This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Synthesis of Imidazo[1,2-α]pyridines: A Decade Update

Avik Kumar Bagdi, a Sougata Santra, a Kamarul Monir a and Alakananda Hajra a,

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

Imidazopyridine ‘the imidazole moiety fused with the pyridine ring’ is an important class of biologically active nitrogen containing heterocycle. Among the various imidazopyridine derivatives, imidazo[1,2-α]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.1-12 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),18 olprinone (3, for the treatment of acute heart failure),19 zolimidine (4, used for the treatment of peptic ulcer),20 necopidem and saripidem (5 and 6, both work as an anxiolytic agent)21 available in the market which contain imidazo[1,2-α]pyridine moiety (Fig. 1). The optically active GSK812397 is a drug for the treatment of HIV infection.22 The antibiotic drug Rifaximin also contains this fused heterocyclic moiety.23 In addition, some abnormal N-heterocyclic carbenes are also prepared based on imidazo[1,2-α]pyridines.24-26

They are also important in the field of optoelectronics as the imidazo[1,2-α]pyridine moiety bearing 2-hydroxyphenyl substituent at 2-position (11) exhibits excited state intramolecular proton transfer (ESIPT) (Fig. 2).27

Accordingly, there is continuous effort towards the development of new methods for the synthesis of imidazo[1,2-α]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-α]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-α]pyridines is presented here according to the reaction type (Fig. 3).

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

Fig. 2 Imidazo[1,2-α]pyridine scaffold as ESIPT.
Condensation reaction: From α-haloketones:

A traditional approach for the synthesis of imidazo[1,2-α]pyridine derivatives is by the condensation reaction of α-haloketones with the 2-aminopyridines. 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). They synthesized various imidazopyridines employing this method. The Chen and Wu group showed that the imidazo[1,2-α]pyridines could be synthesized from α-bromo/chloroketones and 2-aminopyridines under catalyst and solvent-free condition at 60 °C. 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.

Cyranski and Gryko et al synthesized imidazo[1,2-α]pyridine derivatives from the ketones by the in situ generation of α-iodoketones (Scheme 2). 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-α]pyridines possessing a 2-hydroxyphenyl substituent at 2-position exhibit excited-state intramolecular proton transfer (ESIPT). They also described that the imidazo[1,2-α]pyridines possessing aryl substituents at 2-position display strong emission bands in the blue region.

Scheme 2 Imidazo[1,2-α]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-α]pyridines. The copper-catalyzed reaction between α-diazoketones (15) and 2-aminopyridines afforded these heterocycles with good selectivity and good yields (Scheme 3). This Cu(OTf) catalyzed reaction is equally effective for both the aromatic and aliphatic diazoketones. Other Lewis acids like In(OTf), Bi(OTf), InCl, InBr, Sc(OTf) and Brønsted acids like heteropolyacid, 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. 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-α]pyridines starting from the ketone or alcohol (Scheme 5). 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 K₂CO₃ 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-α]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)sulfonyloxyiodo]benzene.

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). Only K₂CO₃ in chloroform is effective to carry out the reaction. The reaction proceeds through the [3,3]-sigmatropic rearrangement followed intramolecular cyclization.

Scheme 6 Proposed reaction mechanism.

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-α]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). Among the various additives like K₂CO₃, Cs₂CO₃, NaHCO₃, NaOAc, Et₃N, pyridine, AcOH; NaHCO₃ 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). This ZnCl₂-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.

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). 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 HNO₂.
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-arylhydrazino[1,2-a]pyridine derivatives (36) (Scheme 12).\(^\text{37}\) FeCl\(_2\) was more suitable compared to the other iron salts for this transformation. A library of 3-methyl-2-arylhydrazino[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-arylhydrazino[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).\(^\text{38}\) The bielectrophilic nature of the nitroolefin was demonstrated by selecting the 2-aminopyridine as the suitable bineucleophilic molecule. FeCl\(_2\) was the most efficient catalyst among the Lewis acids such as AlCl\(_3\), ZnCl\(_2\), LaCl\(_3\), BF\(_3\)-Et\(_2\)O, In(OTf)\(_3\), Cu(OTf)\(_2\) etc. for this reaction. This FeCl\(_2\)-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).
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). The Fe(III)-catalyzed three-component cross-coupling reaction of 2-aminopyridine, aldehyde and nitroalkane offered a new strategy for the straightforward access to imidazo[1,2-a]pyridine rings. Aldehydes containing electron-withdrawing substituents afforded higher yield compared to the electron-donating group well 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$_2$O. 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.

![Scheme 14](image1)

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

![Scheme 15](image2)

**Scheme 15** Three-component approach.

![Scheme 16](image3)

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

![Scheme 17](image4)

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

**Multicomponent reaction of 2-aminopyridine, aldehyde and isonitrile:**

A rapid and efficient synthesis of various 2,6-disubstituted-3-aminimidazopyridines (48) using a microwave-assisted one-pot cyclization/Suzuki coupling approach was described by DiMauro and co-workers (Scheme 18). 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](image5)

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

In 2007, Rousseau et al. and Adib et al. independently reported the multicomponent synthesis of imidazo[1,2-a]pyridines using 2-aminopyridine, aldehyde and isonitrile...
was dependent on the ratio of the reactant and the best result was obtained by carrying out the reaction using aminopyridine, benzaldehydes and imidazoline-2,4,5-trione (Scheme 19). For both the cases 3-aminoimidazopyridine derivatives were obtained in high yields. The Adib group demonstrated that the reaction proceeded well in aqueous 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 °C (Scheme 20). The yield of the reaction was dependent on the ratio of the reactant and the 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 carbones (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). Aquous H₂SO₄ 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-yl)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 aqueous solution and acetonitrile.
Scheme 23 Synthesis of imidazo[1,2-α]pyridines via a one-pot, three-component condensation reaction.

An efficient method for the synthesis of imidazo[1,2-α]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). 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-α]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-α]pyridines from a variety of alcohols (Scheme 25). 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-α]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-α]pyridine derivatives (68) by the copper-catalyzed three-component coupling reaction of aldehydes, 2-aminopyridines and terminal alkynes (Scheme 26).

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

The employment of 2-aminquinoline and 2-aminoisoquinoline as coupling partners in this transformation led to imidazooquinoline and imidazooisoquinoline 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 CuSO4/TsOH catalytic system (Scheme 28, path a). Copper(II) salts were more efficient as the catalyst compared to the copper(I) and Ag(I) salts. Benzilic 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 Benzilic acids, TsOH was the most efficient co-catalyst. The methodology was applicable to various aminopyridines, alkynes and aldehydes having different sensitive functional groups (MOM, NO2, Cl).

Ghosh and co-worker have also developed an efficient one-pot method for the synthesis of diverse imidazo[1,2-α]pyridines through copper(I) iodide-NaHSO4-SiO2 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).

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-α]pyridines by means of coupling of 2-aminopyridine, aldehyde, and alkyne using indium(III) as catalyst in dry toluene under reflux conditions. Among the indium(III)
Multicomponent reaction of 2-aminopyridine, aldehyde and alkyne carboxylic acid:
The Lee group used alkyne carboxylic acids and propiolic acids as alkyne sources in multicomponent-coupling reactions. They have synthesized various imidazo[1,2-α]pyridine derivatives through multicomponent coupling reactions of 2-aminopyridines, aldehydes, and alkyne carboxylic acids in the presence of 10 mol% CuI/Cu(OTf)$_2$ (Scheme 29).

**Scheme 29** Copper-catalyzed synthesis of imidazo[1,2-α]pyridines employing alkyne carboxylic acid.

The Xamena and Corma group examined the catalytic activities of copper-containing MOFs. 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 imidazo[1,2-α]pyridazines.

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). 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'-coupling and cascade cycloisomerization: synthesis of versatile N-fused imidazoles.

Singh and co-workers have demonstrated the catalytic use of magnetic nano-Fe$_3$O$_4$−KHSO$_4$·SiO$_2$ for an efficient one-pot synthesis of imidazo[1,2-α]pyridines (Scheme 31, Method A). The Bharate and Vishwakarma group also developed a method for the synthesis of imidazo[1,2-α]pyridines using the same approach of A'-coupling reaction (Scheme 31, Method B). The Cu−Mn catalyzed domino three-component coupling of 2-aminopyridines, aldehydes and alkynes followed by 5-exo-dig cycloisomerization produced imidazo[1,2-α]pyridines in good yields. Both the groups demonstrated the reusability of the catalyst for several times.

**Scheme 31** Synthesis of imidazo[1,2-α]pyridines using nano-Fe$_3$O$_4$ and Cu–Mn bimetallic catalysts.

Reaction between propargylic alcohols and 2-aminopyridine:
Lei and Lin et al. synthesized imidazo[1,2-α]pyridines by the reaction of 2-aminopyridines and propargylic alcohols through tandem amination/cycloisomerization (Scheme 32). 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.

Aminoxygenation and hydroamination:
The Zhu group described an unexpected and novel intramolecular dehydrogenative aminooxygenation reaction for the construction of imidazo[1,2-\(a\)]pyridines containing a formyl group (Scheme 33). 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.

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

Mechanistic studies in \(^{18}\)O 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).

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). 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.

Intramolecular hydroamination of N-(prop-2-yn-1-yl)pyridine-2-amines (87) in aqueous medium without any catalyst under argon atmosphere also afforded the methylimidazo[1,2-\(a\)]pyridines (88) (Scheme 37). 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).
reaction significantly by its ability to facilitate formation of 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 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 cocatalyzed 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). 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

Scheme 38 Proposed mechanism.

N-(Prop-2-yn-1-yl)pyridin-2-amines in presence 2 mol% of AgNO₃ 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). 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 S₆Ar (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.

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). 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
The Liu group developed a synthetic methodology for the synthesis of imidazo[1,2-\(\alpha\)]pyridines and imidazo[1,2-\(\alpha\)]isoquinolines with important pharmacological properties.

They proposed a mechanism in accordance with their findings and controlled experiments and this is represented in the Scheme 43. First step is the coordination of the (RCO\(_2\))\(_2\)Cu\(^{11}\) with substrate and the intermediate 100 is formed. This intermediate 100 on subsequent intramolecular nucleophilic attack by the amidine on the activated arene (\(\eta^2\pi\) complex) generates the \(\sigma\)-alkyl Cu\(^{11}\) species 101. The intermediate 101 afforded the product via \(\beta\)-hydride elimination along with generation of RCO\(_2\)CuH which on reductive elimination forms the Cu\(^{1}\) and RCO\(_2\)H. Cu\(^{1}\) regenerates the (RCO\(_2\))\(_2\)Cu\(^{11}\) via oxidation in presence of oxygen and RCO\(_2\)H.

They proposed a mechanism in accordance with their findings and controlled experiments and this is represented in the Scheme 43. First step is the coordination of the (RCO\(_2\))\(_2\)Cu\(^{11}\) with substrate and the intermediate 100 is formed. This intermediate 100 on subsequent intramolecular nucleophilic attack by the amidine on the activated arene (\(\eta^2\pi\) complex) generates the \(\sigma\)-alkyl Cu\(^{11}\) species 101. The intermediate 101 afforded the product via \(\beta\)-hydride elimination along with generation of RCO\(_2\)CuH which on reductive elimination forms the Cu\(^{1}\) and RCO\(_2\)H. Cu\(^{1}\) regenerates the (RCO\(_2\))\(_2\)Cu\(^{11}\) via oxidation in presence of oxygen and RCO\(_2\)H.

Employing the strategy of oxidative coupling:

Oxidative coupling between 2-aminopyridine and alkene:

Donohoe et al. synthesized imidazopyridines directly from the alkynes (102) through the in situ formation of \(\alpha\)-iodo ketones 103 (Scheme 44).

This regioselective synthetic strategy offered a new way to synthesize these derivatives from the readily available alkynes under room temperature.

Oxidative coupling of alkyne with aminopyridine:

The Liu group developed a synthetic methodology for the synthesis of imidazopyridines through the copper(II)/iron(III) co-catalyzed intermolecular diamination of alkynes (104) (Scheme 45).

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-\(\alpha\)]pyridines and imidazo[1,2-\(\alpha\)]isoquinolines with important pharmacological properties.

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 oxidized 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.

The direct coupling of terminal alkynes (111) with the 2-aminopyridines mediated by the silver salt afforded the imidazo[1,2-\(\alpha\)]pyridines selectively in dioxane medium under nitrogen atmosphere (Scheme 47). Among the silver salts Ag\(_2\)CO\(_3\) 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\(_2\)CO\(_3\). 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-aminooquinoline and 2-aminouquinoline. However this procedure is unsuccessful for the internal alkynes such as prop-1-yny1benzene, 1,2-diphenylethyne and dimethyl but-2-ynedioate.
Scheme 47 Synthesis of imidazo[1,2-α]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-α]pyridines by the oxidative coupling between haloalkynes (114) and 2-aminopyridines (Scheme 50). This copper triflate catalyzed intermolecular oxidative dimerization 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-α]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-α]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 dimerization of haloalkynes.
aminopyridines: 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 imidazopyridines 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 °C 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.

\[
\begin{align*}
\text{R}_1\text{NO}_2 + \text{R}_2\text{NH}_2 & \xrightarrow{\text{CuBr} (10 \text{ mol\%})} \text{R}_1\text{N} = \text{N} - \text{R}_2 \quad \text{DMF, 80 °C, 4h} \\
\end{align*}
\]

\textbf{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-\(a\)]pyridines (129) compared to the direct coupling of nitroolefins with the 2-aminopyridines.

\[
\begin{align*}
\text{R}_1\text{NO}_2 + \text{R}_2\text{NH}_2 + \text{ArCHO} & \xrightarrow{TBAI (10 \text{ mol\%}), \beta\text{-diketone}} \text{R}_1\text{N} = \text{N} - \text{Ar} \quad \text{DMF, 80 °C, 4h} \\
\end{align*}
\]

\textbf{Scheme 54} Three-component oxidative cyclization reaction of 2-aminopyridines, aromatic aldehydes, and MeNO\(_2\).

Xu and Li \textit{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).\(^{71}\)

\[
\begin{align*}
\text{R}_1\text{NO}_2 + \text{R}_2\text{NH}_2 + \text{ArCHO} & \xrightarrow{\text{Cu (BDC) MOF}} \text{R}_1\text{N} = \text{N} - \text{Ar} \\
\end{align*}
\]

\textbf{Scheme 55} Oxidative coupling between nitroolefins and 2-aminopyridines employing TBAI and Cu(BDC) catalytic system.

\textbf{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 \(\beta\)-diketone and \(\beta\)-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 \textit{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.
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). 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 °C 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). 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·H₂O 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).

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

During the same time Adimurthy et al. reported similar methodology employing CuI as the catalyst in DMF solvent (Scheme 62) and Kumar et al. reported a ligand-free approach for the synthesis of these derivatives using CuI in dioxane medium (Scheme 63). 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). 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). 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.

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

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

Scheme 61 Functionalization of 3-unsubstituted imidazo[1,2-a]pyridine.
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). The combination of I$_2$ (1.5 equiv.) in DMSO produced the products within 1-2 hours (Scheme 67).

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

![Scheme 62](image)

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

![Scheme 63](image)

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

![Scheme 64](image)

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

![Scheme 65](image)

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

![Scheme 66](image)

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

![Scheme 67](image)

**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). The reaction occurred well in presence of acyclic 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.

![Scheme 68](image)
optimized reaction conditions to produce the corresponding amines, imidazols, and alcohols, or thiols were reacted well under the component reaction of pyridin-2-amines, imidazol-[1,2-a]pyridines (one-pot reaction in acetonitrile medium. Various pyridin-2-aminopyridine to form another intermediate which provided the pyridinium intermediate via the condensation reaction finally leading to the product. The mechanism proposed by them is represented in the scheme (Scheme 70).

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). AcOH was the most effective catalyst for this regioselective one-pot reaction in acetonitrile medium. Various pyridin-2-aminopyridines, imidazol-[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 of C-2 position as the major one. This procedure is applicable for the gram scale synthesis of Zolimidine (an antulcer drug).

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

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

Imidazol[1,2-a]pyridines have been synthesized by copper-catalyzed oxidative C-H functionalization of the pyridine derivatives (Scheme 72). The reaction involves N-N bond cleavage of the N-(alkylidene)-4H-1,2,4-triazol-4-aminos (156) followed by functionalization of the aryl C-H bond of pyridines. This protocol afforded the optimum yield in presence of Cul as the catalyst in DMSO at 110 °C under oxygen atmosphere and it is suitable for the synthesis of 3-unsaturated imidazol[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.

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

Scheme 72 Imidazol[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)-4H-1,2,4-triazol-4-amine (156) followed by functionalization of the aryl C-H bond of pyridines.
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.

Oxidative cyclization of pyridines with ketone oxime esters: Imidazo[1,2-α]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). Copper(II)-salts were totally ineffective and Li₂CO₃ 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.

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-arylimidazo[1,2-α]pyridines (173) by the copper-catalyzed oxidative coupling between 2-aminopyridines and chalcones under oxygen atmosphere (Scheme 75). 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-α]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-α]pyridine derivatives under this reaction conditions. This simple strategy offers a new route to 3-arylimidazo[1,2-α]pyridines employing oxygen as an oxidant.

The probable mechanism of this methodology has also been

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

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

Scheme 75 Synthesis of 3-arylimidazo[1,2-α]pyridines by Hajra et al.
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 \( \alpha,\beta \)-unsaturated ketone form 174 which is in tautomerism with 175. After that, pyridinium nitrogen binds with copper acetae 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.](image)

20 Conclusions

During the last decade significant developments have been made on the synthesis of imidazo[1,2-\( \alpha \)]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-\( \alpha \)]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-\( \alpha \)]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

* Department of Chemistry, Visva-Bharati (A Central University), Santiniketan 731235, India. Fax: XX XXXX XXXX; Tel: XX XXXX XXXX; E-mail: alakananda.hajra@visva-bharati.ac.in