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Metal-free synthesis of imidazo[1,5-*a*]pyridines *via* elemental sulfur mediated sequential dual oxidative Csp^3-H amination

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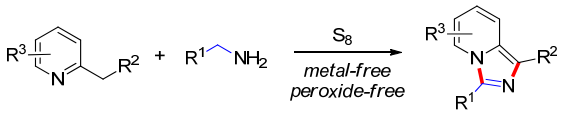
Jie Sheng,[a] Jidan Liu,*[a,b] He Zhao,[a] Liyao Zheng[a] and Xingchuan Wei*[a]

A simple and efficient approach has been developed for the synthesis of imidazo[1,5-*a*]pyridines using elemental sulfur mediated sequential dual oxidative Csp^3-H amination of 2-pyridyl acetates and amines under metal- and peroxide-free conditions. Broad substrate scope, operational simplicity and gram-scale ability make this chemistry very practical.

Fused nitrogen heterocycles occur widely in natural products and biologically active molecules which are important building blocks in both material chemistry and pharmaceutical industry.[1] In particular, the imidazo[1,5-*a*]pyridines are a class of aza-fused heterocyclic skeletons found in many pharmacologically important compounds.[2] Meanwhile, the imidazo[1,5-*a*]pyridines skeleton (2-azaindolizines) has potential applications in organic light-emitting diodes (OLEDs)[3] and organic thin-layer field effect transistors (FETs).[4] In addition, the 2-azaindolizine structure could also be considered as a precursor for *N*-heterocyclic carbene.[5]

Due to the great value in pharmaceuticals and material chemistry, considerable attention has been paid to the development of general and efficient methods for the synthesis of imidazo[1,5-*a*]pyridines and their derivatives. Traditionally, the synthesis of molecules with such a scaffold involves the Vilsmeier-type cyclization of *N*-2-pyridylmethylamides.[6] Another attractive tool is the direct C-H amination/cyclization strategy. For instance, in 2013, Wang reported a novel protocol to form imidazo[1,5-*a*]pyridines *via* sequential dual oxidative amination of C(sp^3)-H bonds with stoichiometric amount of *N*-iodobutanimide and oxidant.[7] Zeng and Xu group have independently investigated the efficient synthesis of imidazo[1,5-*a*]pyridines through copper-catalyzed aerobic oxidative reaction of *N*-heteroaryl aldehydes



Scheme 1 Elemental sulfur mediated sequential dual Csp^3-H amination

or ketones with alkylamines, respectively.[8] Later, Adimurty and co-workers developed a copper-catalyzed aerobic oxidative synthesis of imidazo[1,5-*a*]pyridines employing either pyridotriazoles or 2-pyridyl acetates as substrates.[9] Among the mentioned methods and others,[10] most of them require the use of a copper catalyst or peroxide as an oxidant, in view of the concerns about the influences of trace metals on human consumption drugs and the efficiency of organic electronic devices. Therefore, to explore a new protocol for the synthesis of imidazo[1,5-*a*]pyridines from simple and readily available starting materials under metal- and peroxide-free conditions is highly desirable.

Elemental sulfur widely exists in nature which is nontoxic, stable, odorless and easy handling under normal conditions, and exists in numerous oxidation states, ranging from -2 to +6.[11] It is an inexpensive raw material for sulfur chemistry which is employed for the vulcanization of rubber, the synthesis of sulfuric acid, as well as other sulfur-containing compounds.[12,13] Moreover, elemental sulfur could also serve as a highly efficient and traceless oxidizing agent in oxidative coupling reactions to form a variety of nitrogen-containing heterocycles.[14] As our continuing interest in the synthesis of fused nitrogen heterocycles,[15] we herein disclose a metal-free and peroxide-free oxidative cyclization reaction of 2-pyridyl acetates with alkylamines to construct various imidazo[1,5-*a*]pyridine skeletons, in which elemental sulfur was found to be the key for the success of this oxidative annulation process (Scheme 1).

We started our investigation by taking readily available ethyl 2-(pyridin-2-yl)acetate **1a** and benzylamine **2a** as the model substrates to optimize the reaction conditions (Table 1).

[a] School of Chemistry and Chemical Engineering, Guangzhou University, Guangzhou 510006, P. R. China. E-mail: xing6363@126.com, jdliu@gzhu.edu.cn
[b] Key Laboratory of Functional Molecular Engineering of Guangdong Province, South China University of Technology, Guangzhou 510640, P. R. China

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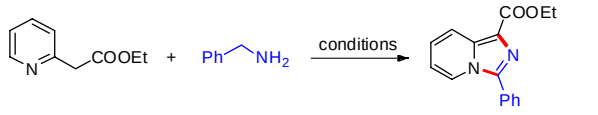
Table 1 Screening of optimal conditions[a]



1a 2a 3a

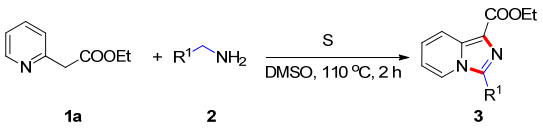
Entry	S	Solvent	T (^{o}C)	Yield[b] (%)
1	S (0.6 mmol)	NMP	110	56
2	S (0.6 mmol)	DMF	110	70
3	S (0.6 mmol)	DMSO	110	88
4	S (0.6 mmol)	Dioxane	110	0
5	S (0.6 mmol)	CH_3CN	110	0
6	S (0.6 mmol)	Toluene	110	0
7	S (0.6 mmol)	DCE	110	0
8	S (0.6 mmol)	H_2O	110	0
9	S (0.6 mmol)	DMSO	120	85
10	S (0.6 mmol)	DMSO	100	76
11	S (0.6 mmol)	DMSO	110	78[c]
12	S (0.6 mmol)	DMSO	110	64[d]
13	S (0.4 mmol)	DMSO	110	73
14	S (0.8 mmol)	DMSO	110	86
15	S (0.6 mmol)	DMSO	110	85[e]
16	—	DMSO	110	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), sulfur (0.6 mmol), solvent (1.0 mL), 110 ^{o}C, under air for 2 h. [b] Isolated yield. [c] **2a** (0.2 mmol, 1 equiv.). [d] **2a** (0.3 mmol, 1.5 equiv.). [e] Under N_2.

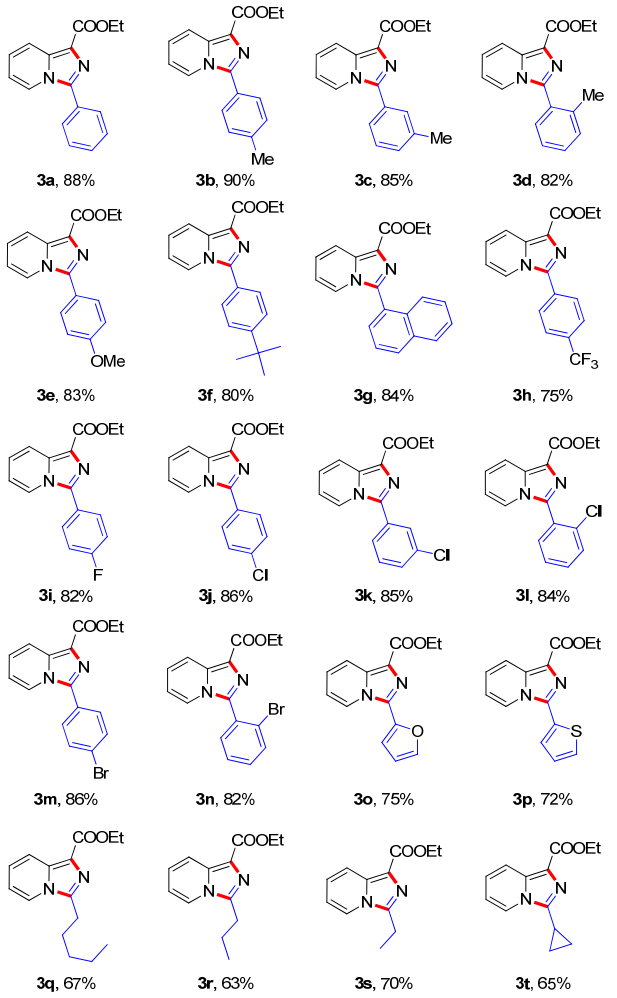
To our utmost delight, the desired ethyl 3-phenylimidazo[1,5-*a*]pyridine-1-carboxylate **3a** was successfully isolated in 56% yield in the presence of elemental sulfur (3.0 equiv.) in NMP at 110 °C for 2 h (Table 1, entry 1). Encouraged by this result, various solvents were tested for this transformation to improve the yield (Table 1, entries 1-8), and DMSO was found to be the best, and the desired product **3a** was afforded in 88% yield (Table 1, entry 3). It is found that increasing the reaction temperature to 120 °C, or reducing the reaction temperature to 100 °C, did not further increase the yield of the target product (Table 1, entries 9 and 10). Furthermore, changing the equivalent of elemental sulfur and benzylamine **2a** did not further improve the reaction either (Table 1, entries 11-14). A similar yield was achieved when the reaction was carried out under nitrogen atmosphere which indicates that elemental sulfur is the only oxidant (Table 1, entries 15). Finally, the control experiment revealed that no desired product **3a** was formed in the absence of elemental sulfur (Table 1, entry 16).

With the aforementioned optimized reaction conditions in hand (Table 1, entry 3), we next set out to examine the scope of the present oxidative annulations. First, a wide range of alkylamines were tested with ethyl 2-(pyridin-2-yl)acetate **1a**. As can be seen from the results of Table 2, the reactions of aromatic benzylamines bearing either electron-donating substituents (such as Me, OMe, and *t*-Bu) or electron-withdrawing substituents (such as F, Cl, Br, and CF_3) on the benzene ring proceeded smoothly to deliver the desired products in moderate to good yields (Table 2, **3b**-**3n**). Halogen groups substituted at the aromatic ring of benzylamines, such as fluro, chloro, and even bromo, were all well tolerated, which provided the possibility for further synthetic elaboration. It is worthwhile to mention that the presence of a variety of electron-donating/withdrawing groups in benzylamine moieties at either (o/m/p) position had almost no effect on the

Table 2 Substrate scope of various amines[a,b]



1a 2 3



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), sulfur (0.6 mmol), DMSO (1.0 mL), 110 °C, under air for 2 h. [b] Isolated yield.

reaction efficiency. Notable, hetero amines including furan and thiophene derivatives also were found to be suitable substrates to afford the desired products (Table 2, **3o** and **3p**). Additionally, the present system is also applicable to simple aliphatic amines, and the corresponding imidazo[1,5-*a*]pyridine derivatives **3q-3t** were obtained in moderate yields.

Next, we turned our attention to the scope of various pyridyl ester derivatives and the results were summarized in Table 3. As expected, substrates with various common ester groups, such as -COOMe, -COO^{i}Pr, -COO^{n}Bu and -COO^{t}Bu, were well tolerated to deliver the desired products **3u**-**3x** in good to excellent yields. In addition, ethyl 2-(quinolin-2-yl)acetate could also participate in this transformation to give **3y** in 90% yield. Moreover, pyridyl acetates with methyl and chloro groups on the pyridine ring as well as pyridyl acetamide produced the desired products **3z**–**3ac** in good yields. However, when R^2 was a cyano or COPh group, no desired product **3ad**

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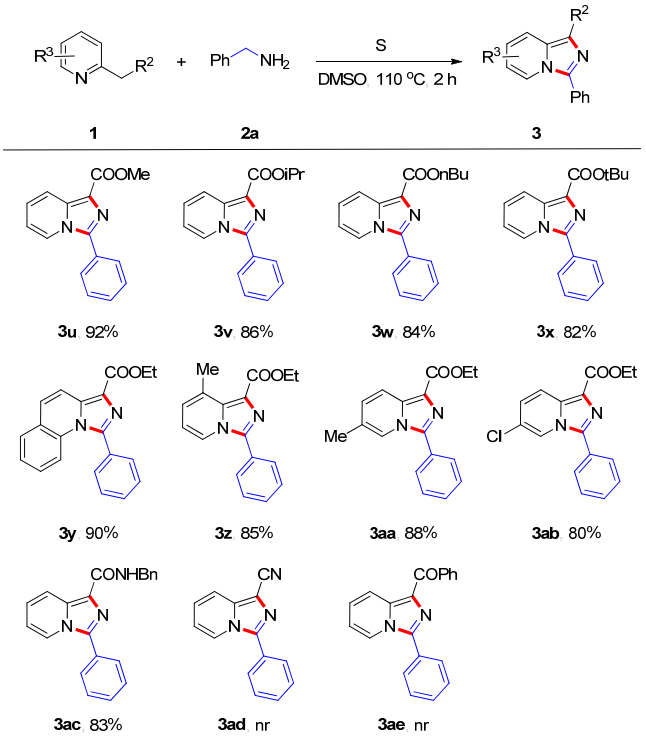
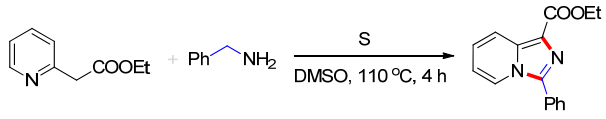
Table 3 Substrate scope of pyridyl esters[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), sulfur (0.6 mmol), DMSO (1.0 mL), 110 °C, under air for 2 h. [b] Isolated yield.

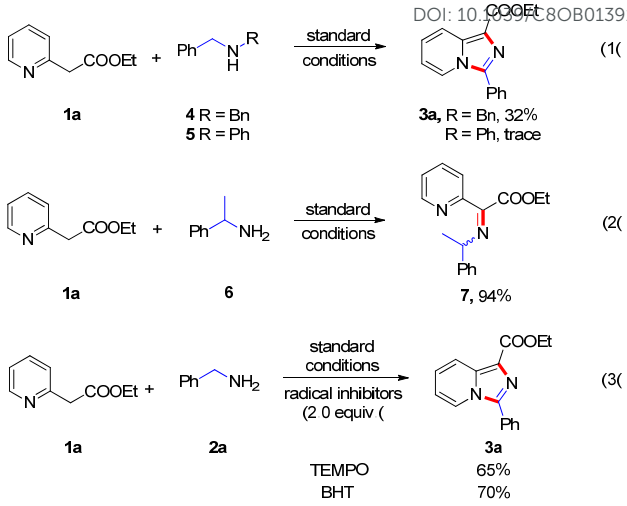
or **3ae** was detected in the reaction mixture, presumably due to the incompatibility of the two functional groups and amine under elevated temperature.

To further demonstrate the practicability of this one-pot protocol, a gram-scale reaction was also performed using 8 mmol of **1a** (1.32 g) under the optimal conditions. This transformation proceeded smoothly to afford the corresponding **3a** in 80% isolated yield without significant loss of reaction efficiency (Scheme 2).



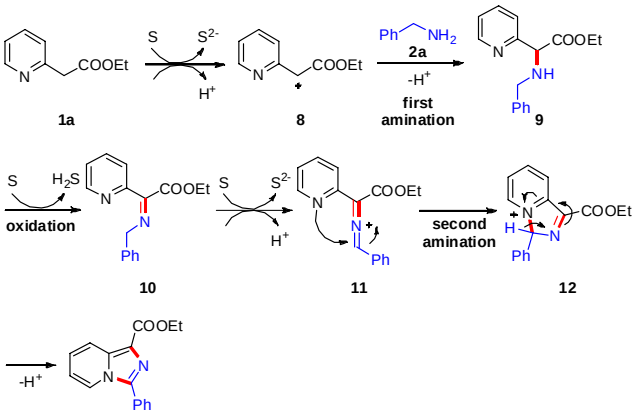
Scheme 2 Gram scale reaction

To elucidate the reaction mechanism, several control experiments shown in scheme 3 were conducted. First, when secondary amine, like dibenzylamine **4** or *n*-phenyl benzylamine **5** was applied, respectively, in the system instead of benzylamine **2a**, the desired product **3a** was not produced efficiently which demonstrates that a free amine is necessary for the success of the tandem reaction. Moreover, when the reaction of **1a** with 1-phenylethanamine **6** was carried out under the standard conditions, an imine product **7** was isolated in 94% yield which indicates that a methyl group at the *α*-position of benzylamine prevented the second amination process. Finally, the model reaction was not



Scheme 3 Control reactions

inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT), as a radical scavenger, was added to the reaction under the standard conditions. This meant that a radical pathway might not be involved in this reaction.



Scheme 4 Plausible reaction mechanism

Although the exact reaction mechanism is still unknown at this stage, based on the results described above and literature reports,[7,9,16] a plausible mechanism was proposed (Scheme 4). Initially, the substrate **1a** undergoes oxidation to give the corresponding carbocation **8** in the presence of elemental sulfur as an oxidant.[16b] The nucleophilic addition of **2a** to **8** generates an intermediate **9**, intermediate **9** undergoes oxidative dehydrogenation to form imine intermediate **10** in the presence of elemental sulfur. Subsequently, **10** undergoes further oxidation to provide the intermediate **11**, which can be further attacked by the nitrogen of pyridine to deliver the intermediate **12**. Finally, oxidative aromatization of **12** will afford the desired imidazo[1,5-*a*]pyridine **3a**.

In summary, we have developed a novel elemental sulfur mediated oxidative cyclization of 2-pyridyl acetates and amines leading to various imidazo[1,5-*a*]pyridines in moderate to excellent yields. This procedure avoids the employment of

metal catalysts, peroxides and extra additives, which makes this reaction very attractive for potential synthetic applications. A wide range of functional groups are proved to be compatible with the standard conditions. Moreover, gram-scale reaction of **1a** and **2a** demonstrates the practicality of the protocol. Deep studies into the detailed reaction mechanism and further synthetic applications are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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