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One-Pot Three-Component Synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine Derivatives Using Air as an Oxidant

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In modern drug discovery, to design a highly efficient chemical reaction, which provides structural diversity with few synthetic steps and simple compounds is a major challenge. One of the ways to achieve this goal is to develop multicomponent reactions.[1] Multicomponent reactions have received considerable interest, because they not only allow more than two reactants to combine sequentially, which is timesaving, highly efficient, and atom economic, but also can give rise to complex structures by simultaneous formation of two or more bonds. Therefore, developing multicomponent reactions has been recognized as one of the most important topics in recent years.

Imidazopyridine[2] as an important pharmacophore is widely found in many bioactive compounds. Especially, imidazo[1,2-*a*]pyridines are one of the most important heterocyclic compounds. They have tremendous applications in material science,[3] medicinal chemistry,[4] and drug synthesis.[5] They are found in many pharmacological compounds, such as the clinical antiulcer compound soraprazan (Figure 1, **I**), alpidem (a nonsedative anxiolytic, **II**),[6] and zolpidem (a hypnotic drug, **III**).[7] Imidazo[1,2-*a*]pyridines show antiinflammatory, antiviral,[8] antibacterial,[9] antipyretic,[10] analgesic,[11] hypnoselective, and anxioselective activities. Therefore, they have attracted significant attention from organic chemists. Recently, with the development of transition metal catalyst tandem reactions[12] and multicomponent[13] reactions, new approaches based on N–H and C–H activations[14] have been developed to gain access to the substituted imidazo[1,2-*a*]pyridine rings.[15] Although synthetic methods for the synthesis of these important structures have been reported, most of them are limited because of expensive oxidants or multistep preparation of the starting materials.[16] As a result, a simple and efficient way to construct imidazo[1,2-*a*]pyridine is still necessary.

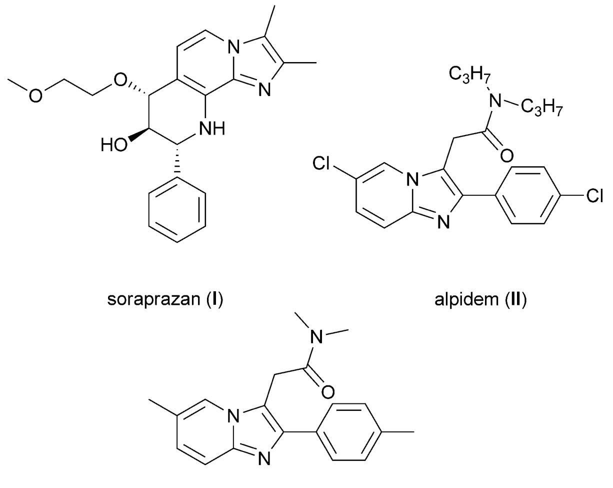
soraprazan (**I**)
alpidem (**II**)
zolpidem (**III**)

Figure 1. Selected examples of imidazo[1,2-*a*]pyridines with biological activities.

The development of a green oxidant is extremely important for future industrial applications, therefore using an environmentally friendly oxidant to construct heterocycles with simple and readily accessible substrates is highly desirable and urgent. Air is the ideal oxidant owing to its abundance, low cost, and sustainability. As a part of our continuing study on the utilization of oxygen in organic chemistry,[17] we paid attention to developing a new strategy for the synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine derivatives through a one-pot three-component reaction (Scheme 1). Herein, we wish to report this simple one-pot synthesis of 3-nitro-2-aryl-imidazo[1,2-a]pyridines in the presence of air.

In the initial experiment, pyridin-2-amine (**1a**) with benzaldehyde (**2a**) and $MeNO_2$ (**3**) were chosen as the model substrates for the reaction, as shown in Table 1. Firstly, the reaction was carried out with CuI in air at 80 °C for 8 hours, the desired 3-nitro-2-phenylimidazo[1,2-*a*]pyridine (**4aa**) was isolated in 78 % yield (Table 1, entry 1). Then different

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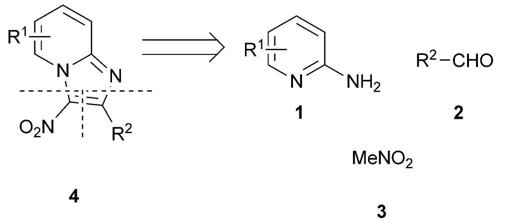
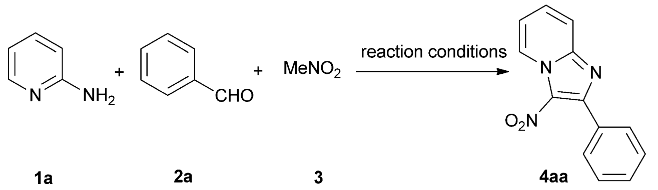


Scheme 1. Retrosynthesis of imidazo[1,2-*a*]pyridines.

copper salts were evaluated, CuBr was superior to CuCl, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, CuOTf, and $Cu(OAc)_2{\cdot}H_2O$, and showed the highest activity for this reaction, affording the desired product in 80 % yield (Table 1, entries 2–8). In addition, without metal copper salts as the catalyst, no desired product was obtained (Table 1, entry 9). When the reaction time was reduced to 4 hours, the product **4aa** was obtained in only 50 % yield (Table 1, entry 10). Meanwhile, when the temperature changed to 60 °C or 100 °C, the yields also decreased (Table 1, entries 11 and 12). When O_2 was employed as the oxidant, there was no improvement in the yield (Table 1, entry 13). Therefore, the optimized conditions were identified (Table 1, entry 2).

Having established the optimal reaction conditions, the scope of this one-pot three-component reaction was examined, the results are illustrated in Table 2. Generally, the reaction of 2-aminopyridines with aromatic aldehydes and $MeNO_2$ mostly proceeded smoothly and led to the desired product in moderate to good yields. To our delight, we found this transformation to be very general for a wide range of aromatic aldehydes and 2-aminopyridines, thus providing easy access to 3-nitro-2-arylimidazo[1,2-*a*] pyridine derivatives. It is observed that the nature of the substituent on the aromatic rings had some influence on the yields of the products. The aromatic aldehydes with electron-donating groups, such as methyl and methoxy groups (Table 2, entries 2–6) gave higher yields than those with electron-withdrawing groups, such as chloro and bromo groups (Table 2, entries 7–12). To our disappointment, when other electron-withdrawing groups such as *o*-NO_2, *p*-NO_2, and CN were tested, only a complex mixture was detected and no desired products were obtained. Furthermore, the reaction of the aromatic aldehyde (Table 2, entry 13) and heteroatom-containing aromatic aldehydes also proceeded efficiently (Table 2, entries 14 and 15). Additionally, the substrate scope of 2-aminopyridines was further investigated **1b–1f**, and similar results were observed. These results indicated that electron-rich 2-aminopyridines were successfully employed (Table 2, entries 16 and 17), and gave higher yields than those with electron-deficient substituents (Table 2, entries 19 and 20). However, **1d** reacted with **2a** to produce **4da** in only 58 % (Table 2, entry 18); this may be owing to the steric hindrance on the pyridine ring. Furthermore, different 2-amino heterocycles were also tested. When 2-aminopyrimidine was subjected to the reaction system, no reaction was observed. 2-Aminobenzimidazole was also tested, however, the desired product was not isolated, and only a trace amount of product was detected. Several aliphatic

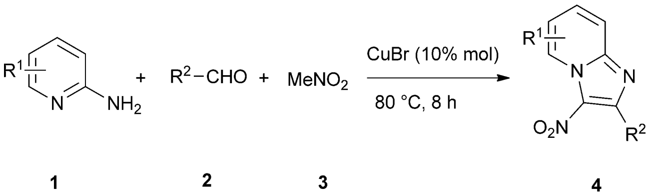
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	*t* [h]	*T* [°C]	Yield [%]
1	CuI	8	80	78
2	**CuBr**	**8**	**80**	**80**
3	CuCl	8	80	78
4	$CuBr_2$	8	80	74
5	$Cu(OAc)_2$	8	80	76
6	Cu(OT f)$_2$	8	80	75
7	CuOTf	8	80	77
8	$Cu(OAc)_2{\cdot}H_2O$	8	80	76
9	–	8	80	0
10	CuBr	4	80	50
11	CuBr	8	60	60
12	CuBr	8	100	78
13	CuBr	8	80	70[b]

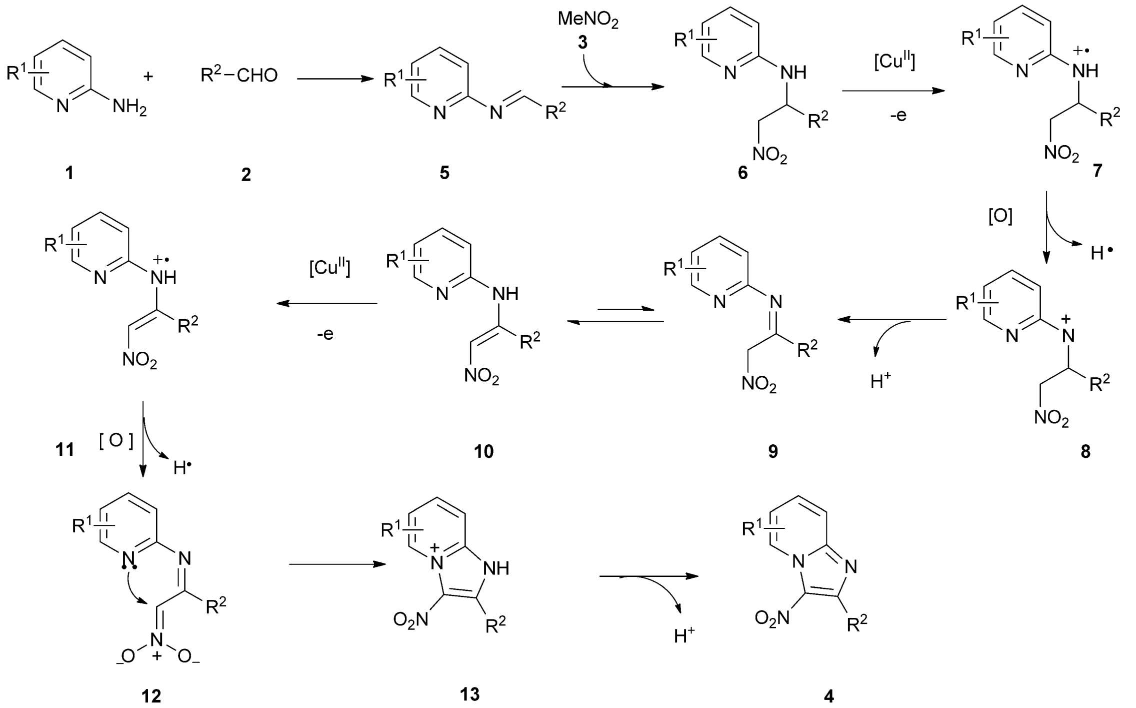
[a] The reaction was carried out using **1a** (0.30 mmol), **2a** (0.36 mmol), and **3** (20 equiv) with catalyst (0.03 mmol) under air. [b] The oxidant is O_2 (1 atm).

Table 2. Synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine derivatives from aminopyridines, aromatic aldehydes and $MeNO_2$[a]



Entry	R1		R2		Product	Yield [%]
1	**1a**	H	**2a**	Ph	**4aa**	80
2	**1a**	H	**2b**	3-Me-Ph	**4ab**	86
3	**1a**	H	**2c**	4-Me-Ph	**4ac**	82
4	**1a**	H	**2d**	3,4-diMe-Ph	**4ad**	88
5	**1a**	H	**2e**	2-MeO-Ph	**4ae**	84
6	**1a**	H	**2f**	4-MeO-Ph	**4af**	78
7	**1a**	H	**2g**	2-Cl-Ph	**4ag**	73
8	**1a**	H	**2h**	3-Cl-Ph	**4ah**	67
9	**1a**	H	**2i**	4-Cl-Ph	**4ai**	75
10	**1a**	H	**2j**	2-Br-Ph	**4aj**	62
11	**1a**	H	**2k**	3-Br-Ph	**4ak**	52
12	**1a**	H	**2l**	4-Br-Ph	**4al**	50
13	**1a**	H	**2m**	1-naphthyl	**4am**	44
14	**1a**	H	**2n**	piperonyl	**4an**	30
15	**1a**	H	**2o**	2-furyl	**4ao**	60
16	**1b**	3-Me	**2a**	Ph	**4ba**	78
17	**1c**	5-Me	**2a**	Ph	**4ca**	78
18	**1d**	6-Me	**2a**	Ph	**4da**	58
19	**1e**	5-Cl	**2a**	Ph	**4ea**	67
20	**1f**	4-COOEt	**2a**	Ph	**4fa**	73

[a] The reaction was carried out using **1** (0.3 mmol), **2** (0.36 mmol), and **3** (20 equiv) in the presence of air at 80 °C for 8 h catalyzed by CuBr.



Scheme 2. Plausible reaction mechanism.

aldehydes, such as *n*-butyraldehyde and *iso*-butyraldehyde were unsuitable substrates to produce 3-nitro-2-arylimidazo[1,2-*a*]pyridines.

On the basis of the results obtained, the above mechanism has been proposed (Scheme 2). The first step involves the reaction of substrates **1** and **2** to produce the imine **5**. Then **3** reacts with imine **5** by Michael addition to form intermediate **6**. Intermediate **6** is then oxidized into the radical cation **7** by the copper catalyst, and subsequent hydride-atom abstraction with oxidant forms nitrenium ion **8**. The intermediate **9** that is produced by proton elimination from nitrenium ion **8** isomerizes into enamine **10** easily. Similarly, intermediate **10** generates radical cation **11** by losing one electron to the copper catalyst. A hydride-atom abstraction of radical cation **11** with oxidant forms the imino nitronate ion **12**, which undergoes nucleophilic addition to produce **13**. Finally, intermediate **13** undergoes proton elimination and affords product **4**.

In summary, we have successfully developed a novel one-pot three-component synthesis of 3-nitro-2-arylimidazo[1,2-*a*] pyridine derivatives. In this system, the starting materials were commercially available without preparation. The procedure, using air as oxidative agent, is simple, environmentally friendly, and sustainable. Various functional groups are tolerated in this reaction system, which proceed well in moderate to good yields.

Experimental Section

A tube was charged with **1** (0.30 mmol), **2** (0.36 mmol), and CuBr (4.3 mg, 0.03 mmol). Then **3** (20 equiv) was added to the reaction system. The reaction was stirred at 80°C under air for 8 h. After cooling to room temperature, the residues were purified by silica-gel column chromatography, eluting with petroleum ether/EtOAc to afford pure **4**.

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Keywords: copper • green chemistry • heterocycles • multicomponent reactions • oxidation

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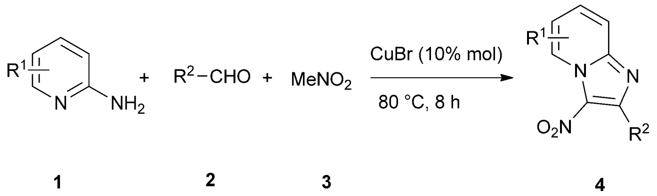

A novel one-pot three-component synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridines has been easily achieved with 2-aminopyridines, aromatic aldehydes, and $MeNO_2$, and is catalyzed by CuBr under air. The procedure, using air as an oxidative agent, is simple, low cost, and sustainable. Various functional groups are tolerated in this reaction system, and it proceeds well with moderate to good yields.

Multicomponent Reactions

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One-Pot Three-Component Synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine Derivatives Using Air as an Oxidant