Bu_4NI-Catalyzed Synthesis of Imidazo[1,2-*a*]pyridines via Oxidative Coupling of Aminopyridines with Nitroolefins

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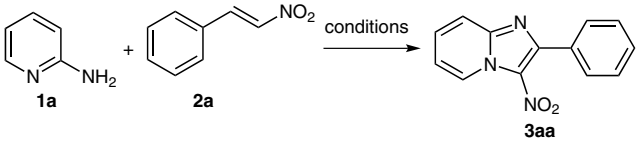
Abstract: A metal-free method for the synthesis of imidazo[1,2-*a*]pyridines via double C–N oxidative coupling of aminopyridines with nitroolefins using TBAI as the catalyst and TBHP as oxidation agent has been developed.

Key words: TBAI, imidazo[1,2-*a*]pyridines, oxidative coupling, aminopyridines, nitroolefins

The imidazo[1,2-*a*]pyridines are an important class of heterocycles which widely exist in medicinal chemistry[1] and material science.[2] Traditional approaches for the formation of imidazo[1,2-*a*]pyridines rely on condensation reaction of 2-aminopyridines with α-halocarbonyl compounds.[3] Recently, the direct transition-metal-catalyzed oxidative coupling of unfunctionalized starting materials, including ketones,[4] alkynes,[5] nitroolefins,[6] β-keto esters[7] with 2-aminopyridines has attracted much attention. In particular, Huang demonstrated CuBr-catalyzed synthesis of imidazo[1,2-*a*]pyridine by mild oxidative double C–N coupling of nitroolefins with 2-aminopyridines using air as oxidative agent.[8] In addition, an alternative metal-free method has also been developed. Han and co-workers reported TBAI-catalyzed synthesis of imidazo[1,2-*a*]pyridine though tandem oxidative C–N coupling/condensation of 2-aminopyridines with β-keto esters and 1,3-diones using *tert*-butyl hydroperoxide (TBHP) as the oxidant.[9] However, there is still no published report on metal-free double C–N coupling protocol for the construction of imidazo[1,2-*a*]pyridines. As a part of our continuing research on the TBAI-catalyzed transformation,[10] we herein report the first metal-free, TBAI-catalyzed oxidative coupling of 2-aminopyridines with nitroolefins, representing a new method for the construction of imidazo[1,2-*a*]pyridines.

We commenced our reaction with pyridin-2-amine (**1a**) and (*E*)-(2-nitrovinyl)benzene (**2a**) as model substrates (Table 1). Gratifyingly, the desired 3-nitro-2-phenylimidazo[1,2-*a*]pyridine (**3aa**) was obtained in 75% yield under the standard conditions established in our previous work (Table 1, entry 1).[10b] When various solvents were examined, DMF gave **3aa** in the highest yield (Table 1, entry 2). Various iodine reagents (Table 1, entries 7–9) and oxidants (Table 1, entries 10–13) were also used, but none of them provided better results. Control experiments indicated that both TBAI and TBHP were required for this transformation (Table 1, entries 14 and 15). The amount of TBAI was also optimized; reducing the amount of TBAI to10 mol% decreased the yield of **3aa** (Table 1, entry 16).

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	TBAI	TBHP	MeCN	75
2	TBAI	TBHP	DMF	83
3	TBAI	TBHP	DCE	72
4	TBAI	TBHP	DMSO	23
5	TBAI	TBHP	H_2O	0
6	TBAI	TBHP	EtOAc	32
7	KI	TBHP	DMF	53
8	I_2	TBHP	DMF	46
9	NaI	TBHP	DMF	48
10	TBAI	TBPB	DMF	39
11	TBAI	H_2O_2	DMF	20
12	TBAI	$K_2S_2O_8$	DMF	0
13	TBAI	MCPBA	DMF	0
14	–	TBHP	DMF	0
15	TBAI	–	DMF	0
16[c]	TBAI	TBHP	DMF	56

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), TBAI (20 mol%), oxidant (2 equiv), solvent (2 mL) at 80 °C for 4 h.
[b] Isolated yield.
[c] Amount of catalyst used was 10 mol%.

Under the optimal reaction conditions, we investigated the substrate scope of the oxidative coupling (Table 2).[11] First, the reaction of substituted aminopyridines **1** and β-nitrostyrene **2a** proceeded smoothly. Both the steric hin-

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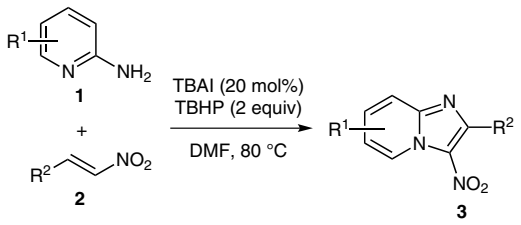
Table 2 Synthesis of Imidazo[1,2-*a*]pyridines **3**[a]

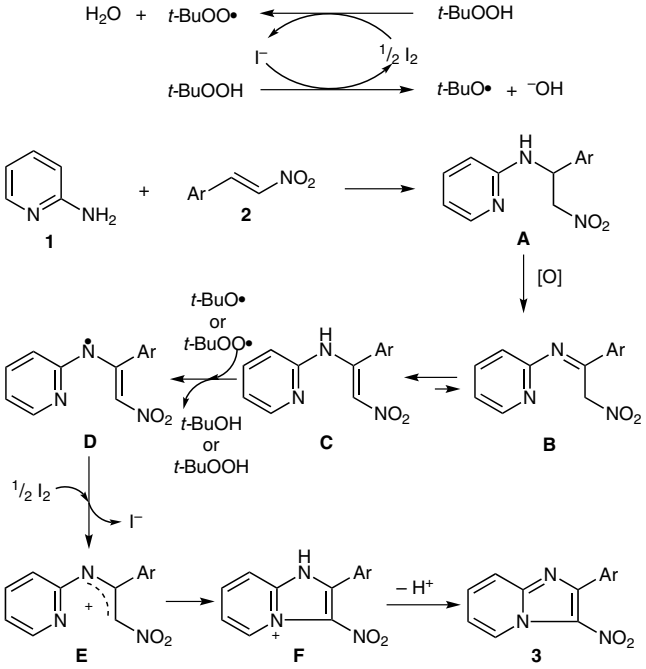


Entry	1	R^1	2	R^2	Product	Yield (%)[b]
1	**1a**	H	**2a**	Ph	**3aa**	83
2	**1b**	3-Me	**2a**	Ph	**3ba**	73
3	**1c**	4-Me	**2a**	Ph	**3ca**	74
4	**1d**	6-Me	**2a**	Ph	**3da**	46
5	**1e**	4-Cl	**2a**	Ph	**3ea**	33
6	**1f**	5-Cl	**2a**	Ph	**3fa**	33
7	**1a**	H	**2b**	4-MeC_6H_4	**3ab**	43
8[c]	**1a**	H	**2c**	4-*i*-PrC_6H_4	**3ac**	62
9	**1a**	H	**2d**	4-$MeOC_6H_4$	**3ad**	50
10	**1a**	H	**2e**	4-FC_6H_4	**3ae**	80
11	**1a**	H	**2f**	4-ClC_6H_4	**3af**	43
12	**1a**	H	**2g**	4-BrC_6H_4	**3ag**	31
13	**1a**	H	**2h**	4-$F_3CC_6H_4$	**3ah**	25
14	**1a**	H	**2i**	4-$MeO_2CC_6H_4$	**3ai**	52
15	**1a**	H	**2j**	3-BrC_6H_4	**3aj**	38
16	**1a**	H	**2k**	3-MeC_6H_4	**3ak**	45
17	**1a**	H	**2l**	2-BrC_6H_4	**3al**	0
18	**1a**	H	**2m**	2-$MeOC_6H_4$	**3am**	0
19	**1a**	H	**2n**	2-thienyl	**3an**	56
20	**1a**	H	**2o**	2-furyl	**3ao**	90

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), TBAI (20 mol%), TBHP (2 equiv, 70% aq solution), DMF (2 mL) at 80 °C for 4 h.
[b] Isolated yield.
[c] Reaction time: 6 h.

drance and the electronic nature of the substituents on the aminopyridines ring had a pronounced effect on the efficiency of the oxidative coupling. For example, aminopyridine with 6-methyl and electron-withdrawing chloride substituents are less effective. Then, the reactions of aminopyridine **1a** with nitroolefin **2** were screened. Both electron-donating Me, *i*-Pr, OMe substituents and electron-withdrawing halide, CF_3, CO_2Me substituents at *para* and *meta* position were compatible with the optimal conditions, whereas *ortho*-substituted nitroolefin **2** did not undergo the cyclization oxidative coupling due to the steric effect. Finally, heterocyclic substituted nitroolefins **2** could also be employed in this reaction to afford the corresponding products.

On the basis of the results described above and in previous reports,[8] a plausible mechanism has been proposed (Scheme 1). Initially, the reaction of aminopyridine with β-nitrostyrene in the presence of TBHP affords enamine **C** via Michael addition of intermediate **A** and imine **B**.[8] The hydrogen abstraction of enamine **C** by the *tert*-butoxyl or *tert*-butylperoxy radicals, generated by TBAI-catalyzed decomposition of TBHP,[12] produces intermediate **D**. Finally, the oxidation of intermediate **D** by I_2[13] and subsequent intramolecular nucleophilic addition of nitrenium ion **E** affords intermediate **F**, which converts to products **3** by proton elimination.



Scheme 1 Proposed mechanism

In summary, we have reported a metal-free process for the oxidative double C–N coupling of aminopyridines with nitroolefins by using TBAI as catalyst and TBHP as oxidation agent. It provides simple and economical access to imidazo[1,2-*a*]pyridines.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **General Experimental Procedure and Spectroscopic Data**: To a solution of **1** (0.5 mmol), **2** (0.6 mmol) and TBAI (0.1 mmol) in DMF (2 mL) was added TBHP (1.0 mmol, 70% aq solution). The reaction mixture was stirred at 80 °C for 4 h. After the mixture was cooled to r.t., the solvent was diluted with CH_2Cl_2 (10 mL), washed with brine (5 mL), and dried over anhyd Mg_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluted with petroleum ether–EtOAc to afford imidazo[1,2-*a*]pyridines. **3aa**: yellow solid; mp 168−170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.52–9.54 (d, *J* = 7.0 Hz, 1 H), 7.90–7.92 (m, 2 H), 7.84–7.87 (d, *J* = 8.9, 1.1 Hz, 1 H), 7.65–7.69 (m, 1 H), 7.50–7.53 (m, 3 H), 7.28–7.31 (q, 1 H).

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