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Mini Review: Recent Developments in Synthesis of Imidazo[1,2-a] pyridines (2016-2020)

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Abstract: Due to having importance in medicinal chemistry, researcher have been showing more interest in the synthesis of Imidazo[1,2-a] pyridines. With various approaches the synthesis has been achieved. We have summarized the approaches for the synthesis of Imidazo[1,2-a] pyridine from 2016-2020 along with its reported possible mechanisms in this review.

Keywords: Imidazo[1,2-a] pyridines, multicomponent reactions, tandem reactions, C-H activations.

1.0 Introduction

Imidazo[1,2-a] pyridinesscaffold showing great importance in an available marketed drugs.[1]Particularly for the synthesis of Imidazo[1,2-a] pyridine have been developed by various approaches, like multicomponent reaction[2]and transition metal catalysed C-H activations[1]. Due to having great potential last two decades' researchershave showing more interest in N-fused imidazole framework. Imidazo[1,2-a] pyridinecontaining compounds are reported for anti-cancer.[2]antiviral activity[3],antitumor[4], antiproliferative[5] and smoothened antagonistic[6] activities. Also it has a corrosion inhibitors properties due to their highly excited state intra-molecular proton transfer which elevates the performances of their adsorption into the metallic surface.[7]The position-3 of this scaffold is having metabolically importance for the several areas of therapeutics and the imidazo[1,2-a] pyridines substituted at C-3 with an amino functionality to get the potent molecules (Figure 1).

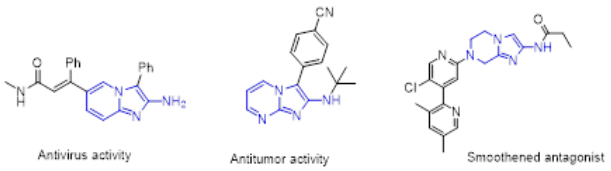


Figure.1 Biological active compounds containing N-fused 2-amino imidazole.

Few commercially available drugs such as alpidem[8], minodronic acid[9]for the treatment of anxiety, heart failure and osteoporosis. Necopidem and saripidem used as sedative and anxiolytic[10]. GSK 812397 clinical active candidate used to treat HIV infection[11].

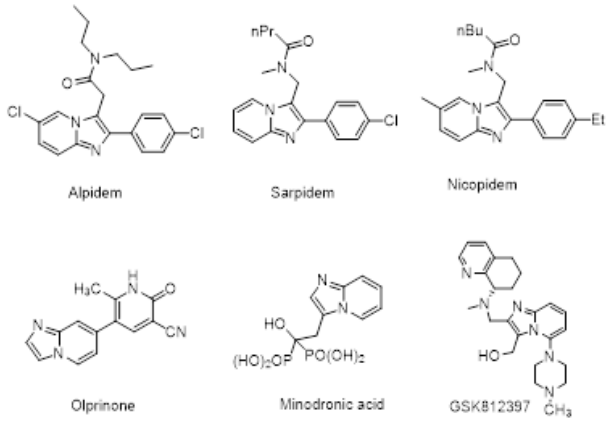
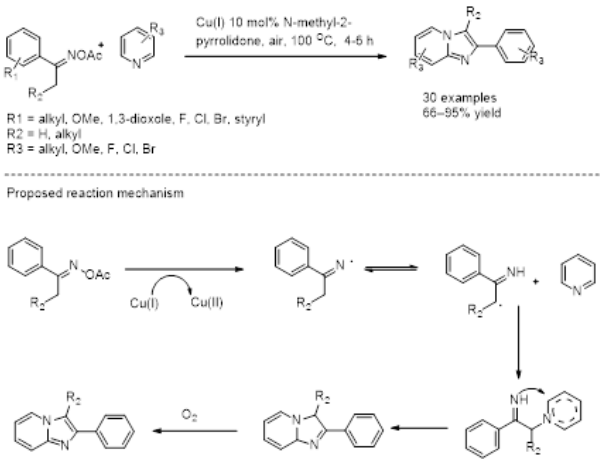


Figure 2. Imidazo[1,2-a] pyridine derived drugs.

2.0 Copper catalysed reaction

2.1 *From ketoxime acetate and pyridine*

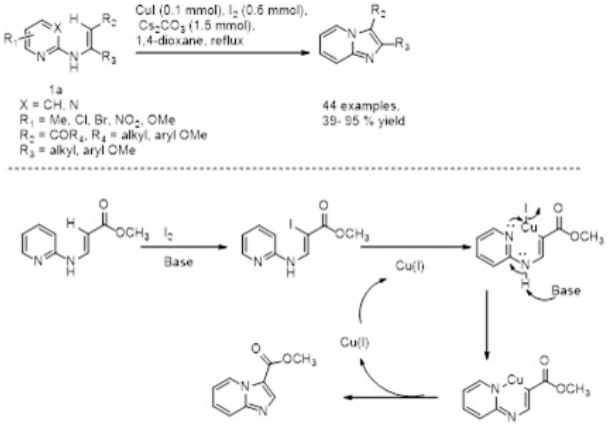
Z.-H. Ren et al.[12]reported a method for the synthesis of imidazo[1,2-*a*]pyridines using copper (I) catalysed aerobic oxidative coupling of ketoxime acetate and pyridine with a variety of functional groups with high yield.Ketoxime can be easily synthesised by doing the condensation of ketone and hydroxyl ammonium salt with quantitative yield. The proposed radical type reaction, active iminium radical and α-carbon radical were reported with Cu(I) catalysed reaction.[13]To perform the reaction various solvent including *N,N*-dimethylformamide (DMF), acetonitrile, toluene, 1,4-dioxane, dimethyl sulfoxide (DMSO), dimethylacetamide (DMA) and N-methyl-2-pyrrolidone (NMP)were screened but NMP gave the best results. For catalyst screening copper(I) bromide, copper(II) bromide, copper(II) chloride, copper (I)iodide, copper acetatewas tried, the combination of copper(I) iodide (10 mol%) in NMP at 100 °C provides the great results.



2.2 *From N-heteroaryl or N-aryl substituted iodine (oxidant)*

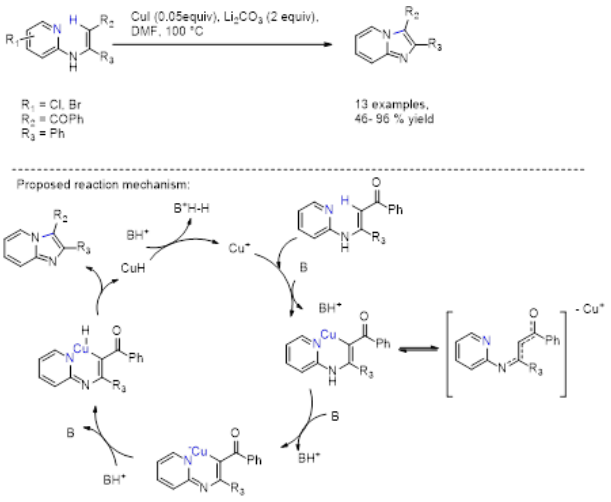
An efficient and versatile method for the synthesis of imidazo[1,2-a]pyridine and indole derivatives using *N*-heteroaryl or *N*-aryl substituted iodine (oxidant) and copper iodide (catalyst), new approach of oxidative C−N and C−C bond formation, respectively has developed by Wenquan Yu,and Junbiao Chang et al.[14]Advantage of this method is reaction proceed without any ligand. Crude enamine intermediate used for the next stage without any purification. Enamine synthesis achieved though p-toluenesulphononic acid (p-TsOH) catalysed condensation of pyridine-2-amine and 1,3-cyclohexanedione. Isolated crude enamine was further treated with CuI/I_2 and caesium carbonate (Cs_2CO_3) in 1,4-dioxane at reflux temperature to obtainimidazo[1,2-a] pyridine with 88% yield. The substituent like methyl and

halogens on pyridyl moiety support to achieve the cyclization reaction smoothly.



2.3 *From N-(2-pyridinyl) enaminones*

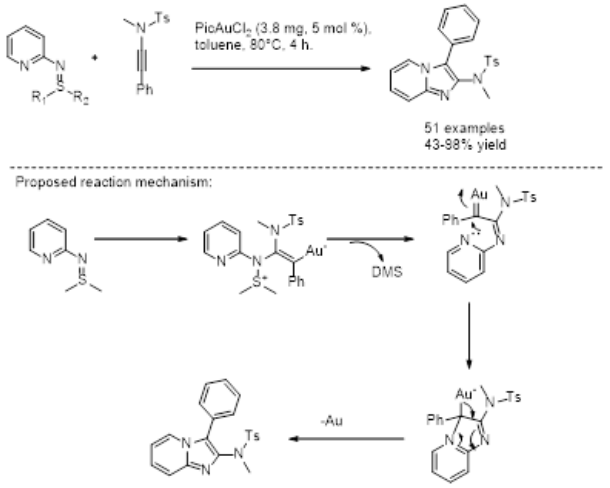
Sandro Cacchia et al.[15]reported new approach using copper iodide (CuI) as a catalyst for the synthesis of substituted imidazo[1,2a]pyridine scaffold from *N*-(2-pyridinyl)enaminones. β-enaminones has specific properties such as a peculiar electronic and ambient electronic character, make it useful in variety of cyclization, including transition metal catalysed cyclization.[16] To explore the impact of solvents tried are1,4-dioxane and acetonitrile. Whereas ligands include *N*,*N*-dimethylethylenediamine, L-proline, triphenylphosphine (PPh_3), and 1,2-Bis(diphenylphosphino)ethane. With respect to bases like potassium carbonate (K_2CO_3), lithium carbonate (Li_2CO_3) for the optimization of reaction condition. Obtained yield in the range of 54-67 %. In absence of ligand and catalyst loading 0.05 equivalent gave very less yield. Doing NMR study to know the role of copper iodide, ithas been observed that the Cu-enaminone complex restrict the cyclisation which has prevented by generating stable complex.



3.0 Gold catalysed approach.

From N-pyrimidinylaminide and ynamide

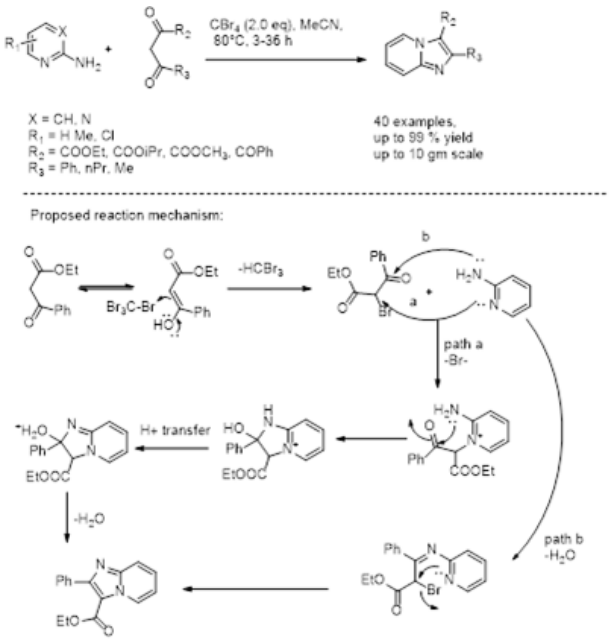
A gold-catalysed ring formation between *N*-pyrimidinylaminide and ynamide for the synthesis of 2-amino fused imidazole reported by a group of Stephen K. Hashmi et al.[17]a reaction of *S,S*-dimethyl-N-(pyridin-2-yl)-sulfilimine and ynamide performed in toluene using 5mol % of 1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene) gold chloride(IPrAuCl) / silver triflimide ($AgNTf_2$) as catalyst at 80 °C which provides 25-29 % yield. However, another gold catalyst chloro(triphenylphosphine)gold(I) [PPh3AuCl]/silver triflimide[AgNTf] leads to 31 % yield, whilepotassium tetrabromoaurate ($KAuBr_4$) delivered good yield. Another dichloro(2-pyridinecarboxylato) gold [$PicAuCl_2$]catalyst resulting 95% yield of desired imidazo[1,2-*a*] pyridines derivatives. Dichloroethane and tetrahydrofuran can be used for the reaction that provides a good yield. Sulfilimine bearing electron donating group on pyridine reaction proceed very fast to convert imidazopyridine, sulfilimine with trifluromethyl or halogen substitution delivered 90 % yield. Only trisubstituted ylide end up with low yield around 76 %.



4.0 Carbon tetrabromide mediated approach

From 2-amino pyridine and 1,3 dione or β-keto ester

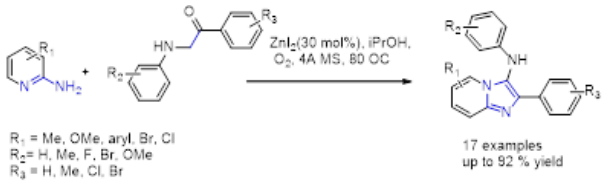
A metal free synthesis of imidazo[1,2-a] pyridines using carbon tetrabromide (CBr_4) mediated C- bond formation reaction of 2-amino pyridine and 1,3 diones or β-keto ester in acetonitrile at 80 °Creported by Congde Huo et al. [18] Recently tetrabutylammonium iodide/borontrifluoride etherate/tertbutyl hydroperoxide[24]or $Fe/I_2/O_2$-catalyzed oxidative coupling of the C−N bond formation reaction discoveredfor the N-fused scaffold.[19]Sources of halogen analogues such as *N*-chlorosuccinamide (NCS), *N*-bromosuccinamide (NBS), *N*-iodosuccinamide (NIS), 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH), and bromine (Br_2) were tried, it found to be less promising as compare to CBr_4. Other sources are $BrCH_2CH_2Br$, $CHBr_3$, CH_2Br_2, copper(II) bromide, and KBr/H_2O_2 were found to be inactive for this transformation. Carbon tetrabromide (CBr_4)loading 1.0-3.0 eq provides 80-83% yield, whereas if reduce to 0.5 eq. get down to 43 % yield. The solventsscreened for the optimization are toluene, tetrahydrofuran (THF), methanol (MeOH), dichloromethane (DCM), water produce yield in the range of 17 to 77 %.



5.0 Zinc catalysed approach

From 2-amino pyridine and α-amino carbonyl compounds

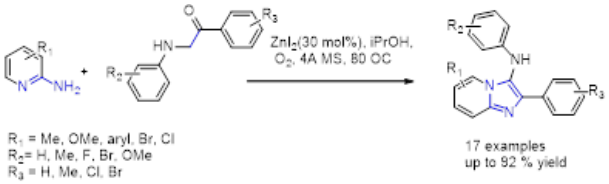
A lewis acid catalysed reaction of 2-amino pyridines and α-amino carbonyl compounds in the presence of oxygen for the synthesis of 3-aminoimidazo[1,2-*a*] pyridine have reported byGuosheng Huang et al. [20]For the optimization of reaction condition, initially used 2-aminopyridine and 1-phenyl-2-(*p*-tolylamino)ethan-1-one and cerium(III) chloride in isopropyl alcohol under oxygen atmosphere at 80 °C to obtain2- phenyl-*N*-(*p*-tolyl) imidazo[1,2-*a*] pyridin-3-amine with 55%.Also to investigate the impact of other Lewis acids have examined zinc chloride, zinc bromide, zinc triflate and samarium(III) triflate in *N*-*N* dimethylformamide (DMF) anddimethyl sulfoxide (DMSO). It has observed that none of these provides satisfactory yield. Whereas zinc iodide provides 77 % yield. Reason could be the generated water in reaction were trapped using 4^0A molecular sieves. Iso-propanol provides the better yield as compare to other alcohol.



6.0 Imidazo[1,2-a] pyridines synthesis using triflic anhydride

From cyclodehydration-aromatization

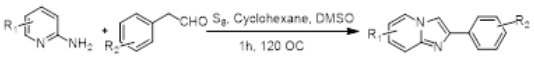
Andre´ B. Charette et al.[21]have reported the synthesis of 3-Aminoimidazo[1,2-a] pyridines via cyclodehydration-aromatization using readily available amides. Synthesis involved the activation of boc-protected amide with triflic anhydride, 2-methoxypyridine (2-MeOPy) followed by boc deprotection. A broad range of functional group are well tolerated with excellent yield. Using this method reaction has performed on gram scale. Imidazo[1,2-a] pyridines are well-known precursors of N-heterocyclic carbene (NHC) ligands.



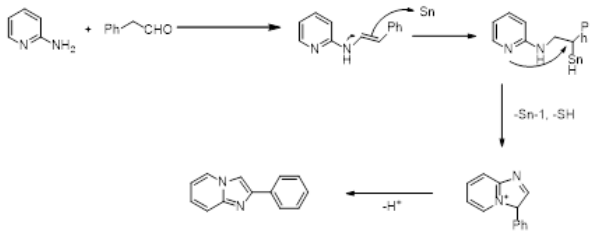
7.0 Sulphur initiated- cyclization of 2-amino pyridine and aldehyde

From 2-amino pyridine and aldehyde

Guo-Jun Deng et al.[22]described a simple and facile method for the synthesis of imidazo[1,2-a] pyridine using 2-amino pyridine and aldehyde. Elemental sulphur promotes the cyclization via oxidative annulation. Apart from aryl acetaldehyde, aliphatic aldehyde also give alkyl substituted imidazo[1,2-a] pyridine with moderate to excellent yield on gram scale. A mixture of cyclohexane and dimethylsuphoxide (DMSO) could enhance the oxidative annulation. Reaction with solvents like *N,N*-dimethylformamide, dimethylacetamide provides less yield. while mixture of cyclohexane and DMSO with their ratio have screened, and 2:4 ratio provides the best results. 2-amino pyridine bearing electron withdrawing group decreases the yield. Whereas the nitrile, ester, ether and methyl functionality offered moderate to excellent yield. This method works well with aminoquinoline and aminoisoquinoline as well. A cyclization reaction of 2-amino pyridine with cyclohexanone and 2-pentanone has failed due to the relatively low reactivity of ketone. This is a metal free and base free approach to access the various substituted imidazo[1,2-a] pyridinefrom an easily available amino pyridine and aldehyde.



Proposed reaction mechanism:



Conclusion

In this review we have summarized the various metal catalyzed, triflic anhydride, and sulfur initiated cyclization approaches for the synthesis of Imidazo[1,2-a] pyridine from 2016-2020 along with its reported possible mechanisms. This will help researcher to explore the possible new approaches for the synthesis of imidazo[1,2-a] pyridine.

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