (**136**) which on subsequent reaction under microwave irradiation at 100 ºC by the 2-aminopyridines afforded the desired products with moderate to good yields.



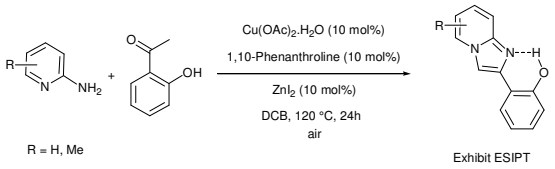
Scheme 57 Synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines.

Oxidative coupling between 2-aminopyridine and ketones:

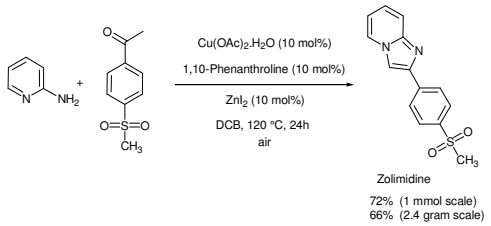
Hajra *et al* demonstrated synthesis of the imidazo[1,2-*a*]pyridine derivatives from the readily available 2-aminopyridines and ketones *via* C-H functionalization of the aryl ketones (Scheme 58).[74] This copper-catalyzed reaction has been carried out under ambient air and zinc-salt as the additive. Among the various copper salts $Cu(OAc)_2.H_2O$ was the most efficient as the catalyst. The methodology is applicable for the synthesis of a wide range of functionalized imidazo[1,2-*a*]pyridine moiety. Imidazo[1,2-*a*]pyridine bearing 2-hydroxy aryl substituent at the 2-position which exhibits ESIPT, has been easily synthesized (Scheme 59). This protocol provided one-step synthesis of antiulcer drug zolmidine on large scale (Scheme 60). Densely substituted imidazo[1,2-*a*]pyridine derivatives (**138**) have also been synthesized employing C-H functionalization of the 3-unsubstituted imidazo[1,2-*a*]pyridine moiety (Scheme 61). The reaction probably proceeds through tandem imine formation followed by the intramolecular oxidative amination.



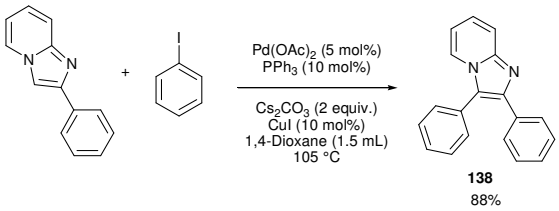
Scheme 58 Hajra's synthesis of imidazo[1,2-*a*]pyridines from the 2-aminopyridines and ketones.



Scheme 59 Synthesis of imidazopyridines which exhibit ESIPT.

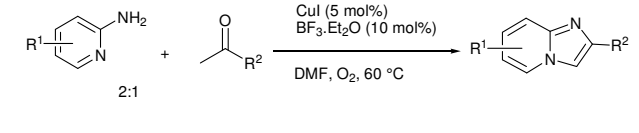


Scheme 60 One-pot gram-scale synthesis of zolimidine.



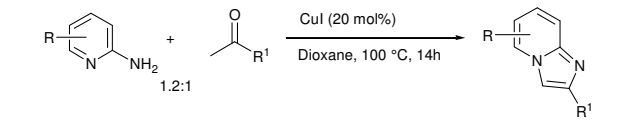
Scheme 61 Functionalization of 3-unsubstituted imidazo[1,2-*a*]pyridine.

During the same time Adimurthy *et al* reported similar methodology employing CuI as the catalyst in DMF solvent (Scheme 62)[75] and Kumar *et al* reported a ligand-free approach for the synthesis of these derivatives using CuI in dioxane medium (Scheme 63).[76] Later Ji and his co-workers reported copper(I) iodide/boron trifluoride etherate-cocatalyzed synthetic method for the heteroaromatic imidazo[1,2-*a*]pyridines using 3 equivalents of aminopyridine under oxygen atmosphere (Scheme 64).[77] An improved method was developed by Zhang and Zu *et al*. Aliphatic, aromatic as well as unsaturated ketones were effectively used to synthesize functionalized imidazo[1,2-*a*]pyridines (Scheme 65).[78] Unsaturated ketones afforded the 'potential optical materials' alkenyl-substituted imidazoheterocycles (**140**) which were not synthesized previously. Only 1 mol% $In(OTf)_3$ was sufficient as the additive to carry out the reaction.



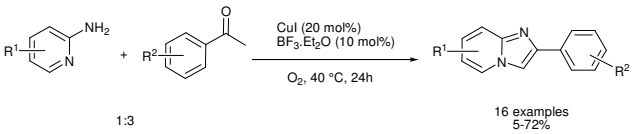
R^1 = H, Me,Ph, Cl, Br, I
R^2 = Ph,4-MePh, 4-MeOPh, 4-ClPh, 2-ClPh, 2-FPh, 4-BrPh, $C_{10}H_7$, Me, C_4H_9, CH=CHPh, 2-OHPh, 4-CF_3Ph, 4-CH_3COPh, C_5H_4N, C_4H_3O,C_4H_3S

Scheme 62 Synthesis of imidazo[1,2-*a*]pyridines from ketones.

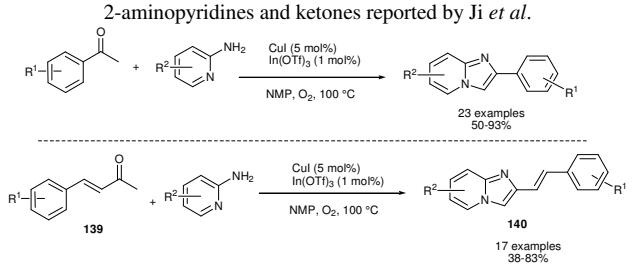


R = H, Me
R^1 = Ph, 4-OCH_3Ph, 2-BrPh, 4-BrPh, 4-FPh, 4-ClPh, Napth, 3-CH_3Ph, 4-CH_3Ph, 3-NO_2Ph, 4-NO_2Ph, 3,4-$(OCH_3)_2$Ph, 2-OCH_3Ph, 2-OHPh, thiophene

Scheme 63 Kumar's additive-free synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines from ketones.

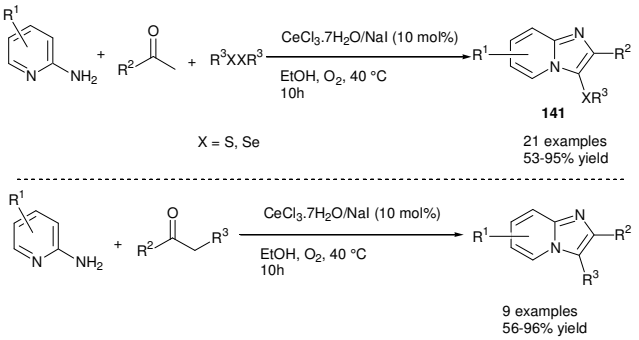


Scheme 64 Synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines from the 2-aminopyridines and ketones reported by Ji *et al*.



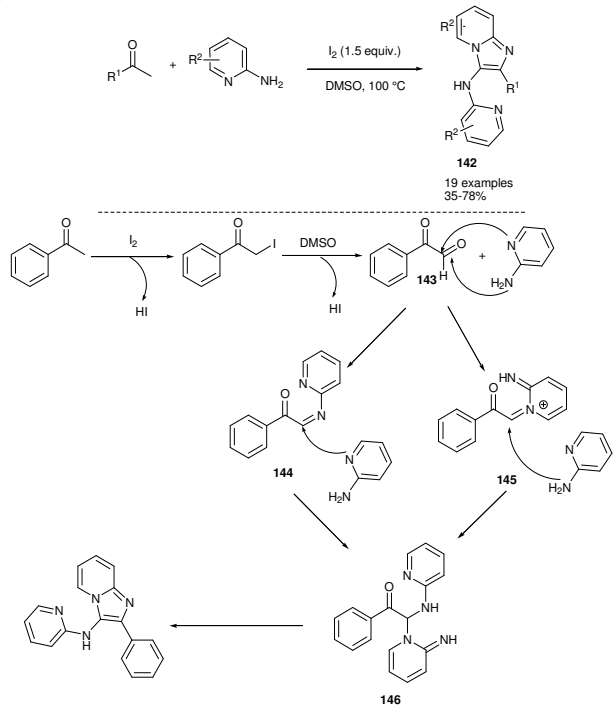
Scheme 65 Improved method by Zhang and Su *et al* for the synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines from ketones.

Wei *et al* developed an aerobic $CeCl_3 \cdot 7H_2O$/NaI-catalyzed method for the synthesis of 3-sulfenylimidazo[1,2-*a*]pyridines (**141**) from easily available ketones, 2-aminopyridines, and disulfides (Scheme 66).[79] This three-component tandem reaction proceeds through the formation of imidazo[1,2-*a*]pyridines followed by Friedel–Crafts sulfenylation and applicable for both aliphatic and aromatic ketones. The aryl ketones afforded the imidazo[1,2-*a*]pyridines with excellent yields whereas aliphatic aldehydes gave the imidazo[1,2-*a*]pyridines with moderate yields.



Scheme 66 Synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines from the 2-aminopyridines and ketones reported by Wei *et al*.

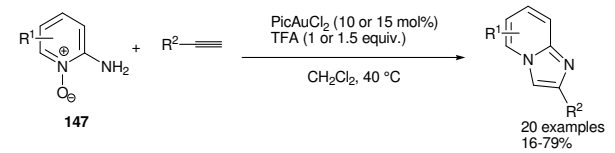
Zhu and Wu *et al* reported an iodine mediated reaction between 2-aminopyridines and methyl ketones in dimethyl sulfoxide (DMSO) for the preparation of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridines (**142**).[80] The combination of I_2 (1.5 equiv.) in DMSO produced the products within 1-2 hours (Scheme 67).



Scheme 67 Synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridines.

Reaction of 2-aminopyridine *N*-oxide and alkynes:

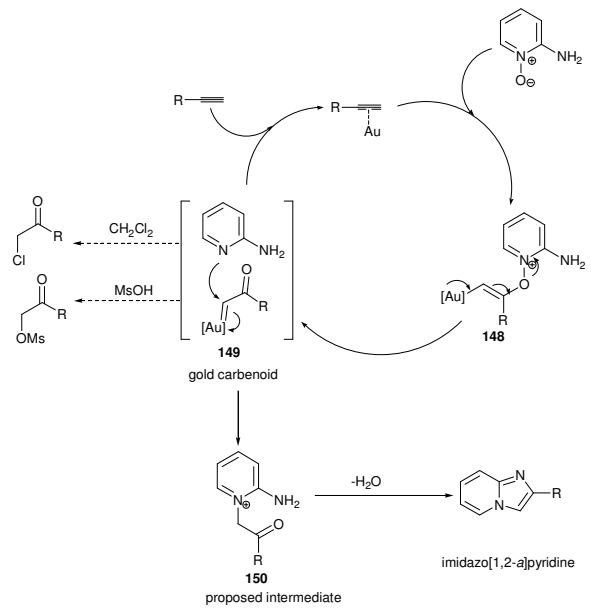
Dean Toste reported dichloro(2-pyridinecarboxylato) gold [$PicAuCl_2$] catalyzed reaction of 2-aminopyridine *N*-oxide (**147**) and alkynes in dichloromethane for the synthesis of imidazo[1,2-*a*]pyridines (Scheme 68).[81] The reaction occurred well in presence of acid additive and among the acids such as MsOH, TFA, *p*-nitrobenzoic acid; TFA (1 equiv.) was most effective one. The acid improved the yield by promoting the dissolution of the sparingly soluble reactant pyridine *N*-oxide. The gold catalysis is essential for this regioselective transformation. The generality of the process was established by employing various alkylalkynes and arylalkynes. The efficiency of the method was proved by synthesizing stereogenic centers adjacent to the imidazo[1,2-*a*]pyridine ring without compromising enantiomeric excess.



Scheme 68 Synthesis of imidazo[1,2-*a*]pyridines from the alkynes and **2**-aminopyridine *N*-oxide.

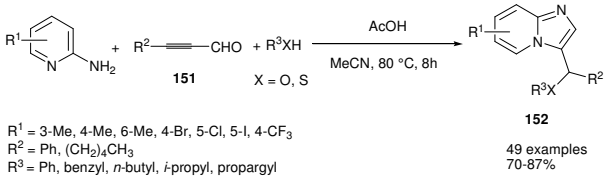
The reaction proceeded through the gold-carbenoid intermediate (**149**) (Scheme 69). First step is the addition of 2-aminopyridine *N*-oxide to the alkyne resulting the vinylgold intermediate (**148**) which is rearranged to form gold-carbenoid

intermediate **149**. The gold-carbenoid intermediate reacts with the newly formed 2-aminopyridine to form another intermediate which provided the pyridinium intermediate **150** *via* the condensation reaction finally leading to the product.



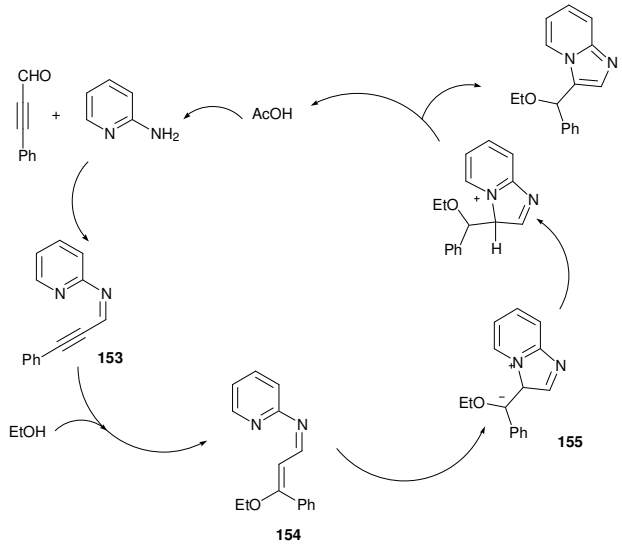
Scheme 69 Probable mechanism for the reaction between 2-aminopyridine *N*-oxide and alkynes as described by Dean Toste *et al*.

The Cao group reported an unprecedented and efficient transition-metal-free three-component reaction for the synthesis of substituted imidazo[1,2-*a*]pyridine derivatives (**152**) (Scheme 70).[82] AcOH was the most effective catalyst for this regiospecific one-pot reaction in acetonitrile medium. Various pyridin-2-amines, ynals, and alcohols, or thiols were reacted well under the optimized reaction conditions to produce the corresponding imidazo[1,2-*a*]pyridines. It represents a simple process for the formation of C–N, C–O, and C–S bonds *via* one-pot, three-component reaction of pyridin-2-amines, ynals (**151**) and alcohols or thiols.



Scheme 70 Synthesis of imidazo[1,2-*a*]pyridine derivatives reported by Cao *et al*.

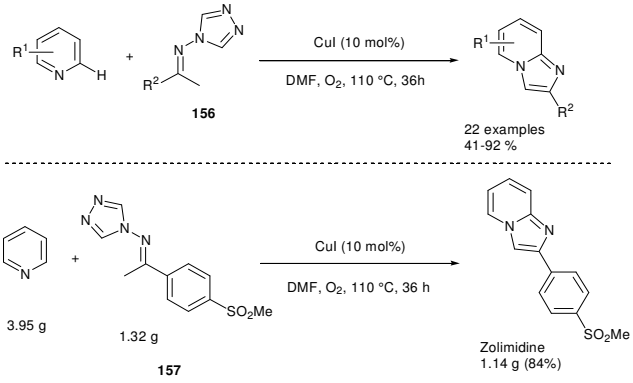
The mechanism proposed by them is represented in the Scheme 71. First step of this reaction is the AcOH-catalyzed condensation between ynals and 2-aminopyridines. The intermediate **153** is formed which undergoes Michael type addition by the RXH to produce the intermediate **155**. Finally the intermediate **155** affords the product through the sequential proton transfer.



Scheme 71 Mechanism to explain the synthesis of imidazo[1,2-*a*]pyridines.

Oxidative C-H functionalization of *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines with pyridines:

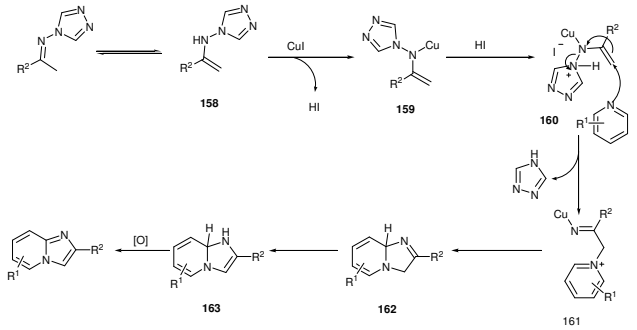
Imidazo[1,2-*a*]pyridines have been synthesized by copper-catalyzed oxidative C-H functionalization of the pyridine derivatives (Scheme 72).[83] The reaction involves N-N bond cleavage of the *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines (**156**) followed by functionalization of the aryl C-H bond of pyridines. This protocol afforded the optimum yield in presence of CuI as the catalyst in DMF at 110 ºC under oxygen atmosphere and it is suitable for the synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines. For the 3-substituted pyridine, both the products by the functionalization of C-2 and C-6 position were formed with the functionalization at C-2 position as the major one. This procedure is applicable for the gram scale synthesis of Zolimidine (an antiulcer drug).



Scheme 72 Imidazo[1,2-*a*]pyridines from pyridines employing C-H functionalization.

The mechanism of this copper-catalyzed oxidative C-H bond functionalization is represented in Scheme 73. The control experiment in presence of TEMPO (a radical scavenger) showed that cleavage of the N-N bond occurs through a non-radical pathway. At first isomerization of the *N*-(alkylidene)-4*H*-1,2,4-

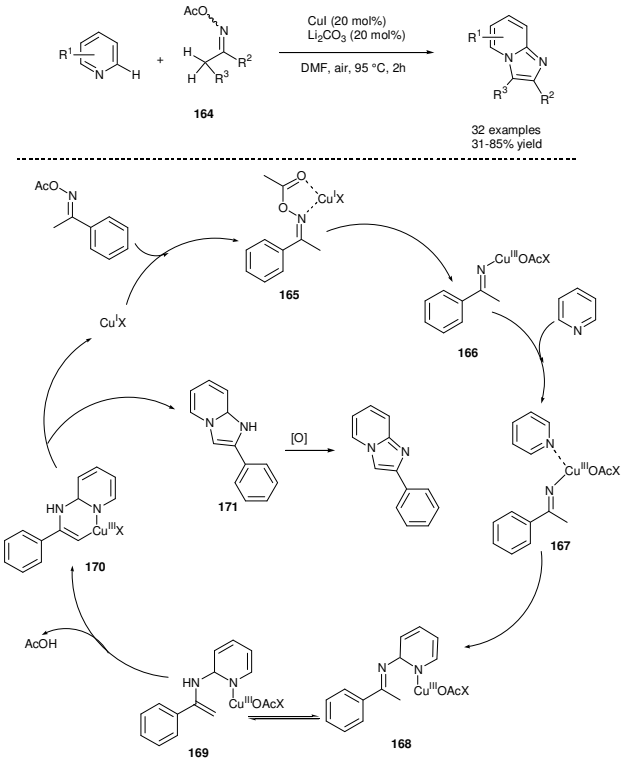
triazol-4-amines produce the enamine intermediate **158** which coordinates with copper(I)-salt to form copper complex **159**. The intermediate **159** was converted into the intermediate **160** by interaction with HI. Through the nucleophilic attack by pyridine, the intermediate **160** was transformed into the pyridium intermediate **161** which on subsequent intramolecular cyclization produced the dihydroimidazopyridine **162**. Isomerization of **162** generates **163** which is readily oxidised to the final products.



Scheme 73 Proposed reaction pathway for the oxidative C-H functionalization of pyridine.

Oxidative cyclization of pyridines with ketone oxime esters:

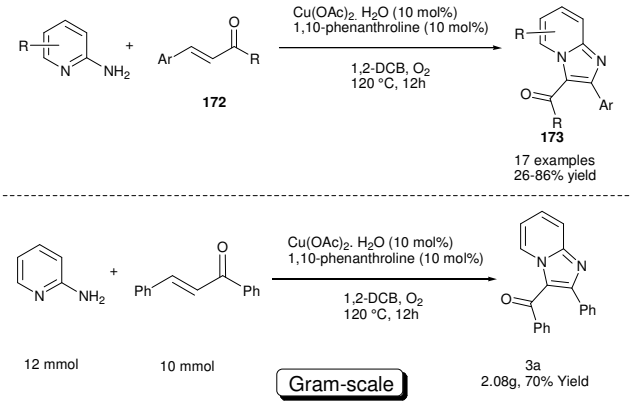
Imidazo[1,2-*a*]pyridines have been directly synthesized from pyridines employing the CuI-catalyzed dehydrogenative cyclization of pyridines with the ketone oxime esters (**164**) under aerobic condition (Scheme 74).[84] Copper(II)-salts were totally ineffective and Li_2CO_3 was the most effective base for this transformation. A variety of ketone oxime esters and pyridines derivatives were subjected to this reaction showing the general applicability and interestingly the 3-substituted pyridines afforded products with the C2-position of the pyridines participating rather than the C6-position. This reaction proceeds through a non-radical pathway and shows no kinetic isotopic effect.



Scheme 74 Dehydrogenative cyclization of pyridines with ketone oxime esters for the synthesis of imidazopyridines.

Oxidative coupling between *α,β*-unsaturated ketones and 2-aminopyridine

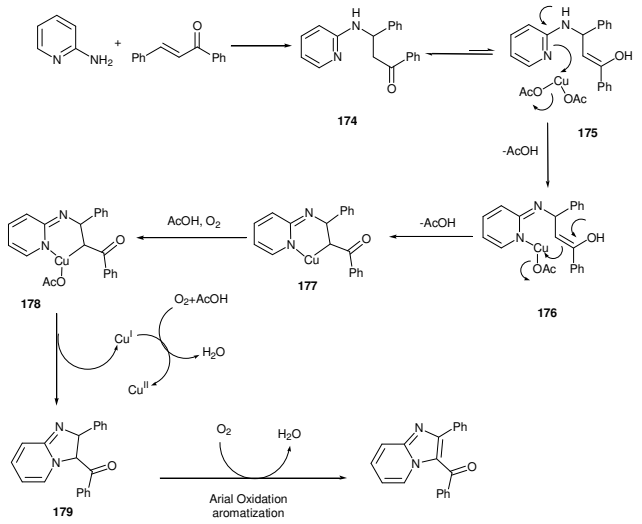
A new methodology has been developed by Hajra *et al* for the construction of 3-aroylimidazo[1,2-*a*]pyridines (**173**) by the copper-catalyzed oxidative coupling between 2-aminopyridines and chalcones under oxygen atmosphere (Scheme 75).[85] The regioselective reaction is suitable for a wide range of 2-aminopyridines and chalcones. This protocol is also applicable for the preparation of aroylimidazo[1,2-*a*]pyridine derivatives on gram-scale. Other activated alkenes such as acrylonitrile, vinyl phosphate, methyl acrylate were not suitable to produce the corresponding imidazo[1,2-*a*]pyridine derivatives under this reaction conditions. This simple strategy offers a new route to 3-aroylimidazo[1,2-*a*]pyridines employing oxygen as an oxidant.



Scheme 75 Synthesis of 3-aroylimidazo[1,2-*a*]pyridines by Hajra *et al*.

The probable mechanism of this methodology has also been

represented on the basis of the control experiments and literature report (Scheme 76). The tandem reaction proceeds through the Michael addition followed by intramolecular oxidative C-N bond formation. At first, Michael addition of 2-aminopyridines to the α,β-unsaturated ketone form **174** which is in tautomerism with **175**. After that, pyridinium nitrogen binds with copper acetate to produce the intermediate **176** which simultaneously reacts with the enol to form the cyclic Cu(II) intermediate **177**. On oxidation by the molecular oxygen the intermediate **177** forms the intermediate **178** in which copper is in the III oxidation state. Reductive elimination of **178** afforded the dihydroimidazopyridine moiety **179** along with the generation of Cu(I) species and finally the product was obtained from the intermediate **179** through spontaneous aromatization. Cu(I) is reoxidized into the Cu(II) by the molecular oxygen.



Scheme 76 Mechanism proposed for the copper catalyzed reaction between 2-aminopyridine and chalcones.

Conclusions

During the last decade significant developments have been made on the synthesis of imidazo[1,2-*a*]pyridines. Majority of these methods have been carried out employing basic chemicals and 2-aminopyridine is used as the coupling partner in most of the cases. Recently, few efficient methodologies have been developed for the preparation of the imidazo[1,2-*a*]pyridine scaffold containing drugs. This review gives ample and updated information on the synthesis of this class of compounds and will be helpful in the development of improved methods for the synthesis of imidazo[1,2-*a*]pyridines as well as other heterocycles.

A. Hajra acknowledges the financial support from CSIR (No.02(0168)/13/EMR-II), New Delhi. We are thankful to DST-FIST and UGC-SAP. AKB and KM thank CSIR and SS thanks UGC for their Fellowship.

Notes and references

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