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Mini-Review

Recent Progress in Metal-Free Direct Synthesis of Imidazo[1,2-*a*]pyridines

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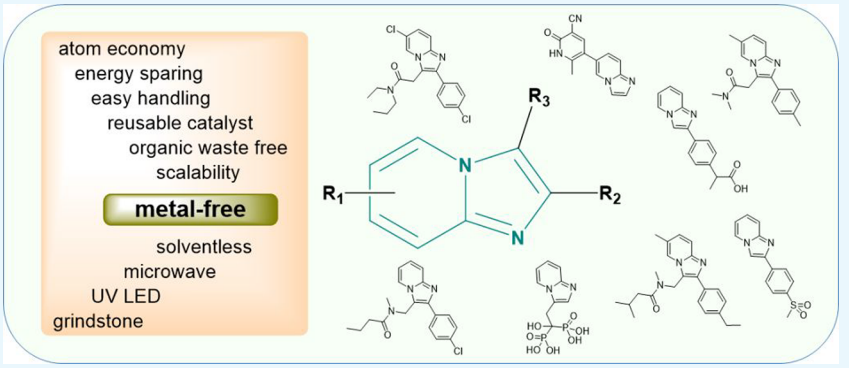

ABSTRACT: This Mini-Review highlights the most effective protocols for metal-free direct synthesis of imidazo[1,2-*a*]pyridines, crucial target products and key intermediates, developed in the past decade. The emphases is given on the ecological impact of the methods and on the mechanistic aspects as well. The procedures efficiently applied in the preparation of important drugs and promising drug candidates are also underlined.

1. INTRODUCTION

Imidazo[1,2-*a*]pyridines are an important class of fused nitrogen-bridged heterocyclic compounds due to the broad spectrum of biological activity profiles displayed,[1] which strongly depend on the substitution pattern. Several representatives are clinically used, like the unsubstituted imidazole fragment cardiotonic agent olprinone, the 2-substituted analgesic miroprofen, the anticancer agent zolimidine, the 3-substituted antiosteoporosis drug minodronic acid, the 2,3-disubstituted derivatives with sedative and anxiolytic properties, alpidem, saripidem, and necopidem, and the agent for the treatment of insomnia and brain disorders, zolpidem (Figure 1). In consequence, several procedures for the synthesis of this fascinating framework are developed, mostly on the basis of metal catalyzed reactions and functionalizations, which are summarized in a series of review articles.[2] The serious ecological problems nowadays provoke scientists to search environmentally benign synthetic strategies as much as possible. This Mini-Review summarizes the most effective recent protocols for the eco-friendly metal-free direct formation of derivatives with an imidazo[1,2-*a*]pyridine skeleton with the hope that no significant contributions in the topic are unintentionally overlooked.

2. RECENT METAL-FREE PROTOCOLS

Considerable efforts have been devoted in the past decade to the development of new synthetic protocols for the construction of an imidazo[1,2-*a*]pyridine core aiming to improve the ecological impact of the classical schemes. The overview of the most efficient and widely applied modern methods provided herein is organized into sections covering the main metal-free methods structured by the type of the reacting species, leading to the formation of similar final products instead of the catalytic systems applied in an attempt to avoid unnecessary drawing duplications.

2.1. Condensation between 2-Aminopyridines and Aldehydes. Most of the synthetic strategies, both classic and recent, for the construction of imidazo[1,2-*a*]pyridines are based on the condensation of 2-aminopyridine with various substrates, mainly carbonyl compounds or alkenes. The condensation between 2-aminopyridine, aldehyde, and isonitrile, known as three component Groebke−Blackburn−

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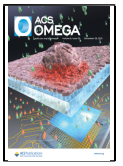

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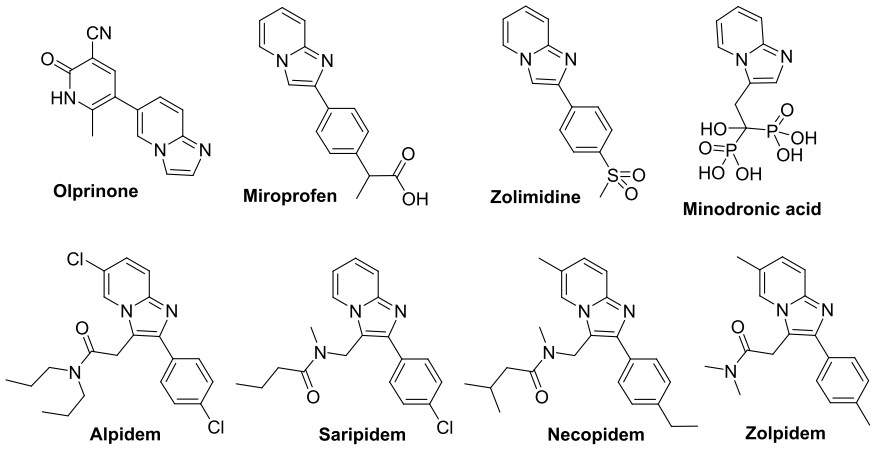

Figure 1. Clinically used drugs with an imidazo[1,2-*a*]pyridine skeleton.

Bienaymé reaction,[3] is among the most widely exploited protocols for the synthesis of 2,3-disubstituted derivatives, usually performed under metal catalysis. Nowadays, the transformation is efficiently applied in the synthesis of compounds with variable substitution patterns by using metal-free catalysts (Scheme 1). Perchloric acid is found to be an effective catalyst in a facile procedure for the preparation of compounds **1**[4a] and **2**[4b] (Scheme 1a), which are further converted into tricyclic molecules of biological interest. An environmentally benign, robust, efficient, and scalable sustainable continuous flow process promoted by a simple hydrochloric acid was developed by Baker et al.[4c] The reaction has shown excellent substrate scope across all three reaction partners, and up to 96% of the product **3** is obtained. An efficient and mild eco-friendly protocol using the nonvolatile green catalyst ammonium chloride in ethanol was performed for the synthesis of derivatives **4**[5a] and **5**[5b] at room temperature or with slight heating, respectively (Scheme 1b). Two independent procedures were developed for the synthesis of compounds **6**: the micellar mediated reaction in the presence of sodium dodecyl sulfate (SDS) in water or catalysis by the nontoxic and biodegradable thiamine hydrochloride solventless method.[5c] The protocols are fast and mild with low catalyst loadings and tolerant with a broad substrate range. Similar derivatives of **6** are efficiently obtained using various catalytic systems. Saccharin is applied in a convenient, fast, and effective protocol with a practical impact.[5d] Esmaielzade Rostami et al.[6a] developed a green approach in the presence of calix[*n*]arene sulfonic acid as the recoverable catalyst and surfactant in water. It is shown that the calixarene hydrophobic cavity is crucial to achieve fast conversion. Bromodimethylsulfonium bromide (BDMS), an easy handling and low cost salt, is found to be a useful catalyst in a simple, high yield one-pot procedure for the synthesis of derivatives with fluorescent properties.[6b] Budhiraja et al.[6c] achieved the first biocatalytic synthesis of clinically important products by applying the *Candida Antarctica lipase B* (CALB) enzyme as a catalyst. The enzyme is further immobilized on mesoporous silica and used as a reusable catalyst with high catalytic efficiency for many cycles. Changunda et al.[6d] developed a successful methodology by using the nonvolatile montmorillonite K-10 clay as a catalyst. The products are further converted into a series of novel tetracyclic derivatives. The fluorescent probes **7**, possessing a bulky substituent at the 2-position (Scheme 1c), are obtained via a fast and efficient microwave-assisted protocol using chloroacetic acid as the catalyst.[6e] Ganesher and Panda[6f] accomplished an effective atom economy procedure for the construction of derivatives **8** catalyzed by trifluoroacetic acid (TFA). The transformation includes sequential Groebke−Blackburn−Bienaymé and intramolecular cyclization reactions in one pot under mild acidic conditions.

A similar three component condensation between 2-aminopyridines, ynals, and alcohols, thiols or 2-aminopyridines instead of isonitriles is efficiently accomplished using acid catalyzed protocols, leading to the construction of a wide range of monosubstituted imidazo[1,2-*a*]pyridines (Scheme 2). Cao et al.[7a] achieved a simple environmentally benign acetic acid catalyzed process for the formation of C−N, C−O, and C−S bonds via a one-pot, three-component approach, leading to the highly decorated products **9** and **10** (Scheme 2a,b). The analogous simple organic acid pivalic acid (PivOH) is shown to aid in the efficiency of the preparation of a series of amino-modified derivatives **11** (Scheme 2c).[7b] A facile microwave-assisted protocol is developed using *p*-toluene sulfonic acid as the catalyst (Scheme 2a).[7c] The reaction is very fast, and the analogous derivatives **9** are isolated in excellent yields. It is proposed that the transformation goes via the subsequent formation of imine, the addition of alcohol to the alkyne moiety, intramolecular cyclization, and *p*-TSA catalyzed dehydration. Tiwari et al.[8] reported a convenient boron trifluoride diethyl etherate promoted condensation of 2-aminopyridine with arylglyoxal and alkyne derivatives leading to 2,3-disubstituted products **12** (Scheme 2d). The key features of procedure are mild reaction conditions, atom economy, easy handling, and scalability.

A mild and efficient one-pot, two-step protocol for the synthesis of derivatives **13** is based on the interaction of 2-aminopyridines and 2-arylacetaldehydes in the presence of *N*-iodosuccinimide (NIS) at room temperature (Scheme 3).[9] It is proposed that an enamine is initially formed followed by the reaction with NIS, cyclization, and deprotonation by sodium bicarbonate. It is shown that a nucleophilic attack by water on the iodo-imine intermediate pushes the equilibrium in favor of an adduct, which is isolated and characterized.

2.2. Condensation between 2-Aminopyridines and Ketones. Ketones are also efficiently applied in three component approaches, leading to various 2,3-disubstituted imidazo[1,2-*a*]pyridine derivatives (Scheme 4). An effective graphene oxide (GO) promoted protocol for the condensation of 2-aminopyridines with acetophenones and thiols is developed

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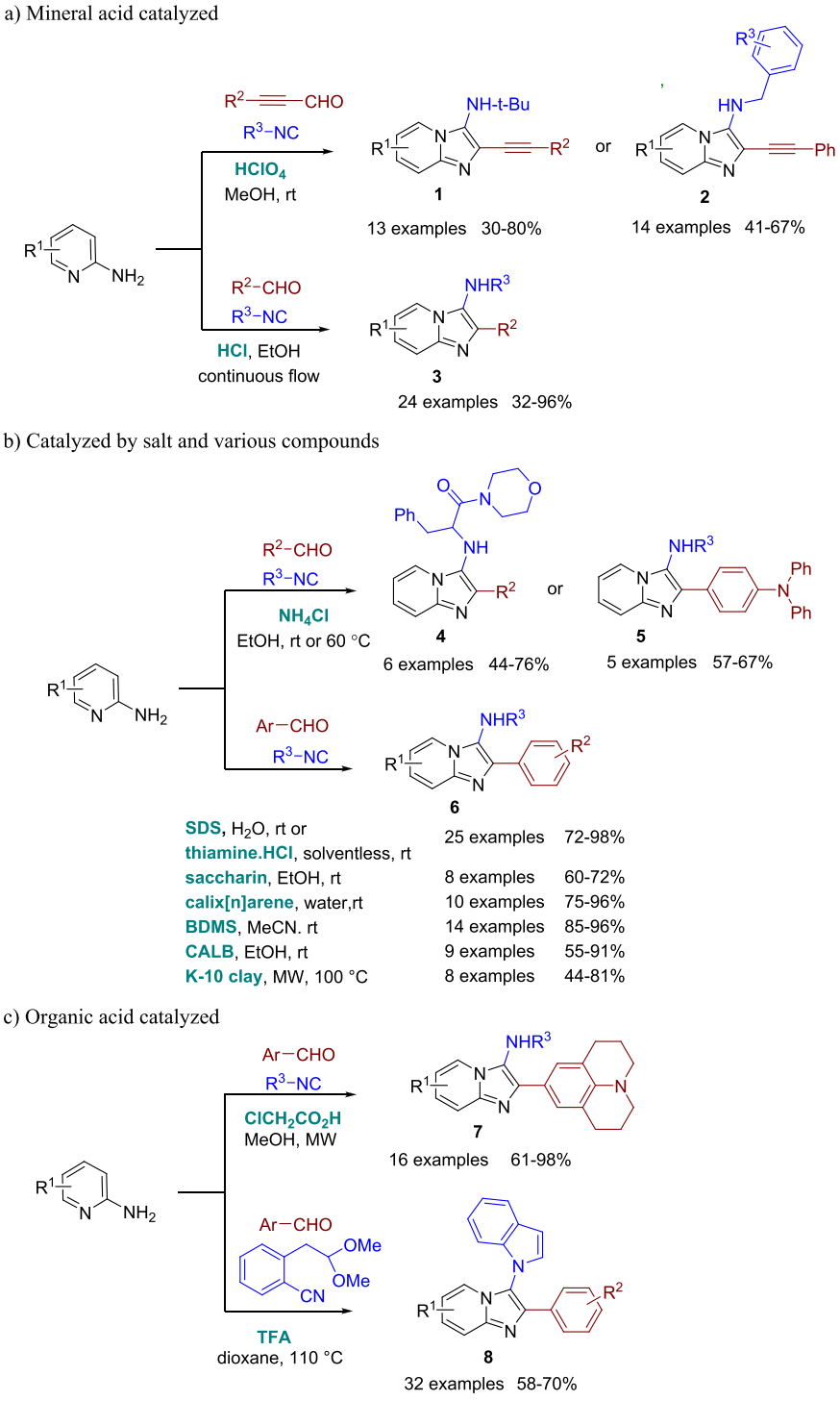
Scheme 1. Three Component Groebke−Blackburn−Bienaymé Reaction



via the initial generation of iodoacetophenone using sodium iodide as an additive followed by an Ortoleva-King type intermediate formation by alkylation of the endocyclic nitrogen atom and subsequent intramolecular cyclization to compounds **14** (Scheme 4a).[10a] It is shown that the reaction is highly selective and tolerant with diverse functional groups and that the carbocatalyst can be recovered and reused. Similar derivatives are obtained by using flavin (Flv)−iodine catalysts.[10b] The protocol involves three aerobic oxidative C−N, S−S, and C−S bond forming transformations enabled by the dual catalytic system. Hu et al.[10c] achieved a scalable molecular iodine catalyzed direct three component reaction between 2-aminopyridines, ketones, and sulfonyl hydrazides in the presence of triphenylphosphine as an additive going to derivatives **15** by following a similar reaction mechanism. The transformation is efficient and mild and tolerates a broad substrate scope. An effective pseudo three component reaction between 2-aminopyridines and two molecules of acetophenones catalyzed by *p*-toluenesulfonic acid (pTSA) or sulfuric acid is accomplished in solventless conditions, leading to an easy separable mixture of compounds **16** and **17**; **16** is predominant in all cases (Scheme 4b).[11a,b] The products' substitution pattern is explained by

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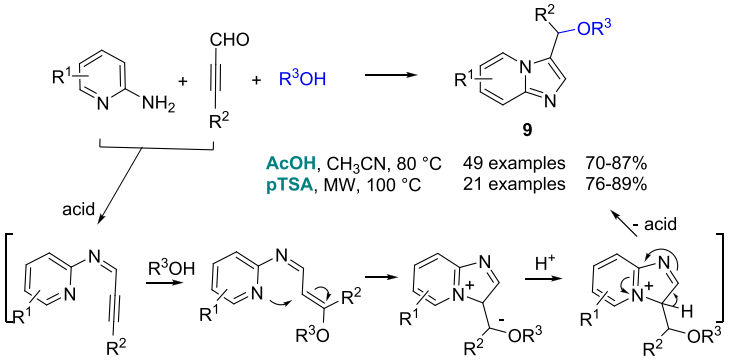
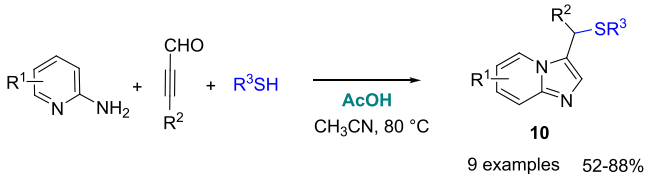
Scheme 2. Three Component Acid Catalyzed Reaction between 2-Aminopyridines, Aldehydes, and Third Reagents

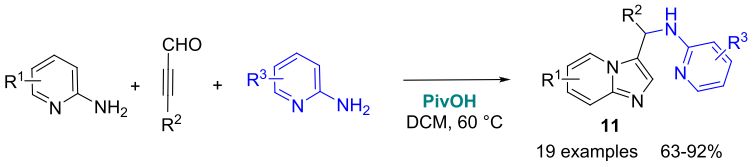
a) Alcohols as third reagents



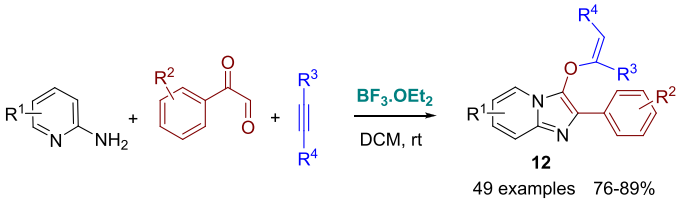
b) Thiols as third reagents



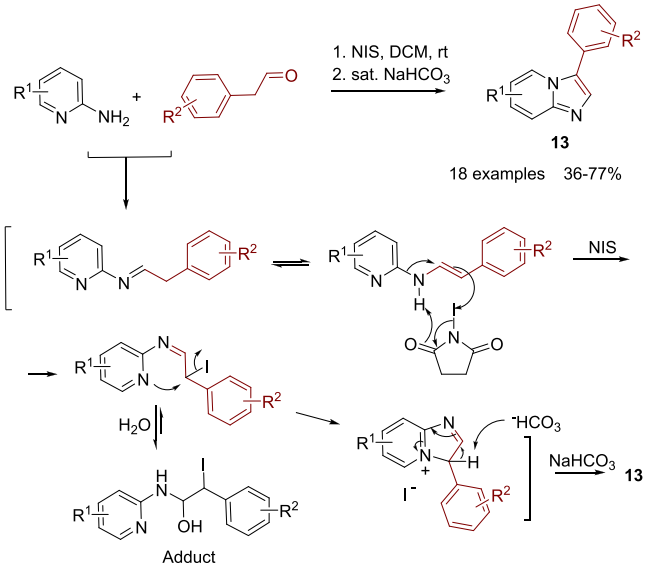
c) 2-Aminopyridines as third reagents



d) Alkynes as third reagents



Scheme 3. Two Component Reaction between 2-Aminopyridines and 2-Arylacetaldehydes



concurrent ketimine and Ortoleva−King type reaction intermediate transformations, leading to derivatives **16** and **17**, respectively.[11b] It is shown that pTSA tolerates ketimine formation, while sulfuric acid catalyzes both reactions. Several carboxylic and sulfonic acids are further tested as catalysts, and it is found that isoquinoline-5-sulfonic acid is the most effective in this particular transformation.[11c] It is observed that the reaction output is strongly dependent on the substituents of both reactants, independent of the catalyst used.

Several series of 2-aryl (**18**) and 2-heteroaryl (**19**) substituted imidazo[1,2-*a*]pyridines are obtained using various metal-free catalysts (Scheme 5). The iodine promoted reactions of 2-aminopyridine with acetophenones or heteroaryl analogues are performed via two independent protocols.[12a] The SDS-derived micellar media transformation is achieved with slight heating, while the "on-water" procedure is carried out at room temperature under mild acidic conditions in the presence of ammonium chloride. It is found that the micellar media reaction is more efficient, and its scope is validated by the gram scale synthesis of the market drug zolimidine. The proposed plausible mechanistic pathway includes the initial imine formation as the slowest step, followed by iodine catalyzed tautomerization, intramolecular cyclization, and oxidative aromatization. Ghosh

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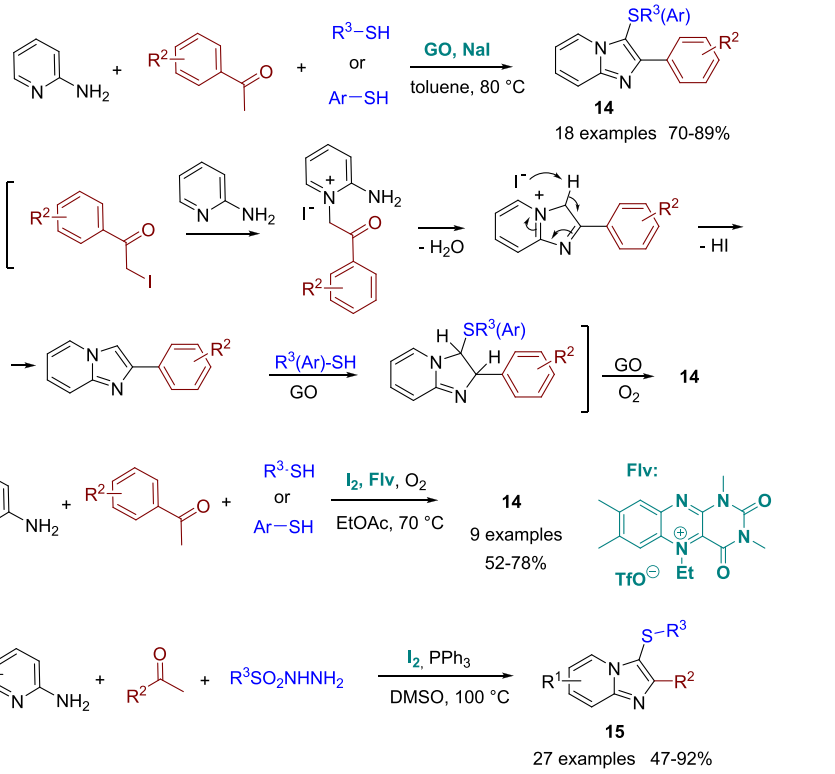
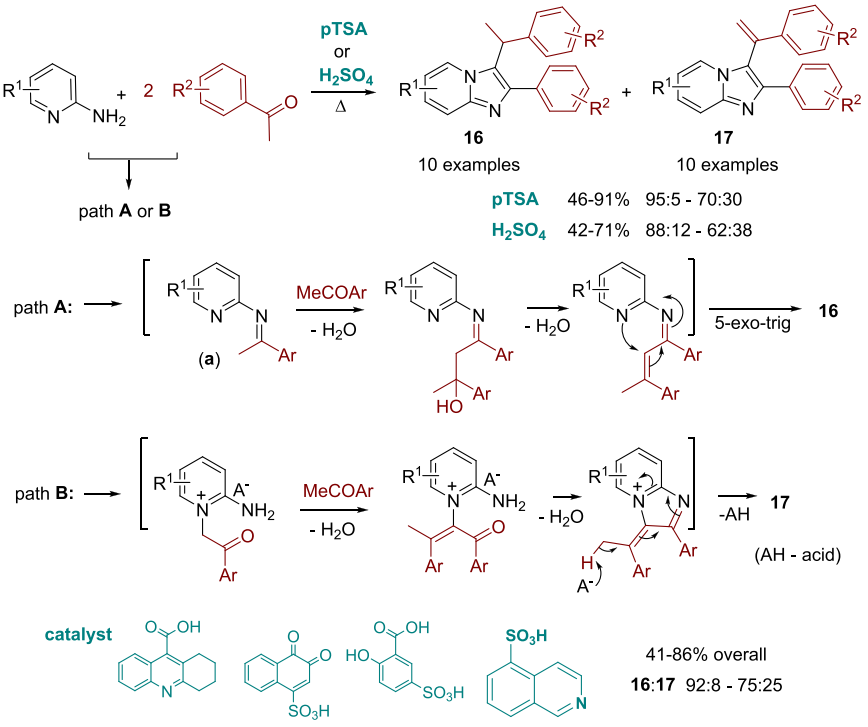
Scheme 4. Three Component Reaction between 2-Aminopyridines and Acetophenones

a) Reaction between 2-aminopyridines, acetophenones and thiols or sulfonyl hydrazides



b) Pseudo three component reaction between 2-aminopyridines and acetophenones



et al.[12b] devised an efficient, additive-free, green protocol for the synthesis of similar derivatives catalyzed by iodine in cyclohexane via consequent enolization of acetophenones, iodination, coupling with the endocyclic nitrogen, and cyclization. The method offers several practical advantages like mild reaction conditions at ambient atmosphere, short reaction times, and broad functional group tolerance. The same iodine promoted synthesis is performed by Das et al.[12c] under a mechanochemical method at ambient temperature by adopting automated grindstone chemistry. The reaction outcome is explained by the initial iodine catalyzed condensation between the ketone and exocyclic amino group and subsequent tautomerization, cyclization, and oxidative aromatization. A series of derivatives **18** is obtained by mild effective procedures using iodine as the

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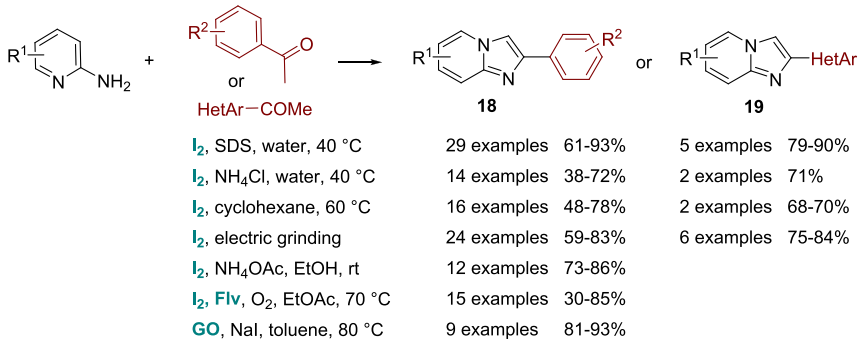
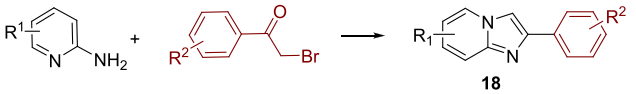
Scheme 5. Two Component Reaction between 2-Aminopyridines and Acetophenones



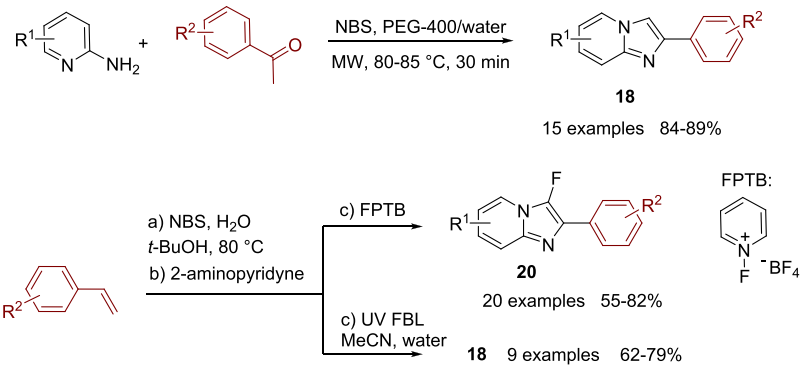
Scheme 6. Reaction between 2-Aminopyridines and Bromoacetophenones

a) Reaction with bromoacetophenones



K_2CO_3, DMF, rt	15 examples	70-88%
DMF, Δ	8 examples	41-59%
EtOH, Δ	12 examples	60-66%
TBHP, ethyl acetate, 90 °C	34 examples	19-97%
NaHCO3, MeOH, MW, 80 °C, 1 min	20 examples	24-99%
GSP, rt, 3-5 min	30 examples	96-99%

b) Reaction with *in situ* generated bromoacetophenones



catalyst and ammonium acetate as the additive,[12d] via a flavin−iodine dual catalyzed aerobic oxidative C−N bond-forming process[10b] or in the presence of the green carbocatalyst graphene oxide (GO) and sodium iodide as the additive.[10a]

2.3. Condensation between 2-Aminopyridines and α-Halogenocarbonyl Compounds. Several articles report on the synthesis of the analogous imidazo[1,2-*a*]pyridines **18** by condensing 2-aminopyridines with bromoacetophenones (Scheme 6) via the initial alkylation of the ednocyclic nitrogen atom followed by intramolecular condensation. Recently, the catalyst-free versions were achieved by applying variable eco-friendly techniques. Kwong et al.[13a] performed the reaction at room temperature in DMF, i.e., high boiling solvent, in the presence of potassium carbonate as the base (Scheme 6a). The same protocol was accomplished in the absence of base in refluxing DMF[13b] or ethanol.[13c] Liu et al.[13d] developed an operative one-pot tandem cyclization/bromination protocol in the presence of *t*-butyl hydroperoxide (TBHP) using α-haloketone as both the substrate and bromine source. The method has high atom economy and possesses excellent functional group tolerance and scalability. Rodríguez et al.[13e] accomplished a fast and efficient protocol under microwave irradiation in methanol and sodium bicarbonate as a base, and the target products were isolated in up to 99% yields. An ecologically favorable solventless grindstone procedure (GSP) has been established nowadays.[13f] It has been shown that the method is fast, effective, free of organic wastes, and tolerant to a broad substrate scope and has a simple water workup. Alternatively, the reaction is achieved by in situ generation from acetophenones and *N*-bromosuccinimide (NBS) bromoacetophenones, thus avoiding the need of preliminary isolation of a reagent with a lachrymatory nature (Scheme 6b).[14a] The conversion is performed in polyethylene glycol (PEG-400) and water as a green media. Said et al.[14b] developed a facile, three-step, one-pot procedure for the regioselective synthesis of 3-fluoro-imidazopyridine derivatives **20** starting from styrene. The subsequent bromination, condensation, and fluorination are carried out in *tert*-BuOH−water as the solvent. It is shown that both NBS and 1-fluoropyridinium tetrafluoroborate play dual roles of an oxidant and bromine source and of a fluorine source and base, respectively. Similarly, Das and Thomas[14c] achieved a three-step, one-pot protocol to form products **18** by applying

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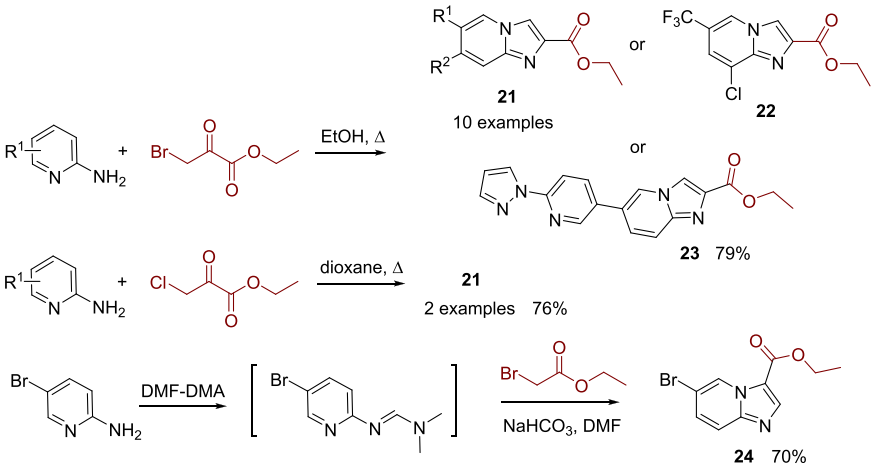
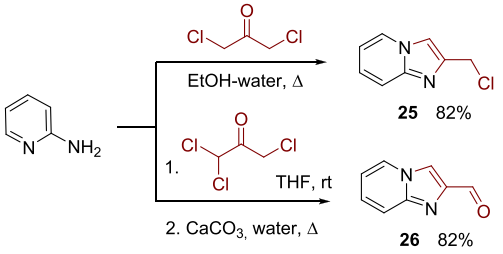
Scheme 7. Reaction between 2-Aminopyridines and Halogenoesters

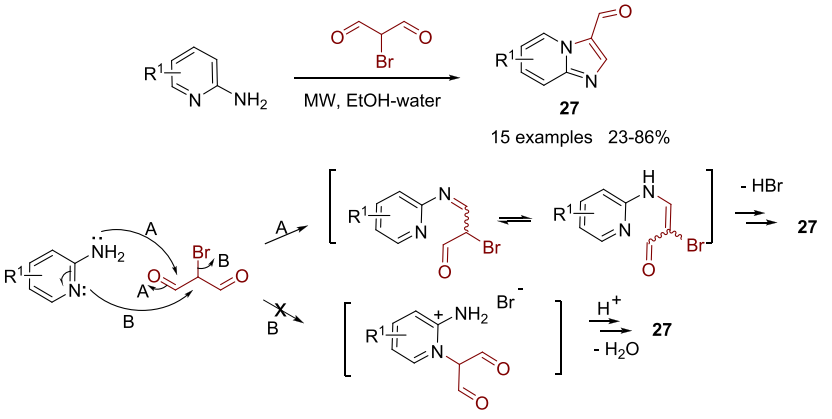


Scheme 8. Reaction between 2-Aminopyridines and Halogenated Carbonyl Compounds

a) Reaction with chlorinated ketones



b) Reaction with bromomalonaldehyde



sensitizer, catalyst, and additive-free UV LED fluorescent black light (UV FBL) irradiation in acetonitrile−water as the last step.

2.4. Condensation between 2-Aminopyridines and Other Carbonyl Compounds. Variable monosubstituted imidazo[1,2-*a*]pyridines are obtained in eco-friendly catalyst-free conditions by condensation of 2-aminopyridine with halogenoesters and are further converted into libraries of derivatives with important properties (Scheme 7). Feng et al.[15a] obtained a series of key intermediates **21** in the synthesis of highly potent respiratory syncytial virus fusion inhibitors by simply refluxing a mixture of 2-aminopyridine and ethyl bromopyruvate in ethanol. The same protocol was recently applied in the preparation of libraries of antibacterial,[15b] anticancer,[15c] and antitubercular[15d] agents via 2-ethyl carboxylate intermediates **22**, **23**, and **21**, respectively, the latter being obtained while refluxing dioxane instead of ethanol. The regioisomeric 3-substituted compound **24** was generated by Zhang et al.[15e] via an efficient one-pot, two-step procedure as a key step in the synthesis of CLK1 inhibitors. The transformation includes the initial formation of an imine between the aminopyridine exocyclic amino group and dimethylacetamide followed by direct condensation with bromoethyl acetate without the isolation of imine.

Two 2-substituted compounds, 2-chloromethyl **25**[16a] and 2-carbaldehyde **26**,[16b] are obtained as key intermediates in the multistep procedures for the generation of libraries of bioactive imidazo[1,2-*a*]-pyridines by condensation of 2-aminopyridine and 1,3-dichloroacetone or 1,1,3-trichloroacetone, respectively (Scheme 8a). Kusy et al.[16c] developed a mild and rapid microwave-assisted protocol for the construction of 3-carbaldehyde substituted compounds **27** by the condensation of diversely substituted 2-aminopyridines and bromomalonal-

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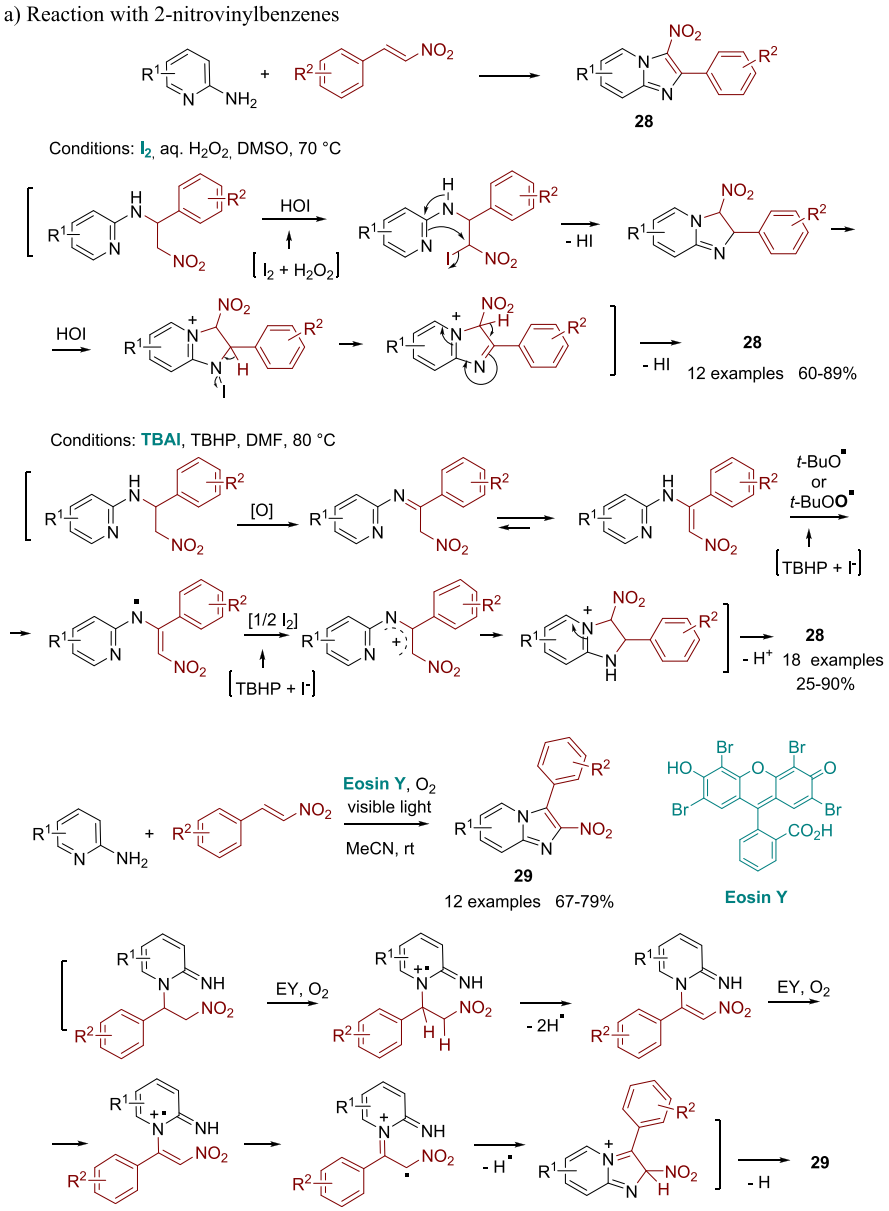
dehyde in ethanol−water media (Scheme 8b). An intermediate enamine is isolated, thus confirming one of the two mechanisms for analogous reactions proposed in the literature, namely, the initial attack of the exocyclic amine on bromomalonaldehyde, followed by the elimination of water, intramolecular cyclization, and expulsion of the bromide anion.

2.5. Condensation between 2-Aminopyridines and Compounds with Multiple Bonds. Several protocols are based on condensation between 2-aminopyridines and alkenes under variable catalysis, leading to 2,3-disubstituted products in general (Scheme 9). Tachikawa et al.[17a] achieved an environmentally friendly iodine catalyzed synthetic protocol for 3-nitroimidazo-[1,2-*a*]pyridines **28** by intermolecular oxidative cyclization of nitroalkenes and 2-aminopyridines using aqueous hydrogen peroxide as a terminal oxidant (Scheme 9a). The suggested plausible mechanism involves the initial Michael addition of 2-aminopyridine to nitroalkene followed by iodination at the α-position with respect to the nitro group by HOI, generated from iodine and hydrogen peroxide, intramolecular nucleophilic substitution, and subsequent oxidation with HOI. Similar derivatives are obtained via oxidative double C−N coupling using tetrabutylammonium iodide (TBAI) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidation agent.[17b] The plausible proposed mechanism includes the initial Michael addition to an imine and subsequent isomerization, hydrogen abstraction by the *tert*-butoxyl or *tert*-butylperoxy radicals, generated by the TBAI-catalyzed decomposition of TBHP, oxidation by iodine, intramolecular nucleophilic addition of nitrenium ion, and proton elimination. Yadav et al.[17c] accomplished visible light-catalyzed aerobic oxidative cyclization in the presence of the photoredox catalyst Eosin Y, an inexpensive organic dye, and atmospheric oxygen as the oxidant, leading to regioisomeric derivatives **29**. It is proven that the presence of oxygen is essential to achieve the reaction. The protocol is tolerant with a broad range of functional groups. Nair et al.[18a] developed a catalyst-free, one-pot, room temperature reaction between Morita-Baylis-Hillman (BMH) acetates of nitroalkenes and 2-aminopyridines (Scheme 9b), taking

Scheme 9. Reaction between 2-Aminopyridines and Nitroalkenes



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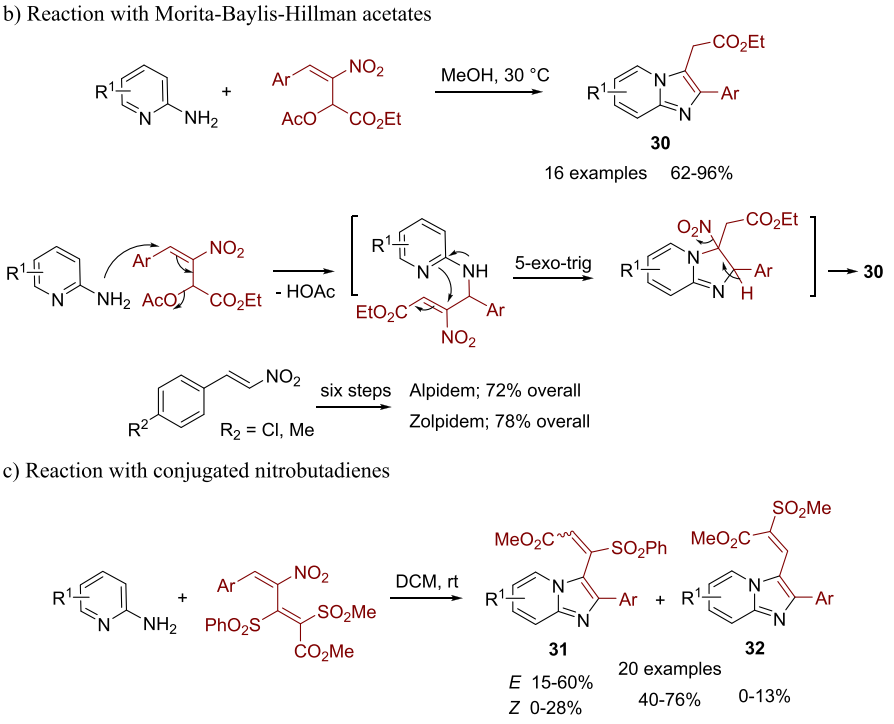
Scheme 9. continued

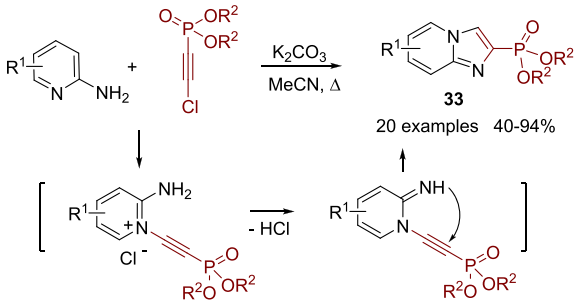


advantage of the binucleophilic character of 2-aminopyridines and the bielectrophilic character of the acetates. The transformation proceeds via Michael addition of 2-aminopyridine, involving an exocyclic amino group as the nucleophilic center, to BMH acetate and the subsequent elimination of acetate in an overall S_N2' reaction, intramolecular Michael addition involving the pyridine endocyclic nitrogen in a regioselective 5-exo trig fashion, and elimination of HNO_2 to form the target compounds **30**. The methodology is successfully applied for the efficient synthesis of the anxiolytic drug alpidem and hypnotic drug zolpidem. Conjugated nitrobutadienes are applied in a similar catalyst-free reaction to furnish a collection of 2-aryl-3-vinylimidazo[1,2-*a*]pyridines **31** and **32** as chromatographically separable mixtures (Scheme 9c).[18b] It is shown that the aza-Michael addition of 2-aminopyridine on a nitrovinyl moiety is the starting point of classic approaches and that the final structures are the result of a cascade process made possible by the particular functionalization on the conjugated systems.

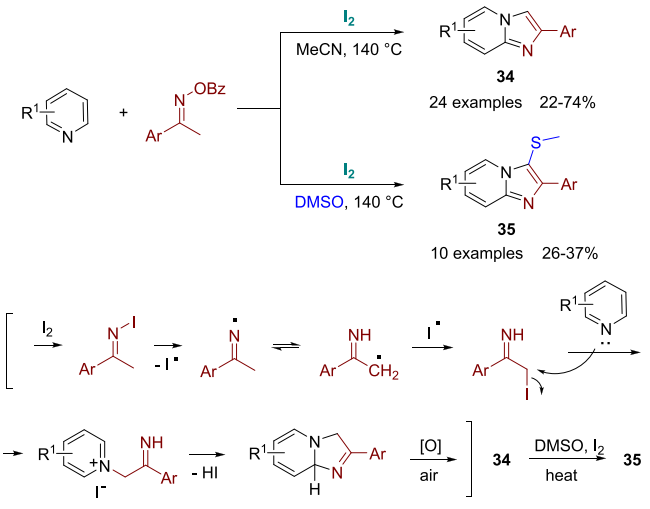
A successful catalyst-free and simple approach for the regio- and chemoselective synthesis of novel 2-phosphonylated imidazo[1,2-*a*]pyridines **33** from 2-aminopyridine and phosphorylated alkynes under mild conditions was developed by Krylov et al. (Scheme 10).[19] It is assumed that the transformation includes an initial attack of the pyridine nitrogen atom at the triple bond, followed by hydrogen chloride cleavage and ring closure.

2.6. Miscellaneous. Several protocols for the construction of an imidazo[1,2-*a*]pyridine core are based on the condensation of other pyridine derivatives with variable reagents. Singh et al.[20] disclosed a simple molecular iodine catalyzed approach to deliver pharmaceutically active 2-substituted compounds **34** from pyridines and oxime esters (Scheme 11). It is proposed that iodine triggers the cleavage of the N−O bond in oxime esters to generate reactive iminyl radicals that regioselectively couple with pyridines. The protocol is further extended toward 3-methylthiolated analogues **35** by performing the transformation in dimethyl sulfoxide, which plays a dual role of solvent and methyl-sulfenylating agent.

Scheme 10. Reaction between 2-Aminopyridines and Phosphorylated Alkynes

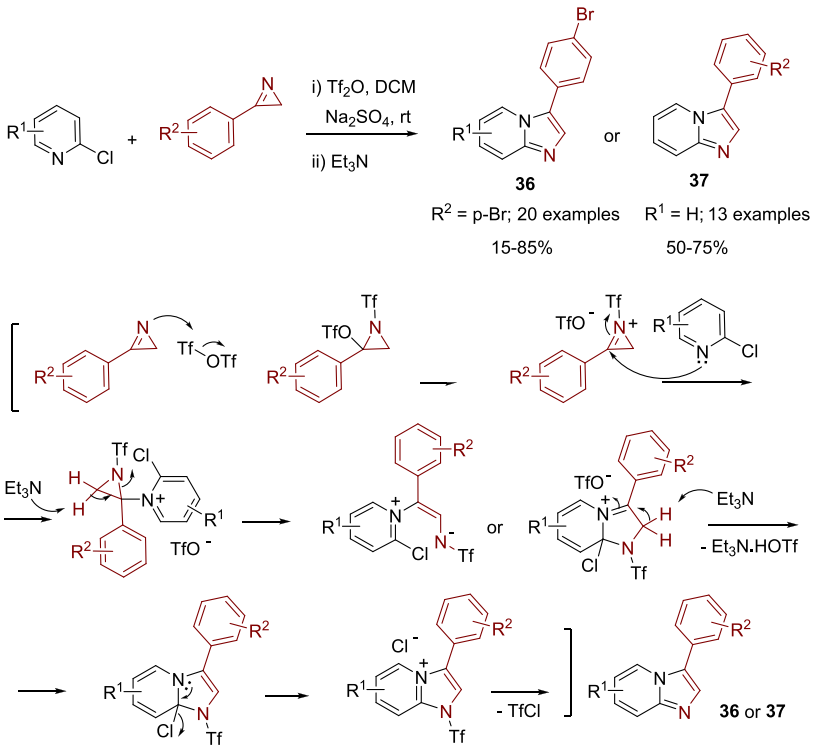


Scheme 11. Reaction between Pyridines and Oxime Esters

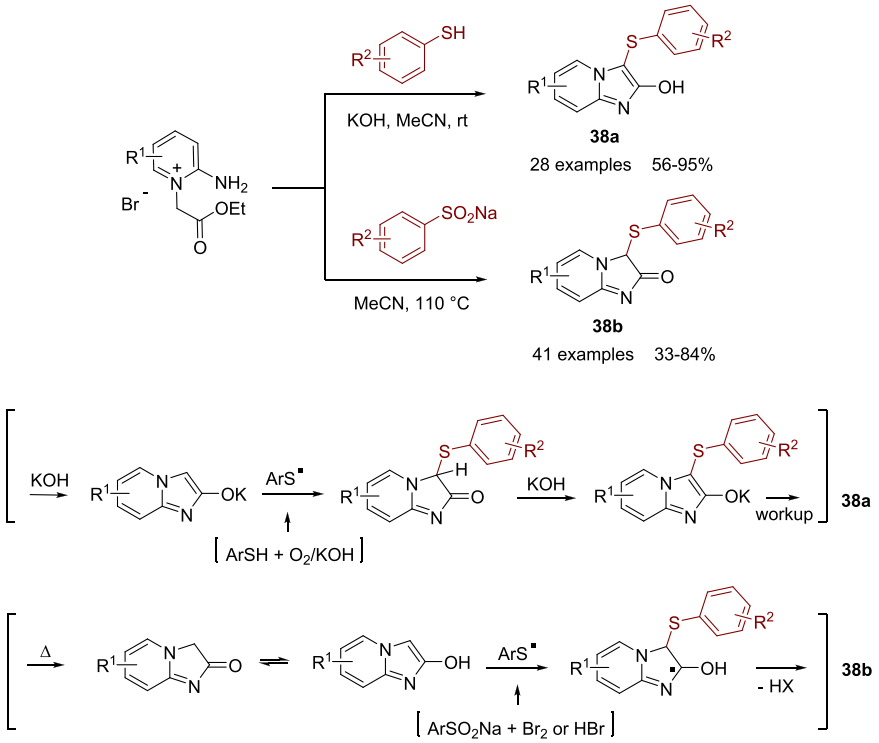


https://doi.org/10.1021/acsomega.1c03476
ACS Omega 2021, 6, 35173−35185

Scheme 12. Reaction between 2-Chloropyridines and 2*H*-Azirines



Scheme 13. Reaction between 2-Aminopyridinium Bromides and Thiophenols



A two-step, one-pot sequence for the synthesis of 3-substituted derivatives **36** from 2-chloropyridines and 2*H*-azirines (Scheme 12) is reported by Vuillermet et al.[21] The proposed mechanism involves the formation of an electrophilic 1-trifloyl-aziridin-2-yl triflate species by the reaction of 2*H*-azirines with triflic anhydride and further condensation with 2-chloropyridine to transient pyridinium salts followed by treatment with trimethylamine.

Kumar's group simultaneously published two independent articles on the formation of 3-(arylthio)imidazo[1,2-*a*]pyridin-2-ols **38a**[22a] or their keto analogues **38b**[22b] from 2-amino-pyridinium bromides and thiophenols or sodium sulphinates (Scheme 13). The developed protocols are mild, efficient, and

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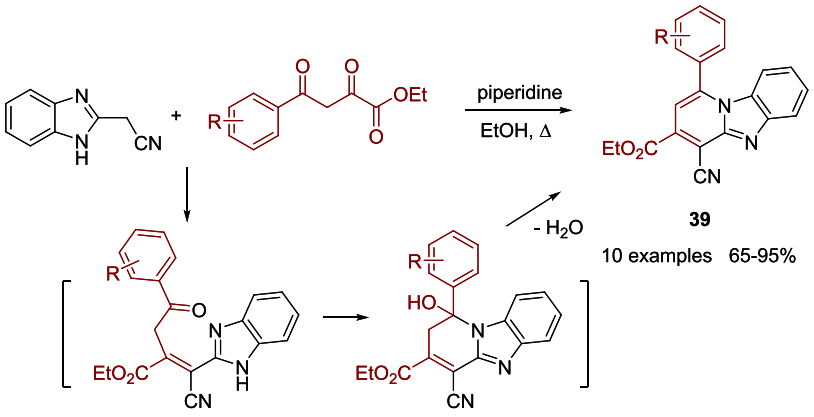
Scheme 14. Reaction between 2-(1*H*-Benzo[*d*]imidazol-2-yl)acetonitrile and Ethyl 2,4-Dioxo-4-arylbutanoates



environmentally benign and include a potassium hydroxide-mediated reaction at ambient temperature for the construction of **38a** and reaction at reflux in the absence of a base for **38b**. The reaction outputs are explained by similar pathways starting with base or a heat mediated intramolecular amidation reaction of 2-aminopyridinium bromide to form imidazopyridin-2-ol or its potassium salt. The next step involves the insertion of a thiophenol substituent at the 3-position by in situ formed species. Finally, a proton abstraction leads to the formation of 3-sulfenylimidazo[1,2-*a*]pyridin-2-(3*H*)-ones **38b**, which tautomerize into enol to form **38a** after an acidic workup.

A series of benzo[4,5]imidazo[1,2-*a*]pyridine derivatives **39** are obtained via eco-friendly catalyst-free condensation of 2-(1*H*-benzo[d]imidazol-2-yl)acetonitrile with various ethyl 2,4-dioxo-4-arylbutanoates in the presence of piperidine as a base (Scheme 14).[23] The proposed mechanism includes the initial Knoevenagel condensation and subsequent intramolecular nucleophilic attack of the nitrogen on the carbonyl group as well as water elimination.

3. SUMMARY

This Mini-Review covers the most efficient protocols for metal-free direct imidazo[1,2-*a*]pyridine core construction developed in the past decade. As seen, the tendency nowadays is to accomplish as eco-friendly as possible procedures. The key features of the methods include atom economy, energy savings, easy handling, reusable catalysts, and scalability and being free of organic waste. Several mineral or organic acids, substrates such as saccharin or calixarenes, enzymes, iodine, low or nonvolatile salts, and clays are applied as catalysts to obtain compounds with variable substitution patterns. Numerous methods involve catalyst-free conditions; some use high boiling solvent in an attempt to minimize environment contamination. Recently, the trend to develop even more environmentally benign protocols has resulted in a series of solventless procedures and the application of modern green techniques like microwave and light irradiation, grindstone chemistry, and continuous flow processes.

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Notes

The author declares no competing financial interest.

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