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I_2/TBPB mediated oxidative reaction of aryl acetaldehydes with amidines: synthesis of 1,2,5-triaryl-1*H*-imidazoles†

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A direct method for the synthesis of 1,2,5-triaryl-1*H*-imidazoles was achieved easily from cyclization of aryl acetaldehydes with amidines catalyzed by I_2. Various substitued groups can be employed, and this reaction proceeds smoothly in moderate to good yields.

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Introduction

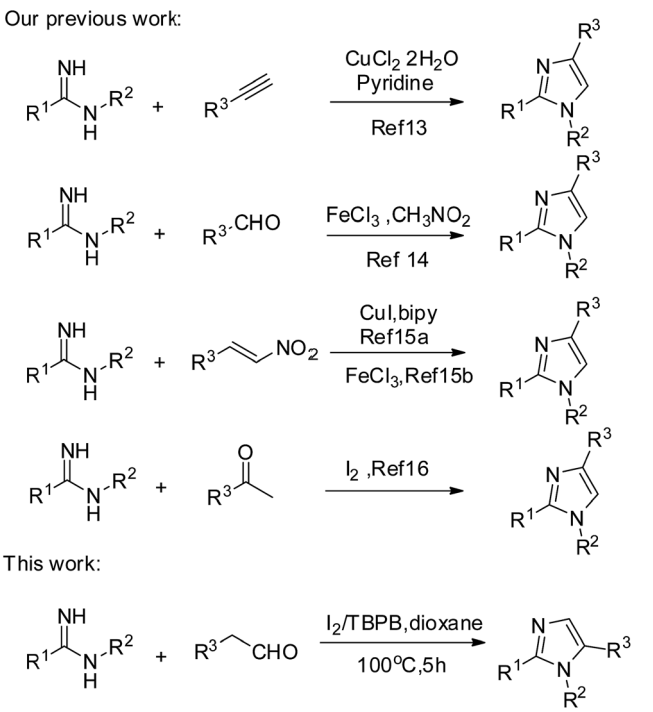
As one of the most valuable types of N-heterocyclic compound, imidazoles have been found in numerous natural products[1] and functional materials.[2] They also have good biological activities, such as antitumor,[3] antimicrobial,[4] antihypertensive[5] and protein kinase inhibitory activities.[6] In addition, they can also act as organocatalysts,[7] ionic liquids,[8] and precursors of N-heterocyclic carbenes.[9]

Due to their indisputable importance and great application prospects, more and more researchers are dedicating effort to constructing imidazoles. As for tri-substituted imidazoles, a number of methods have been developed. The existing synthetic methodologies have mostly focused on 1,2,4-triarylated imidazoles[10] and 2,4,5-triarylated imidazoles.[11] The most common route for producing 1,2,4-triarylated imidazoles is combining amidines with terminal alkynes and nitroolefins with ketones. Besides, most of the reported methods for obtaining 2,4,5-triarylated imidazoles involve the condensation of 1,2-diketones and aldehydes with amines or ammonia. However, until now only a few methods have been developed for making 1,2,5-triarylated imidazoles.[12] Therefore, it is a big challenge for organic chemists to find an efficient and simple way to construct 1,2,5-triarylated imidazoles.

Our group is dedicated to the efficient synthesis of 1,2,4-triarylated imidazoles by employing amidines and alkynes *via* metal-catalyzed oxidative processes.[13] In recent years, our group has been interested in the synthesis of 1,2,4-triarylated imidazoles by employing amidines and aldehydes[14]/nitroolefins[15]/ketones.[16] We herein report a more environment-friendly and efficient methodology to construct 1,2,5-triaryl-1*H*-imidazoles[17] which uses I_2/TBPB mediated oxidative formal [3 + 2] cycloaddition of aryl acetaldehydes with amidines Scheme 1.[18]

Results and discussion

To elucidate the optimal reaction conditions, we initially studied the reaction of *N*-phenylbenzimidamide **1a** (0.20 mmol)



Scheme 1 Synthesis of imidazole from amidine.

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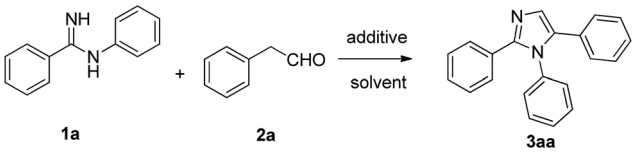
Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

Entry	Catalyst (mol%)	Oxidant (equiv.)	Solvent (mL)	T (°C)	Yield[b] (%)
1	I_2(20)	—	Dioxane	100	40
2	I_2(20)	TBHP(1)	Dioxane	100	78
3	**I_2(20)**	**TBPB(1)**	**Dioxane**	**100**	**93**
4	I_2(20)	DTBP(1)	Dioxane	100	38
5	I_2(20)	H_2O_2(1)	Dioxane	100	42
6	I_2(20)	$K_2S_2O_8$(1)	Dioxane	100	12
7	I_2(20)	O_2	Dioxane	100	41
8	KI(20)	TBPB(1)	Dioxane	100	69
9	TBAI(20)	TBPB(1)	Dioxane	100	54
10	NIS(20)	TBPB(1)	Dioxane	100	65
11	PIDA(20)	TBPB(1)	Dioxane	100	31
12	I_2(20)	TBPB(1)	Dioxane	80	66
13	I_2(20)	TBPB(1)	Dioxane	110	68
14	I_2(20)	TBPB(1)	DMF	100	42
15	I_2(20)	TBPB(1)	DMSO	100	50
16	I_2(20)	TBPB(1)	Toluene	100	88
17	I_2(20)	TBPB(1)	DCB	100	85

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (20 mol%), oxidant (1 eq), solvent (2 mL), in air for 5 h; TBHP = *tert*-butyl hydroperoxide (70% in water); TBPB = *tert*-butyl peroxybenzoate; DTBP = di-*tert*-butyl peroxide; TBAI = tetrabutylammonium iodide; NIS = niodosuccinimide; PIDA = iodosobenzene diacetate. [b] Isolated yield.

with phenylacetaldehyde **2a** (0.24 mmol) in the presence of I_2 (20 mol%) in dioxane at 100 °C in air for 5 h. As expected, the desired product 1,2,5-triphenyl-1*H*-imidazole **3aa** was obtained in 40% yield (Table 1, entry 1). In order to improve the yield of **3aa**, we further screened different oxidants, such as TBHP, TBPB, DTBP, H_2O_2, $K_2S_2O_8$ and O_2 for this reaction in the presence of iodine (Table 1, entries 2–7). Among them, TBPB was found to be the most optimal oxidant for the transformation. Next, the reaction proceeded less efficiently in other iodine-containing catalysts such as KI, TBAI, NIS, and PIDA (Table 1, entries 8–11). Then, the reaction did not give a superior result with variations in temperature (80, 110 °C, Table 1, entries 12–13). Furthermore, different solvents such as DMF, DMSO, toluene and DCB were failed to improve the yield (Table 1, entries 14–17). After several experimental iterations, the optimal reaction conditions emerged with *N*-phenylbenzimidamide **1a** (0.20 mmol) with phenylacetaldehyde **2a** (0.24 mmol) in the presence of I_2 (20 mol%) and TBPB (1 eq.) in dioxane (2 mL) at 100 °C in air for 5 h (Table 1, entry 3)

With the optimized conditions in hand, we proceeded to examine the substrate scope (Table 2). First, we studied the R^1-substituted arylamidines. A variety of 1,2,5-trisubstituted imidazoles could be obtained by employing various arylamidines (**1**) and phenylacetaldehyde (**2a**) giving 44–85% yields (Table 2, entries 1–5). Generally, electron donating groups substituents (4-Me, 4-MeO) as well as some electron withdrawing groups (4-CF_3, 2-Cl) provided moderate yields (Table 2, entries 1–4). In addition, the substrate *N*-p with the pyridine ring could also be applied to this strategy, even with a relatively low yield (Table 2, entry 5).

We next examined the substrate scope of this reaction using R^2-substituted arylamidines. Electron-rich-substituted arylamidines such as 4-OMe, 4-Me, 2-Me, 3,4-diMe were easily converted into the corresponding products in excellent yields (Table 2, entries 6–9). Moreover, the substrate with ethyl at the *ortho*-position afforded the corresponding product **3ka** in 86% yield (Table 3, entry 10). Electron-deficient arylamidines bearing halide (4-F, 4-Cl) groups reacted under the standard conditions to afford the desired products in moderate yields (Table 2, entries 11–12).

In addition, bifunctional amidines were also studied, and were well compatible in this transformation in 72–92% yields (Table 2, entries 13–17).

To further study the scope and generality of the present protocol, various aryl acetaldehyde **2** were studied for the cycloaddition reactions with *N*-phenylbenzimidamide **1a** under the optimized reaction conditions (Table 3). Substrates bearing electron-donating groups (4-OMe, 4-Me, 3-Me, 2-Me, 3,4-diMe and 2-Et) at the aromatic ring produced the corresponding products in moderate yields (Table 3, entries 1–6). The presence of electron-withdrawing substituents (2-F, 4-F) reduced the efficiency of the reaction, as the corresponding products could be isolated in slightly lower yields (Table 3, entries 7–8).

Based on the results and the literature reports,[19] a plausible mechanism was proposed as shown in Scheme 2. Initially, the intermediate **A** is produced by the condensation reaction of *N*-

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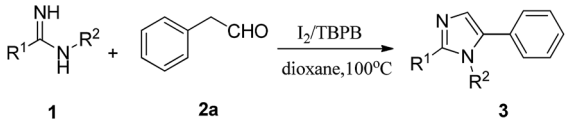
Table 2 Reactions of amidines **1** with phenylacetaldehyde **2a**[a]

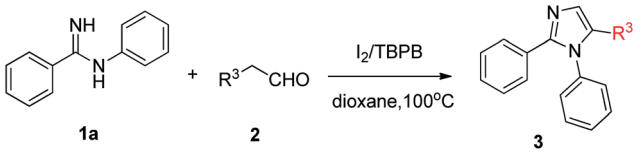


1 **2a** **3**

Entry	R^1	R^2	Product	Yield[b] (%)
1	4-MeOC_6H_4	Phenyl	**3ba**	81
2	4-Me C_6H_4	Phenyl	**3ca**	85
3	4-CF_3 C_6H_4	Phenyl	**3da**	78
4	2-Cl C_6H_4	Phenyl	**3ea**	79
5	2-Pyridyl	Phenyl	**3fa**	44
6	Phenyl	4-MeO C_6H_4	**3ga**	95
7	Phenyl	4-Me C_6H_4	**3ha**	92
8	Phenyl	2-Me C_6H_4	**3ia**	90
9	Phenyl	3,4-diMe C_6H_3	**3ja**	91
10	Phenyl	2-Et C_6H_4	**3ka**	86
11	Phenyl	4-F C_6H_4	**3la**	86
12	Phenyl	4-Cl C_6H_4	**3ma**	89
13	4-MeO C_6H_4	4-Me C_6H_4	**3na**	92
14	4-Me C_6H_4	4-Me C_6H_4	**3oa**	91
15	(3-Br,4-Me)C_6H_3	4-Me C_6H_4	**3pa**	78
16	4-Cl C_6H_4	4-Me C_6H_4	**3qa**	76
17	4-Br C_6H_4	4-Me C_6H_4	**3ra**	72

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), I_2 (20 mol%), TBPB(1 eq.), dioxane (2 mL), 100 °C in air for 5 h, unless otherwise stated. [b] Isolated yields.

Table 3 Reactions of *N*-phenylbenzimidamide **1a** with aryl acetaldehydes **2**[a]

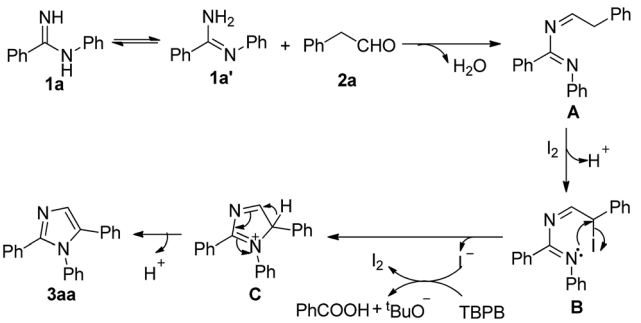


1a **2** **3**

Entry	R^3	Product	Yield(%)[b]
1	4-MeO C_6H_4	**3ab**	85
2	4-Me C_6H_4	**3ac**	83
3	3-Me C_6H_4	**3ad**	81
4	2-Me C_6H_4	**3ae**	78
5	3,4-diMe C_6H_3	**3af**	80
6	4-Et C_6H_4	**3ag**	81
7	4-F C_6H_4	**3ah**	78
8	2-F C_6H_4	**3ai**	72

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), I_2 (20 mol%), TBPB(0.2 mmol), dioxane (2 mL), 100 °C in air for 5 h, unless otherwise stated. [b] Isolated yields.

phenylbenzamidine **1a** with phenylacetaldehyde **2a**. Subsequently, the iodo compound **B** is formed from the **A** after attack by a molecule of iodine, at the same time with release of H^+. There follows an intramolecular cyclization of the iodo compound **B** to form the immediate **C** by leaving of I^- along



Scheme 2 Plausible reaction pathway.

with a catalytic cycle of I^- being oxidized to I_2 by TBPB. Then, a subsequent oxidation of **C** to give the desired product **3aa**.

Conclusion

In conclusion, we have successfully described a practical and efficient strategy for one-pot synthesis of 1,2,5-triaryl-1*H*-imidazoles which uses I_2/TBPB mediated oxidative formal [3 + 2] cycloaddition of aryl acetaldehydes with amidines. The reaction is carried out smoothly and the corresponding products are formed in good to excellent yields with excellent regioselectivity. Importantly, operational simplicity, inexpensive catalysts, an excellent functional groups tolerance to the desired compounds from easily available starting materials. And further studies with respect to the details on the subject remain in progress.

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