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Review Paper

Recent advances in synthesis of nitrogen fused imidazoheterocycles via double C-N bond formation

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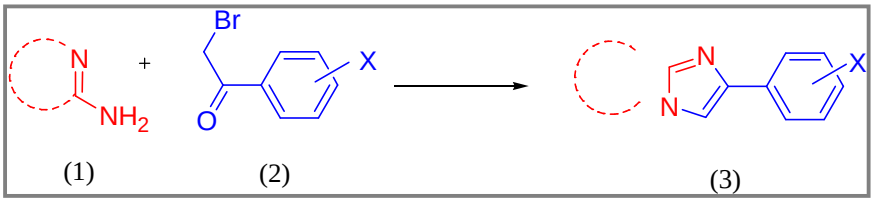
ABSTRACT

Several compounds has more than one nitrogen contained fused bicyclic heterocycles were important structural motifs found in numerous natural products and bioactive molecules. In recent years, the synthesis of bicyclic compounds possessing N-bridge heterocycle central core has been the focus of great interest. They are associated with diversified biological activities.

Graphical Abstract



Keywords: Fused heterocycles, Imidazoheterocycles, Imidazopyridine, C-N bond formation.

INTRODUCTION

Over the past decades, the majority of chemist's interest has been on heterocyclic compounds and their various derivatives as well as their uses in the pharmaceutical and chemical fields. Nitrogen and sulphur containing privileged heterocyclic scaffolds has received considerable attention because of their potential utility in the modern synthetic chemistry and plays an important role in medicinal chemistry due to their promising biological and pharmaceutical activities [**1**]. More than one nitrogen containing fused bicyclic heterocycles are important structural motifs found in numerous natural products and bioactive molecules [**2, 3**]. In recent years, the synthesis of bicyclic compounds possessing *N*-bridge heterocycle central core has been the focus of great interest. Amongst these bicyclic nitrogen fused heterocycles, imidazoheterocycles are privileged scaffolds with wide range of biological activities, especially as antiulcer [**4**], anticancer [**5**], anti-inflammatory [**6**], antiviral [**7**], immunomodulatory [**8**], immunosuppressive [**9**], antitumor [**10**], anti-rhinoviral [**11**], antimicrobial [**12**], antiarthritic [**13**], cardiotonic [**14**], antiarrhythmic [**15**], antitubercular [**16**], hypertensive [**17**],

anxyolitic [18], antiprotozoal [19] agents and in the treatment of cystic fibrosis [20]. Furthermore, imidazoheterocycles containing molecules have also been used as selective cyclin-dependent kinase inhibitors [21], calcium channel blockers [22], β-amyloid formation inhibitors [23] and benzodiazepine receptor agonists [24].

Several commercially nitrogen fused imidazole drugs, such as imidazopyridine core containing drugs (Figure 1) are alpidem [25], zolimidine[26], zolpidem [27], necopidem [28], saripidem [28], olprinone [29], imidazo[2,1-*b*]thiazole core containing levamisole [30] and benzo[*d*]imidazo[2,1-*b*]thiazole derivatives are YM-201627 [31] as well as ^{11}C-labelled imidazo[2,1-*b*]benzothiazole [32] have been developed by the modification of imidazole fused with either pyridine, thiazole or benzothiazole heterocyclic nuclei.

Apart from the above, the imidazoheterocycle system is also used in many other compounds such asherbicides [33], styryl dyes [34] and in material sciences [35].

Due to an interesting biological importance display over broad range of therapeutic classes, in the recent years the synthesis of nitrogen bridge bicyclic imidazo [2,1-*b*]pyridine/thiazole or benzothiazole derivatives have received significant attention from the pharmaceutical industries [36, 37].

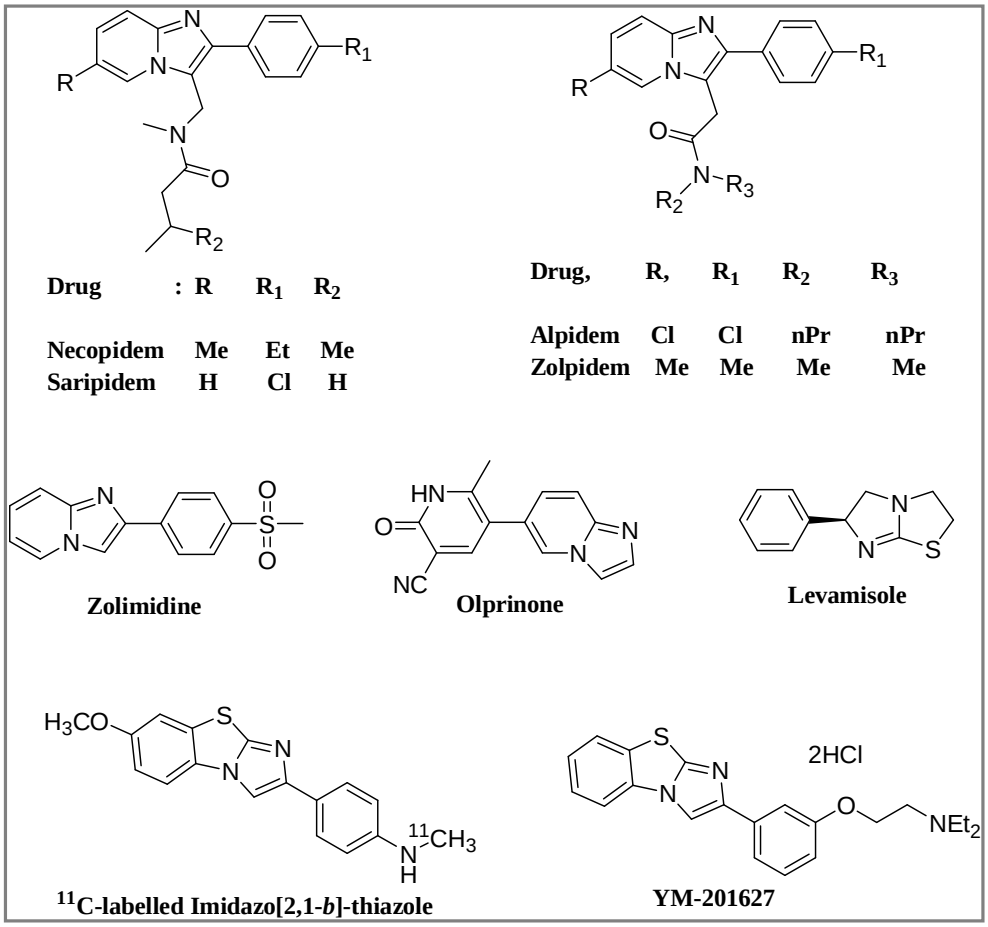
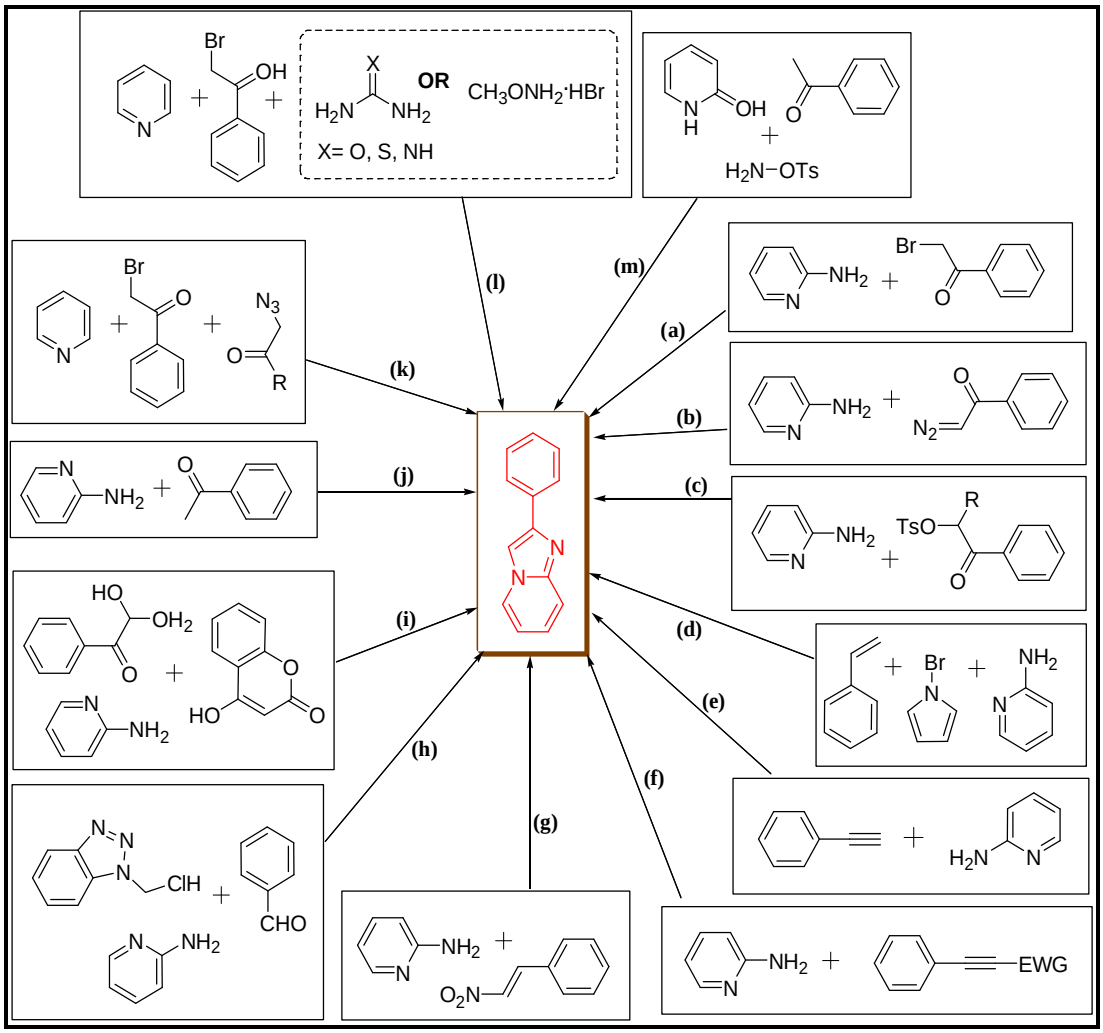


Figure 1. Fused Imidazoheterocycles based drugs.

In past, few synthetic strategies have been developed for the preparation of imidazoheterocycles (Scheme 1-Route a-l), which can be achieved by the condensation reaction of 2-aminopyridine or 2-aminothiazole with two carbon synthones such as phenacyl halide (Route a) [38-47], diazo aryl ketone

(Route b) [48] or α-tosyl ketones (Route c) [49, 50] derivatives in the presence of the basic or neutral conditions [36, 37]. In addition to this a styrenes and NBS reacts with 2-aminopyridine in water (Route d) [51], consequently new alternative method also described which includes silver-catalyzed oxidative C-N coupling of 2- aminopyridines with terminal alkynes (Route e) [52], One more method involves transition metal free base-catalyzed cyclocondensation of electron withdrawing group alkynoatesor alkynyl(phenyl)- iodonium salts with 2-aminopyridine (Route f) [53, 54], subsequently other techniques also reported which includes Fe-catalyzed method using 2-aminopyridines and nitro-olefins (Route g) [55]. Also, DBU catalysed one pot three-component coupling of 2-aminopyridine with aldehyde and 1-chloromethylbenzotriazole has been reported (Route h) [56]. In another process molecular iodine mediated three-component coupling of arylglyoxals, cyclic 1,3-dicarbonyls and 2-aminopyridine (Route i) [57].

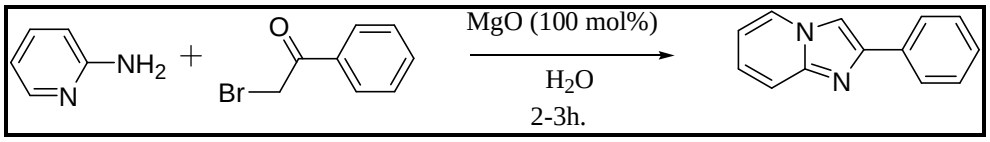


Scheme 1. Literature available methods for the synthesis of imidazopyridines.

In addition to this several methods involving Cu-catalyzed oxidative coupling of unactivated methyl ketones with 2-aminopyridines in the presence of ligands or additives have been reported (Route j) [58-63] and also condensation of pyridine with bromocarbonyl compound and phenacyl azide (Route k) [64] or urea [65] or O-methyloxime hydro bromide salt [66] are reported (Route l). one of the method also reports the synthesis of fused imidazo-heterocycles by the multicomponent reaction via C-H activation/tandem addition-cyclization process of O-tosylhydroxyl amine and acetophenones using ionic liquid containing copper salt under microwave irradiation (Route l) [67].

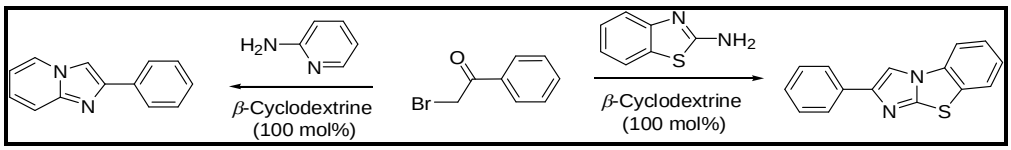
Condensation of bromocarbonyl compound [**38-47**] with 2-amino pyridine/thiazole compounds refluxing in acetone or ethanol or using different catalysts and reaction conditions require long reaction time [**36, 37**]. Some selected literature reports are given as follows,

V. D. Bobade and co-workers (2016) [**38**] reported the synthesis of various imidazolo[1,2-*a*]pyridines via condensation of 2-amino pyridines and aromatic phenacyl bromides by one step C-N bond formation process in the presence of MgO (100 mol%) in aqueous medium at room temperature. (Scheme 2).



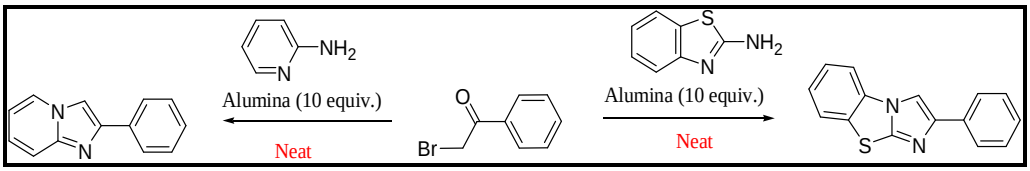
Scheme 2.

S. Kumar and D. P. Sahu (2008) [**39**] has reported an aqueous phase *β*-cyclodextrin catalysed reaction for the synthesis of bridgehead imidazoheterocycle from various 2-amino-azaheterocycle (2-aminopyridine, 2-aminopyrimidine and 2-aminobezothiazole) with α-bromoketones (Scheme 3). The reactions were carried out by dissolving *β*-cyclodextrin (100 mol%) in water warmed to 50-55°C. By using this method 2-aryl substituted benzo[*d*]imidazo[2,1-*b*]thiazoles and azaindolizines were synthesized in good to excellent yield.



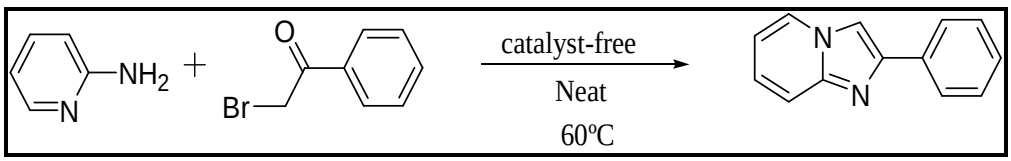
Scheme 3.

S. Ponnala *et al.*, (2005) [**40**] reported that the neutral alumina (10 equiv.) is an efficient medium for the synthesis of imidazo[1,2-*a*]pyridine or benzo[d]imidazo[2,1-b]thiazoles derivatives by the condensation reaction of α-haloketones with the 2-aminopyridines or 2-aminobenzothiazole without solvent at room temperature for 3h (Scheme 4).



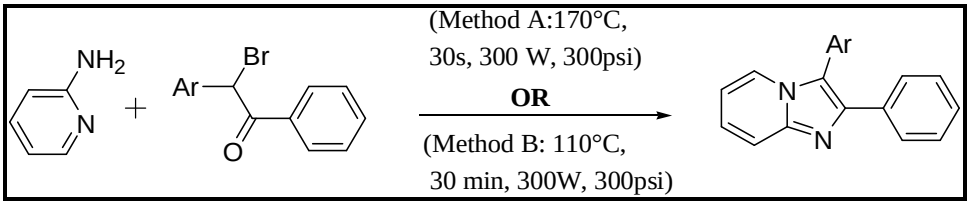
Scheme 4.

D. J. Zhu *et al.*, (2009) [**41**] reported the methodology for the synthesis of imidazo[1,2-a]pyridine derivatives by the condensation reaction of α-haloketones with the 2-aminopyridines under catalyst and solvent-free condition at 60ºC affording imidazopyridine derivatives in good to excellent yields (Scheme 5). They have showed that the nucleophilic substitution of bromide by the pyridine-nitrogen in the 2-aminopyridine is the key step of these reactions.



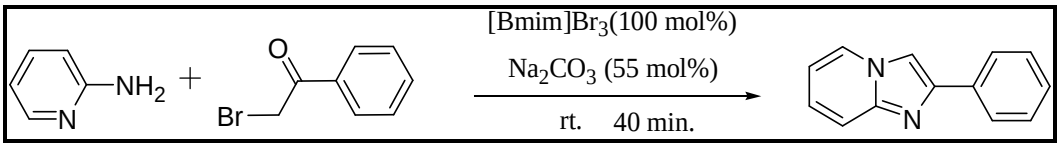
Scheme 5.

L. Cai and co-workers (2006) [**42**] reported the Lewis acid titanium(IV) chloride (75 mol%) promoted microwave assisted process for syntheses of 2,3-Diaryl-l*H*-imidazo[1,2-*a*]pyridine derivatives by the condensation reaction of α-halo ketones with the 2-aminopyridinesinto a microwave reaction tube in presence the dichloromethane and chloroform mixture as solvent to afford good yields (Scheme 6).



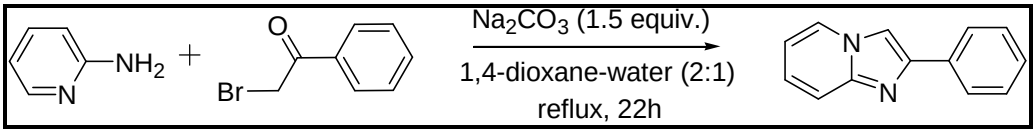
Scheme 6.

Z. G. Le and group (2012) [**43**] have reported the one-pot synthesis of imidazo[1,2-*α*]pyridines from acetophenone,2-aminopyridine in ionic liquid [Bmim]Br_3(100 mol%) under solvent-free conditions in the presence of Na_2CO_3 (55 mol%) at rt, gave the good yields ranging from 72% to 89% (Scheme 7).



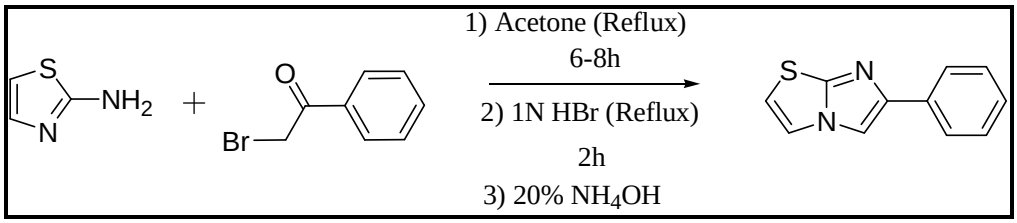
Scheme 7.

H. Tomoda *et al.*, (1999) [**44**] have reported the synthesis of 2-aryl substituted imidazo[1,2-a]pyridine derivatives from 3-aminopyridine condense with 2-bromo-1-(4-substituted phenyl)-ethanone in 1,4-dioxane-water (2:1) solution was refluxed for 30min, to which Na_2CO_3 (1.5 equiv.) added and reflux for 22h,affording imidazopyridine derivatives in good yields(Scheme 8).



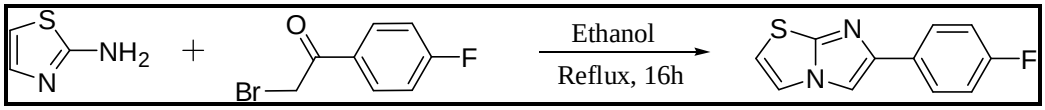
Scheme 8.

A. Andreani and his group(1996) [**45**] have reported the synthesis of imidazo[2,1-*b*]-thiazole in three steps from 2-aminothiazole and various phenacyl bromide in acetone at reflux for 6-8h, followed by the resulting salt was refluxed for 2 h with 1 N HBr. Before complete cooling, the resulting solution was carefully basified with 20% NH_4OH to precipitate the imidazo[2,1-*b*]thiazoles yields (50-60%) (Scheme 9).



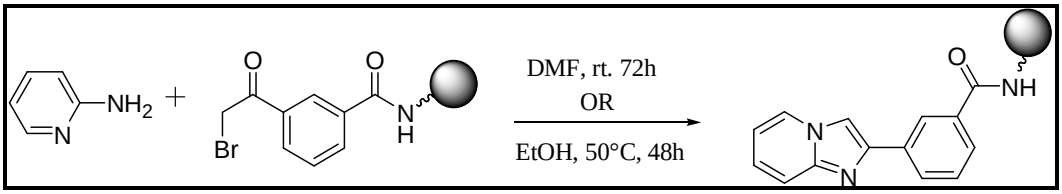
Scheme 9.

M. S. Abdel-Maksoud *et al.*, (2015) [**46**] have reported the synthesis of 6-(4-fluorophenyl) imidazo[2,1-*b*]thiazole by the cyclisation of α-bromo-4-fluoroacetophenone with 2-aminothiazole in ethanol under reflux condition for 16 h gave 86% yield (Scheme 10).



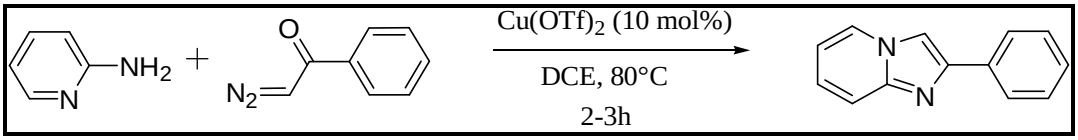
Scheme 10.

S. El Kazzouli *et al.*, (2003) [**47**] have reported the new synthesis process of imidazo[1,2-a]pyridine derivatives by condensation between an α-bromoketone which was bound to polystyrene solid support and various 2-aminopyridine in DMF, rt, 72 h or EtOH, 50°C, 48 h (Scheme 11).



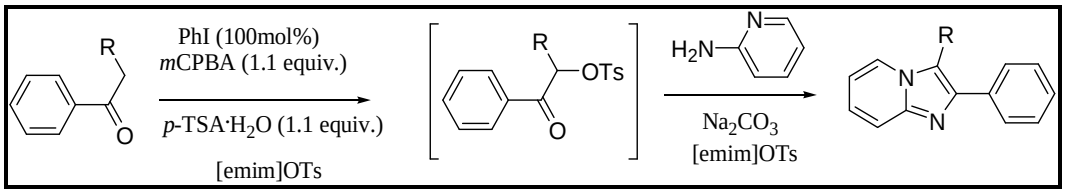
Scheme 11.

J. S. Yadav *et al.*, (2007) [**48**] reported the new process in which the *α*-Diazoketones undergo smooth coupling with 2-aminopyridines in the presence of copper(II) triflate (10 mol%) in DCE at 80°C to produce the corresponding 2-substituted imidazo[1,2-*a*]pyridine derivatives in good to excellent yields(Scheme 12).



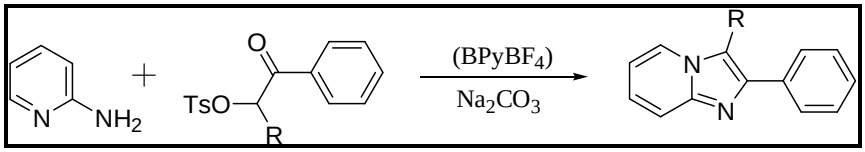
Scheme 12.

Ya-Li Chang *et al.*, (2010) [**49**] have reported the new process of iodobenzene (100 mol%) catalyzed synthesis of imidazo[1,2-*a*]pyridines from aryl ketones with *m*CPBA as a cooxidant and PTSA in ionic liquidethylmethylimidazolium tosylate ([emim]OTs) at room temperature without isolation of α-tosyloxyketones.Nucleophilic substitution reaction of α-tosyloxyketones with 2-aminopyridine to gave imidazo[1,2-a]pyridine in good to excellent yields(Scheme 13).



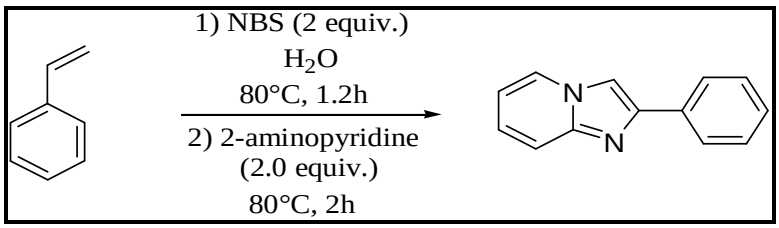
Scheme 13

Y. Y. Xie *et al.*, (2002) [**50**]reported theroom temperature ionic liquid n-butylpyridinium tetrafluoroborate ($BPyBF_4$) is used as a recyclable alternative to classical molecular solvents for the cyclocondensation of α-tosyloxyketones with 2-aminopyridine in presence of Na_2CO_3 (55 mol%) stirred at rt for 1h to gave imidazo[1,2-a]pyridine in good yields(Scheme 14).



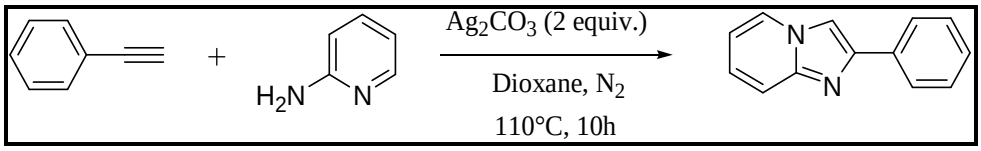
Scheme 14.

M. H. Shinde and U. A. Kshirsagar (2015) [**51**] reported the method for the synthesis of imidazopyridines derivatives in one pot manner by just heating of styrenes (1.0 equiv.) with NBS (2.0 equiv.) in water followed by reaction with 2-aminopyridines (2.0 equiv.). The condensation reaction proceed via co-oxidant free, in-situ formation of α-bromoketone using NBS as bromine source as well as oxidant followed by trapping with 2-aminopyridine as nuclephile to provide imidazo[1,2-*a*] pyridine in good yields (Scheme 15).



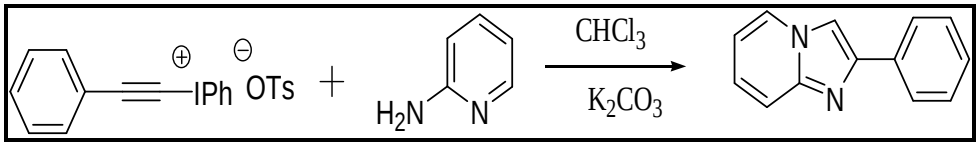
Scheme15.

C. He *et al.*, (2012) [**52**] reported new alternative method for the synthesis of imidazo[1,2-*a*]pyridine using oxidative C-N coupling of 2- aminopyridines with terminal alkynes mediated by the silver salt Ag_2CO_3 (2.0 eqiuv.) in dioxane medium under nitrogen atmosphere at 110°C for 10h afforded the imidazo[1,2-*a*]pyridines selectively. In this oxidative coupling procedure, no terminal alkyne homo coupling by product was observed. On the other hand this reaction is failed for the internal alkynes (Scheme 16).



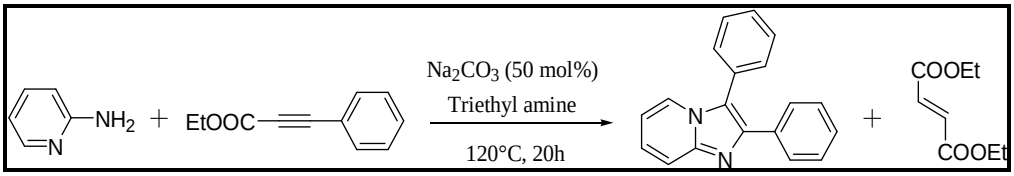
Scheme 16.

Z. Liu*et al.*, (2004) [**53**] reported the new synthesis process for the synthesis of 2-substituted-imidazo[1,2-*a*]pyridines by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-amino pyridine occurred easily in $CHCl_3$ under reflux in the presence of K_2CO_3(60 mol%) offered moderate to good yield (Scheme 17).



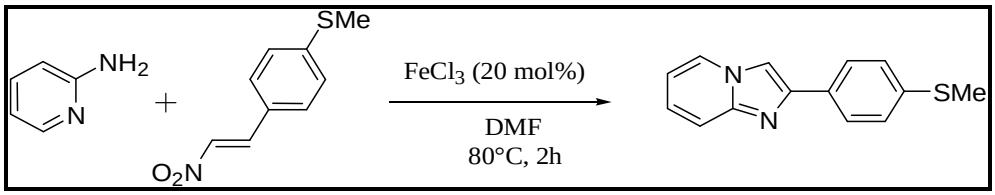
Scheme 17.

Z. Chen *et al.*, (2016) [**54**] reported a base Na_2CO_3/triethyl amine catalysed cyclization reaction of substituted 2-aminopyridines and alkynoates for the synthesis of 2,3-diarylimidazo[1,2-*α*]pyridines. This reported method is marked by the cleavage of C-C bond and the formation of new $C(sp^2)$-$C(sp^2)$ bond in transition-metal-free conditions (Scheme 18).



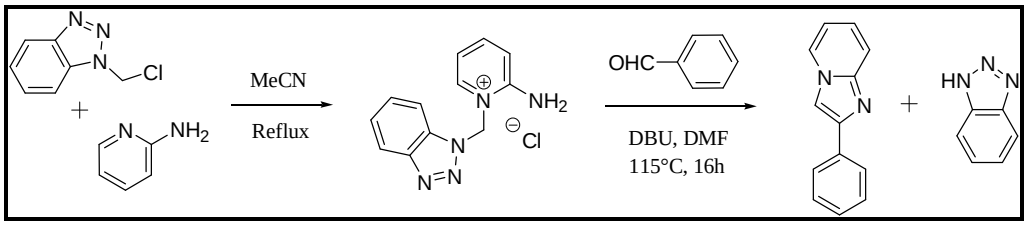
Scheme 18.

S. Santra *et al.*, (2013) [**55**] developed a methodology for the synthesis of 3-unsubstituted imidazo[1,2-*a*]pyridines by the cascade reaction between bielectrophilic molecular nature of the aromatic or aliphatic-nitroolefins and binucleophilic molecule 2-aminopyridines in presence as $FeCl_3$ (20 mol%) as homogeneous Lewis acid catalyst in DMF at 80°C for 2h results in good yields (Scheme 19).



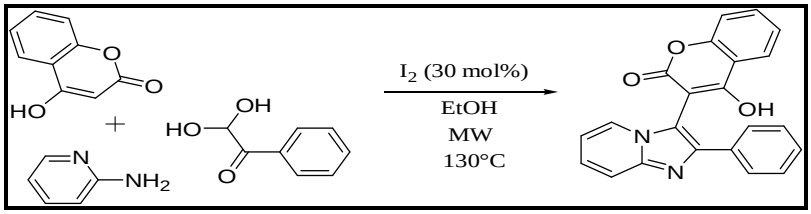
Scheme 19.

A. R. Katritzky *et al.*, (2000) [**56**] have developed a new facile two step reaction method for the synthesis of imidazolo[1,2-*a*]pyridines. In the first step 2-aminopyridines reacts with 1-chloromethyl benzotriazole in acetonitrile under refluxed condition gave a salt of 2-amino-1-[α-benzotriazol-1-ylmethyl]pyridinium chlorides. Followed by the obtained salt react with aryl aldehydes by using DBU as base in DMF at 115°C for 16h to afforded imidazolo[1,2-*a*]pyridines in good yields. The benzotriazolyl group in 2-aminopyridinium salts plays a dual role: (i) it activates the methylene group for easy deprotonation and (ii) it serves as a good leaving group in the subsequent elimination step leading to the target products imidazolo[1,2-*a*]pyridines (Scheme 20).



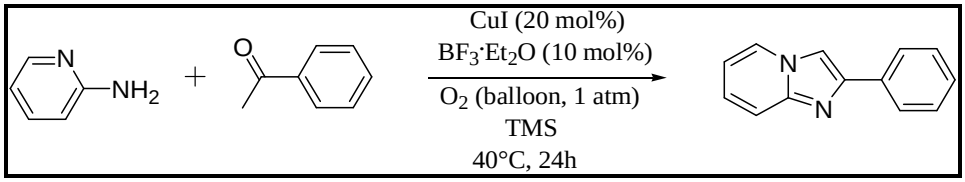
Scheme 20.

S. Karamthulla *et al.*, (2015) [**57**] have developed an molecular iodine(30 mol%) mediated one-pot metal-free, three component reaction of arylglyoxals, cyclic 1,3-dicarbonyls and 2-aminopyridines in ethanol for the synthesis of 2,3-disubstituted imidazo[1,2-a]pyridines under microwave irradiation for 15 min, keeping temperature at 130°C. Imidazo[1,2-*a*]pyridine derivatives can be synthesized in good yields with water as the only benign by-product (Scheme 21).



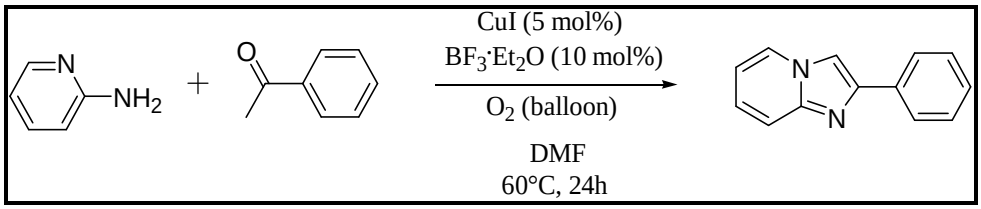
Scheme 21.

Z. J. Cai *et al.*, (2013) [**58**] reported the construction of heteroaromatic imidazo[1,2-a]pyridines through CuI (20mol%)/$BF_3{\cdot}Et_2O$ (10 mol%) catalyzed molecular oxygen mediated (O_2 balloon, 1 atm) dehydrogenative reactions of aryl alkyl ketones with 2-aminopyridines under neat conditions at 40°C for 24h. In this reaction 4 hydrogen atoms are removed and two new C-N bonds are formed in one step via the imine formation and oxidative C(sp^3)-H functionalization to affords good yields (Scheme 22).



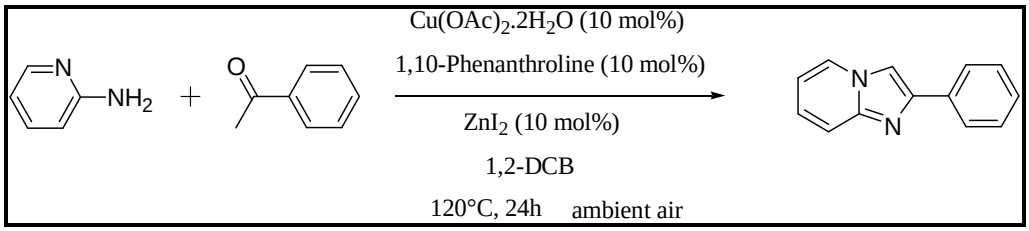
Scheme 22.

M. D. Chandra *et al.*, (2013) [**59**] reported the copper-catalysedsynthesis of imidazo[1,2-*a*]pyridines through C-H activation with aerobic oxidative linkage of two C-N bonds using molecular oxygen as a sole oxidant. They have developed the dehydrogenative annulation of 2-aminopyridine with acetophenone by combination of CuI (5 mol%) is an homogeneous catalyst with $BF_3{\cdot}Et_2O$ (10 mol%) as an additive in DMF at 60°C for 24h under an oxygen atmosphere (balloon) used for the C–N bond formation reaction (Scheme 23).



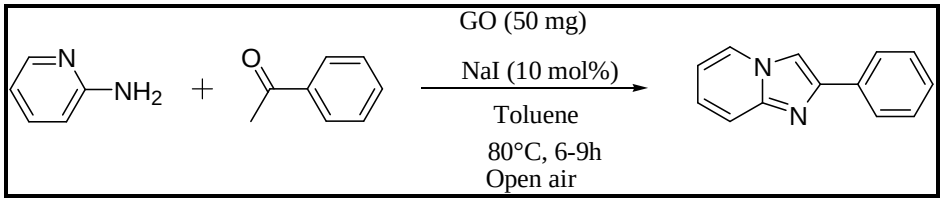
(Scheme 23.

A. K. Bagdi *et al.*, (2013) [**60**] developed the method for the copper-catalyzed oxidative cyclization via C-H amination between 2-aminopyridines and methyl aryl ketones under air for the synthesis of imidazo[1,2-a]pyridines. Imidazo[1,2-a]pyridines containing a wide range of functional groups have been synthesized from 2-aminopyridines and methyl aryl ketones by using $Cu(OAc)_2.2H_2O$ (10 mol%) as homogeneous catalyst with ligand 1,10-Phenanthroline (10 mol%) and ZnI_2 (10 mol%) is an oxidative additive in 1,2-DCB at 120°C for 24h to afforded good yields (Scheme 24).



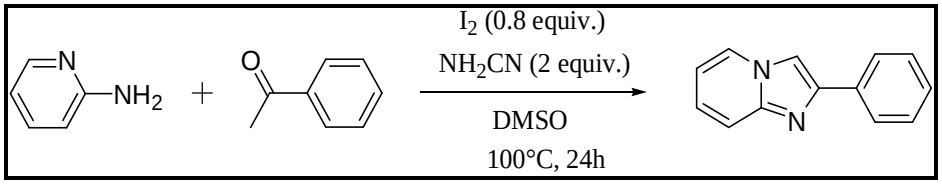
Scheme 24.

S. Kundu and B. Basu (2015) [**61**] have demonstrated that catalytic amounts of graphene oxide (GO) (50mg) in combination with NaI (10 mol%) is the additive utilized for selective and expedient synthesis of imidazo[1,2–*a*]pyridines via one-pot multi–component reactions of 2-aminopyridine with various substituted alkyl aryl ketones in toulene at 80°C for 6h produce a single product in good yield (Scheme 25).



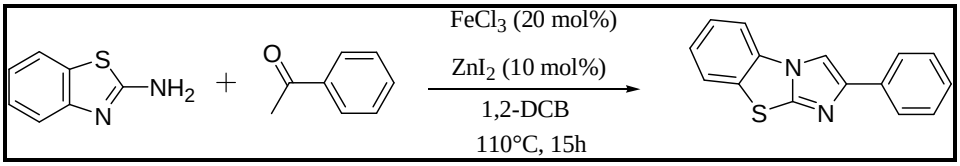
Scheme 25.

S. Liu *et al.*, (2015) [**62**] reported the construction of 6-iodo-3-methylthioimidazo[1,2-*a*]pyridines from aryl methyl ketones and 2-aminopyridines in the presence of NH_2CN (2 equiv.) and I_2 (0.8 equiv.) in DMSO at 100°C for 24 h. Remarkably, this reported four-component coupling reaction allowed for the formation of C-I and C-S bonds with construction imidazo[1,2-*a*]pyridines heterocycles (Scheme 26).



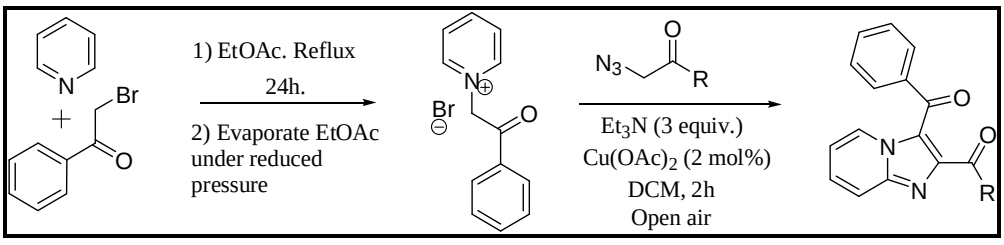
Scheme 26.

S. Mishra *et al.*, (2014) [**63**] have reported the $FeCl_3$ (20 mol%)/ZnI_2 (10 mol%) catalyzed aerobic oxidative double C-N bond formation reaction between 2-aminobenzothiazole and alkyl aryl ketone proceeds through in situ formation of α-iodo ketone followed by intramolecular cyclization for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles in 1,2-DCB at 110°C for 16h. A variety of fused benzoimidazothiazole derivatives were obtained in good yield (Scheme 27).



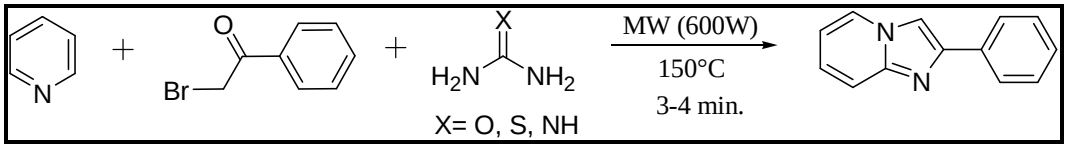
Scheme 27.

A. Kamal *et al.*, (2015) [**64**] have reported the new method for the region selective synthesis of imidazo[1,2-*a*]pyridines utilizing in situ generated imines. The pyridinium salt was prepared by refluxing equimolar mixture of substituted pyridine with various phenacyl bromide in EtOAc. Next the crude pyridinium salt was reacted with phenacyl azide in presence of $Cu(OAc)_2$ (2 mol%) and Et_3N mediated oxidative coupling utilizing molecular oxygen as a green oxidant to formation of imidazo[1,2-*a*]pyridine were synthesized in high yields (71-92%) (Scheme 28).



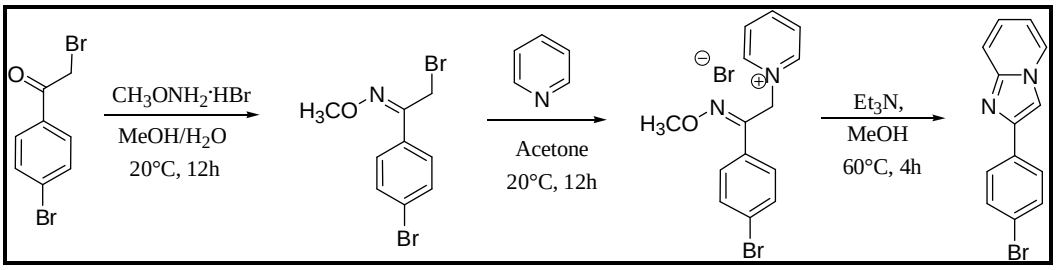
Scheme 28.

K. Motevalli *et al.*,(2012) [**65**] reported the synthesis of 2-phenyl-H-imidazio[1,2-α] pyridines from a one-pot, three-component reaction between pyridine, urea (guanidine or thiourea) and phenacylbromide under microwave irradiation at 150°C and solvent-free conditions, resulted in good yields (78-85%)(Scheme 29).



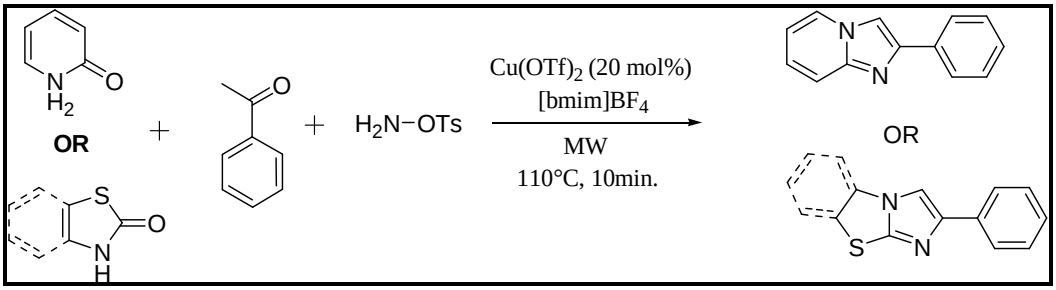
Scheme 29.

V. A. Artyomov *et al.*, (1996) [**66**] reported the multistep synthesis of 4-bromophenylimidazo [1,2-a]pyridine derivatives from 4-bromophenacyl bromide O-methyloxime condense with pyridines in acetone to form the corresponding pyridinium salts which, when heated in methanol in the presence of triethyl amine, undergo cyclisation followed by elimination of methanol to gave imidazo[1,2-*a*] pyridine derivatives (Scheme 30).



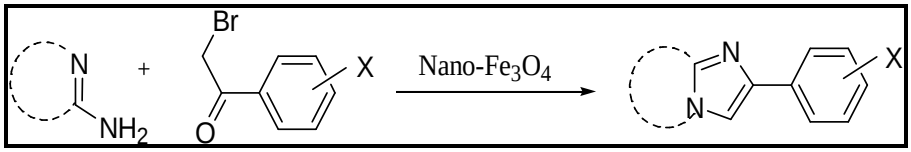
Scheme 30.

G. S. Kumar *et al.*, (2015) [**67**] reported an efficient synthesis of fused imidazo-heterocycles via C-H activation/tandem addition-cyclization process using $Cu(OTf)_2$ (20 mol%) in $[bmim]BF_4$ by the multicomponent reaction of pyridin-2(1*H*)-one or thiazol/benzo[*d*]thiazol-2(3*H*)-ones reactedwith acetophenones and O-tosyl hydroxyl amine at 110°Cunder microwave irradiation. The ionic liquid containing $Cu(OTf)_2$was recovered and reused upto four times. This method involved the formation of three new C-N bonds in a cascade pathway (Scheme 31).



Scheme 31.

B. R. Chaudhari *et al.*, (2018) [**68**] described a mild and efficient approach to synthesis of imidazoheterocycle derivatives through double C-N bond formation by using nano-Fe_3O_4 as catalyst (scheme32). To the best of our knowledge, there has been no report on nano-ferrite catalysed synthesis of fused azaheterocycles. The proposed reaction process involves the crucial steps for the formation of two C-N bonds, first through nucleophilic substitution of bromide by nitrogen of 2-aminoheterocycle and second through dehydrative condensation and deliver the N-fused heterocyclic scaffold (Scheme 32).



Scheme 32.

APPLICATION

Several compounds has more than one nitrogen contained fused bicyclic heterocycles were important structural motifs found in numerous natural products and bioactive molecules. These important motifs have been developed by the modification of imidazole fused with pyridine, thiazole or benzothiazole heterocyclic nuclei. In recent years, the synthesis of bicyclic compounds possessing N-bridge heterocycle central core has been the focus of great interest. They are associated with diversified biological activities.

CONCLUSION

In this review, we have reporting various methods for the synthesis of N-fused heterocyclic scaffold through C-N bond formation reactions.

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