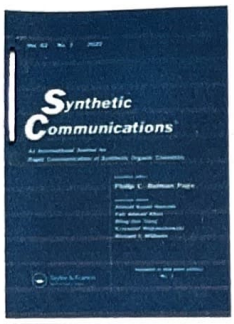

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Synthetic strategies in development of 3-aroylimidazo[1,2-a]pyridines and 2-aroylimidazo[1,2-a]pyridines: A decade update

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Introduction

Imidazo[1,2-a]pyridines are prominent nitrogen-bridgehead fused heterocyclic compounds investigated for their pharmacological properties in medicinal chemistry.[1] These molecules exhibit wide range of biological activities, such as antiviral,[2] anticancer,[3] antifungal,[4] antipyretic,[5] antibacterial,[6] antiparasitic,[7] anti-inflammatory,[8] anticonvulsant,[9] antituberculosis,[10] antiprotozoal,[11] anti-anxiety,[12] etc. They are also examined for $GABA_A$ and benzodiazepine receptor agonists, β-amyloid detecting ligands, MCH1R antagonists, and kinase inhibitors for CDK, RET, P13K, FLT3 and IRAK.[13–21] The core structure of this scaffold is present in several commercial drugs including alpidem, saripidem and necopidem (anxiolytic agents), zolimidine (anti-ulcer agent), olprinone (cardiotonic), zolpidem (for treating insomnia), miroprofen (anti-inflammatory), minodronic acid (for treating osteoporosis), GSK812397 (for treating HIV), telacebec (Q203) (antituberculosis agent) and soraprazan (inhibition of gastric acid secretion)[22–28] (Figure 1).

Owing to the medical relevance of this scaffold, numerous strategies have been employed expeditiously to synthesize functionalized imidazo[1,2-a]pyridines.[29–33] One of the most sought after transformation is, the regioselective synthesis of an aroyl group at C-3/C-2 position of imidazo[1,2-a]pyridines. In past, aroyl functionality has shown elevated biological applications in numerous heterocycles.[34] Earlier, direct introduction of aroyl group at C-3 position of imidazo[1,2-a]pyridine was unsuccessful by using Friedel-Crafts acylation

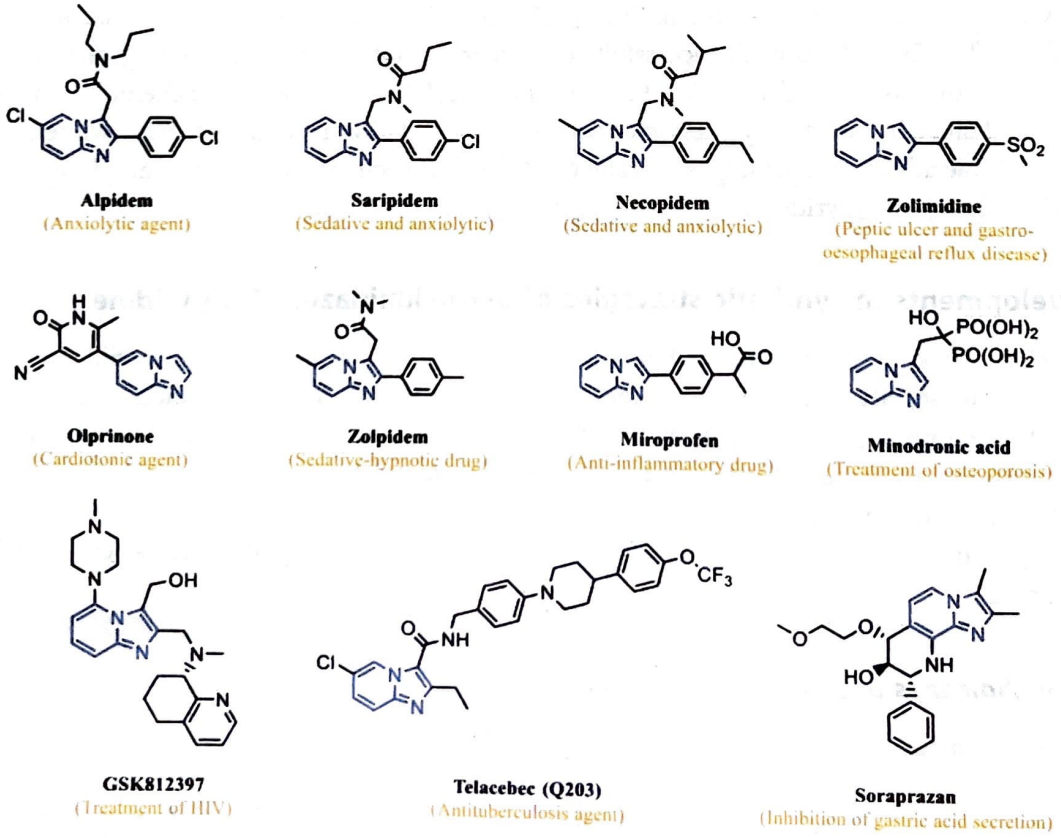
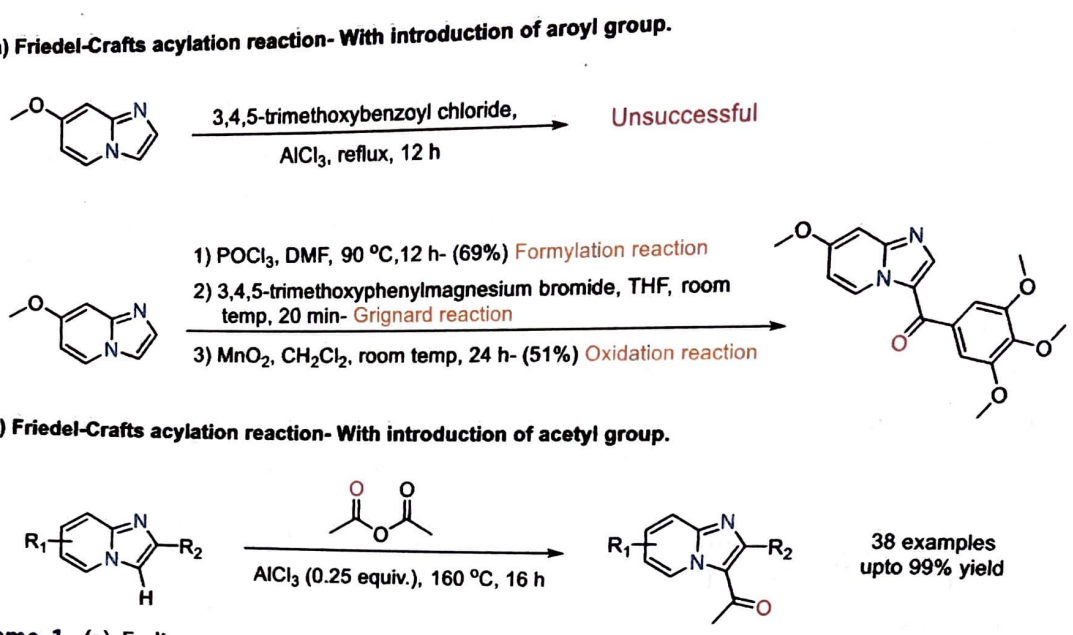


Figure 1. The core structure of imidazo[1,2-a]pyridines present in bio-active drugs.



Scheme 1. (a) Earlier unsuccessful attempt of Friedel–Crafts acylation reaction for aroylation of imidazo[1,2-a]pyridine resulted in a three-step long strategy as the only source to access 3-aroylimidazo[1,2-a]pyridine. (b) Friedel–Crafts acylation reaction for acetylation at C-3 position of imidazo[1,2-a]pyridine.

reactions. This had left chemists with three-steps long and exhausting protocol for synthesis of 3-aroylimidazo[1,2-a]pyridine which included; (a) Formylation of imidazo[1,2-a]pyridine, (b) Grignard reaction on 3-formylimidazo[1,2-a]pyridine and (c) Oxidation of secondary alcohol.[35] In 2018, Frett et al. successfully demonstrated introduction of acetyl group at C-3 position of this scaffold by using Friedel–Crafts acylation reaction[36] (Scheme 1). As a result of failure in direct aroylation via Friedel–Crafts acylation reaction, we have witnessed a remarkable advancements in past decade toward regioselective synthesis of 3-aroyl- and 2-aroyl imidazo[1,2-a]pyridines.

Developments in synthetic strategies of 3-aroylimidazo[1,2-a]pyridines

Direct synthesis of functionalized imidazo[1,2-a]pyridines from easily accessible/available precursors are possible by synthetic strategies such as transition metal catalyzed oxidative coupling, C-H functionalization, metal supported on molecular sieves catalyzed, superparamagnetic nanoparticle catalyzed, metal-free approach, multicomponent reactions (MCR) and tandem processes. Herein, we have discussed these strategies on the basis of substrates used and various catalytic systems employed (Figure 2).

From chalcones and 2-aminopyridines

Transition metal catalyzed reactions have proved to be one of the most robust and direct approaches for many organic transformations.[37] Among them, copper is highly abundant, economically cheap, undergoes C–C and C-heteroatom bond formation reactions.[38] It also participates in many cross-coupling reactions, somehow notably similar

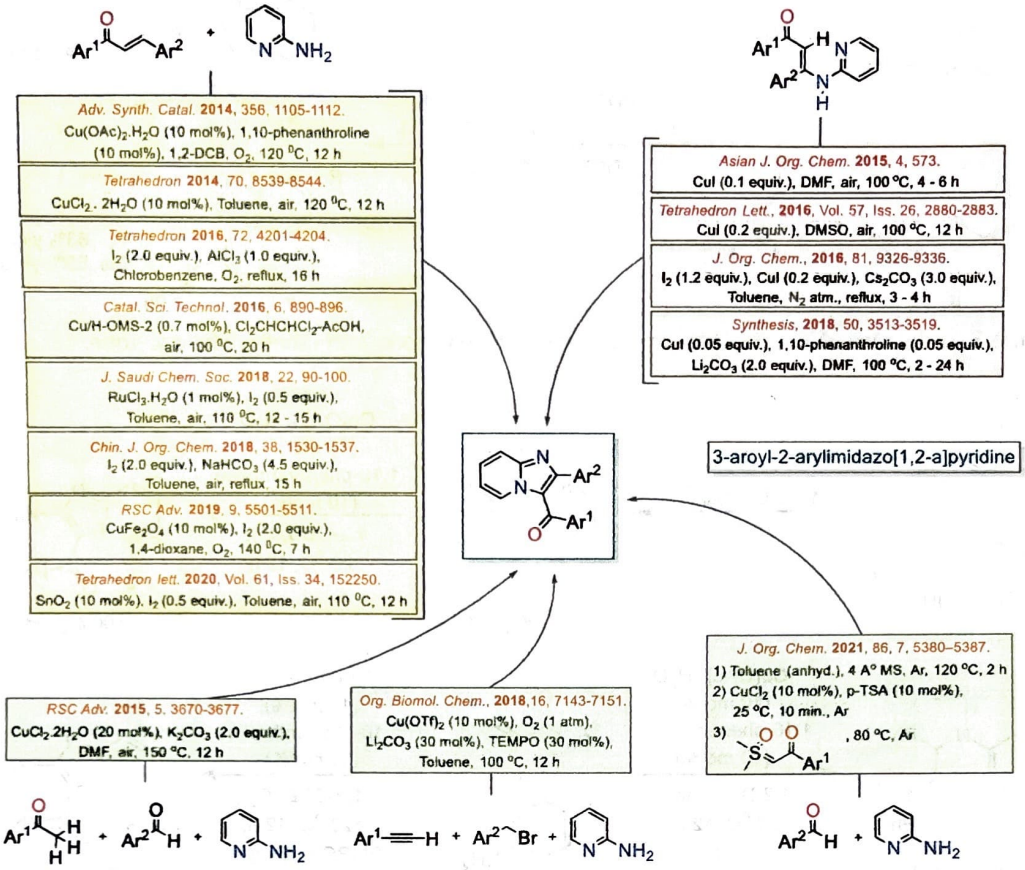
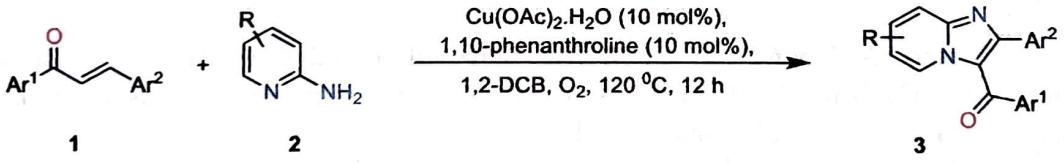


Figure 2. Different strategies employed for regioselective synthesis of 3-aroylimidazo[1,2-a]pyridines.



1 2 3

R= H, 3-Me, 4-Me, 5-Cl, 5-Br, 5-I
Ar^1= C_6H_5, 4-ClC_6H_4
Ar^2= C_6H_5, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, piperonyl

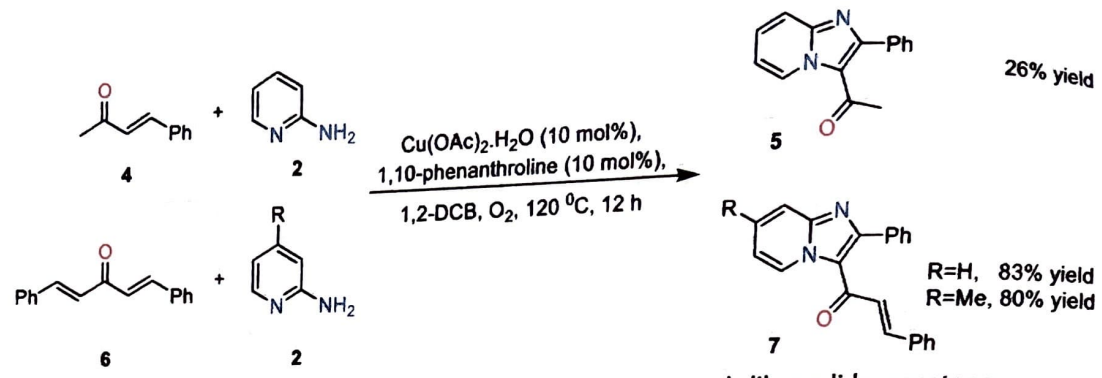
14 examples
74-86% yield

Scheme 2. $Cu(OAc)_2 \cdot H_2O$ catalyzed synthesis of 3-aroylimidazo[1,2-a]pyridines.

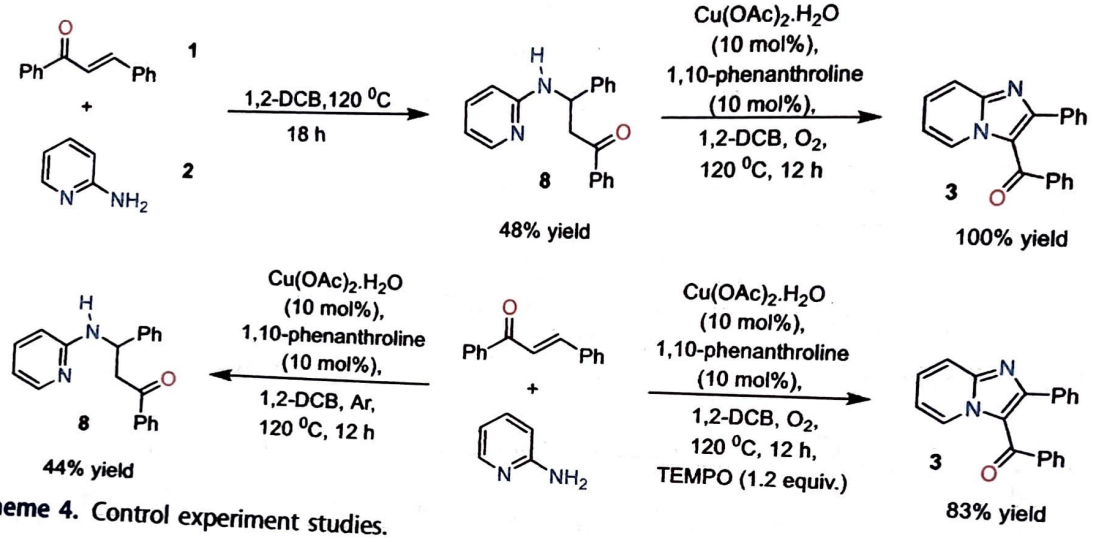
to palladium.[39] Similarly, nonmetal like iodine is extensively used to promote several reactions due to its nontoxic, inexpensive and readily available nature.[40]

Copper catalyzed reactions

Copper (II) acetate and 1,10-phenanthroline catalyzed. The search for regioselective, straightforward, and efficient method to synthesize 3-aroylimidazo[1,2-a]pyridine **3** from readily accessible substrates ended in 2014 when Hajra et al. became the first to develop it. They reported oxidative coupling between chalcones **1** and 2-aminopyridines **2** by employing Cu(II) catalyst under oxygen atmosphere as an oxidant[41] (Scheme 2). This strategy involves Michael addition followed by intramolecular oxidative coupling



Scheme 3. Tolerance of the protocol toward benzylideneacetone and dibenzylideneacetone.



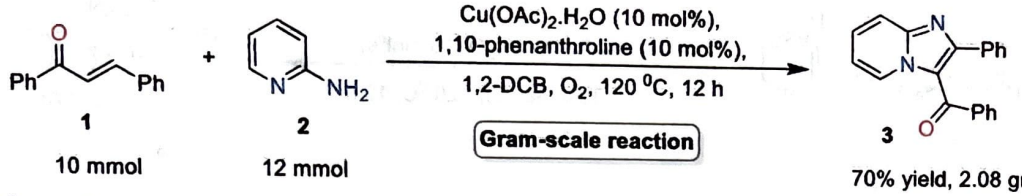
Scheme 4. Control experiment studies.

which leads to C–N bond formation. They screened several Cu(I) and Cu(II) salts, among them $Cu(OAc)_2{\cdot}H_2O$ worked excellent. Similarly, numerous ligands were also screened and 1,10-phenanthroline worked best.

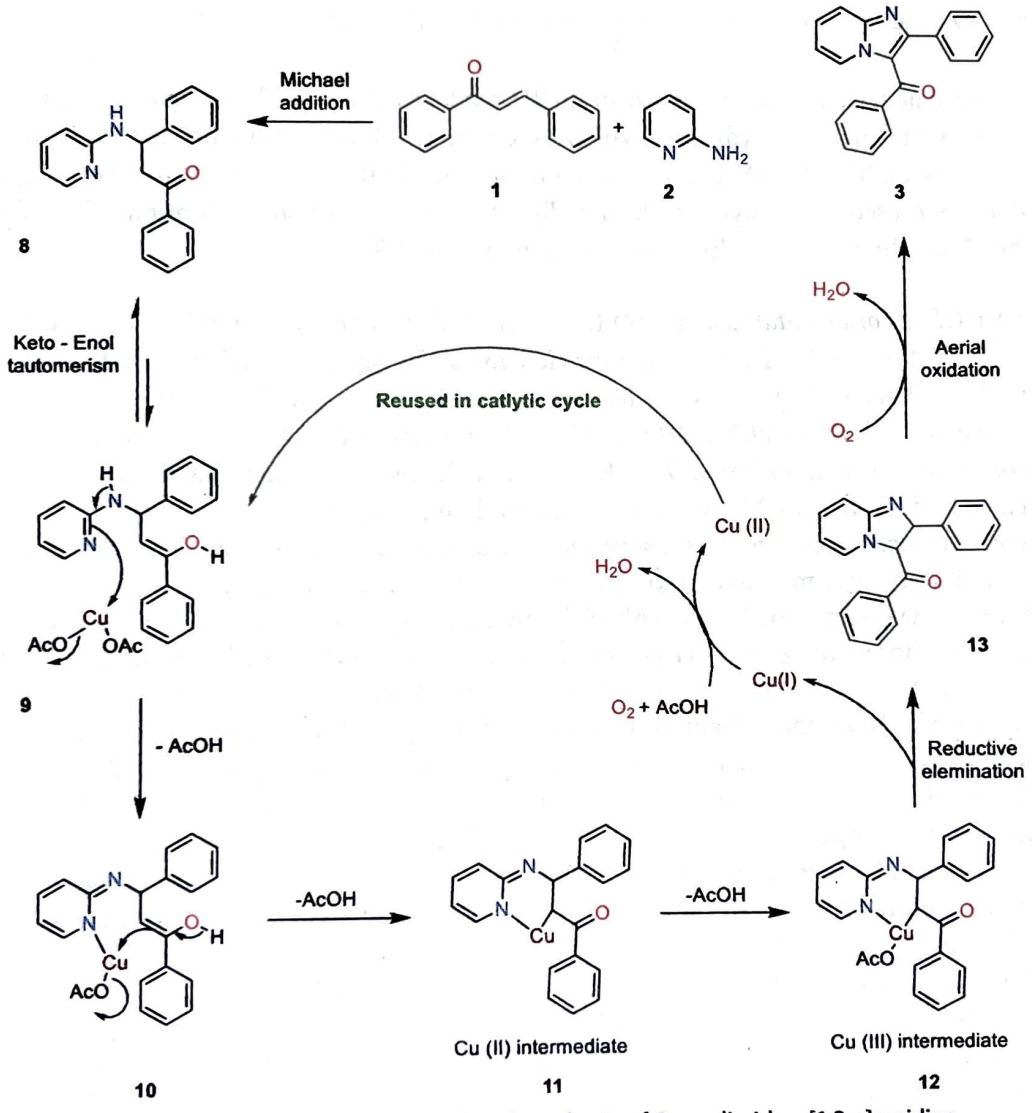
This protocol shows a wide substrate scope for 2-aminopyridines and chalcones. In case of 2-aminopyridine, the methyl group substituted at 3rd and 4th position; chloro, bromo, and iodo groups at 5th position resulted in good yields. But, substituents like 2-amino-6-methylpyridine were incompatible due to steric hindrance. Whereas, chalcones substituted with methoxy group remain unchanged. Michael acceptors such as acrylonitrile, methyl acrylate, and vinyl phosphate did not work under this methodology. Also, 2-Cyclohexenone and trans-3-nonen-2-one did not furnish the expected product. However, substrate such as benzylideneacetone **4** afforded lower yield than chalcones. In contrast, when dibenzylideneacetone **6** was used, it gave higher yield by just consuming one equivalent of 2-aminopyridine **2** (Scheme 3).

In control experiment studies (Scheme 4), they noticed that- (a) Initially, Michael adduct **8** was formed. (b) Cu salt was required for oxidative cyclization. (c) Oxygen undergoes oxidation of Cu(I) salt to Cu(II) salt and aromatization of dihydroimidazopyridine scaffold. Interestingly, gram-scale reaction afforded 70% yield by this protocol (Scheme 5).

The plausible mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridine **3** is outlined in (Scheme 6). Firstly, exocyclic amine group of 2-aminopyridine **2** undergoes Michael

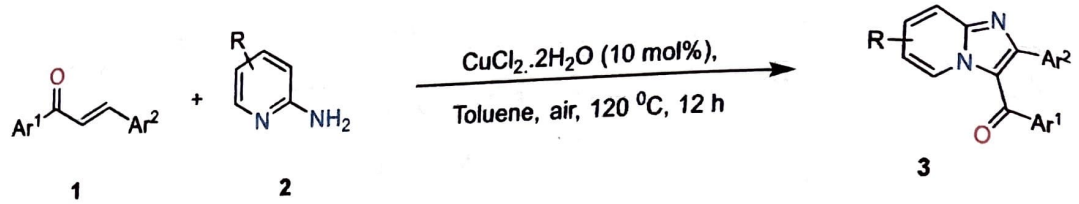


Scheme 5. Application of methodology on gram-scale.



Scheme 6. Mechanism for $Cu(OAc)_2 \cdot H_2O$ catalyzed synthesis of 3-aroylimidazo[1,2-a]pyridine.

addition on α,β-unsaturated ketone **1** to form Michael adduct **8**, which shows keto – enol tautomerism with **9** form. Then, pyridinium nitrogen binds up with copper acetate which results in intermediate **10**. Simultaneously **10** reacts with enol to form cyclic Cu(II) intermediate **11**.[39] Further, the molecular oxygen undergoes oxidation of **11** to



1 2 3

R= H, 3-Me, 4-Me, 5-Me, 6-Me, 5-Br
Ar^1= C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$
Ar^2= C_6H_5, 2-FC_6H_4, 3-$MeOC_6H_4$, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4

19 examples
38-86% yield

Scheme 7. $CuCl_2{\cdot}2H_2O$ catalyzed synthesis of 3-aroylimidazo[1,2-a]pyridines.

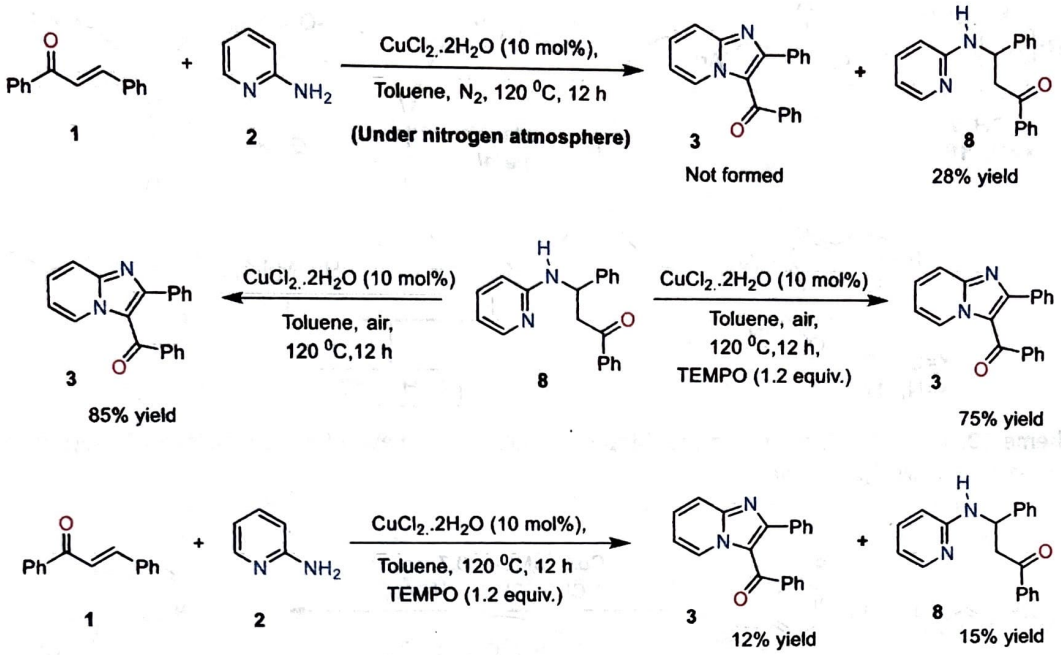
form intermediate **12** which has Cu in +(III) oxidation state.[42] Then, reductive elimination of **12** results in dihydroimidazopyridine moiety **13** and simultaneous formation of Cu (I) species. This Cu(I) species is reoxidised into Cu(II) species by molecular oxygen, and further used in catalytic cycle. Finally, the spontaneous aromatization of **13** furnishes 3-aroylimidazo[1,2-a]pyridine as a final product **3**.

Copper (II) chloride catalyzed. In 2014, Kumar et al. demonstrated Cu(II) catalyzed oxidative coupling, and a ligand free approach for synthesis of 3-aroylimidazo[1,2-a]pyridine **3**.[43] This strategy involves reaction of chalcones **1** and 2-aminopyridines **2** in presence of 10 mol% $CuCl_2{\cdot}2H_2O$ at 120°C in toluene for 12 h. under aerobic atmosphere as an oxidant (Scheme 7). The reaction proceeds through initial formation of Michael adduct, followed by intramolecular oxidative coupling.

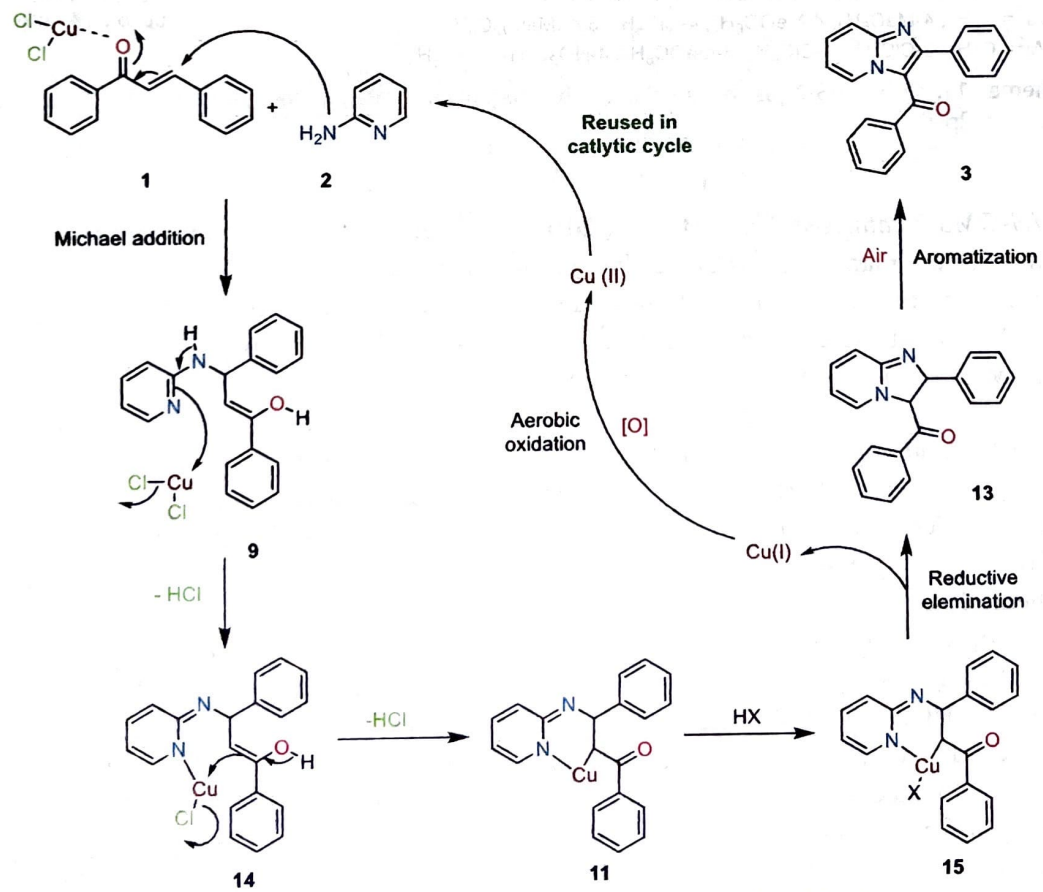
This protocol shows wide substrate scope, among them chalcones substituted with groups like methyl, methoxy, fluoro, chloro, bromo, nitro, and cyano gave good yields. Whereas, chalcones substituted with electron donating groups gave higher yields than electron withdrawing groups. However, 2-aminopyridine substituted with bromo at 5th position and methyl group at 3rd, 4th and 5th position gave moderate to good yields. Due to steric hindrance, 2-amino-6-methylpyridine gave lower yield. Interestingly, no product was obtained when 2-amino-5-nitropyridine was employed. The alluring features of this method include atom economy, straight forward, ligand free, high yields, wide substrate scope and aerobic reaction condition.

From control experiment studies (Scheme 8), they observed that, (a) Aerobic condition was required for oxidative cyclization, (b) Michael adduct was the key intermediate, (c) Reaction proceeded through non-radical pathway. (This was confirmed by using TEMPO, a radical scavenger which did not show an appreciable decrease in yield).

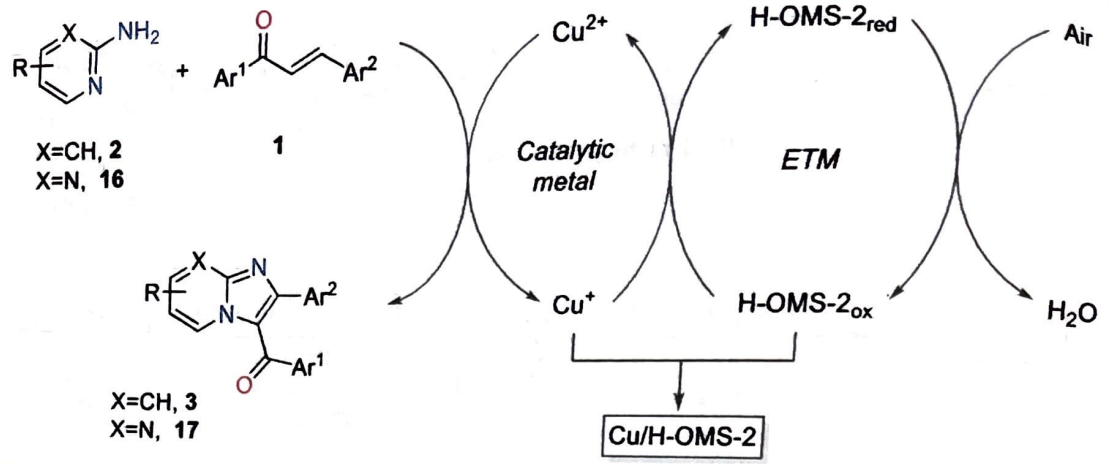
A plausible mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridine based on control experiments study is outlined in (Scheme 9). Firstly, with assistance of $CuCl_2$, Michael addition of 2-aminopyridine **2** on chalcone **1** leads to the formation of Michael adduct **9**. Further, simultaneous binding of pyridinium nitrogen followed by enolic carbon to the Cu salt produces intermediate **11** via intermediate **14**. In next step, intermediate **11** undergoes oxidation to form **15**, followed by reductive elimination which produces **13**. Finally, intermediate **13** undergoes spontaneous aromatization under aerobic condition to furnish 3-aroylimidazo[1,2-a]pyridine **3** as a final product. The Cu(I) salt generated, is reoxidised to Cu(II) salt under aerobic condition and further reused to complete the catalytic cycle.[44]



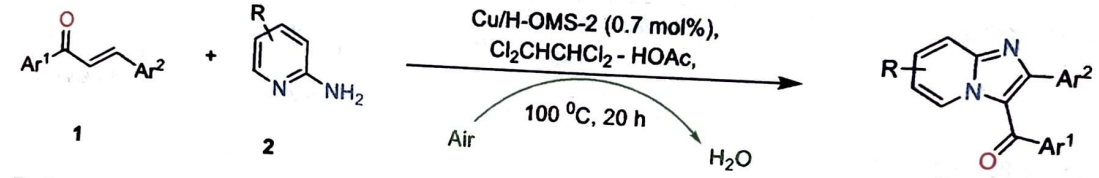
Scheme 8. Control experiment studies.



Scheme 9. Mechanism for $CuCl_2 \cdot 2H_2O$ catalyzed synthesis of 3-aroylimidazo[1,2-a]pyridine.



Scheme 10. Cu/H-OMS-2 promoted multistep oxidation for synthesis of 3-aroylimidazo[1,2-a]pyridines and 3-aroylimidazo[1,2-a]pyrimidines.



R= H, 3-Me, 4-Me, 5-Me, 4-CF_3, 3-Br, 5-Br, 4-Cl, 5-Cl
Ar^1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$
Ar^2= C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4

23 examples
up to 88% yield

Scheme 11. Cu/H-OMS-2 as a biomimetic heterogeneous catalyst for synthesis of 3-aroylimidazo[1,2-a]pyridines.

Cu/H-OMS-2 catalyzed. Zhao et al. in 2016, described the role of copper supported on acid-modified manganese oxide octahedral molecular sieves (Cu/H-OMS-2) as a catalyst in synthesis of 3-aroylimidazo[1,2-a]pyridine **3** by using chalcone **1** and 2-aminopyridine **2** as a substrate in presence of air as an oxidant.[45] Previously, OMS-2 has been employed as a support catalyst[46] and redox catalyst due to its superior properties like excellent structural stability, mixed valence, large surface areas, electron conducting properties and oxygen reduction abilities.[47] The Cu/H-OMS-2 catalytic system has low loading Cu as a catalytic metal and support H-OMS-2 as an electron transfer mediator (ETM), which sequentially lowers the redox energy barrier and generates low energy pathway for synthesis of 3-aroylimidazo[1,2-a]pyridine **3** in a biomimetic way (Scheme 10).

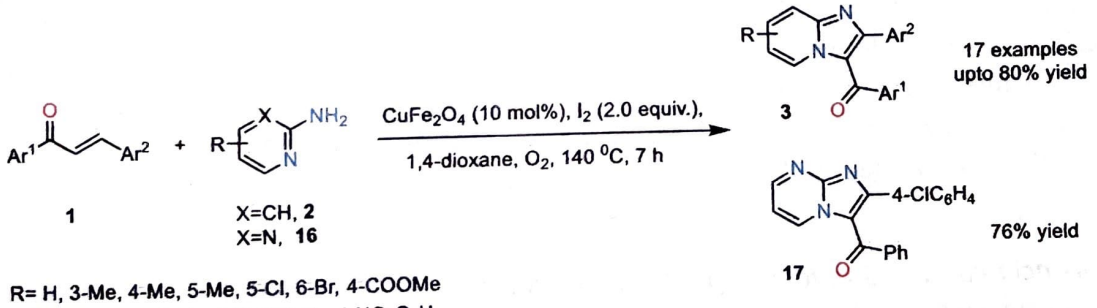
For optimization, several solvents were screened; they found apolar $Cl_2CHCHCl_2$ gave the highest 41% yield of 3-aroylimidazo[1,2-a]pyridine without any by-products. Whereas, HOAc gave 0% yield of 3-aroylimidazo[1,2-a]pyridine, but 59% yield of Michael adduct was observed within 3 h under catalytic system of Cu/H-OMS-2. Hence, they used mixed solvent system of $Cl_2CHCHCl_2$ and HOAc. This strategy can be employed for synthesis of 3-aroylimidazo[1,2-a]pyrimidines too, by replacing 2-aminopyridine with 2-aminopyrimidine. The optimized reaction condition for oxidative cyclization is shown in (Scheme 11).

This protocol shows wide substrate scope, among them chalcones substituted with electron withdrawing groups gave higher yields than those having electron donating groups. Reaction did not proceeded in 2-chlorochalcone due to steric hindrance of chloro group. Whereas, in case of 2-aminopyridine, those substituted with electron donating groups showed higher activity than those with electron withdrawing groups like halogens. Many multi-halogen-substituted 3-aroylimidazo[1,2-a]pyridines were synthesized in 42-64% yield. 2-aminopyridines having –CN and –COOMe groups, quickly decomposed because of HOAc of solvent system. This strategy is valid for one pot, three component reaction of ketones, aldehydes and 2-aminopyridine too for synthesis of 3-aroylimidazo[1,2-a]pyridine. Recyclability study showed that, Cu/H-OMS-2 could be reused up to four times; after that catalytic activity dropped to 48% due to leached copper species which were catalytically inactive.

$CuFe_2O_4$ superparamagnetic nanoparticle catalyzed. In past two decades, nanoparticles have emerged as a catalyst in many chemical transformations.[48] The catalytic activity of the nanoparticle depends upon the active site present on its surface. They have advantages like, large surface area, high activity, excellent stability, high selectivity; however, it has a downside when it comes to separation and recovery. Interestingly, employing superparamagnetic nanoparticles as a catalyst would be beneficial due to ease in separation by magnetic decantation instead of filtration or centrifugation.

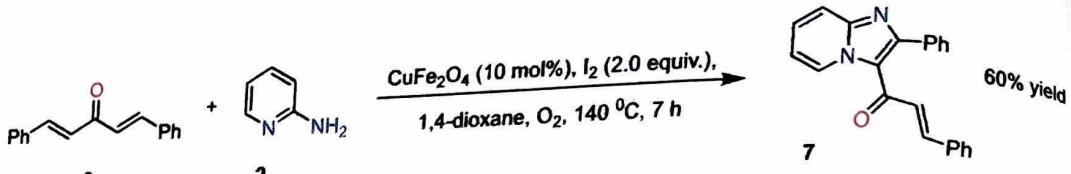
Phan et al. in 2019, successfully employed $CuFe_2O_4$ superparamagnetic nanoparticle as a catalyst for aerobic coupling of 2-aminopyridines **2** with trans-chalcones **1** to afford 3-aroylimidazo[1,2-a]pyridine **3**.[49] The reaction performed best in 10 mol% $CuFe_2O_4$ and 2 equiv. of iodine in 1,4-dioxane solvent system at 140 °C for 7 h under oxygen atm. as an oxidant (Scheme 12). The superiority of this method comes from base free and ligand free approach, the copper ferrite could easily separate by magnetic decantation and reused up to 5 times without any substantial loss in catalytic activity. This strategy also works for synthesis of 3-aroylimidazo[1,2-a]pyrimidines **17** by just replacing 2-aminopyridine **2** with 2-aminopyrimidine **16**.

They also verified whether there was any possibility of getting a double annulated product by using highly conjugated chalcone. Interestingly, they noticed only mono annulated product **7** when dibenzylideneacetone **6** were used to couple with two equivalents of 2-aminopyridine **2** under optimized condition (Scheme 13).

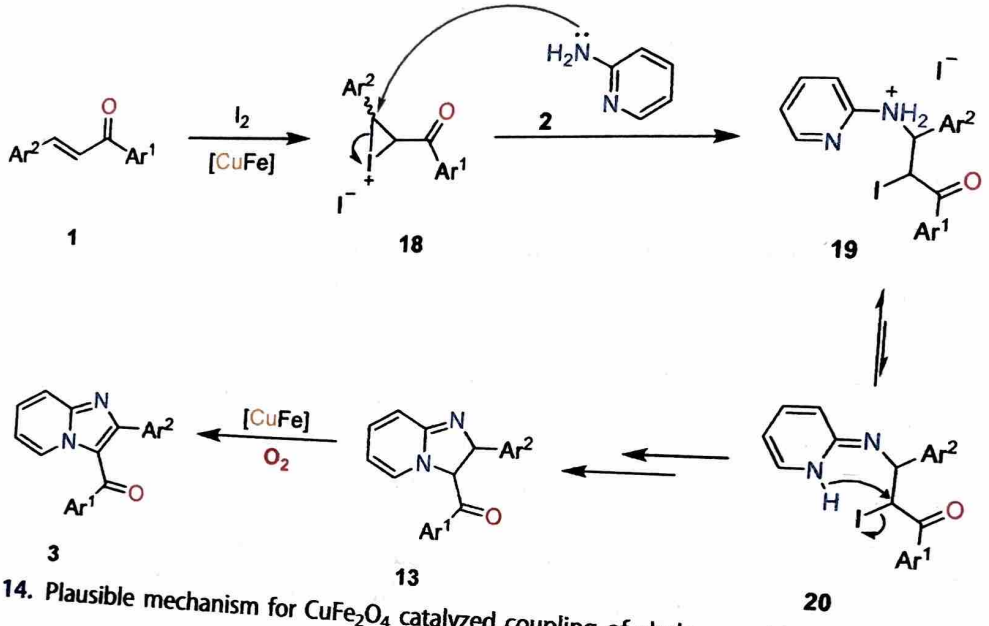


R= H, 3-Me, 4-Me, 5-Me, 5-Cl, 6-Br, 4-COOMe
Ar^1= C_6H_5, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
Ar^2= C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 12. $CuFe_2O_4$ catalyzed coupling of chalcones with 2-amino pyridines/pyrimidines.



Scheme 13. $CuFe_2O_4$ catalyzed coupling of dibenzylideneacetone with 2-aminopyridine.



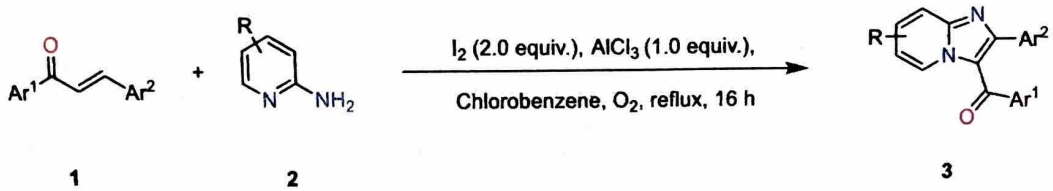
Scheme 14. Plausible mechanism for $CuFe_2O_4$ catalyzed coupling of chalcone with 2-aminopyridine.

The substrate scope for this strategy was explored; trans-chalcones substituted with chloro, bromo, methoxy groups gave good yield. But, nitro-chalcone afforded low yield. Chalcone replaced by nitroalkene gave moderate yield. Whereas, 2-aminopyridines having substitutions like methyl group at 3rd, 4th and 5th position, chloro at 5th and bromo at 6th position gave good yields. These halogenated products have further advantage of getting used up in cross-coupling reactions.

The plausible mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridine **3** is outlined in (Scheme 14). They postulated that, reaction proceeds by formation of some α-iodo ketone type compounds.[50,51] The electrophilicity of carbon-carbon double bond increases due to binding of copper iron oxide, this promotes first nucleophilic substitution on intermediate **18** to get **19**. Further, second nucleophilic attack by endocyclic pyridine nitrogen of 2-aminopyridine **2** generates intermediate **13**. Finally, aromatization of **13** occurs in presence of $CuFe_2O_4$ and oxygen to furnish 3-aroylimidazo[1,2-a]pyridine **3** as a final product.

Lewis acid catalyzed reactions promoted by iodine

$AlCl_3$ catalyzed and Iodine promoted. In 2016, Li et al. reported a unique, facile, and efficient strategy for the synthesis of 3-aroylimidazo[1,2-a]pyridines **3** from chalcones **1** and 2-aminopyridines **2** by using I_2 induced aerobic oxidative coupling.[51] The reaction



1 2 3

R= H, 4-Me, 5-NO_2, 5-Br
Ar^1= C_6H_5, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, naphthyl, 2-thienyl, 2-furyl
Ar^2= C_6H_5, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

22 examples
up to 82% yield

Scheme 15. Iodine and $AlCl_3$ induced synthesis of substituted 3-aroylimidazo[1,2-a]pyridines.

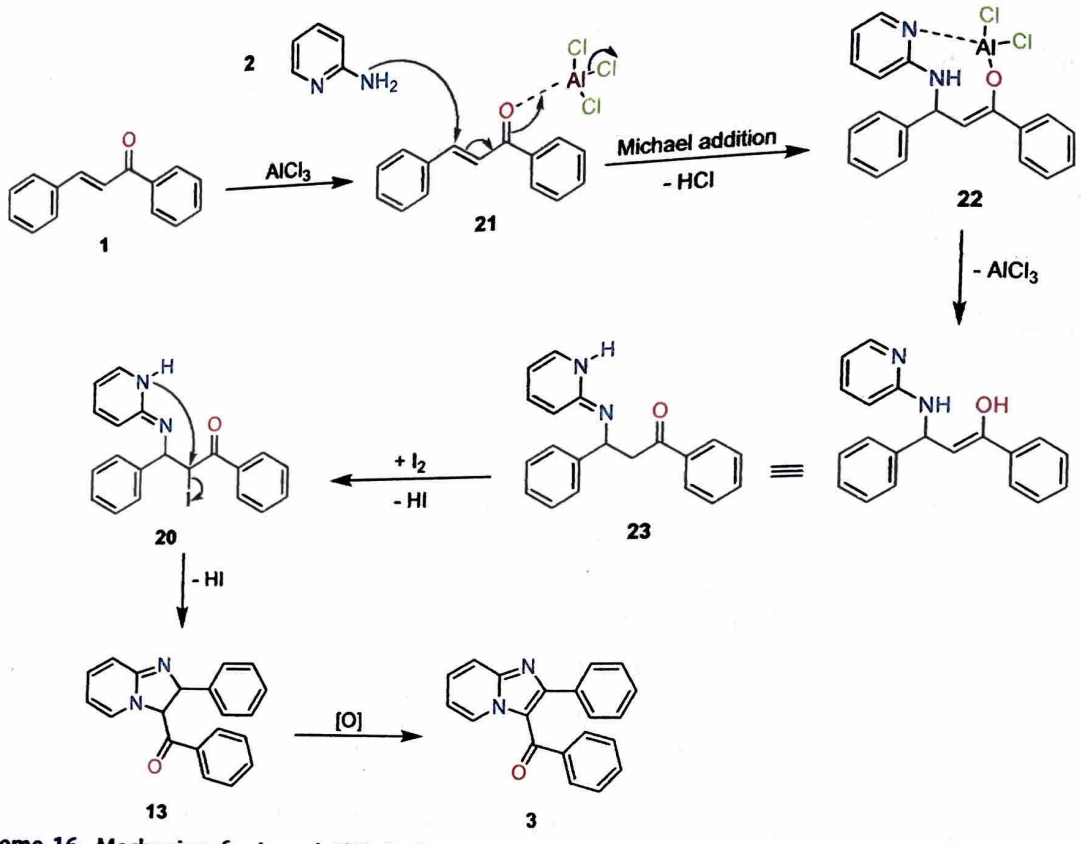
proceeds through $AlCl_3$ catalyzed tandem Michael addition, followed by intramolecular oxidative amination. The superiority of this reaction comes from high regioselectivity, transition metal free and good functional group tolerance.

In optimization studies, they noticed that tandem cyclization was not detected in absence of iodine. They screened various additives like TsOH, $AlCl_3$, K_2CO_3 and DBU; among them $AlCl_3$ worked best. Chlorobenzene proved to be the most effective solvent. Excellent yield was obtained under reflux condition. When reactions were carried out in presence of N_2 and open air atmosphere, low yields were reported. But, under an O_2 atmosphere, increment in yield was observed. The optimized condition is represented in (Scheme 15).

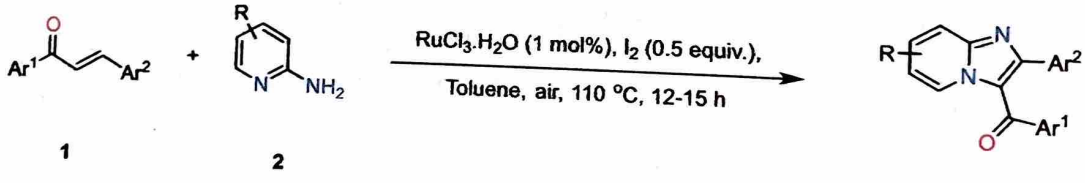
This protocol shows wide substrate scope, among them chalcones substituted with groups like methoxy, methyl, nitro, chloro and bromo were well tolerated and gave good yields. By considering electronic effects, chalcones having electron donating group gave higher yields than electron withdrawing ones. Moreover, heteroaryl chalcones such as 2-furyl, 2-thienyl, and 2-naphthyl reacted easily with 2-aminopyridine to yield corresponding imidazo[1,2-a]pyridines in good yield. Whereas, 2-aminopyridine substituted with groups like methyl at 4th position, nitro and bromo at 5th position were well tolerable and afforded moderate to good yields.

The plausible mechanism based on previous report[52] for $AlCl_3/I_2$ induced aerobic oxidative coupling between 2-aminopyridine and chalcone is outlined in (Scheme 16). Initially, chalcone **1** gets activated by $AlCl_3$ which is followed by Michael addition of exocyclic amine group of 2-aminopyridine **2** on activated chalcone **21** and generates enolate **22**, with release of HCl. Subsequently, the key intermediate **23** is formed by elimination of $AlCl_3$. Further, intermediate **23** reacts with iodine to furnish intermediate **20**. Later, **20** undergoes intramolecular cyclization and forms intermediate **13**. Finally, oxidation by oxygen furnishes 3-aroylimidazo[1,2-a]pyridine **3** as a final product.

$RuCl_3$ catalyzed and iodine promoted. In 2018, Kamal et al. reported a simple and efficient strategy for construction of densely functionalized 3-aroylimidazo[1,2-a]pyridine **3** from 2-aminopyridine **2** and chalcone **1** by using $RuCl_3.H_2O/I_2$ catalytic system.[53] The superiority of this method comes from low catalyst loading, broad substrate scope, operationally simple procedure, good functional group tolerance and high yields. In past, $RuCl_3$ has been used in many organic transformations.[54–56] During optimization studies they screened catalysts such as $Ag(OAc)_2$, Ag_2CO_3, $Bi(OTf)_3$, $Yb(OTf)_3$, and



Scheme 16. Mechanism for I_2 and $AlCl_3$ induced synthesis of 3-aroylimidazo[1,2-a]pyridine.



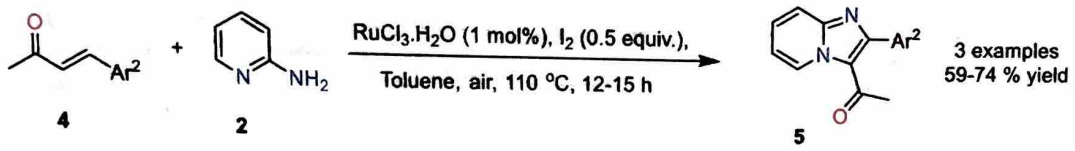
R= H, 3-Me, 6-Me, 4-Cl, 5-NO_2, 5-Br
Ar^1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4,5-$(MeO)_3C_6H_2$
Ar^2= C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 2,3,4-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$, 2-thienyl

19 examples
up to 86% yield

Scheme 17. Iodine and $RuCl_3$ induced synthesis of substituted 3-aroylimidazo[1,2-a]pyridines.

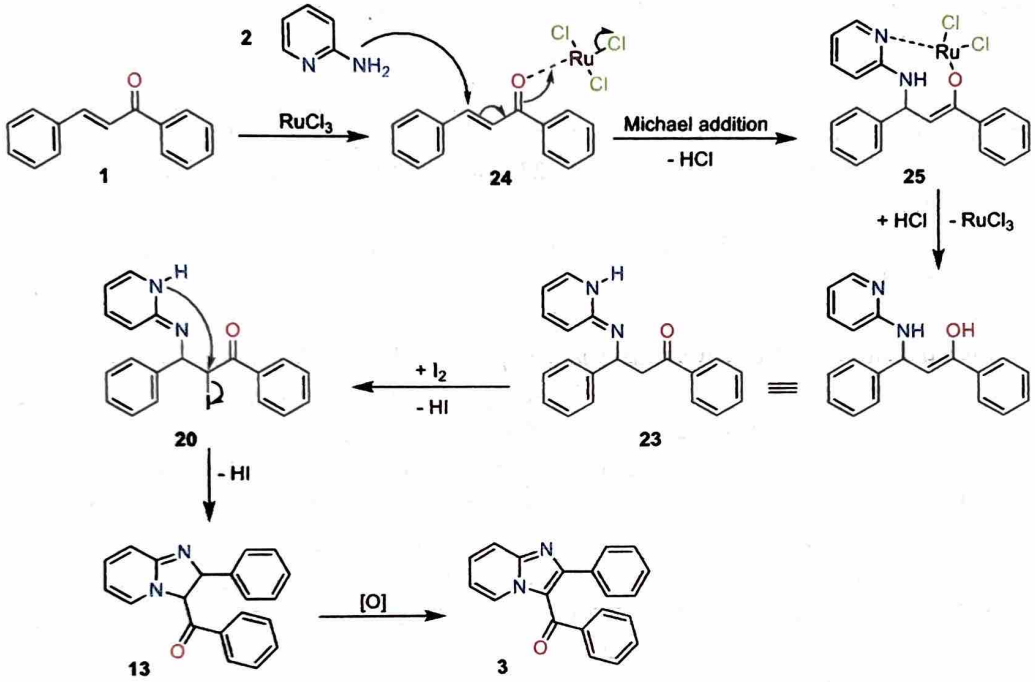
$Zn(OTf)_2$. But, $RuCl_3{\cdot}H_2O$ worked best in terms of reaction time and yield. Highest yield was obtained with 1 mol% of $RuCl_3{\cdot}H_2O$ and 0.5 equivalent of I_2 in toluene. Iodine has emerged as a green, versatile, economic reagent for many organic transformations.[49–51,57] In absence of iodine, the reaction performed sluggishly; whereas in absence of $RuCl_3$, no desired product was detected. The optimized reaction condition is shown in (Scheme 17).

From control experiment studies, they observed that; (a) Reaction carried out in N_2 atmosphere just gave Michael adduct in moderate yield and no desired product was obtained, this indicates that aerobic oxidation is necessary for reaction to occur, (b) Reaction proceeded through Michael adduct, as it was the key intermediate, (c) Radical



Ar^2= C_6H_5, 2,3,4-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$

Scheme 18. Application of optimized method on benzylideneacetone and 2-aminopyridine.

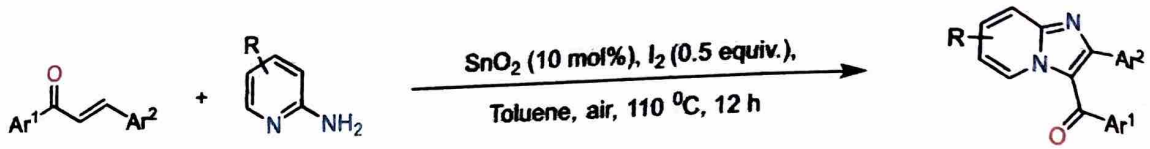


Scheme 19. Mechanism for I_2 and $RuCl_3$ induced synthesis of 3-aroylimidazo[1,2-a]pyridine.

scavenger like TEMPO did not decrease the yield appreciably, this rules out the possibility of radical pathway. In substrate scope, chalcones bearing substitution like methyl, methoxy and chloro were well tolerated to afford the desired product in moderate to good yields. Heteroaryl chalcone such as, 2-thienyl chalcone performed smoothly and gave moderate yield. Moreover, benzylideneacetone **4** afforded moderate yields of desired product **5** (Scheme 18).

Whereas, several 2-aminopyridines bearing groups like 3-Me, 6-Me, 5-Br, 4-Cl, and 5-NO_2 gave desired products in moderate to good yields. Surprisingly, the effect of steric hindrance on yield was not observed in 3-methyl-2-aminopyridine and 6-methyl-2-aminopyridine when treated with chalcones. Moreover, effective coupling was observed in 2-amino-5-nitropyridine and 6-methyl-2-aminopyridine. Gram-scale reaction under this method gave 85% yield of 3-aroylimidazo[1,2-a]pyridine with 5 gm of 2-aminopyridine and 11.05 gm of chalcone.

The plausible mechanism based on control experiments and literature reports[51] is outlined in (Scheme 19). Firstly, $RuCl_3$ activates chalcone **1** which is followed by Michael addition of exocyclic amine group of 2-aminopyridine **2** on activated chalcone



1 2 3

R= H, 4-Me, 5-Me, 3-NO_2-5-Cl
Ar^1= C_6H_5, 4-MeC_6H_4, 3-FC_6H_4, 3,4-$(F)_2C_6H_3$, 3-$CF_3C_6H_4$, 3-Me-4-FC_6H_3, 2-thienyl
Ar^2= C_6H_5, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

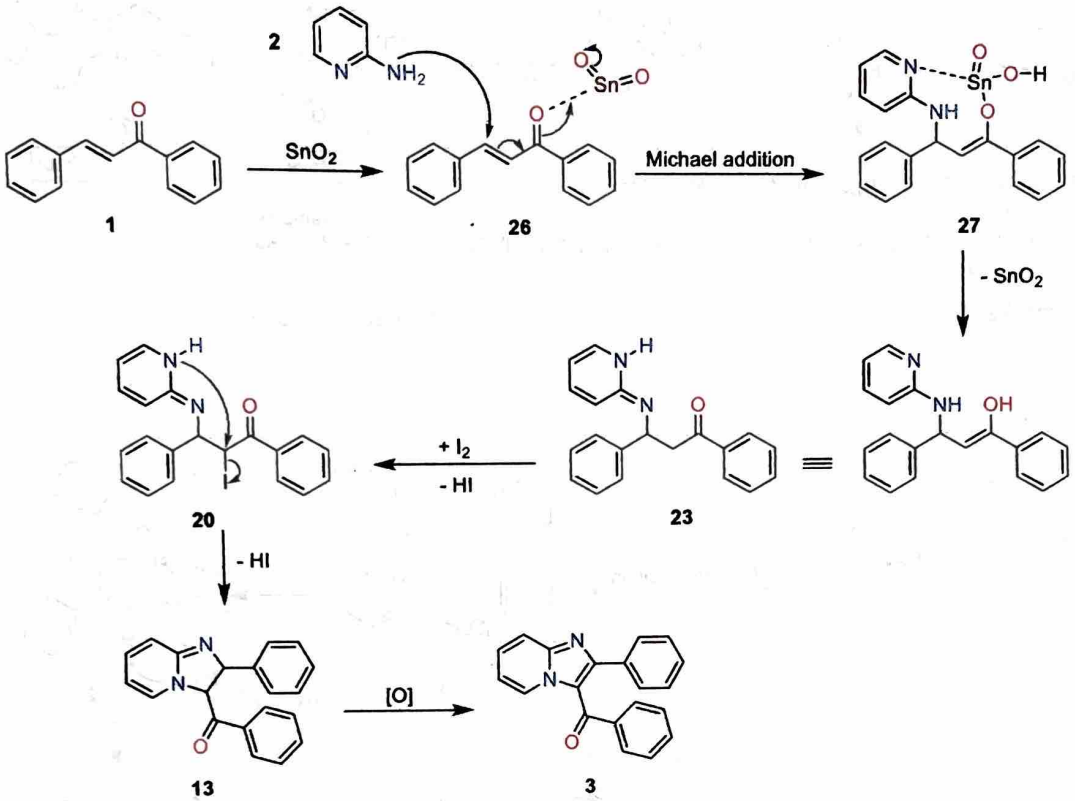
22 examples
up to 84% yield

Scheme 20. Iodine and SnO_2 NPs induced synthesis of 3-aroylimidazo[1,2-a]pyridines.

24 and generates enolate **25**, with release of HCl. Subsequently, elimination of $RuCl_3$ generates the key intermediate **23**. Further, **23** reacts with iodine to furnish intermediate **20**, followed by intramolecular cyclization to generate dihydroimidazopyridine **13**. Finally, under aerobic oxidation, the intermediate **13** undergoes aromatization to afford the desired product **3**.

SnO_2 nanoparticles (NPs) catalyzed and iodine promoted. **In 2020, Pawar et al. successfully demonstrated cascade synthesis of 3-aroylimidazo[1,2-a]pyridines 3 from chalcones 1 and 2-aminopyridines 2 by using SnO_2/I_2 as a catalytic system, and toluene as a solvent system under aerobic condition.[58] This protocol has several merits such as, high catalytic activity and chemical stability of SnO_2 NPs, ligand free and transition metal free approach, column free purification and easy workup with good yields. In the SnO_2/I_2 catalytic system, SnO_2 NPs catalyzes Michael addition of 2-aminopyridine on chalcone, and I_2 induces intramolecular oxidative C-N bond formation. In optimization studies, they screened catalysts such as ZnO, TiO_2, SnO_2, ZrO_2 and SiO_2. Among them, SnO_2 was the most active catalyst. The reaction did not proceed in the absence of both, SnO_2 and I_2. Also, the reaction did not proceed at room temperature, even if kept for a long duration. But, when refluxed for 12 h in ambient air, it gave best yield. The optimized reaction condition is shown in (Scheme 20).**

This protocol shows a wide substrate scope with different substituted chalcones and 2-aminopyridines. Surprisingly, chalcones bearing electron withdrawing groups as well as electron donating groups showed similar reactivity patterns and afforded good yields. Chalcone substituted with fluoro, nitro, methyl and trifluoromethyl were well tolerated and afforded 55–84% yield. Even, heteroaryl chalcone like 2-thienyl reacted smoothly and gave 59–64% yields. Whereas, 2-aminopyridines bearing methyl group at 4th and 5th position reacted efficiently to give 51–77% yield. In case of 2-amino-3-nitro-5-chloro-pyridine on reaction with chalcone, it just gave traces of corresponding product. This was due to –R and –I effect of nitro and chloro group on 2-aminopyridine. One pot, three component reaction of acetophenone, benzaldehyde and 2-aminopyridine under optimized reaction condition gave 55–76% yields. In recycle study of SnO_2 NPs, they observed that the catalyst was found indistinguishable by XRD pattern even after ten catalytic cycles. This indicates high chemical stability of SnO_2 NPs.

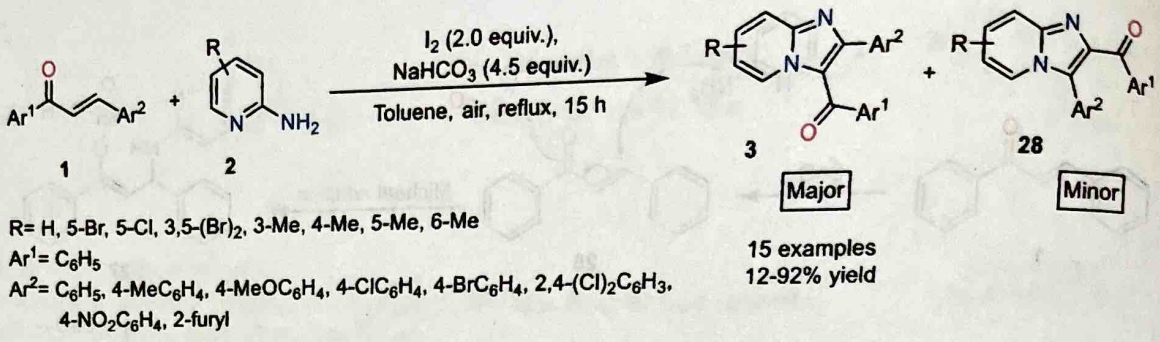


Scheme 21. Mechanism for I_2 and SnO_2 NPs induced synthesis of 3-aroylimidazo[1,2-a]pyridine.

The plausible mechanism for this strategy is outlined in (Scheme 21). Initially, SnO_2 activates chalcone **1** which leads to Michael addition of an exocyclic amine group of 2-aminopyridine **2** on activated chalcone **26** to form an enolate **27**. Subsequently, elimination of SnO_2 generates key intermediate **23**. Further, **23** reacts with iodine to furnish intermediate **20**, followed by intramolecular cyclization to generate dihydroimidazopyridine **13**. Finally, under aerobic oxidation, the intermediate **13** undergoes aromatization to afford the desired product **3**.

Iodine and base promoted reaction

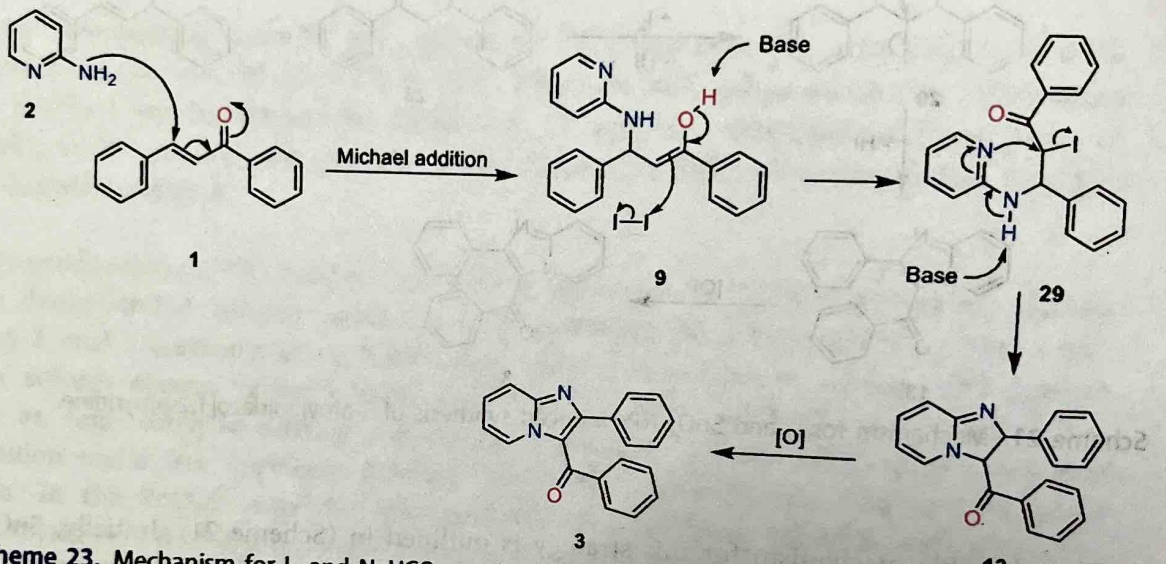
Iodine and $NaHCO_3$ promoted reaction in toluene. Yu et al. in 2018, regioselectively synthesized 3-aroylimidazo[1,2-a]pyridines **3** through iodine mediated diamination of chalcones **1** with 2-aminopyridines **2**.[59] They demonstrated regioselective synthesis of 3-aroyl and 2-aroylimidazo[1,2-a]pyridines by just changing the solvent system and substituents on 2-aminopyridines. While optimization, they screened solvents such as 1,4-dioxane, ACN, DMSO, DCE and toluene in presence of $NaHCO_3$ and K_2CO_3 as a base. Among them, toluene significantly improved the yield and gave regioselectively 3-aroylimidazo[1,2-a]pyridine **3** with trace amount of 2-aroylimidazo[1,2-a]pyridine **28**. Whereas, base such as $NaHCO_3$ resulted in excellent yield than K_2CO_3. However, they choose a high stoichiometric amount to optimize the reaction condition. For (0.5 mmol) chalcone, they used (2.0 mmol) 2-aminopyridine, (1.0 mmol) iodine and (2.25 mmol) $NaHCO_3$. The optimized reaction condition is shown in (Scheme 22).



R= H, 5-Br, 5-Cl, 3,5-$(Br)_2$, 3-Me, 4-Me, 5-Me, 6-Me
Ar^1= C_6H_5
Ar^2= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2,4-$(Cl)_2C_6H_3$, 4-$NO_2C_6H_4$, 2-furyl

15 examples
12-92% yield

Scheme 22. Iodine and $NaHCO_3$ induced synthesis of 3-aroylimidazo[1,2-a]pyridines.



Scheme 23. Mechanism for I_2 and $NaHCO_3$ mediated synthesis of 3-aroylimidazo[1,2-a]pyridine.

Substrate scope was explored by reacting chalcones with several halogenated 2-aminopyridines; they noticed, unsubstituted chalcone formed 3-aroyl isomer regioselectively. However, 2-aminopyridine bearing electron withdrawing group like 3,5-dibromo gave moderate yield. The regioselectivity and yield remained unaffected in case of chalcones bearing electron rich groups like methyl, methoxy and mono halogens like Cl, Br. Also, heteroaryl chalcone such as 2-Furyl chalcone gave good yield. Whereas, chalcones bearing electron withdrawing groups or aliphatic group lowered the yield of 3-aroyl isomer and increased the yield of 2-aroyl isomer. Moreover, unsubstituted 2-aminopyridine and those bearing methyl groups favored the formation of undesired 2-aroyl isomer. Surprisingly, 6-methyl-2-aminopyridine gave regioselectively 3-aroyl isomer. This was due to steric hindrance induced by 6-methyl group. The plausible mechanism is outlined in (Scheme 23). At first, chalcone **1** undergoes Michael addition by exocyclic amine group of 2-aminopyridine **2** to give intermediate **9**. Further, iodine mediated cyclization of **9** generates dihydroimidazopyridine **13** via intramolecular Ortoleva-King reaction.[60] Finally, aromatization of **13** furnishes the desired product **3**.

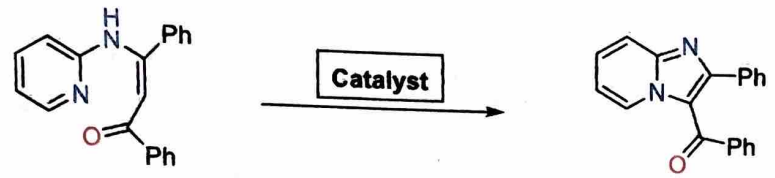
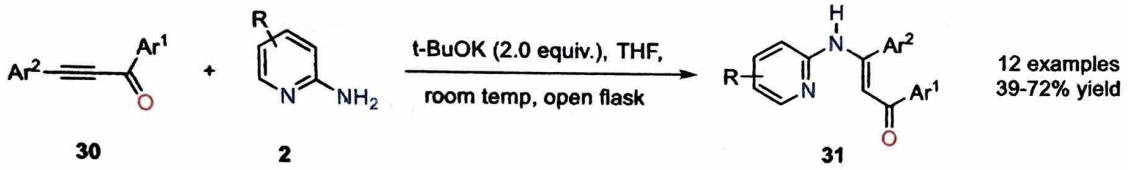


Figure 3. Strategy based on C-H amination of N-aryl enaminones.



R= H, 5-F, 5-Cl, 5-Br, 5-I, 4-CN, 6-Me
Ar^1= C_6H_5, 4-(t-Bu)C_6H_4, 2-thienyl
Ar^2= C_6H_5, 3-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4

Scheme 24. Synthesis of N-pyridyl enaminones from α,β-ynones and 2-aminopyridines.

From N-heteroaryl enaminones

Enaminones are a class of very stable, easily available and versatile reactive compound having widespread application in organic synthesis. β-enaminones are very useful synthetic intermediate due to their peculiar electronic properties. They possess ambident electrophilic character at enone moiety and ambident nucleophilic character at enamine moiety.[61, 62] Direct cross-dehydrogenative amination of C(sp^2)–H bonds by using transition metal catalyst has emerged as a straightforward method.[63] Previously, many protocols have been developed for intramolecular direct C–N bond formation by using either catalytic amount of Pd-complexes[64] or Cu-salts.[65] But, most of the C–N bond formation of C(sp^2)–H via C–H activation was carried out on aryl systems. In this section, we have discussed C-H amination via copper-catalyzed intramolecular oxidative coupling in alkene system in the form of N-aryl enaminones to access 3-aroylimidazo[1,2-a]pyridines (Figure 3).

Copper (I) iodide catalyzed in DMF

In 2015, Das et al. reported a general Cu(I) catalyzed intramolecular oxidative C-H amination of N-heteroaryl enaminones **31** to access 3-aroylimidazo[1,2-a]pyridine **3** under ligand and base free condition.[66] This open air protocol is also applicable for synthesis of substituted imidazo[1,2-a]pyrimidines and imidazo[1,2-a]pyrazines. Initially, they synthesized N-pyridyl enaminones **31** via conjugate addition of 2-aminopyridine **2** with α,β-ynones **30** in THF solvent and t-BuOK as a base (Scheme 24).

Similarly, enaminones containing pyrazine, pyrimidine and benzothiazole were also prepared using same protocol. While optimization for 3-aroylimidazo[1,2-a]pyridine **3**, they performed C–H amination on N-pyridyl enaminone **31** by using 1,10-phenanthroline as a ligand and K_2CO_3 as a base. To investigate the role of ligand and base, they performed a reaction in the absence of ligand and base. Surprisingly, the reaction proceeded best without base and ligand to afford 90% yield. Several Cu(I) and Cu(II) salts

R= H, 5-F, 5-Cl, 5-Br, 5-I, 4-CN, 6-Me
Ar^1= C_6H_5, 4-(t-Bu)C_6H_4, 2-thienyl
Ar^2= C_6H_5, 3-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4

Scheme 25. Oxidative C–N bond formation for synthesis of 3-aroylimidazo[1,2-a]pyridines.

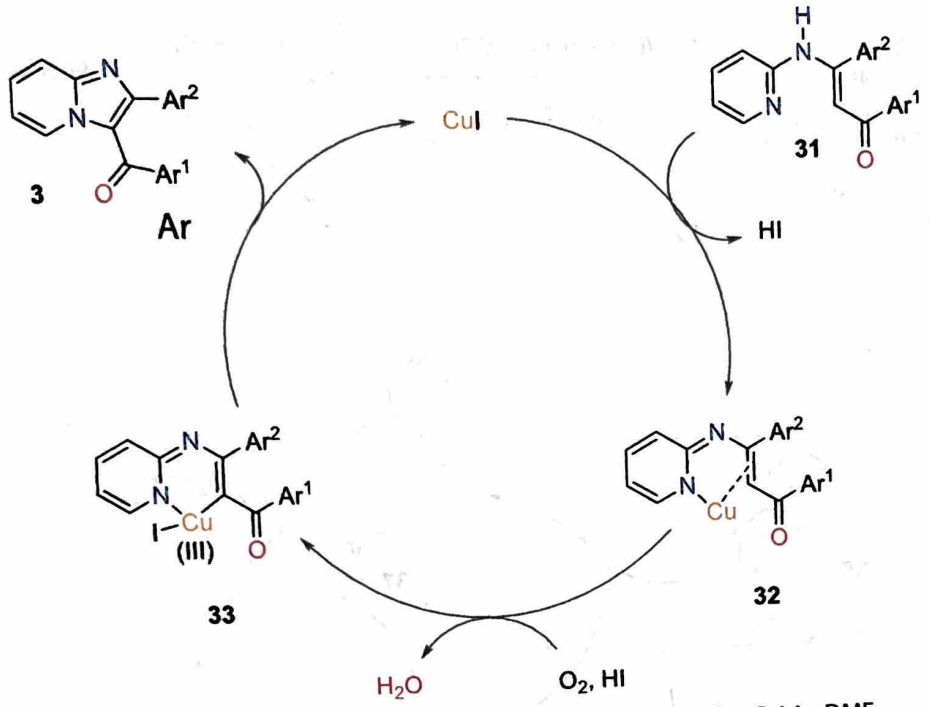
were screened, such as CuCl, CuBr, CuI, Cu_2O, $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$ and $Cu(OAc)_2$ in DMF; among them CuI gave best yield. Whereas, solvents such as EtOAc, EtOH, CH_3CN, THF gave poor yields. However, reaction under O_2 atmosphere did not improve the yield and under N_2 atmosphere it gave poor yield. The optimized reaction condition is shown in (Scheme 25).

Substrate scope for a wide variety of N-pyridyl enaminones was studied. Several functional groups present on enone and N-pyridyl fragment were well tolerated, including heteroaryl moiety and entire range of halogens (fluoro, chloro, bromo, iodo) to afford the corresponding 3-aroyl-2-arylimidazo[1,2-a]pyridine **3** in good yields (73–90%). N-pyridyl bearing cyano was well efficient to give 85% yield. However, in 2-amine-6-methylpyridine derivative, the steric congestion due to 6-methyl group was well tolerated to afford the desired product in 73% yield. Same protocol was efficient for constructing imidazo[1,2-a]pyrazine and imidazo[1,2-a]pyrimidine framework by just replacing N-pyridyl enaminone with pyrazine and pyrimidine derived enaminone respectively to afford desired product in good yields (76–88%). Medically important framework like di-substituted benzo[d]imidazo[2,1-b]thiazole were also synthesized using this protocol to afford 66% yield.

The plausible mechanism is outlined in (Scheme 26). At first, N-pyridyl enaminone **31** undergoes coordination followed by complexation of the pyridine ring with CuI to generate intermediate **32**. Further, intermediate **32** gets oxidized to Cu(III) complex **33** by O_2 in air, followed by reductive elimination to give the desired product **3**.

Copper (I) iodide catalyzed in DMSO

Wan et al. in 2016, reported a Cu(I) catalyzed intramolecular C(sp^2)–H amination of N-pyridinyl enaminones **35** to afford 2-unsubstituted 3-aroylimidazo[1,2-a]pyridines **36** under aerobic condition.[67] Previously 2,3-disubstituted imidazo[1,2-a]pyridines were synthesized by β-enaminones bearing free NH group and additional β-substituent.[68] As predetermined by the structure of starting material, those β-enaminones could not afford 2-unsubstituted imidazo[1,2-a]pyridine. To do so, they identified transamination between N,N-disubstituted 3-enaminones for generating –NH bearing 2-enaminones.[69] They applied this protocol to access N-pyridinyl 2-enaminones **35** by reacting enaminones **34** and 2-aminopyridines **2**. Further, the obtained N-pyridinyl 2-enaminones **35** undergoes intramolecular C–H amination for constructing 2-unsubstituted 3-aroylimidazo[1,2-a]pyridine **36** (Figure 4).



Scheme 26. Mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridines by CuI in DMF.

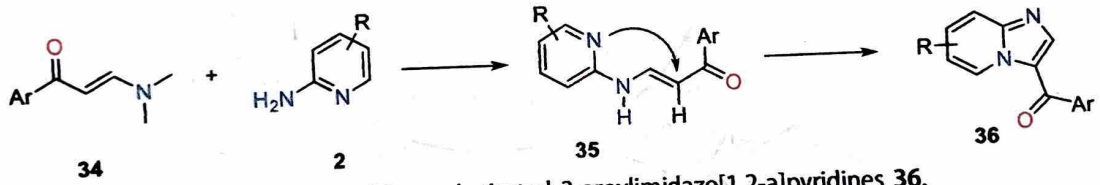
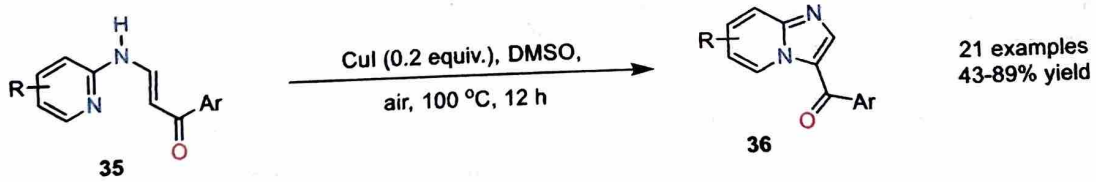


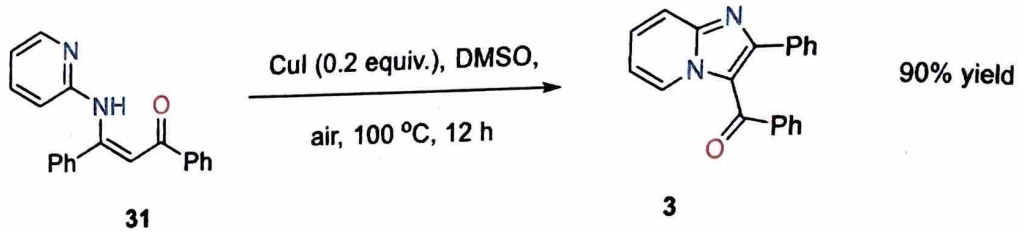
Figure 4. Strategy for synthesis of 2-unsubstituted 3-aroylimidazo[1,2-a]pyridines **36**.



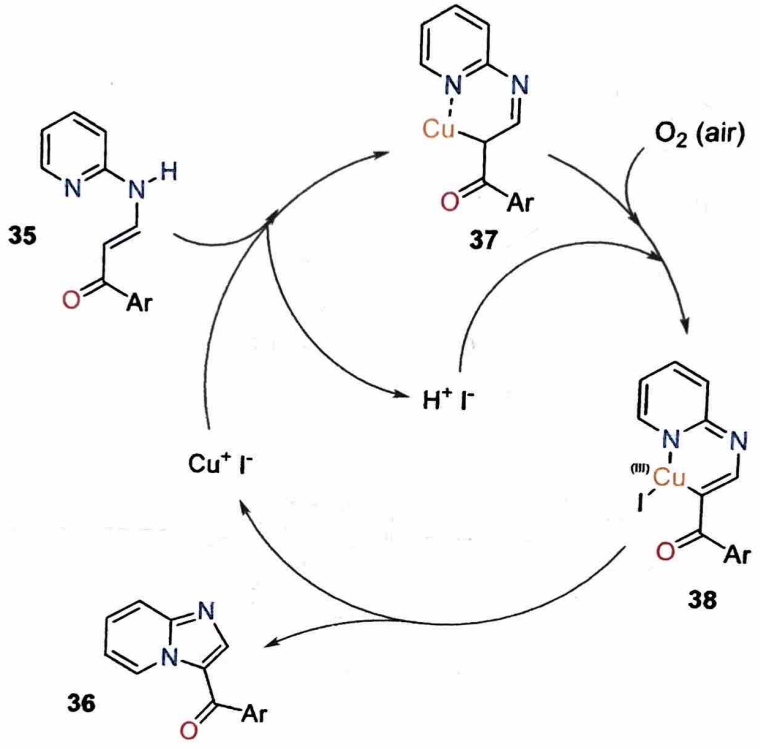
R= H, 6-Me, 4-Me, 4-Cl
Ar= C_6H_5, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$(Cl)_2C_6H_3$, 4-CNC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2-$(OH)C_6H_4$, piperonyl, 2-thienyl, naphthalen-2-yl

Scheme 27. Transformation of N-pyridyl enaminone to 3-aroylimidazo[1,2-a]pyridine.

The optimized reaction condition is shown in (Scheme 27). N-pyridinyl enaminone **35** were subjected to various Cu(I) and Cu(II) salts such as CuI, CuBr, CuCl, $Cu(OAc)_2$, and $CuCl_2$; among those, only 20 mol% CuI worked efficiently at 100 °C. Reaction did not proceed without CuI. Among the various solvent systems screened, DMSO gave good yields. Substrate scope of this protocol was explored. In the aryl ring system associated with 3-aroyl group, electron donating and withdrawing groups were well tolerated and afforded the corresponding 3-aroylimidazo[1,2-a]pyridine **36** in moderate to excellent yield. Whereas, pyridine ring system bearing electron withdrawing



Scheme 28. Synthesis of 3-aroyl-2-arylimidazo[1,2-a]pyridine **3** from **31**.



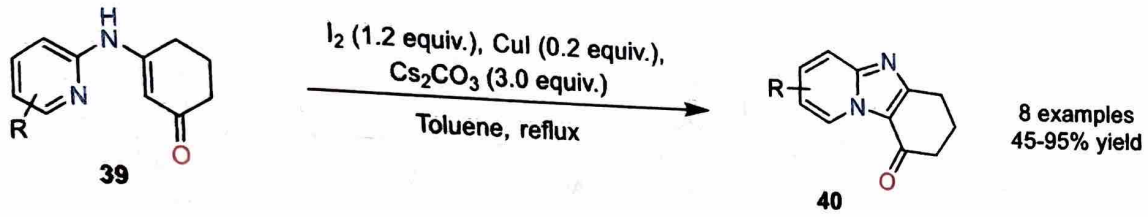
Scheme 29. Mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridines by CuI in DMSO.

group lowered the yield of desired product. Moreover, the same protocol also worked on N-pyridinyl enaminone bearing phenyl substitution at β-position to afford the corresponding product in excellent yield (Scheme 28).

The plausible mechanism is outlined in (Scheme 29). At first, enaminone **35** react with Cu(I) ion through N-chelating site of the pyridine ring to generate cuprous intermediate **37**. Further, aerobic oxidative addition of intermediate **37** generates intermediate **38** bearing Cu(III). Finally, intermediate **38** undergoes reductive elimination to furnish the desired product **36** and the Cu(I) salt released is reused in next catalytic cycle.

Iodine mediated and copper (I) iodide catalyzed

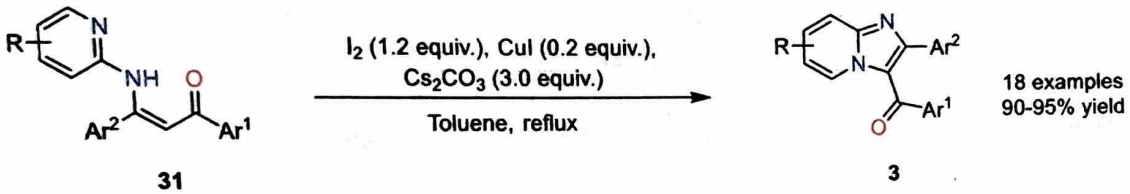
In 2016, Chang et al. reported an efficient and versatile method for synthesis of diverse imidazo[1,2-a]pyridines **40, 3** using N-heteroaryl substituted enamine **39, 31** via I_2-mediated oxidative C–N bond formation.[70] This C–H functionalization also works for



39 40

R= H, 6-Me, 5-Me, 4-Me, 3-Me, 5-Cl, 5-Br, 3,5-$(Br)_2$

Scheme 30. Synthesis of fused imidazo[1,2-a]pyridine from enamine **39**.



31 3

R= H, 6-Me, 5-Me, 4-Me, 3-Me, 5-Cl, 5-Br, 3,5-$(Br)_2$
Ar^1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-$CF_3C_6H_4$, 2-$MeOC_6H_4$, naphthalen-2-yl, 2-thienyl
Ar^2= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

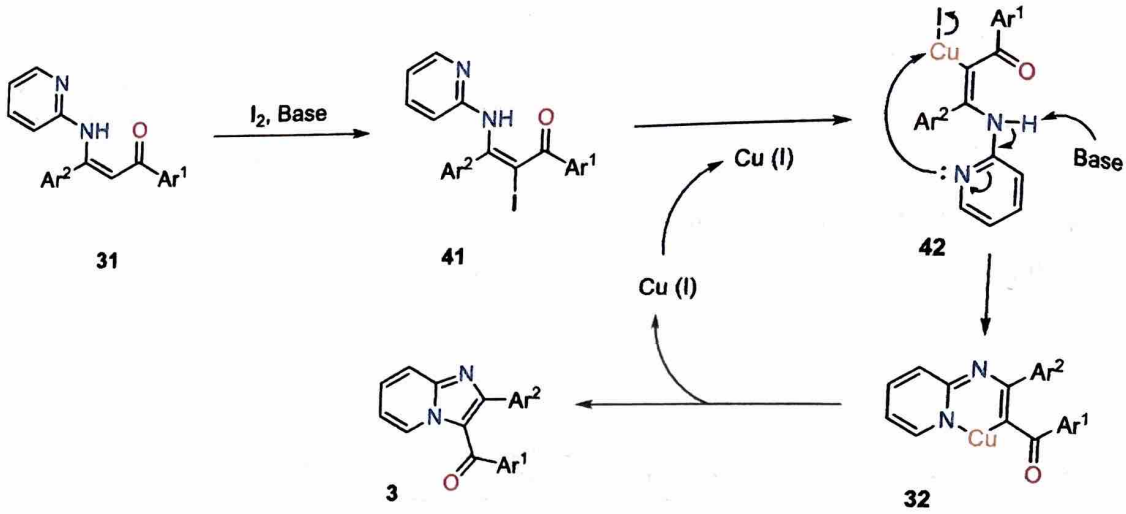
Scheme 31. Synthesis of 3-aroylimidazo[1,2-a]pyridines **3**.

synthesis of indoles by using N-aryl substituted enamines. In this catalytic system, I_2 works as a sole oxidant in presence of CuI. Initially, they developed a protocol for constructing fused imidazo[1,2-a]pyridine **40** from N-pyridylcyclohexenamine **39** via I_2/CuI mediated C–H functionalization in presence of Cs_2CO_3 and refluxing in 1,4-dioxane. On further screening of solvent, toluene was found more efficient than 1,4-dioxane (Scheme 30). Further, the same protocol was employed for constructing 3-aroylimidazo[1,2-a]pyridine **3** which resulted in excellent yields by using N-pyridyl enaminone **31** for C–H functionalization (Scheme 31). Substrate scope of the protocol revealed well tolerance of pyridine ring system bearing electron withdrawing and electron donating groups. They even extended this protocol for synthesis of indole by using N-phenylenamines via oxidative C–C bond formation.

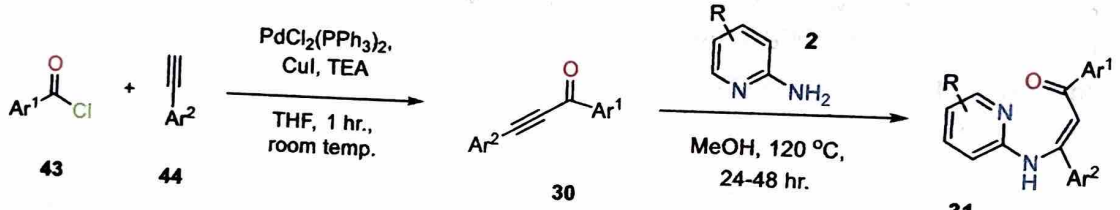
The plausible mechanism for this protocol is outlined in (Scheme 32). Initially, N-(2-pyridyl)enaminone **31** reacts with I_2 under basic condition to generate β-iodoenamide **41**, followed by oxidative addition of Cu(I) to form copper complex **42**. Further, base promoted cyclization of intermediate **42**, results in formation of intermediate **32**, followed by reductive elimination to furnish the desired 3-aroylimidazo[1,2-a]pyridine **3**. The released Cu(I) salt is reused in the next catalytic cycle.

Copper (I) iodide and 1,10-phenanthroline catalyzed

In 2018, S. Cacchi et al. developed an efficient and facile protocol for synthesis of multi-substituted imidazo[1,2-a]pyridines **3** from N-(2-pyridinyl)enaminones **31** by using Cu (I) catalyzed C-N bond formation via C-H functionalization.[71] The required substrate, N-(2-pyridinyl)enaminones **31** were prepared via Sonogashira cross-coupling between



Scheme 32. Proposed mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridine 3.



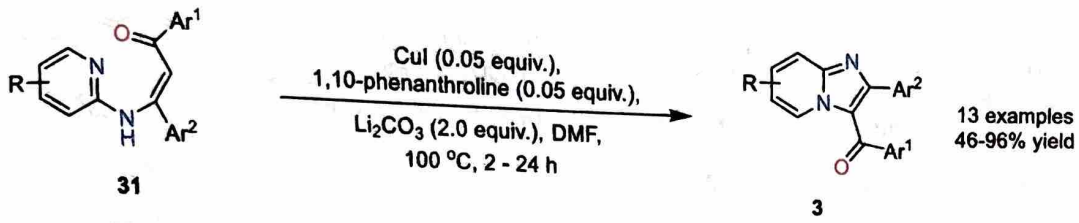
R= H, 5-Br, 5-Cl, 3-Br-5-Me
Ar^1= C_6H_5, 4-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-$CF_3C_6H_4$, 4-FC_6H_4, 4-PhC_6H_4, 3,5-$(MeO)_2C_6H_3$
Ar^2= C_6H_5, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-BrC_6H_4, 4-CNC_6H_4, 3-$(MeCO)C_6H_4$

Scheme 33. Synthesis of N-(2-pyridinyl)enaminones 31.

terminal alkynes 44 and aroyl chloride 43 to afford α,β-ynones 30; followed by conjugate addition of 2-aminopyridine 2 to give the desired enaminones 31 (Scheme 33).[72]

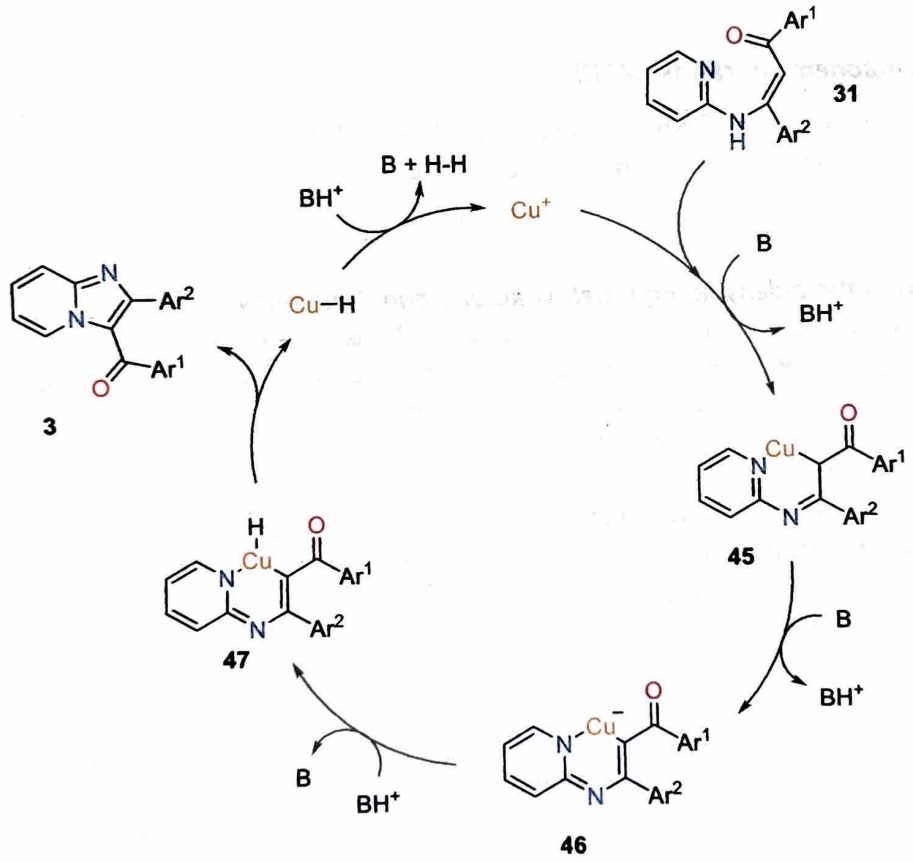
In optimization study, they subjected N-(2-pyridinyl)enaminone 31 to CuI as the catalyst at 100 °C, and various ligands, bases and solvent systems were screened to afford the corresponding imidazo[1,2-a]pyridine 3. Reaction did not proceed in absence of CuI and ligand. Solvent systems such as dioxane gave a trace amount of product; whereas, MeCN afforded nothing. Ligand systems such as, L-proline and dppe resulted in low yields; whereas, PPh_3 and DMEDA afforded 60% and 67% yield respectively. However, 1,10-phenanthroline gave best result. Among bases, Li_2CO_3 furnished better yield than K_2CO_3. The optimized reaction condition is shown in (Scheme 34).

When the role of ligand were investigated by using NMR study; they noticed formation of copper-enaminone complex which restricted the cyclization process. To overcome this problem, generation of stable copper-ligand complex such as copper-1,10-phenanthroline is vital for efficient synthesis of 3-aroylimidazo[1,2-a]pyridine. This protocol shows wide substrate scope with good to excellent yields and well tolerance toward functional groups such as fluoro, chloro, bromo, cyano, trifluoromethyl and ether.



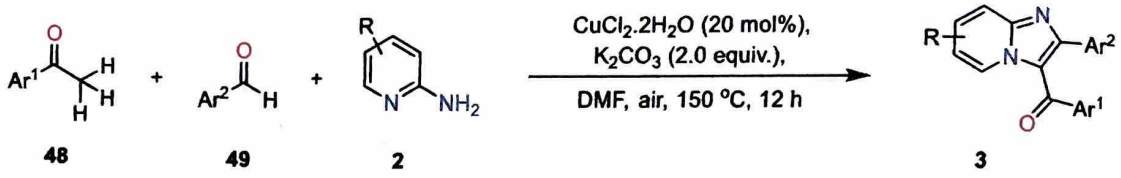
R= H, 5-Br, 5-Cl, 3-Br-5-Me
Ar^1= C_6H_5, 4-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-$CF_3C_6H_4$, 4-FC_6H_4, 4-PhC_6H_4, 3,5-$(MeO)_2C_6H_3$
Ar^2= C_6H_5, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-BrC_6H_4, 4-CNC_6H_4, 3-$(MeCO)C_6H_4$

Scheme 34. Synthesis of 3-aroylimidazo[1,2-a]pyridines **3**.



Scheme 35. Proposed reaction mechanism for synthesis of **3** from **31**.

The plausible mechanism is outlined in (Scheme 35). Firstly, N-(2-pyridinyl)enaminones **31** react with CuI in the basic medium to generate complex **45**. Then, base abstracts proton attached to carbon α to the carbonyl group, this leads to intramolecular nucleophilic attack of pyridine nitrogen on the copper of complex **45**. Further, the generated complex **46** converts to complex **47** due to protonation. Finally, reductive



48 49 2 3

R= H, 3-Me, 4-Me, 5-Me, 5-Br
Ar^1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2-thienyl
Ar^2= C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 2-FC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl

16 examples
26-82% yield

Scheme 36. One-pot, three-component tandem reaction for synthesis of **3**.

elimination of CuH furnishes the desired product **3**. Later, CuH is converted to Cu (I) via reaction with conjugate acid of base and reused in next catalytic cycle.

Multicomponent reactions (MCR)

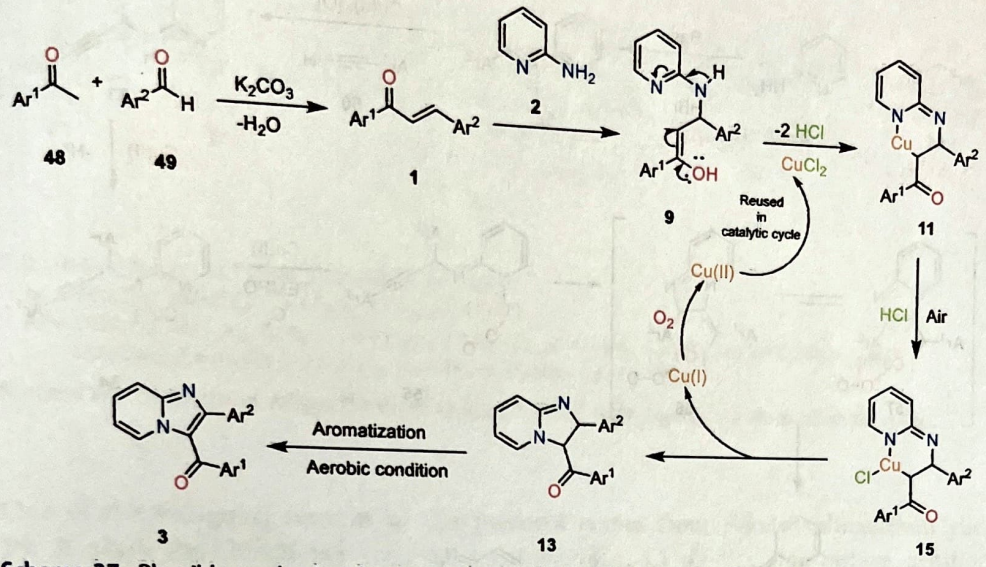
In modern synthetic chemistry, MCR fused with tandem sequences is one of the remarkable strategies applied to carry out coupling reactions in construction of fused heterocycles.

From aromatic aldehyde, aryl methyl ketone and 2-aminopyridine

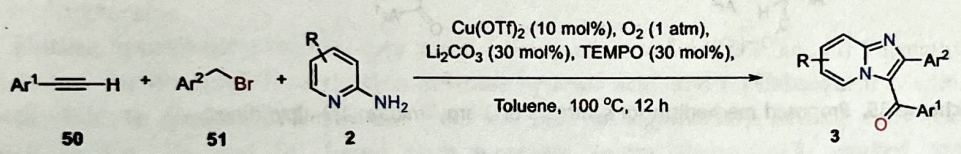
Kumar et al. in 2015, demonstrated a facile synthesis of 3-aroylimidazo[1,2-a]pyridines **3** by using one pot, three component tandem reaction of acetophenone **48**, aromatic aldehydes **49** and 2-aminopyridines **2** in presence of catalytic amount of copper (II) chloride and air as an oxidant.[73]

The prime features of this method includes, atom economical, one step procedure, readily accessible precursors, simple isolation, moderate to good yields, and good functional group tolerance. In their initial study, they expected by-products such as, (a) Naphthyridine, and (b) 2-phenylimidazo[1,2-a]pyridine. However, naphthyridine was not detected. But, 2-phenylimidazo[1,2-a]pyridine were detected in minor quantity due to reaction between acetophenone and 2-aminopyridine. To overcome this problem, they reduced the rate of formation of this by-product by increasing the rate of reaction between aromatic aldehyde and acetophenone. To achieve that, they kept acetophenone as a limiting reagent. During optimization they found K_2CO_3 improved the yield slightly. Whereas, DMF as a solvent enhanced the yield smoothly. The optimized reaction condition is shown in (Scheme 36). The substrate scope was explored. 2-aminopyridines bearing methyl at 3-, 4-, 5- position gave moderate to good yield. Also, highly sensitive bromo group on 2-aminopyridine were well tolerated. However, aromatic aldehydes bearing electron withdrawing groups like 4-Cl, 2-F and 4-NO_2 afforded high yields; whereas those bearing electron rich groups afforded 2-arylimidazo[1,2-a]pyridine instead of 3-aroylimidazo[1,2-a]pyridine, due to faster rate of reaction between acetophenone and 2-aminopyridine as compared to acetophenone and aromatic aldehyde.

The plausible mechanism is outlined in (Scheme 37). Initially, crossed aldol condensation between aromatic aldehyde **49** and acetophenone **48** generates chalcone **1**, followed by Michael addition of 2-aminopyridine **2** on chalcone affords Michael adduct **9**.



Scheme 37. Plausible mechanism for the synthesis of 3-aroylimidazo[1,2-a]pyridines.



R= H, 3-Cl, 5-Cl, 3-Br, 5-Br, 6-COOEt
Ar^1= C_6H_5, 2-BrC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 2,4-$(Cl)_2C_6H_3$
Ar^2= C_6H_5, 4-$CF_3C_6H_4$, 2-ClC_6H_4, 2-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3-$CF_3C_6H_4$, 4-$(COOEt)C_6H_4$, 1-naphthalene, 5-Me-2-furan, 2-thienyl

23 examples
53-87% yield

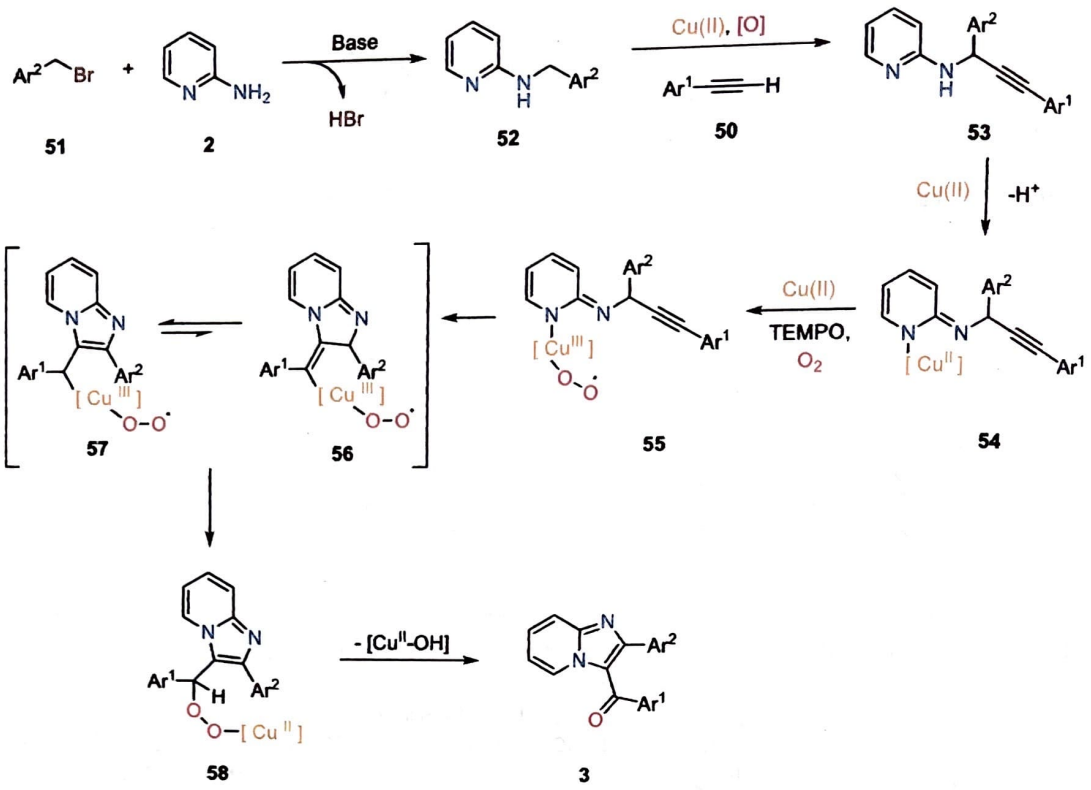
Scheme 38. Oxidative cascade reaction for synthesis of 3-aroylimidazo[1,2-a]pyridines.

Pyridinium nitrogen and enolic carbon of Michael adduct interacts with copper salt to generate intermediate **11**. Further oxidation of Cu(II) salt to Cu(III) salt generates intermediate **15**, which later undergoes reductive elimination to give dihydroimidazopyridine **13** and Cu(I) salt. In the presence of air, Cu(I) salt oxidizes to Cu(II) salt and further used in next catalytic cycle. Finally, aromatization of intermediate **13** under aerobic condition furnishes the desired product **3**.

From 2-aminopyridine, benzyl bromide and terminal alkyne

In 2018, Liu et al. reported a general and efficient copper-catalyzed oxidative cascade reaction comprising of terminal alkyne **50**, 2-amino N-heterocycle **2**, benzyl or allylic bromide **51** for synthesis of imidazo fused heterocycles with molecular oxygen.[74] During optimization study, they noticed $Cu(OTf)_2$ as a catalyst, Li_2CO_3 as a base, TEMPO and molecular oxygen as an oxidant in toluene solvent system, gave the desired 3-aroylimidazo[1,2-a]pyridine in (87%) best yield (Scheme 38).

No product was obtained by using Pd (II) and Mn (II); whereas, Cu (I) and Fe (III) showed lower efficiency. Replacing $Cu(OTf)_2$ with HOTf gave no yield, suggesting the



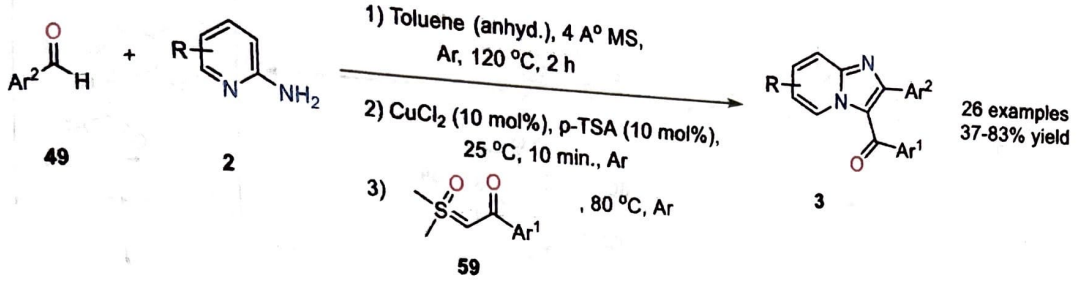
Scheme 39. Proposed mechanism for synthesis of 3-aroylimidazo[1,2-a]pyridines.

vital role of copper salt. Under the N_2 atmosphere, just a trace amount of product was obtained, which indicates the crucial role of O_2 in transformation. Substrate scope for this protocol was explored. 2-aminopyridine bearing electron donating groups were more efficient than those with electron withdrawing groups. Fused arenes or heterocycles such as, naphthalene, furan and thiophene corresponding to bromo substrate gave the desired products in good yields. Important functionalities like, methoxy, ester, trifluoromethyl were well tolerated at different positions. This protocol is also applicable for synthesis of benzo[d]imidazo[2,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[1,2-b]pyridazine and imidazo[1,2-c]pyrimidine fused heterocycles by just making changes in 2-amino N-heterocycles.

Based on control experiment studies, the plausible mechanism is shown in (Scheme 39). Initially, 2-aminopyridine **2** undergoes S_N2 reaction with benzylic bromide **51** to generate intermediate **52**, followed by cross dehydrogenative coupling of **52** with terminal alkyne **50** in presence of Cu (II)-catalyzed oxidative condition to generate intermediate **53**. Further, **53** coordinates with Cu (II) catalyst to generate complex **54**. Subsequently, SET process occurs with molecular oxygen, which might be assisted by TEMPO to generate peroxy-Cu (III) intermediate **55**. Further, sequence of intramolecular amino-cuperation of alkynes and oxygenative carbonylation furnishes the desired product **3**.

From aromatic aldehyde, 2-aminopyridine and sulfoxonium ylide

Recently, Guchhait et al. reported a protocol involving [4 + 1]-annulation of in-situ generated heterocyclic azine-aldimines with β-keto sulfoxonium ylides for construction of multisubstituted imidazole-fused heterocycles via noncarbenoid route (Scheme 40).[75]



R= H, 3-($PhCH_2O$), 5-Cl, 3-Me, 4-COOMe, 5-Br, 5-Me
Ar^1= 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$
Ar^2= 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-OHC_6H_4, 3,5-$(MeO)_2$-4-$(OH)C_6H_2$, quinolin-3-yl, quinolin-4-yl, naphthalen-1-yl

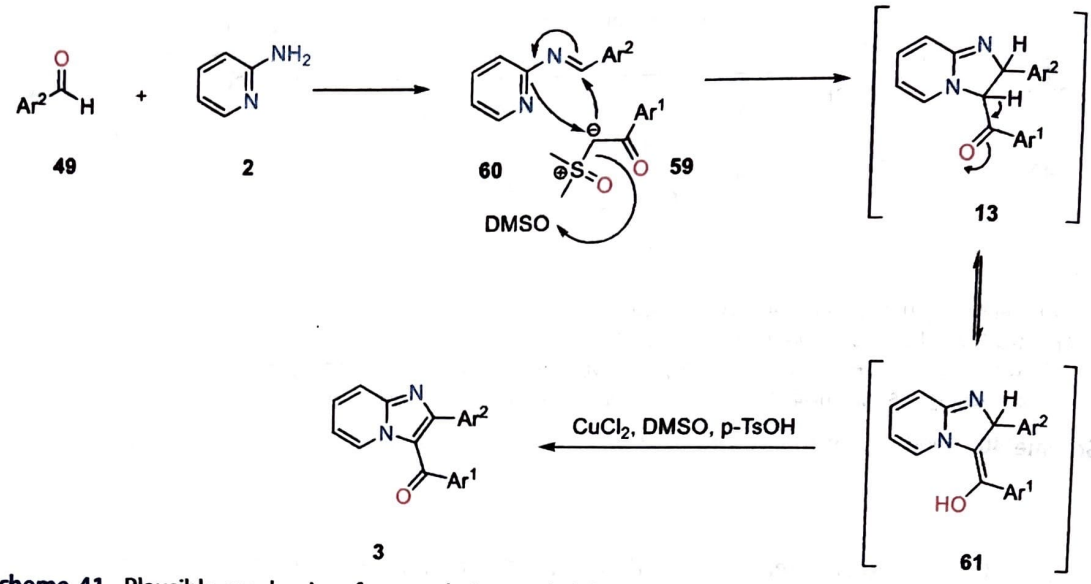
Scheme 40. Synthesis of multisubstituted imidazole-fused heterocycles via noncarbenoid route.

One of the intriguing features of this protocol comes from β-keto sulfoxonium ylide **59**; it plays dual-functional role, as a nucleophilic 1,1-dipolar one-carbon synthon, and a source of DMSO which acts as an internal oxidant to promote in-situ dehydrogenation.

During optimization studies, they studied the sequence of reaction i.e., (a) Formation of imine, (b) Electrophilic activation of imine by lewis acid, and (c) Subsequent reaction with ylide. In absence of lewis acid, the yield reduced significantly. Several lewis acids such as Cu, Yb and Sc- based were screened; among them $CuCl_2$ worked best. Moreover, addition of p-TSA as an additive improved the yield. As imine formation is reversible and sensitive to pH, they screened various bronsted acids having different pKa values. They noticed acids with pKa range between (-2.0 to 0.3) were more efficient. Among them, TFA and p-TSA worked best. But, they chose p-TSA due to its operational simplicity. They even tried other transition metal catalysts like Pd, Ru and Rh to determine whether the reaction followed the carbenoid pathway; as it was expected from oxosulfonium ylides. But, it showed significant decrease in yield, suggesting the non-carbenoid pathway was followed by the reaction.

The substrate scope for this protocol was explored. Phenacylsulfoxonium ylides bearing Cl, F, OMe and CF_3 groups on aromatic ring worked smoothly and gave overall good yields. Moreover, moieties such as –OH, $-CO_2Et$ and –CN were well tolerated. Whereas, reaction with aliphatic acylsulfoxonium ylide or aliphatic aldehyde were not feasible. However, this protocol also gave access to N-fused imidazoles, imidazo[1,2-a]pyrazines and pyrimidines. Gram-scale reaction (12 mmol) were tolerable and afforded the desired product without significant decrease in yield (70%).

Based on control experiment studies, the plausible mechanism is shown in (Scheme 41). Initially, aromatic aldehyde **49** and 2-aminopyridine **2** react to form aldimine **60**. Further, nucleophilic addition of sulfoxonium ylide carbon **59** on aldimine **60**, followed by intramolecular substitution of ring- N's nucleophilic attack at α-carbon of sulfonium-carbonyl forms annulated C–N bond to afford fused imidazoline ring intermediate **13**, and removal of DMSO simultaneously. Intermediate **13** shows tautomerism with intermediate **61**. Finally, dehydrogenative aromatization furnishes 3-aroylimidazo[1,2-a]pyridine **3**.



Scheme 41. Plausible mechanism for annulation and dehydrogenative aromatization.

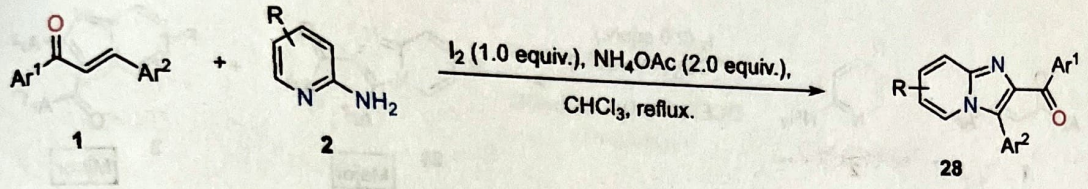
Developments in synthetic strategies of 2-aroylimidazo[1,2-a]pyridines

Iodine – NH_4OAc mediated

In 2018, Kapoor et al. reported a simple, efficient, one-pot, and metal free strategy for regioselective synthesis of 2-aroylimidazo[1,2-a]pyridines **28** from chalcones **1** and 2-aminopyridines **2** by using Iodine-NH_4OAc system.[50] When 2-aminopyridine react with chalcone, either exo-amine group[41,43,67,73] or endocyclic pyridine nitrogen[76,77] of 2-aminopyridine **2** will undergo the first nucleophilic attack on chalcone **1**, generating two possibilities of regioisomers (2-aroylimidazo[1,2-a]pyridine **28** and 3-aroylimidazo[1,2-a]pyridine **3**). Their protocol involved formation of 3-membered iodonium complex[78] of chalcone by using I_2 as a reagent, followed by attack on β-carbon of iodonium intermediate by endo-nitrogen of 2-aminopyridine via Ortoleva-King type intermediate.[60,79,80]

In optimization study, they screened solvents such as, $CHCl_3$, DCE, EtOH, CH_3CN, DMF, 1,4-dioxane, toluene and chlorobenzene; among them $CHCl_3$ was most suitable. Different additives were also screened such as, NH_4Cl, DABCO, p-TsOH, NH_4OAc, NaOAc, DBU, and $(NH_4)_2SO_4$; among these NH_4OAc improved the yield best. Interestingly, 2-aroylimidazo[1,2-a]pyridine was not formed in absence of I_2. The optimized reaction condition is shown in (Scheme 42).

Substrate scope of this protocol was explored. Chalcones bearing electron donating groups like –Me, –OMe, and electron withdrawing groups like $-NO_2$, –Cl, –Br reacted efficiently to give desired product in very good yields (72–85%). Similarly, 2-aminopyridines bearing electron donating group like -Me, and electron withdrawing group like $-NO_2$ worked efficiently. Moreover, heteryl ring systems were also tolerable to this protocol. Further, one pot, three-component reactions were also investigated by using aryl methyl ketone, arylaldehyde and 2-aminopyridine under the optimized reaction condition. However, the yields of three component reaction were slightly less than two component reaction. When reaction was carried out in presence of radical scavenger

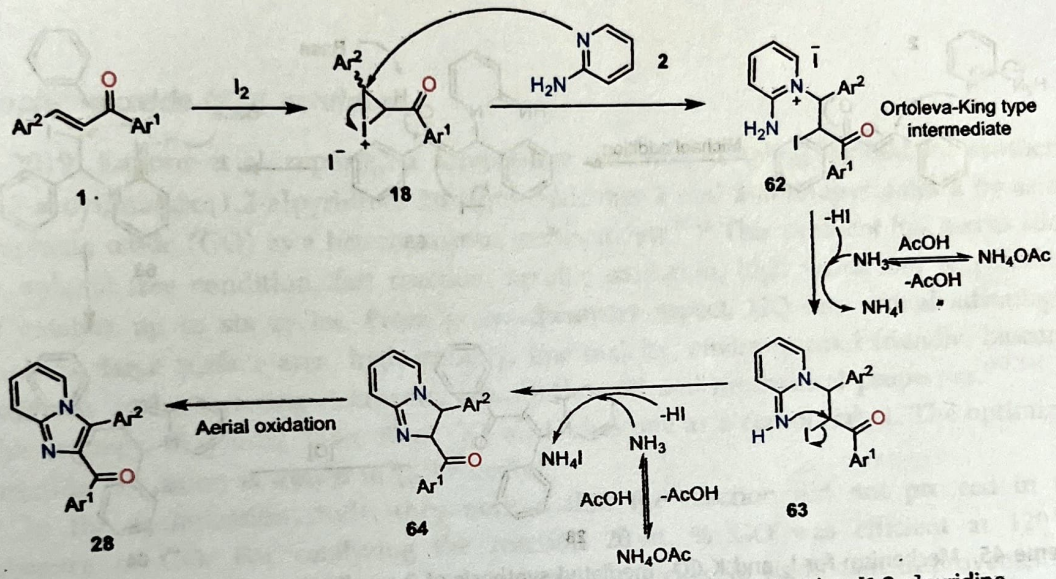


1 2 28

R= H, 5-Me, 3-NO_2, 5-NO_2
Ar^1= C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl
Ar^2= C_6H_5, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 2-pyridyl, 2-thienyl

13 examples
72-85% yield

Scheme 42. Regioselective synthesis of 2-aroyl-3-arylimidazo[1,2-a]pyridines 28.



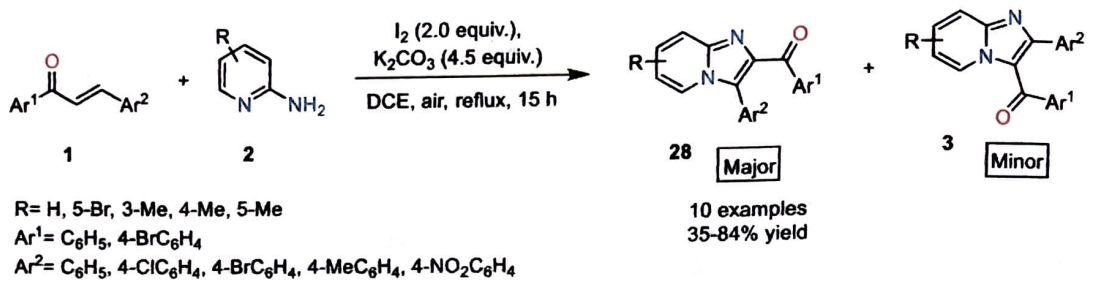
Scheme 43. Plausible reaction mechanism for synthesis of 2-aroyl-3-arylimidazo[1,2-a]pyridine.

like TEMPO, the yield of 2-aroylimidazo[1,2-a]pyridine did not decreased significantly. This indicates the non-radical pathway of reaction.

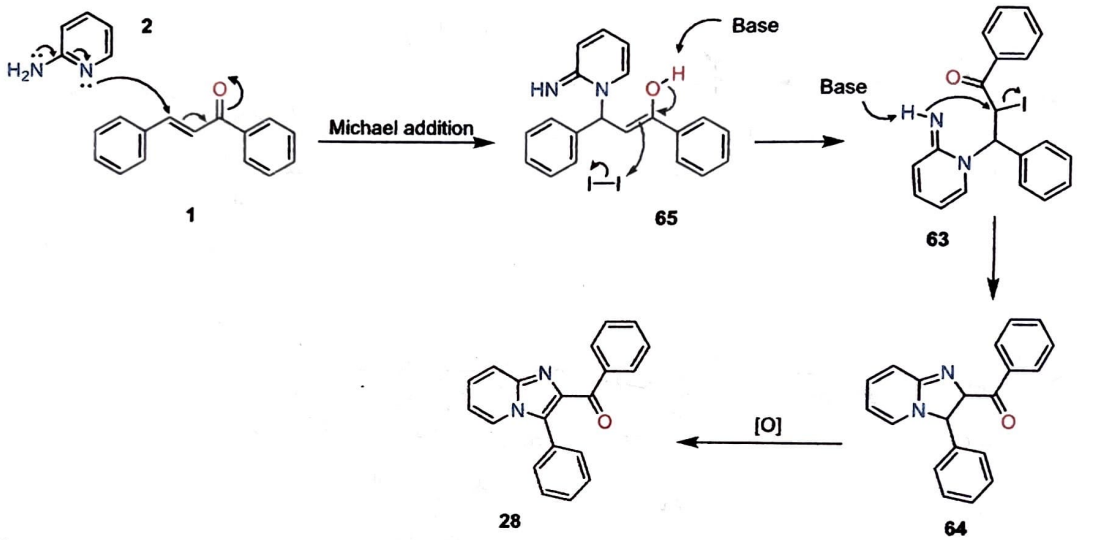
To validate the proposed mechanism, they analyzed mass spectrum of the reaction mixture at different time intervals. A plausible mechanism is outlined in (Scheme 43). Initially, iodine reacts with chalcone **1** to form iodonium intermediate[78] **18**. Then endocyclic pyridine nitrogen of 2-aminopyridine **2** undergoes first nucleophilic attack on the β-position of iodonium intermediate[81] generating intermediate **63** via Ortoleva-King type intermediate[60,79,80] **62**. Further, intramolecular cyclization of intermediate **63** due to nucleophilic attack of exocyclic amine group of 2-aminopyridine lead to the formation of intermediate **64**, followed by aerial oxidation to furnish the desired product **28**.

Iodine and K_2CO_3 promoted reaction in 1,2-dichloroethane

In 2018, Yu et al. regioselectively synthesized 2-aroylimidazo[1,2-a]pyridines **28** through I_2 mediated diamination of chalcones **1** with 2-aminopyridines **2**.[59] They performed this by just changing the solvent system, base, and substitution on 2-aminopyridines. During optimization of 3-aroylimidazo[1,2-a]pyridine **3** they noticed, toluene when



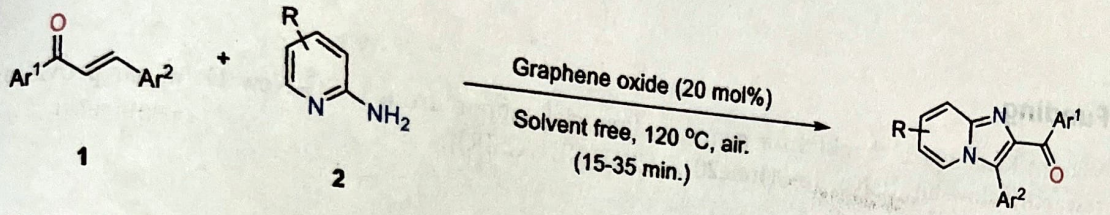
Scheme 44. Iodine and K_2CO_3 induced synthesis of 2-aroylimidazo[1,2-a]pyridines.



Scheme 45. Mechanism for I_2 and K_2CO_3 mediated synthesis of 2-aroylimidazo[1,2-a]pyridine.

replaced by DCE in presence of $NaHCO_3$ as a base, afforded 25% of 2-aroylimidazo[1,2-a]pyridine **28** along with 3-aroyl isomer in 46% yield. Interestingly, when $NaHCO_3$ was replaced by stronger base like K_2CO_3, the yield and selectivity toward 2-aroyl isomer was improved. However, they choose a high stoichiometric amount to optimize the reaction condition. For (0.5 mmol) chalcone, they used (2.0 mmol) 2-aminopyridine, (1.0 mmol) iodine and (2.25 mmol) K_2CO_3. The optimized condition is shown in (Scheme 44).

Substrate scope for this protocol was explored. When diamination reaction were carried out on chalcone **1** by alkyl- or unsubstituted 2-aminopyridines **2**, it afforded the corresponding 2-aroylimidazo[1,2-a]pyridines **28**. Even 5-bromo-2-aminopyridine gave 2-aroyl isomer as a major product in DCE solvent. Whereas, 6-methyl-2-aminopyridine was consistent in furnishing only 3-aroylimidazo[1,2-a]pyridine due to the steric effect induced by 6-methyl group. The plausible mechanism is outlined in (Scheme 45). At first, chalcone **1** undergoes Michael addition by endocyclic pyridine nitrogen of 2-aminopyridine **2** to give intermediate **65**. Further, I_2 mediated cyclization of **65** generates dihydroimidazopyridine **64** via intramolecular Ortoleva–King reaction.[60,82,83] Finally, aromatization of **64** furnishes the desired product **28**.



1 2 28

R= H, 5-Me, 3-NO_2
Ar^1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, piperonyl, 2-thienyl
Ar^2= C_6H_5, 4-MeC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl

10 examples
76-87% yield

Scheme 46. Graphene oxide (GO) catalyzed synthesis of 2-aroylimidazo[1,2-a]pyridines.

Graphene oxide (GO) catalyzed

In 2019, Kapoor et al. reported a solvent-free oxidative coupling method for synthesis of 2-aroylimidazo[1,2-a]pyridines **28** from chalcones **1** and 2-aminopyridines **2** by using graphene oxide (GO) as a heterogeneous carbocatalyst.[84] This protocol has merits such as, solvent-free condition, fast reaction, aerobic oxidation, high yields and recyclability of catalyst up to six cycles. From green chemistry aspect, GO has several advantages such as, large surface area, high stability, low toxicity, environmental friendly, biocompatibility and interesting electronic, optical, thermal and mechanical properties.[85,86] In this strategy, they used 20 wt. % of GO w.r.t. chalcone as a carbocatalyst. The optimized reaction condition is shown in (Scheme 46).

In the optimization study, they noticed that the reaction did not proceed in the absence of GO. For catalyzing the reaction 20 wt. % GO was efficient at 120 °C. Moreover, 10 wt. % and 30 wt. % GO lowered the yield. No significant improvement in yield was observed in presence of solvents such as EtOH, toluene, CH_3CN, DMF and dioxane. In this strategy, chalcones bearing electron withdrawing groups like chloro, bromo, nitro and electron rich groups like methoxy, methyl afforded appreciable corresponding yields. Interestingly, this protocol was well tolerated by oxymethylene moiety and heteryl ring systems. Recyclability of GO catalyst indicates no significant loss of catalytic activity for up to five consecutive runs.

Conclusion

In the last decade, we have witnessed remarkable developments in regioselective synthesis of 3-aroylimidazo[1,2-a]pyridine and 2-aroylimidazo[1,2-a]pyridine. These scaffolds are endowed with diverse applications. But, inaccessibility of these functionalized imidazo[1,2-a]pyridines by direct Friedel-Crafts acylation reaction had left chemists with three-steps long protocol to access it. In this regard, we believe the current review provides ample information on the synthetic strategies reported in the last decade toward direct functionalization of imidazo[1,2-a]pyridines with aroyl group at C-3 and C-2 position by using readily available precursors in step-economic pathway.

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