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ABSTRACT

A facile synthesis of 2-(imidazo[1,2-*a*]pyridin-3-yl)acetonitriles *via* $FeCl_3$-catalyzed site-selective C(sp^2)−H alkylation of imidazo[1,2-*a*]pyridines with diazoacetonitrile is presented. This new method features with an environmentally benign catalyst, easily obtainable substrates, and oxidant- and ligand-free reaction conditions. Moreover, the importance of the products thus obtained is showcased by their ready transformation into some synthetically and pharmaceutically interesting products with good efficiency.

Introduction

Imidazo[1,2-*a*]pyridine and its derivatives have attracted considerable attention due to their wide applications in medicinal chemistry and material sciences. For examples, numerous functionalized imidazo[1,2-*a*]pyridines, especially the C−3 substituted ones, are found to possess pharmaceutical and biological activities such as antitumor, antiviral, antiprotozoal, antiapoptotic, antipyretic, analgesic as well as antitubercular.[1,2] This could be well exemplified by a number of imidazo[1,2-*a*]pyridine-containing commercial drugs such as zolpidem, alpidem, saripidem, and necopidem, etc. (Figure 1). In addition, many imidazo[1,2-*a*]pyridine derivatives have demonstrated unique photo-physical properties, and have thus been developed as a new class of fluorescent probes and luminophores.[3] On the other hand, (hetero)arylacetonitrile is a privileged scaffold widely found in clinical drugs or drug candidates.[4] More attractively, the derivatives of (hetero)arylacetonitrile are versatile synthetic intermediates owing to their distinctive structural characteristics: 1) the acidic methylene unit makes them good nucleophiles;[5] 2) the cyano group enables them to be ready candidates for amides, amines, ketones, acids, esters, etc.;[6] 3) the acetonitrile moiety as a whole could be used as a building block for the construction of various *N*-heterocycles.[7] Given the importance of both C−3 functionalized imidazo[1,2-*a*]pyridines and (hetero)arylacetonitriles, the development of efficient and practical methods for the preparation of 2-(imidazo[1,2-*a*]pyridin-3-yl)acetonitriles constitutes an important topic for the synthetic community.

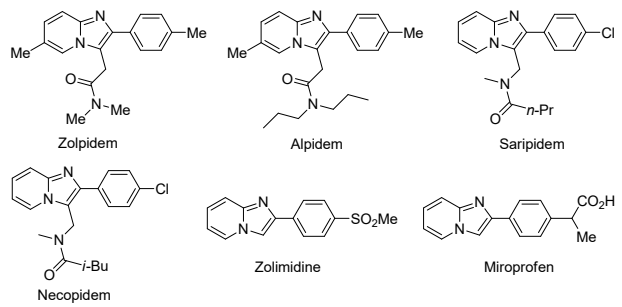
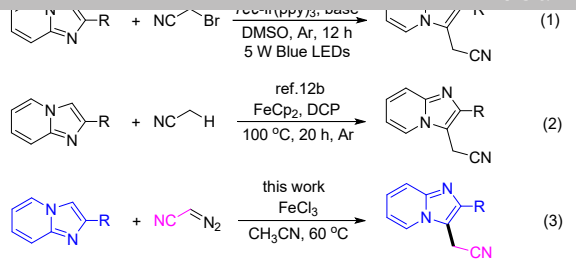


Figure 1. Selected pharmaceuticals containing an imidazo[1,2-*a*]pyridine scaffold.

In recent years, direct functionalization of inert C(sp^2)−H bonds is emerging as a highly valuable tool for organic synthesis due to its excellent step-economy and atom-efficiency. In this regard, extensive studies have been made on the efficient introduction of diverse functional groups onto the C−3 site of the imidazo[1,2-*a*]pyridine scaffold through regioselective C(sp^2)−H bond functionalization reactions.[8] Inspired by those elegant pioneering studies and as a continuation of our own interests in transition metal-catalyzed C(sp^2)−H functionalization of 2-arylimidazo[1,2-*a*]pyridines[9] and in diazo compounds as a class of efficient coupling partners for Rh(III)-catalyzed C–H bond derivations,[10] we have explored the reaction of imidazo[1,2-*a*]pyridines with diazoacetonitrile.[11] From this study, a facile and convenient synthesis of 2-(imidazo[1,2-*a*]pyridin-3-yl) acetonitriles was successfully established (Scheme 1 (3)). It is worthwhile to note herein that although some excellent synthetic protocols toward 2-(imidazo[1,2-*a*]pyridine-3-yl)acetonitriles via C(sp^2)−H functionalization have already been developed[12] (Scheme 1 (1) and (2)), an alternative method to fulfill this task by using the cheap and sustainable $FeCl_3$ as a catalyst under oxidant- and ligand-free conditions has not been reported previously. Herein, we wish to present our detailed results in this regard.



Scheme 1. Different approaches toward 2-(imidazo[1,2-*a*]pyridine-3-yl)acetonitriles.

Results and discussion

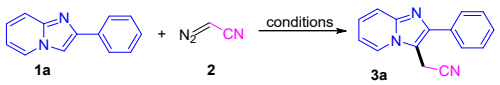
Our study was initiated by treating a mixture of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and diazoacetonitrile (**2**) in CH_3CN with $[RhCp^*Cl_2]_2$ and $AgSbF_6$ at 40 °C under air for 6 h. From this reaction, the desired 2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetonitrile (**3a**) was obtained in 21% yield (Table 1, entry 1). In the absence of $AgSbF_6$, **3a** was formed in a similar yield of 22% (entry 2), indicating that the presence of an additive is not necessary. Next, $PdCl_2$, $Fe(ClO_4)_2$, $Fe(acac)_3$, $FeCl_3$, $CuCl_2{\cdot}2H_2O$ or $Cu(OAc)_2$ was tried as catalyst for this reaction (entries 3-8). Among them, the economically and environmentally sustainable $FeCl_3$ was found to be the most effective to afford **3a** in 47% yield (entry 6). Further study on the effect of different temperatures showed that the yield of **3a** could be improved to 57%, 66% or 58% when this transformation was carried out at 50 °C, 60 °C or 70 °C, respectively (entries 9-11). Next, THF, DCM, DMF and toluene were tried as the reaction media. Among them, DCM gave similar result as that with CH_3CN while others were much less effective (entries 12-15). As another aspect, varying the molar ratio of **1a** to **2a** from 1:3 to 1:2 or 1:4 gave **3a** in yields of 46% and 67%, respectively (entries 16 and 17). It was also found that prolonging the reaction period from 6 h to 8 h did not improve the yield of **3a** obviously (entry 18) while a shortened reaction period resulted in decreased efficiency (entry 19). When the reaction was carried out under nitrogen instead of air, the yield of **3a** decreased to 53% (entry 20). Finally, a control experiment showed that **3a** could not be formed in the absence of the iron catalyst (entry 21).

After having established the optimal reaction conditions, the scope of substrates for this reaction was then explored. First, a series of 2-phenylimidazo[1,2-*a*]pyridines (**1**) bearing various substituents on different sites of the imidazo[1,2-*a*]pyridine scaffold were tested. The results listed in Table 2 showed that **1** with a methyl, methoxy, chloro or trifluoromethyl group attached on the 6-position were well suitable for this reaction to give products **3b-3e**. Meanwhile, the electronic nature of the imidazo[1,2-*a*]pyridine unit rendered some effect on this reaction as those bearing electron-donating groups (EDGs) generally resulted in higher yields than those bearing electron-withdrawing groups (EWGs) (**3b**, **3c** vs **3d**, **3e**). Next, imidazo[1,2-*a*]pyridine with a methyl, methoxy or bromo unit attached on the 7-position or a methyl or fluoro group attached on the 8-position were let to react with diazoacetonitrile under standard conditions. It turned out that the corresponding reactions proceeded smoothly to give products **3f-3j** in yields ranging from 45% to 62%. In comparison, 5-methyl-2-phenylimidazo[1,2-*a*]pyridine (**1k**) exhibited lower reactivity toward **2**, most likely due to higher steric hindrance.

Next, a number of 2-phenylimidazo[1,2-*a*]pyridines (**1**) bearing various substituents on different positions of the 2-phenyl unit were tried. It turned out that **1** with either EDGs such as methyl and methoxy or EWGs such as halides and trifluoromethyl on the *ortho*-, *meta*- or *para*-position of the 2-phenyl moiety were compatible with the reaction conditions to give **3l-3w** in moderate to good yields. In comparison, *para*-substituted substrates were more efficient than their *ortho*-substituted counterparts. Besides 2-phenylimidazo[1,2-*a*]pyridines, reactions of 2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridine, 2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine and 2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine proceeded equally well to give **3x**, **3y** and **3z**. Furthermore, substrates **1** with substituent attached on both the imidazo[1,2-*a*]pyridine scaffold and the 2-phenyl unit took part in this reaction smoothly to afford **3aa-3dd** in moderate yields. When 2-methylimidazo[1,2-*a*]pyridine was subjected to the standard conditions for 6 h, it remained almost intact and the desired product **3ee** was not obtained.

As for possible mechanism accounting for the formation of **3a**, we noticed that Koenigs et al. have proposed that FeTPPCl-catalyzed alkylation of indoles with diazoacetonitrile should proceed via a radical pathway since the alkylation was completely inhibited by 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) as a radical scavenger.[11i] To explore if this $FeCl_3$-catalyzed alkylation of imidazo[1,2-*a*]pyridines with diazoacetonitrile is also a radical process, the reaction of **1a** with **2** was conducted in the presence of 1 equiv., 2 equiv., or 3 equiv. of TEMPO. Under these circumstances, **3a** was obtained in 42%, 18% or 16% yield, respectively. The fact that the alkylation of

Optimization studies for the formation of **3a**[a]

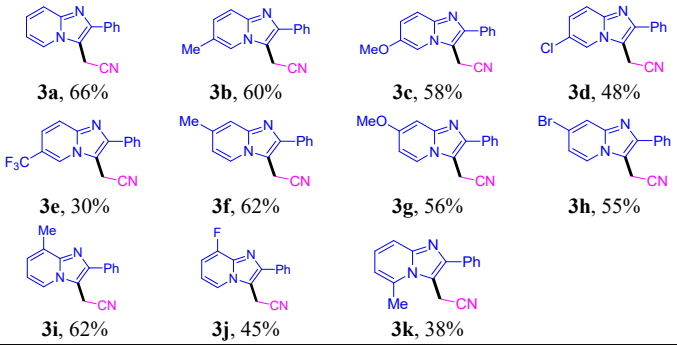


Entry	Catalyst	Solvent	T (°C)	Yield (%)[b]
1[c]	$[RhCp^*Cl_2]_2$	CH_3CN	40	21
2	$[RhCp^*Cl_2]_2$	CH_3CN	40	22
3	$PdCl_2$	CH_3CN	40	20
4	$Fe(ClO_4)_2$	CH_3CN	40	25
5	$Fe(acac)_3$	CH_3CN	40	26
6	$FeCl_3$	CH_3CN	40	47
7	$CuCl_2{\cdot}2H_2O$	CH_3CN	40	17
8	$Cu(OAc)_2$	CH_3CN	40	18
9	$FeCl_3$	CH_3CN	50	57
10	$FeCl_3$	CH_3CN	60	66
11	$FeCl_3$	CH_3CN	70	58
12	$FeCl_3$	THF	60	53
13	$FeCl_3$	DCM	60	61
14	$FeCl_3$	DMF	60	39
15	$FeCl_3$	toluene	60	26
16[d]	$FeCl_3$	CH_3CN	60	46
17[e]	$FeCl_3$	CH_3CN	60	67
18[f]	$FeCl_3$	CH_3CN	60	68
19[g]	$FeCl_3$	CH_3CN	60	61
20[h]	$FeCl_3$	CH_3CN	60	53
21		CH_3CN	60	ND

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), catalyst (0.05 mmol), solvent (2 mL), air, 6 h.
[b]Isolated yield.
[c]$AgSbF_6$ (0.5 mmol).
[d]**2** (1.0 mmol).
[e]**2** (2.0 mmol).
[f]8 h.
[g]4 h.
[h]Under N_2.

Tab

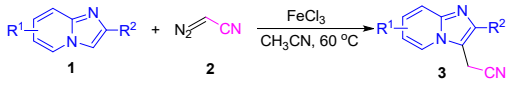
Substrate scope for the synthesis of **3** (I) [a,b]

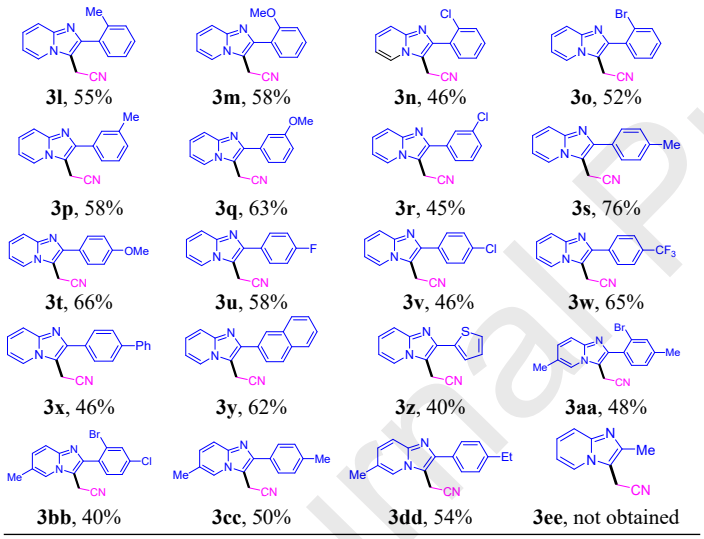


[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $FeCl_3$ (0.05 mmol), CH_3CN (2 mL), 60 °C, 6 h.
[b]Isolated yield.

Table 3

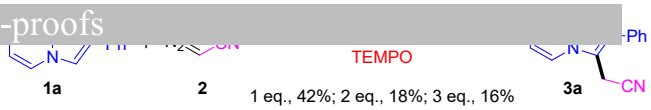
Substrate scope for the synthesis of **3** (II) [a,b]



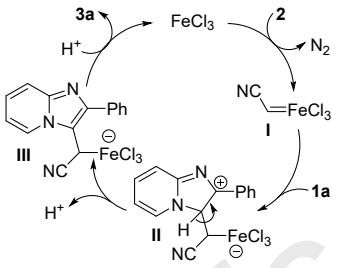


[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $FeCl_3$ (0.05 mmol), CH_3CN (2 mL), 60 °C, 6 h.
[b]Isolated yield.

1a with **2** in the presence of TEMPO is much less efficient than that carried out in the absence of TEMPO suggests that it might also involve the formation of radical intermediate(s) somewhere in the cascade process. Meanwhile, the fact that **3a** could still be obtained in 16% yield even in the presence of 3 equiv. of TEMPO indicates that another pathway involving the formation of a carbene intermediate might also exist as proposed by Zhou[13a] and Moody[13b] in their studies on the reactions of α-diazophenylacetates or 4-diazo-4*H*-imidazoles with various substrates. To be specific, **2** firstly reacts with $FeCl_3$ to form an iron carbene species **I**. Reaction of **I** with **1a** generates a zwitterionic intermediate **II**. Next, a β-elimination occurs with **II** to give intermediate **III**. Finally, protonation of **III** affords product **3a** and releases the catalyst for the next catalytic cycle (Scheme 3). Admittedly, more efforts are still needed to clarify the exact reaction pathway for the formation of **3a**.



Scheme 2. Control experiments in the presence of TEMPO.

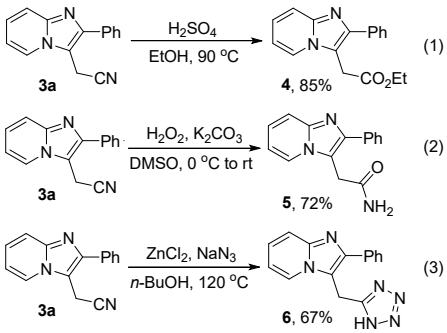


Scheme 3. Plausible mechanism accounting for the formation of **3a**

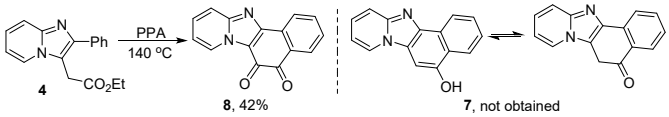
To illustrate the usefulness of the products thus obtained, the following transformations were conducted. First, **3a** was treated with H_2SO_4 in ethanol to afford ethyl 2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetate (**4**) in high efficiency (Scheme 4 (1)).[12a] Second, **3a** was treated with H_2O_2 and K_2CO_3 in DMSO to afford 2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetamide (**5**) in 72% yield (Scheme 4 (2)).[14] Third, a tetrazole derivative (**6**) was obtained through the reaction of **3a** with NaN_3 under the promotion of $ZnCl_2$ (Scheme 4 (3)).[15]

Given the importance of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine derivatives,[9] **4** was then treated with polyphosphoric acid (PPA) with the aim to get naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-ol (**7**) via an envisioned intramolecular Friedel-Crafts acylation (IFCA) followed by a ketone-enol tautomerization. To our surprise, **7** was not isolated from the resulting mixture. Instead, naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5,6-dione (NPDO, **8**) was obtained in moderate yield (Scheme 5). It was soon realized that the formation of **8** is both synthetically and mechanistically attractive since it not only reveals an interesting cascade reaction combining an IFCA and an in situ oxidation of the methylene unit, but also provides a simple and direct alternative synthetic method toward NPDOs, which have been identified as highly reactive substrates of NADPH-dependent single- and two-electron transferring flavoenzymes.[16]

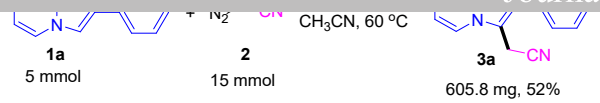
Finally, to see whether this method is suitable for enlarged synthetic missions, the synthesis of **3a** was carried out on 5 mmol scale. It turned out that the corresponding reaction proceeded smoothly to afford **3a** in 52% yield (Scheme 6).



Scheme 4. Structural elaboration of **3a**.



Scheme 5. A novel synthesis of NPDO (**8**).



Scheme 6. Enlarged-scale synthesis of **3a**.

Conclusion

In summary, we have developed a novel C−3 alkylation of imidazo[1,2-*a*]pyridines with diazoacetonitrile, from which an efficient and convenient method for the synthesis of the synthetically and pharmaceutically valuable 2-(imidazo[1,2-*a*]-pyridine-3-yl)acetonitriles was established. Compared with literature methods, the protocol developed herein has advantages such as simple substrates, sustainable catalyst, oxidant- and ligand-free reaction conditions. Further studies to clarify the reaction mechanism and find more applications of diazoaceto-nitrile in C−H bond functionalization are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:

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Declaration of interests

☑The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

$FeCl_3$-catalyzed C−3 functionalization of imidazo[1,2-*a*]pyridines with diazoacetonitrile under oxidant- and ligand-free conditions

Guang Chen, Bin Li*, Bing Hu, Xinying Zhang, Xuesen Fan*

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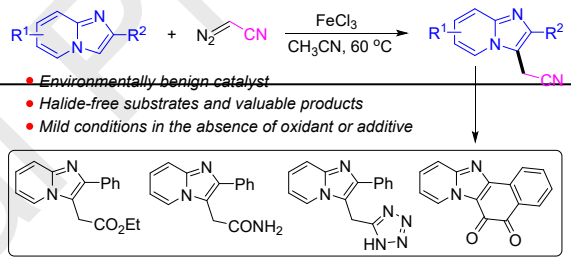

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