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Mild Metal-Free Sequential Dual Oxidative Amination of C(sp^3)−H bonds: Efficient Synthesis of Imidazo[1,5-*a*]pyridines

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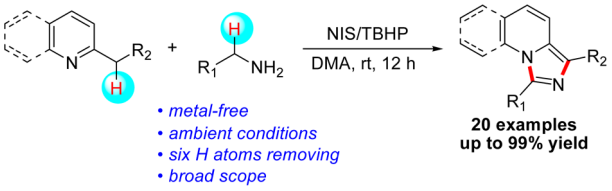
ABSTRACT



A metal-free sequential dual oxidative amination of C(sp^3)−H bonds under ambient conditions was the first developed, affording imidazo[1,5-*a*]-pyridines in good to excellent yields. The reaction was involved in two oxidative C−N couplings and one oxidative dehydrogenation process with six hydrogen atoms removed.

Imidazo[1,5-*a*]pyridines have drawn much attention for their potential photophysical and biological activities.[1] However, only a few synthetic routes are available for these compounds so far.[2] The process of these reported methods mainly relied on traditional Vilsmeier-type cyclizations of *N*-2-pyridylmethylamides. Therefore, developing more practical and efficient synthetic approaches for imidazo[1,5-*a*] pyridines is highly desirable.

Transition-metal-catalyzed intermolecular or intramolecular direct oxidative aminations of the C(sp^3)−H bond have emerged as important methods for C−N bond formations because of economical advantages over the present procedures by employing prefunctionalized substrates.[3−5] However, using expensive transition metals and the substate scope limited their applications in organic synthesis. Recently, Chang[6] and Muniz[7] have, respectively, developed interesting metal-free benzylic and allylic C−H aminations

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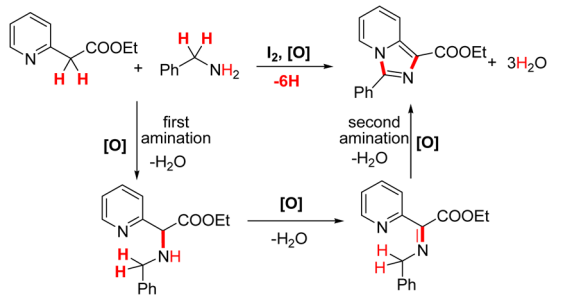
Scheme 1. Initial Hypothesis Pathway for Dual Oxidative C(sp3)−H Aminations

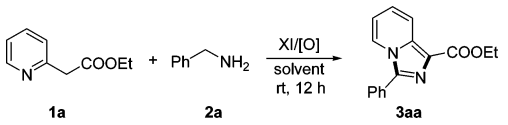


with sulfonamides in the presence of stoichiometric hypervalent iodine(III) reagents. However, large amounts of iodobenzene were generated as waste, and the substrates remained limited to sulfonamides in the absence of transition metal. Therefore, the development of an efficient, and environmentally friendly catalytic system for oxidative C(sp^3)−H amination with primary amine remains challenging.

Recently, our group[8] and other groups[9] have developed iodine-catalyzed intramolecular and intermolecular oxdative C(sp^3)−H amination for the synthesis of heterocycles. As a continuous study on this field, we hypothesized that multisubstituted imidazo[1,5-*a*]pyridine could be synthesized from ethyl 2-(pyridin-2-yl)acetate and benzylamine via iodine-catalyzed C(sp3)−H aminations. The reaction was involved in two oxidative C−N couplings and one oxidative dehydrogenation process with six hydrogen atoms removed (Scheme 1). The reaction could be carried out under metal-free conditions with only water and *tert*-butyl alcohol as waste. To the best of our knowledge, this protocol has been not reported to date.

Initially, we began our study with the reaction of 1 equiv of ethyl 2-(pyridin-2-yl)acetate (**1a**) and 2 equiv of benzylamine (**2a**) in the presence of 3 equiv of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) as the oxidant and 1 equiv of molecular iodine as the catalyst. When the reaction mixture was stirred in 1 mL of *N,N*-dimethylformamide (DMF) in air at room temperature for 12 h, ethyl 3-phenylimidazo[1,5-*a*]pyridine-1-carboxylate (**3aa**) was obtained in 85% isolated yield (Table 1, entry 1). In the absence

Table 1. Optimization of Reaction Conditions[a]



entry	XI	oxidant	solvent	yield[b] (%)
1	I_2	TBHP	DMF	85
2	none	TBHP	DMF	nd
3	NIS	TBHP	DMF	99
4	Bu_4NI	TBHP	DMF	31
5	KI	TBHP	DMF	49
6	PhI	TBHP	DMF	nd
7	NIS	DTBP	DMF	6
8	NIS	$K_2S_2O_8$	DMF	13
9	NIS	O_2(1 atm)	DMF	16
10	NIS	none	DMF	10
11	**NIS**	**TBHP**	**DMA**	**99**
12	NIS	TBHP	THF	31
13	NIS	TBHP	CH_3CN	46
14	NIS	TBHP	EtOH	23
15	NIS	TBHP	H_2O	58
16	NIS	TBHP	Tol.	21
17[c]	NIS	TBHP	DMA	69
18[d]	NIS	TBHP	DMA	28

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), XI (0.3 mmol), oxidant (0.9 mmol), solvent (1 mL), rt, 12 h. [b] Isolated yield. [c] 0.5 equiv of NIS was used. [d] 0.2 equiv of NIS was used.

of iodine, no desired **3aa** was detected, which indicated that iodine was essential to this reaction (Table 1, entry 2). When various iodine reagents were used, *N*-iodosuccinimide (NIS) gave **3aa** in the highest yield (Table 1, entries 3−6). Among the examination of various oxidants, such as di-*tert*-butyl peroxide (DTBP), potassium peroxydisulfate ($K_2S_2O_8$), and oxygen, TBHP gave **3aa** in the highest yield (Table 1, entries 7−9). In the absence of extra oxidant (or only in air), only 10% of **3aa** was detected (Table 1, entry 10). Moreover, various solvents were also examined, and DMA proved to be the best choice (Table 1, entries 11−16). In addition, the amount of NIS was also optimized. Reducing the amount of NIS to 50 or 20 mol % decreased the yield of **3aa** (Table 1, entries 17 and 18). Therefore, the optimal conditions are those described in entry11.

Under the optimal reaction conditions, we investigated the substrate scope of oxidative C−N coupling. First, when various aromatic benzylamines (**2a**−**k**) were employed in this reaction, the corresponding products (**3aa**−**ak**) could be obtained in 80−99% yields (Table 2, entries 1−11). It is noted that benzylamines bearing electron-donating groups (4-Me or 4-OMe) gave the desired products in higher yields than electron-withdrawing groups (4-CF_3 or 4-Cl) on the phenyl ring (Table 2, entries 5, 7, 8, and 11). However, no steric hindrance was observed in the reaction. For example, benzylamines bearing a *p*-methyl or *p*-chlorophenol group on the phenyl ring, respectively, gave the corresponding products in the same yields as that of benzylamine bearing an *o*-methyl or *o*-chlorophenol group (Table 2, entries 5, 6, 8, and 10). Moreover, ring-fused (**2l**) and heterocyclic

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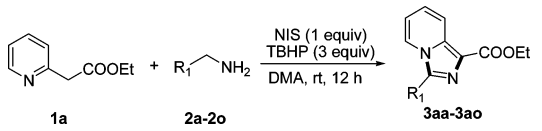
Table 2. Substrate Scope of Benzylamines[a]



1a 2a-2o 3aa-3ao

entry	R^1	product	yield[b] (%)
1	Ph (**2a**)	**3aa**	99
2	4-F-Ph (**2b**)	**3ab**	93
3	3-F-Ph (**2c**)	**3ac**	94
4	2-F-Ph (**2d**)	**3ad**	94
5	4-Cl-Ph (**2e**)	**3ae**	90
6	2-Cl-Ph (**2f**)	**3af**	90
7	4-CF_3Ph (**2g**)	**3ag**	80
8	4-Me-Ph (**2h**)	**3ah**	96
9	3-Me-Ph (**2i**)	**3ai**	96
10	2-Me-Ph (**2j**)	**3aj**	95
11	4-OMe-Ph (**2k**)	**3ak**	92
12	1-naphthyl (**2l**)	**3al**	99
13	2-furyl (**2m**)	**3am**	70
14	2-thienyl (**2n**)	**3an**	81
15	2-pyridyl (**2o**)	**3ao**	nd[c]

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), NIS (0.3 mmol), oxidant (0.9 mmol), solvent (1 mL), rt, 12 h. [b] Isolated yield. [c] Unknown complex mixture.

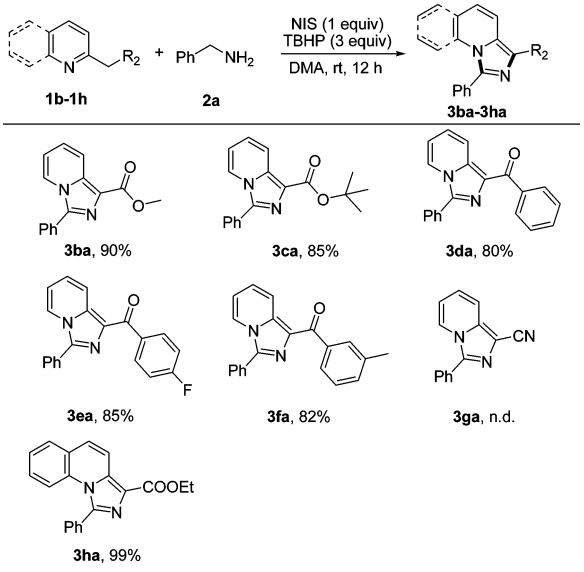
(**2m** and **2n**) benzylamines also gave the corresponding products in good yields (Table 2, entries 12−14).

Subsequently, various substrates **1b**−**h** replacing **1a** were also employed in this reaction, giving the desired products **3ba**−**ha** in good yields (Scheme 2). For example, when R_2 were various ester groups such as COOMe or COO^{t}Bu, 90% of **3ba** and 85% of **3ca** were obtained, respectively. When R_2 was a benzoyl group, the product **3da** was obtained in 80% yield. Similarly, substrates **1e** or **1f** also gave the desired products **3ea** or **3fa** with 85% or 82% yields, respectively. However, when R_2 was a cyano group, an unknown complex mixture was obtained. In addition, ethyl 2-(quinolin-2-yl)acetate (**1h**) also gave **3ha** with an almost quantitive yield.

Recently, our group has also developed some novel methods for the synthesis of heterocycles using amino acids as nitrogen motifs via decarboxylative amination.[10] Therefore, we expected to use amino acids as nitrogen motifs instead of benzylamines for the synthesis of imidazo[1,5-*a*]-pyridines. To our delight, imidazo[1,5-*a*]pyridines could be obtained in moderate yields from **1a** and amino acids **4** under standard conditions (Scheme 3).

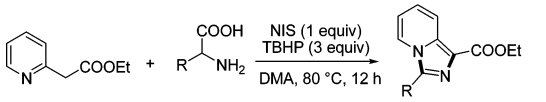
To gain insight into the mechanism, several control experiments were carried out. First, **1a** under standard conditions in the absence of **2a** did not produce the expected iodo intermediate, suggesting that the reaction does not proceed through an α-iodointermediate. When the reaction of ethyl 2-(pyridin-2-yl)propanoate (**1i**) with **2a** was carried out under standard conditions, no amination

Scheme 2. Scope of Substrate **1**[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), NIS (0.3 mmol), TBHP (70% aq, 0.9 mmol), DMA (1 mL), rt, 12 h. Isolated yields are given.

Scheme 3. Synthesis of Imidazo[1,5-*a*]pyridine from Amino Acids



product was obtained because the existence of the methyl group restrained the first amination process (Scheme 4a). Furthermore, when the reaction of **1a** with 1-phenylethanamine (**2p**) was carried out under standard conditions, a new product **5ap** was obtained in 53% yield. The reason for the generation of **5ap** is probably that the existence of a methyl group in 1-phenylethanamine prevented the second amination process (Scheme 4b). Moreover, when stoichiometric hypervalent iodine reagents, such as $PhI(OAc)_2$ or IBX, were employed instead of our catalytic system, no desired product was obtained. This result indicated that the reaction pathway may be not followed in catalysis involving in situ generated hypervalent iodine (III or V) reagents (Scheme 4c). Finally, radical trapping experiments were also carried out.

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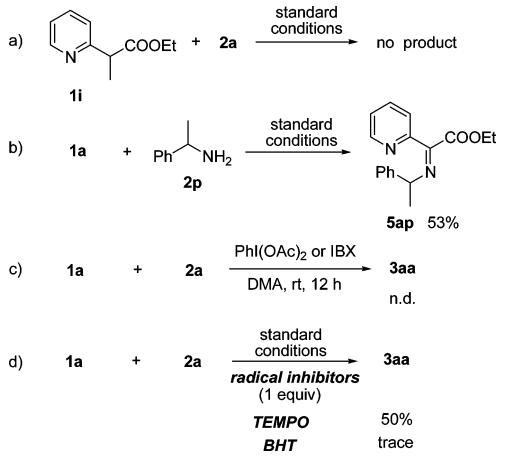
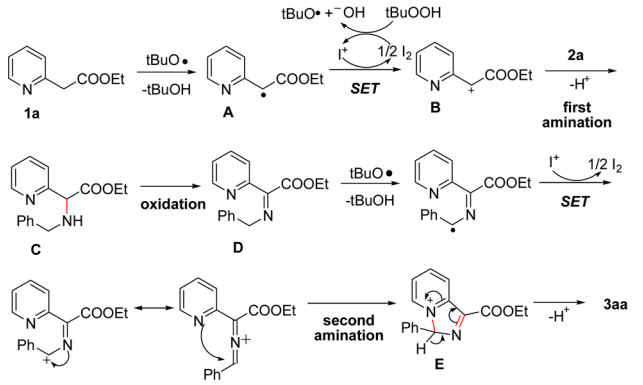
(13) For the imine ion intermediate, see: (a) Li, Z. P.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z. P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

Scheme 4. Control Experiments for Mechanism



Scheme 5. Mechanism for Synthesis of Imidazo[1,5-*a*]pyridine via Dual Oxidative C(sp^3)−H Aminations



We observed that the reaction was obviously inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 4d). This observation implied that the reaction presumably underwent a radical pathway.

On the basis of the results described above and in previous reports,[8,11−13] a plausible mechanism was proposed (Scheme 5). Initially, **1a** is presumably involved a hydrogen abstraction from benzylic C−H bond to give a carbon radical **A**, which generates a benzylic cation **B** via a single-electron-transfer process in the presence of I^+.[6,12] The nucleophilic substitution of **2a** to **B** provides an intermediate **C**. A oxidative dehydrogenation in **C** gives intermediate **D**. Finally, **D** provides the intermediate **E** via a similar radical process to the first amination, which could be further converted to **3aa** by removing a hydrogen ion and rearrangement.[8,13] Overall, the I_2−I^+ redox process[8b,10a] plays a key role in the C−N bond formations by promoting reductive cleavage of O−O bond in the peroxide and the oxidation of the benzylic radical to a benzylic cation or the N-bound carbon radical to an imine ion.

In summary, we have developed a metal-free sequential dual oxidative amination of C(sp^3)−H bonds for the synthesis of imidazo[1,5-*a*]pyridines under mild conditions. Notably, this novel protocol is distinguished by (1) the lack of any expensive transition metals; (2) operational simplicity; (3) room temperature; (4) the fact that an inert atmosphere or dry solvents are not required; (5) a broad substrate scope; and (6) the production of alcohol and water as the only waste. Iodine-catalyzed oxidative C−H aminations for the synthesis of other heterocycles are ongoing in our laboratory.

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Supporting Information Available. General procedure for the reaction and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.