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Iron(III)-catalyzed three-component domino strategy for the synthesis of imidazo[1,2-*a*]pyridines



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ABSTRACT

An efficient, one-pot, three-component domino strategy has been demonstrated for the synthesis of imidazo[1,2-*a*]pyridines using a catalytic amount of Fe(III) chloride in high yields in air. A library of imidazo[1,2-*a*]pyridines was synthesized by the reaction of easily available aldehydes and 2-aminopyridines in a mixture of nitroalkane and DMF (2:1). This transformation presumably occurs by a sequential aza-Henry reaction/cyclization/denitration. The use of readily available chemicals as starting materials, inexpensive metal catalyst, aerobic reaction conditions, tolerance of a wide range of functional groups, and operational simplicity are the notable advantages of this present protocol.

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Recently, significant interest has focused on the development of new protocols for environmentally benign processes that are both economically and technologically practical. Particularly the use of nonhazardous, inexpensive metals has attracted interest in organic synthesis. Iron-based catalysts have been shown to promote a broad range of organic transformations, such as cross-couplings, allylations, hydrogenations, and direct C—H bond functionalizations owing to their low cost, sustainability, ready availability, nontoxicity, and environmental friendliness.¹

Fused imidazoles have proven to be an important structural scaffold in many pharmaceuticals. Interestingly, the fused imidazole containing an embedded pyridine, that is, imidazo[1,2-*a*]pyridine derivatives, have been shown to have a diverse range of biological activities, for instance antiviral, antimicrobial, antitumor, anti-inflammatory, antiparasitic, hypnotic etc.² They are also β -amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotonic agents.³ Imidazo[1,2-*a*]pyridine scaffolds, in particular, constitute the core structure of many currently marketed drugs⁴ such as zolpidem, alpidem, olprinone, zolimidine, necopidem, and saripidem (Fig. 1).

As a consequence, a number of methods to synthesize imidazo[1,2-a]pyridines have been developed in recent times. The most important approaches are the condensation of 2-aminopyridine with α -halocarbonyl compounds,⁵ one-pot condensation of aldehydes, isonitriles, and 2-aminopyridines,⁶ and the coppercatalyzed three-component reaction of 2-aminopyridines, aldehydes, and alkynes⁷/nitromethane.⁸ Recently a few methodologies have also been developed employing C—H amination.⁹ However, most of these methodologies have been developed using expensive reagents, commercially less available alkynes, and α -halocarbonyl compounds which have lachrymatory properties. Therefore, finding a new methodology for the synthesis of imidazo[1,2-*a*]pyridines in terms of using basic chemicals as starting materials, increasing efficiency, operational simplicity, and economic practicability is highly desirable.

Multicomponent domino reactions are one of the best options to generate complex heterocycles and natural products with several degrees of structural diversity by the reaction of three or more simple starting materials in one-pot.¹⁰ In addition, multicomponent reactions (MCRs) are accepted as efficient chemical processes since they avoid time-consuming and costly purification processes, as well as protection–deprotection steps.¹¹ In recent years, MCRs have emerged as a powerful synthetic tool for generating structurally complex molecular entities¹² with fascinating biological properties through the formation of several carbon–carbon and carbon–heteroatom bonds in a one pot operation.¹³ For these reasons, MCRs are particularly well suited for diversity oriented synthesis and library synthesis of drug like compounds, which are an essential part of the research performed in agrochemical and pharmaceutical companies.

Our group is actively researching multicomponent reactions.¹⁴ Recently, we reported a one-pot methodology for the synthesis of β -nitroamines via a three-component coupling of an amine, an aldehyde, and a nitroethane using an aza-Henry reaction.¹⁵ Furthermore, our previous studies revealed that the in situ



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

generated nitro compounds could be transformed into a cyclic compound via a denitration process.¹⁶ These results suggested that an amine having two nucleophilic sites such as 2-aminopyridine could afford a cyclic structure via a sequential aza-Henry reaction/cyclization/denitration process (Scheme 1a). Very recently we reported the synthesis of imidazo[1,2-*a*]pyridines by a cascade reaction between nitroolefins and 2-aminopyridines.^{16a} However, this method is only applicable for the synthesis of 3-unsubstituted imidazopyridines (Scheme 1b). Herein we report a FeCl₃-catalyzed one-pot protocol for the synthesis of substituted imidazo[1,2-*a*]pyridines by a three-component coupling of 2-aminopyridines, aldehydes, and nitroalkanes (Scheme 1).

We started by choosing 2-aminopyridine 1a and 4-chlorobenzaldehyde 2a as the model substrates for this reaction using 20 mol % FeCl₃ as the catalyst in nitromethane as solvent for 5 h at 110 °C. Gratifyingly, the expected product was obtained in 36% yield (entry 1, Table 1). Inspired by this result, we tested various iron salts in different solvents as well as varying the temperature (see Table 1). The use of a mixture of nitromethane and DMF (2:1 v/v) as the solvent yielded **5aaa** in 72% (entry 2, Table 1). It indicated that the binary solvent system might play an important role for this conversion.¹⁷ So, we examined the model reaction with various binary solvent systems such as nitromethane with DMSO, toluene, and CH₃CN. It was found that the use of a mixture of nitromethane and DMF (2:1) afforded the product 5aaa in maximal yield (entry 6, Table 1). Increasing the temperature did not improve the yield whereas decreasing the temperature lowered the yield to 64%. FeCl₃ (20 mol %) was found to be a more effective catalyst compared to other iron salts like FeBr₃ and Fe(OTf)₃. In this case FeBr₃ and Fe(OTf)₃ make strong complexes with 2-aminopyridine which probably suppressed the formation of product. Increasing the amount of catalyst (30 mol %) did not improve the yield noticeably (entry 13, Table 1) whereas decreasing the amount of catalyst (10 mol %) decreased the yield (entry 14, Table 1). In the absence of catalyst no product was observed. Furthermore, the use of other additives, such as piperidine and acetic acid, did not improve the yield of this transformation (entries 7 and 8, Table 1). However, other common Lewis acids like AlCl₃ and ZnCl₂ were not effective for this reaction (entries 16 and 17, Table 1). Thus, optimal reaction conditions were obtained using 2-aminopyridine (**1a**, 1 mmol), 4-chlorobenzaldehyde (**2a**, 1.1 mmol) in presence of 20 mol % of FeCl₃ in a mixture of nitromethane (**3a**) and DMF (2:1) at 110 °C (entry 6, Table 1) in air.

With the optimized reaction conditions in hand, we explored the scope of this reaction (Table 2). Our attention was focused on the use of substituted aldehydes and 2-aminopyridines to prove the general applicability of the reaction conditions (**5aaa–5eba**). It can be seen that electron-rich and electron-deficient aldehydes reacted efficiently with various 2-aminopyridines to afford the desired products with good yields under the optimized reaction conditions without any additives.¹⁸ The chloro- and iodo-substituted benzaldehydes gave the corresponding **5aaa** and **5bja** in 78% and 76% yields respectively. We were pleased to notice that under the stated conditions, aminopyridines substituted with halogens such as –Cl, and –I (**5dba** and **5eba**) smoothly reacted with benzaldehyde without forming any dehalogenated products. The aldehyde containing an electron donating OMe group on the aromatic ring also showed good efficiency (**5ada** and **5bda**).



Scheme 1. Synthesis of imidazo[1,2-a]pyridine derivatives.

Table 1

Optimization of the reaction conditions^a



Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Yield ^b (%)
1 ^c	FeCl ₃ (20)	$MeNO_2$ (3 mL)	110	36
2	FeCl ₃ (20)	MeNO ₂ /DMF (1.5/1.5 mL)	110	72
3	FeCl ₃ (20)	MeNO ₂ /Toluene (1.5/1.5 mL)	110	28
4	FeCl ₃ (20)	MeNO ₂ /DMSO (1.5/1.5 mL)	110	33
5	FeCl ₃ (20)	MeNO ₂ /CH ₃ CN (1.5/1.5 mL)	110	26
6	FeCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	110	78
7 ^d	FeCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	110	76
8 ^e	FeCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	110	74
9	FeCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	90	64
10	FeCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	130	72
11	FeBr ₃ (20)	MeNO ₂ /DMF (2/1 mL)	110	42
12	$Fe(OTf)_3$ (20)	MeNO ₂ /DMF (2/1 mL)	110	37
13	FeCl ₃ (30)	MeNO ₂ /DMF (2/1 mL)	110	79
14	FeCl ₃ (10)	MeNO ₂ /DMF (2/1 mL)	110	64
15	_	MeNO ₂ /DMF (2/1 mL)	110	ND ^f
16	AlCl ₃ (20)	MeNO ₂ /DMF (2/1 mL)	110	Trace
17	$ZnCl_2$ (20)	MeNO ₂ /DMF (2/1 mL)	110	Trace

Entry 6 is the optimized reaction conditions.

^a Reaction conditions: Carried out with 1 mmol of **1a** and 1.1 mmol of **2a** in solvent (3 mL) for 5 h.

^b Isolated yields.

^c Reaction carried out under reflux conditions.

^d 20 mol % piperidine was used as an additive.

^e 20 mol % AcOH was used as an additive.

^f Yields are not determined by TLC.

Table 2

Scope of the iron(III)-catalyzed three-component reaction^a



^a Reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), FeCl₃ (20 mol %), MeNO₂ (**3**a, 2.0 mL), DMF (1.0 mL) at 110 °C for 5 h. All are isolated yields.

 $^{\rm b}$ 1a (20.0 mmol), 2a (22.0 mmol), FeCl_3 (20 mol %), MeNO_2 (3a, 40.0 mL), DMF (20.0 mL) at 110 °C for 5 h.

2-Hydroxybenzaldehyde afforded the corresponding product **5afa** which is very useful for photophysical studies and displays excited-state intramolecular proton transfer (ESIPT).^{5a} In addition,

heteroaryl aldehydes such as furfural and thiophene-2-carboxaldehyde could also participate in the multicomponent reaction to produce the desired products in moderate yields without affecting the heterocyclic moieties (**5aga** and **5bka**). We were delighted to find that the –SMe substituted benzaldehyde was also tolerated under our catalytic conditions with 72% isolated yield (**5aea**). Aliphatic aldehyde isobutyraldehyde also afforded the desired product with moderate yield (**5aha**). This methodology is also applicable on a gram-scale synthesis. We have successfully prepared the imidazopyridine **5aaa** in 72% yield by the reaction of 2-aminopyridine (**1a**, 20 mmol) with 4-chlorobenzaldehyde (**2a**, 22 mmol).

Our synthesized compound **5aea** can be utilized for the synthesis of the marketed drug zolimidine by oxidation employing the reported method.^{9b} We have also successfully synthesized this drug under our present reaction conditions with good yield (Scheme 2).

By virtue of our method, we are able to synthesize substituted imidazo[1,2-*a*]pyridines at the C-3 position. The synthesis of 3-substituted imidazo[1,2-*a*]pyridines is possible by changing nitromethane to other nitroalkanes (Scheme 3). Both nitroethane and nitropropane worked well under the present reaction conditions. The desired 3-substituted imidazo[1,2-*a*]pyridines were obtained in good yields (**6aab**–**7bbc**). An aliphatic aldehyde also reacted under the optimized reaction conditions (**6bhb**).

To understand the reaction mechanism, a few experiments were performed which are represented in Scheme 4. First of all, we synthesized the corresponding imine **A** by reacting with 2-aminopyridine (**1a**) and 4-chlorobenzaldehyde (**2a**) in ethanol. When the imine **A** was subjected to the optimized reaction conditions, the corresponding imidazo[1,2-*a*]pyridine **5aa** was obtained in quantitative yield (Eq. 1). Furthermore, the imine **A** has been isolated from the reaction mixture by quenching the reaction after 30 min. Moreover, the formation of nitrostyrene was not observed in the reaction. This suggests that the imine **A** is the key intermediate for this reaction. No significant decrease in yield was observed when the reaction was carried out in the presence of a



Scheme 2. One-pot synthesis of the drug zolimidine.



Scheme 3. Synthesis of 3-substituted imidazo[1,2-a]pyridines.



Scheme 4. Mechanistic experiments.



Scheme 5. Probable mechanism for the three-component reaction.

radical scavenger, TEMPO (1.5 equiv) (Eq. 2) which favors the formation of imidazo[1,2-*a*]pyridines through the non-radical mechanistic pathway.

From the results of the above experiments, a probable mechanism for the reaction is represented in Scheme 5. Initially, imine **A** is formed by the condensation between 2-aminopyridine and aldehyde. The next step is the formation of the aza-Henry product **B** through the addition of nitromethane to the imine.¹⁵ Likely, FeCl₃ assisted these two steps by increasing the electrophilicity of both the aldehyde and the imine. Intermediate **B** then tautomerizes to intermediate **C**, which undergoes an intramolecular cyclization affording intermediate **D**. The final product results from a subsequent elimination of both water and nitroxyl (HNO).^{16,19} FeCl₃ may further act as a Lewis acid to facilitate the intramolecular cyclization.

In summary, we have developed an iron(III)-catalyzed one-pot three-component domino strategy for the expedient synthesis of imidazo[1,2-*a*]pyridines under ambient atmosphere. Furthermore, the present methodology is also applicable to the synthesis of zolimidine, a useful drug for the treatment of peptic ulcers. The present reaction most likely occurs via a sequential aza-Henry reaction/cyclization/denitration. Readily available chemicals as starting materials, an inexpensive metal catalyst, aerobic reaction conditions, tolerance of a wide range of functional groups, and operational simplicity are the notable advantages of this present approach. These advantages render this protocol facile and suitable to create a diversified library of imidazo[1,2-*a*]pyridine derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014 .07.094.

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