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Original article

Direct one-pot synthesis of zolimidine pharmaceutical drug and imidazo[1,2-a]pyridine derivatives *via* I_2/CuO-promoted tandem strategy

Qun Cai, Mei-Cai Liu, Bi-Ming Mao, Xuan Xie, Feng-Cheng Jia, Yan-Ping Zhu, An-Xin Wu *

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, China

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ABSTRACT

An efficient one-pot synthetic protocol was developed for the synthesis of imidazo[1,2-a]pyridines from easily available starting materials: Aromatic ketones, α,β-unsaturated ketones, β-keto esters and 2-aminopyridines. The present reaction proceeded well in MeOH under the media of I_2/CuO. By using this method, the marketed drug zolimidine could be prepared easily with 95% yield. All these target products were characterized by NMR, HRMS and IR spectra. Furthermore, the target compound **3fa** was determined by X-ray crystallographic analysis.

1. Introduction

Imidazo[1,2-a]pyridines are very important heterocycles which have been found to be the core scaffold of many natural products and drugs (Scheme 1). They have received considerable interest from the pharmaceutical industry because of their important biological activities and interesting therapeutic properties [1], including antibacterial [2a], antifungal [2b,2c], antiviral [2d,2f], antiulcer [2g], and anti-inflammatory behavior [2h]. Moreover, they can also be used in material science and molecular recognition [3].

By now, many synthetic methods for the construction of imidazo[1,2-a]pyridines have been reported. In general, the common strategies were the cyclocondensations of 2-aminopyridines with α-halocarbonyl compounds [4], 1,3-dicarbonyl compounds [5], nitroolefins or alkynes [6]. Besides, the condensation of 2-aminopyridines, aldehydes and isonitriles or alkynes in one-pot was also an efficient method for the synthesis of imidazo[1,2-a]pyridines [7]. Some other novel synthetic approaches have been established in recent years. For example, the transition-metal catalyzed C–H activation or coupling methods have been demonstrated by some research groups recently [8]. Furthermore, several domino protocols have also been proposed for preparation of imidazo[1,2-a]pyridines, which avoided the requirement of any transition-metal [9,10].

In our previous studies, we found that aryl methyl ketones could be quantitatively converted to aryloxoethanals in I_2/DMSO system. The aryloxoethanals generated *in situ* were easily captured by 2-aminopyridines to afford 2,3-disubstituted imidazo[1,2-a]pyridines [10]. Based on these results, this work developed an I_2/CuO-promoted one-pot protocol for the synthesis 2-substituted imidazo[1,2-a]pyridines *via* 2-aminopyridines capturing α-iodo acetophenones generated *in situ* from aryl methyl ketones in MeOH (Scheme 2).

2. Experimental

All aryl methyl ketones, β-ketone esters, 2-aminopyridines, and other reagents were obtained from commercial suppliers and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh).

IR spectra were recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). HRMS were obtained

* Corresponding author.
E-mail address: chwuax@mail.ccnu.edu.cn (A.-X. Wu).

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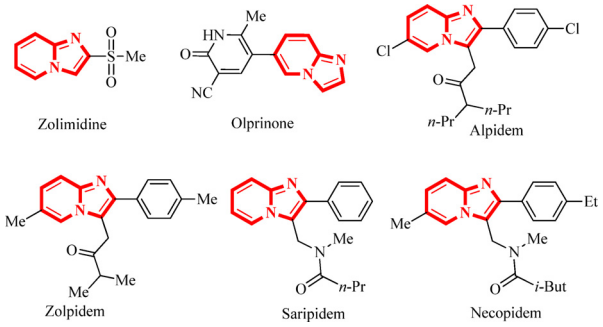


Scheme 1. The drugs containing imidazo[1,2-a]pyridine unit.

on a Bruker Apex-Ultra 7.0T FTMS equipped with an electrospray source (ESI) or atmospheric-pressure chemical ionization (APCI). Melting points were determined using XT-4 apparatus and not corrected.

The synthetic route of the target products was outlined in Scheme 2. Finely powdered CuO (88 mg, 1.1 mmol) and I_2 (279 mg, 1.1 mmol) were added to a solution of acetophenone **1a** (120 mg, 1 mmol) in anhydrous MeOH (20 mL). The mixture was refluxed for 1–10 h. When disappearance of the reactant (monitored by TLC), then added 2-aminopyridine **2a** (94 mg, 1.0 mmol) at reflux for another 2 h. After the reaction completed, the mixture was filtered and the solvent was removed under reduced pressure. The residue was poured into 10% $Na_2S_2O_3$ solution (50 mL), the mixture was extracted with EtOAc (3× 50 mL), and the organic layer was dried (Na_2SO_4). Removal of the solvent and purification of the residue by column chromatography gave the desired product **3aa** as yellow solid 159.1 mg (yield 82%).

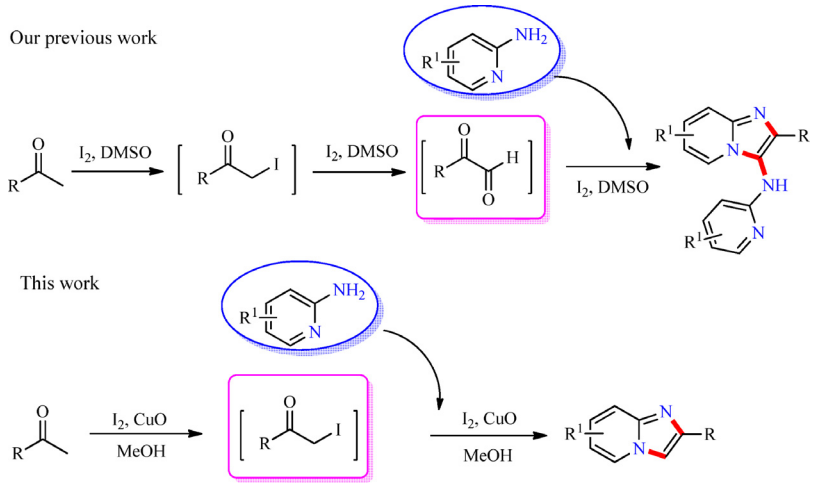
3. Results and discussion

We firstly selected acetophenone (**1a**) and 2-aminopyridine (**2a**) as model substrates to optimize the reaction conditions (Table 1). Several solvents were firstly examined. The reaction could not perform to give the desired product in acetonitrile, tetrahydrofuran, toluene, chloroform, and isopropanol (entries 1, 2, 4, 5, and 8). However, the desired product was obtained in 30% yield when acetophenone (**1a**), 2-aminopyridine (**2a**), I_2 and CuO were heated in DMF at 100 °C for 1–2 h (entry 3). When the reaction was performed in methanol or ethanol, the target product could be obtained in 40% and 35% yields, respectively (entries 6 and 7). To our delight, the yields of the desired product were increased when acetophenone (**1a**), I_2 and CuO were refluxed in methanol or ethanol for 1–2.5 h, with the subsequent addition of **2a** for another 2 h (entries 9 and 10). Next, the equiv. of I_2 and CuO was also optimized. Further elevating the amounts of I_2 or CuO did not increase the yield obviously (entries 11 and 12). Above all, the optimal reaction condition turned out to be acetophenone **1a** (1.0 mmol), I_2 (1.1 mmol) and CuO (1.1 mmol) refluxed in MeOH for 1–2.5 h, then 2-aminopyridine (**2a**) (1.0 mmol) was added at reflux for another 2 h.

With suitable reaction conditions established, the generality of the reaction was explored (Table 2). The substrates with the electron-donating substituents on the benzene ring gave good yields, such as 4-Me, 4-OMe, 2,4-$(OMe)_2$ and 2,6-$O(CH_2)_2O$ groups (80%–86%, **3ba**–**3ea**). The electron-withdrawing substituent groups, such as 4-Cl, 4-Br, 3,4-Cl_2, 3-NO_2 attached to the benzene ring shown a slight decrease in yields (70%–76%, **3fa**–**3ia**). It should be noted that the substrate with a sensitive hydroxy group (4-OH) in the phenyl group presented a moderate yield of **3ja** (65%). Meanwhile, steric hindrance substrates 2-naphthyl methyl ketone and 1-naphthyl methyl ketone were also tolerant to this reaction to afford the desired products **3ka**–**3la** in 79%–80% yields. Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl ketones. The heterocycles, including thiophenyl and benzofuryl, did not affect the overall efficiency, and the corresponding products **3ma**–**3oa** were furnished in 69%–75% yields. The unsaturated methyl ketones and β-ketone esters were also tested under the standard conditions. When unsaturated methyl ketones were selected as substrates, the corresponding products **3pa**–**3qa** were obtained in 55%–58% yields. Moreover, β-ketone esters were also tolerant to the reaction to yield the corresponding products **3ra**–**3ta** in moderate to good yields (55%–73%). Furthermore, the product **3fa** was further determined by X-ray crystallographic analysis (Fig. 1).

To further expand the substrate scope, the substrates 2-aminopyridines were investigated. To our satisfaction, both electron-donating and electron-withdrawing groups attached to 2-aminopyridines were all suitable for this protocol, and provided the corresponding products (**3ab**–**3ae**) in 62%–78% yields. To our delight, 2-aminopyrimidine was also tolerant to the reaction to afford the corresponding product **3af** in 88% yield.

Zolimidine **3ua**, which was the marketed antiulcer drug, could be synthesized in this concise route. As shown in Table 2, by utilizing 1-(4-(methylsulfonyl)phenyl)ethanone and 2-aminopyridine under I_2/CuO-mediated conditions, the cyclization product **3ua** could be generated smoothly in 95% yield.



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

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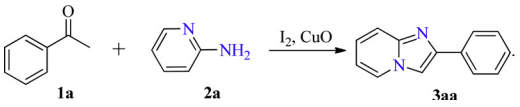
Table 1
Optimization of the reaction conditions.



1a 2a 3aa

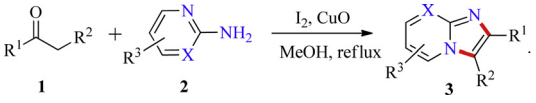
Entry	I_2 (mmol)	CuO (mmol)	Solvent	Yield (%)[b]
1	1.1	1.1	MeCN	n.r.
2	1.1	1.1	THF	n.r.
3	1.1	1.1	DMF/100 °C	30
4	1.1	1.1	Toluene	n.r.
5	1.1	1.1	$CHCl_3$	n.r.
6	1.1	1.1	MeOH	40
7	1.1	1.1	EtOH	35
8	1.1	1.1	*n*-PrOH	n.r.
9[a]	1.1	1.1	MeOH	82
10[a]	1.1	1.1	EtOH	79
11[a]	2	1.1	MeOH	82
12[a]	1.1	2	MeOH	81

Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2, and CuO were heated in one pot for 1–12 h.
[a] **1a** (1.0 mmol), I_2, and CuO were reflux for 1–2.5 h. Subsequently, **2a** was added (1.0 mmol) to this reaction mixture, until the disappearance of **2a**, monitored by TLC. It was a two-step process.
[b] Isolated yield. n.r. = no reaction.

To gain some insight into the mechanism of the reaction process, some control experiments were also performed (Scheme 3). It was found that acetophenone **1a** could be converted into α-iodo ketone **1aa** in 95% yield under I_2/CuO-mediated conditions (Scheme 3a) [11a]. **1aa** with 2-aminopyridine **2a** could perform smoothly to afford product **3aa** in 92% yield in MeOH at reflux conditions. Meanwhile, β-ketone ester **1r** could also be transformed to intermediate **4r** in 78% yield under I_2/CuO-mediated conditions (Scheme 3b). Intermediate **4r** could also react with **2a** to furnish product **3ra** in 90% yield in MeOH at reflux for 2 h.

Based on the above results, a possible mechanism of the present reaction was proposed as follows using acetophenone (**1a**) and 2-aminopyridine (**2a**) as an example (Scheme 4). Initially, the acetophenone **1a** was converted to intermediate α-iodo acetophenone **1aa** in the media of I_2 and CuO [11]. The *in situ* generated intermediate **1aa** underwent an intermolecular nucleophilic substitute with 2-aminopyridine **2a** to obtain intermediate **D**, which was followed by isomerization to furnish intermediate **E**. Finally, intermediate **E** further underwent an intramolecular cyclization to afford the desired product **3aa**. In the whole process, CuO plays multiple roles. It not only acts as the oxidizing agent or catalyst to convert molecular iodine into the reacting iodonium ion (I^+) species, but also act as a weak base to neutralize hydrogen iodide, and reoxidize iodide ion (I^-) into molecular iodine (I_2), which forms together with insoluble copper(I) oxide and water [11a].

Table 2
The scope of ketones and 2-aminopyridines.



1 2 3

Entry	R^1	R^2	R^3	X	Product	Yield (%)[a]
1	C_6H_5	H	–	C	**3aa**	82
2	4-Me–C_6H_4	H	–	C	**3ba**	85
3	4-OMe–C_6H_4	H	–	C	**3ca**	86
4	2,4-OMe_2–C_6H_3	H	–	C	**3da**	80
5	2,6-$O(CH_2)_2O$–C_6H_3	H	–	C	**3ea**	84
6	4-Cl–C_6H_4	H	–	C	**3fa**	76
7	4-Br–C_6H_4	H	–	C	**3ga**	72
8	3,4-Cl_2–C_6H_3	H	–	C	**3ha**	70
9	3-NO_2–C_6H_4	H	–	C	**3ia**	70
10	4-OH–C_6H_4	H	–	C	**3ja**	65
11	2-Naphthyl	H	–	C	**3ka**	80
12	1-Naphthyl	H	–	C	**3la**	79
13	2-Thiophenyl	H	–	C	**3ma**	75
14	3-Thiophenyl	H	–	C	**3na**	73
15	2-Benzofuryl	H	–	C	**3oa**	69
16	$C_6H_5CH{=}CH$	H	–	C	**3pa**	55
17	3,4-OMe_2–$C_6H_3CH{=}CH$	H	–	C	**3qa**	58
18	C_6H_5	CO_2Et	–	C	**3ra**	65
19	3,4-OMe_2–C_6H_3	CO_2Et	–	C	**3sa**	73
20	4-NO_2–C_6H_4	CO_2Et	–	C	**3ta**	55
21	C_6H_5	H	5-Br	C	**3ab**	68
22	C_6H_5	H	3,5-Br_2	C	**3ac**	62
23	C_6H_5	H	6-Me	C	**3ad**	78
24	C_6H_5	H	4-Me	C	**3ae**	76
25	C_6H_5	H	–	N	**3af**	88
26[b]	4-CH_3SO_2–C_6H_4	H	–	C	**3ua**	95

Reaction conditions: **1** (1.0 mmol), I_2 (1.1 mmol), and CuO (1.1 mmol) were reflux in MeOH (3 mL) for 1–10 h, and then added **2** (1.0 mmol) until the disappearance of **2**, monitored by TLC.
[a] Isolated yield.
[b] Reaction conditions: **1u** (1.0 mmol), I_2 (1.1 mmol), and CuO (1.1 mmol) at reflux in MeOH (3 mL) for 12 h, and then added **2a** (1.0 mmol) for another 2 h.

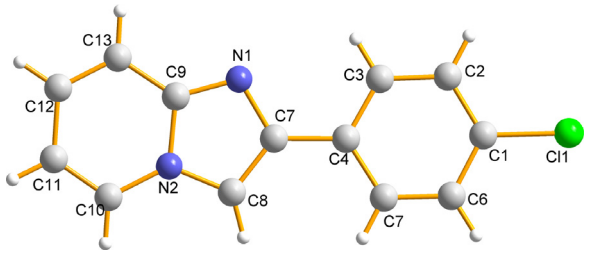
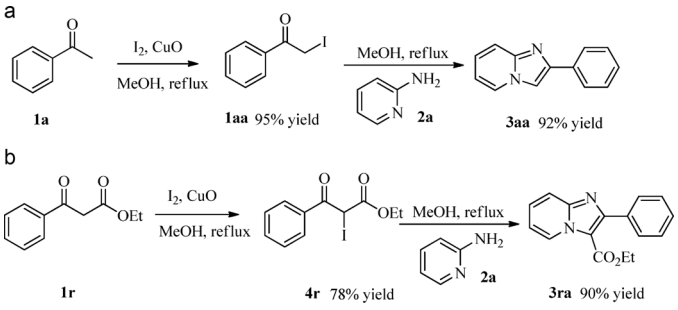
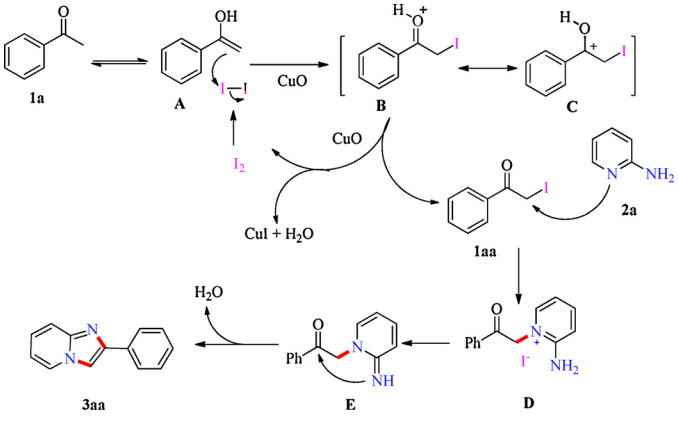


Fig. 1. The X-ray crystal structure of compound **3fa**.



Scheme 3. The control experiments.



Scheme 4. The plausible mechanism of the present reaction.

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4. Conclusion

In conclusion, an I_2/CuO-promoted one-pot tandem strategy has been proposed for the synthesis of imidazo[1,2-a]pyridine derivatives. It is notable that the present reaction has a broad scope of substrates, including aryl methyl ketones, heteroaryl ketones, α,β-unsaturated methyl ketones, β-ketone esters, and substituted 2-aminopyridines. Owing to the generality of the reaction, this protocol should be of great utility in medical chemistry and organic methodology. Further investigations into the scope of this reaction and its applications are ongoing in our laboratory.

Acknowledgments

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