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LETTER

I_2-Catalyzed Diamination of Acetyl-compounds to Achieve the Construction of Multi-substituted Imidazoles

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An expedient and straightforward synthetic route for substituted imidazole derivatives from amidines and ketones catalyzed by I_2 has been reported. The reaction proceeded smoothly, and a series of imidazole scaffolds were produced with good to excellent yields and 100% regioselectivity.

Over the past years, C-H/N-H functionalization and C-N bond formation have been intensely studied,[1] owing to the versatility of C-N bond in numerous N-containing natural products[2] and therapeutically important drug molecules.[3] This process is also prevalent and productive in the synthesis of a broad variety of N-containing organic materials, which was often promoted by transition metal catalysts such as Palladium[4], Iron[5] and Copper[6].

Imidazole is an important fragment found in numerous compounds among diverse heterocyclic molecules,[7] which is widely adopted in natural products, biological and pharmaceutical industry. As a privileged structural motif, its pharmacological properties including antitumor,[8] antimicrobial[9] and antiinflammatory[10] are widely exploited and utilized. In addition, thier photophysical properties are of potential applications in material chemistry, such as, in organic electroluminescent devices (OLED).[11] It is worth noting that imidazole derivatives have been exploited as precursors of ligands or final ligands in synthetic organic.[12, 13]

Given the importance as they are, diverse transition metal catalyzed direct C-N formation via the cleavage of C-H/N-H has been reported.[14] However, effective as they are, most of these methods suffer from one or more limitations, such as the requirement of non-ideal solvents, poor functional group tolerance and the formation of hazardous by-products. [15]

Our group has dedicated to efficiently synthesize multi-substituted imidazoles via metal-catalyzed oxidative process.[16] In recent time, we have reported copper and zinc co-catalyzed synthesis of imidazoles via the activation of sp^3 C-H and N-H bonds. However, the reactions required expensive ligands and high temperature.[17] Thus, we are interested in investigating a direct synthesis of multi-substituted imidazoles in the absence of ligands under mild conditions. To achieve a green procedure involving environmental friendly and atom economy, we first reported a novel and efficient I_2-catalyzed synthesis of trisubstituted imidazoles via oxidative activation of C-H and N-H bonds from amidines and ketones. It showed several advantages comparing our previous method, such as an inexpensive and environmental catalyst, ligand-free conditions, easy operation, and no need of specific atmosphere.

Hence, a simple and economical method for the synthesis of multi-substituted imidazoles is expected in terms of operational simplicity and readily available starting materials. In this procedure, the reactivity and feasibility of a regioselective diamination of acetyl with I_2 as catalyst were investigated.

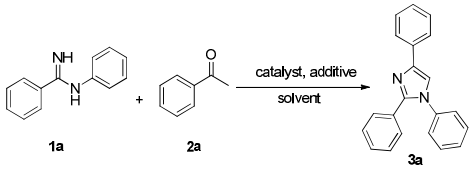


Table 1. Optimization of Reaction Conditions[a]

Entry	I_2 (%)	Lewis acid (%)	Additive (1.0 equiv.)	Solvent	T (°C)	Yield (%)[b]
1	10	-	-	Ph-Me	80	48
2	10	-	-	NMP	80	Trace
3	10	-	-	DMSO	80	Trace
4	10	-	-	Ph-Cl	80	41
5	10	-	-	DMF	80	31
6	10	-	-	EtOH	80	38
7	10	-	-	CH_3CN	80	22
8	10	ZnI_2 (0.1)	-	Ph-Me	80	56
9	10	ZnI_2 (0.1)	-	Ph-Me	100	63
10	10	ZnI_2 (0.1)	-	Ph-Me	60	49
11	10	ZnI_2 (0.1)	-	Ph-Me	120	65
12	10	$FeCl_3$ (0.1)	-	Ph-Me	100	36
13	10	$AlCl_3$ (0.1)	-	Ph-Me	100	42
14	10	$ZnCl_2$ (0.1)	-	Ph-Me	100	55
15	10	PivOH (0.1)	-	Ph-Me	100	28
16	10	ZnI_2 (0.1)	4 Å M.S.	Ph-Me	100	51[c], **85**[d], 87[e]
17	-	ZnI_2 (0.1)	4 Å M.S.	Ph-Me	100	Nr
18	10	ZnI_2 (0.1)	4 Å M.S.	Ph-Me	100	25[f], 84[g]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), Lewis acid, additive, solvent (2.0 mL), 5 h. [b]Isolated yield. [c]2 h. [d]5 h. [e]8 h.

[f]Reaction was carried out under nitrogen atmosphere. [g]Reaction was carried out under oxygen atmosphere. Nr=No reaction.

Initially, we commenced our study by investigating the reaction of *N*-phenylbenzamidine (**1a**) and acetophenone (**2a**) as the model reaction with I_2 (10%) as a catalyst in toluene at 80 °C for 5 h. To our delight, the desired 1,2,4-triphenyl imidazole (**3a**) was obtained in 48% yield (Table 1, Entry 1). In screening of the solvents, toluene was the best solvent among CH_3CN, *N*-methyl-2-pyrrolidone (NMP), Dimethyl Sulphoxide (DMSO), PhCl and EtOH (Table 1, Entries 2-7). Continuing to raising temperature failed to enhance the product yield substantially when the temperature reached to 100 °C (Table 1, Entries 9-11). Fortunately, **3a** was isolated in 63% yield (Table 1, Entry 9) in the presence of the Lewis acid ZnI_2 (10%). Furthermore, with the addition of 4 Å molecular sieves (M.S.) (1.0 equiv.) could improve the yield to 85% (Table 1, Entry 16). Further control experiments indicated that reducing reaction time would decrease the yield, and an increasing reaction time did not show a better result (Table 1, Entry 16). When the reaction was carried out under nitrogen and oxygen atmosphere, yield of the reaction under nitrogen atmosphere was apparently lower, which proved that O_2 in the air played a vital role in the process (Table 1, Entry 18).

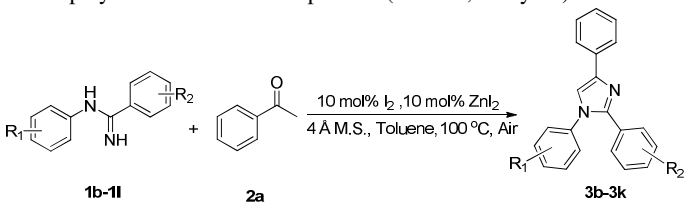
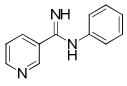
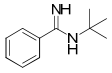


Table 2. Substrate Scope of Amidine[a]

Entry	R_1, R_2	Product	Yield(%)[b]
1	2-Me, H, **1b**	**3b**	88
2	3-ethyl, H, **1c**	**3c**	81
3	4-Me, 4-Me, **1d**	**3d**	92
4	4-Me, 4-Cl, **1e**	**3e**	95
5	4-Cl, H, **1f**	**3f**	94
6	3-Cl, H, **1g**	**3g**	83
7	H, 2-Cl, **1h**	**3h**	82
8	H, 4-CF_3, **1i**	**3i**	62
9	4-Me, 4-OMe, **1j**	**3j**	87
10	 **1k**	**3k**	52
11	 **1l**	-	Nr

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), 4 Å M.S. (1.0 equiv.), ZnI_2 (10%), PhMe (2.0 mL), 100 °C, 5 h. [b]Isolated yields.

With the optimized conditions in hand, we set out to investigate the reactivity of amidines and ketones, as shown in Table 2. A variety of 1,2,4-trisubstituted imidazoles (**3b**-**k**) could be obtained by employing various amidines (**1b**-**l**) and acetophenone (**2a**) giving 52-95% yields (Table 2, Entries 1-11). Generally, halogen substituents as well as some electro-donating groups such as methoxy-, methyl-, and ethyl- provided good to excellent yields (Table 2, Entries 1-7). Nevertheless, the electron-deficient group trifluoromethyl reduced the yields apparently to only 62% (Table 2, Entry 8), which might be attributed to the electronic effect affect the yield. The substrate *N*-phenylnicotinimidamide with pyridine ring can also be applied to this strategy, even with a relatively low yield (Table 2, Entry 10). Disappointingly, we failed to find the target product when *N*-phenylpivalimidamide was applied to the system (Table 2, Entry 11).

On the other hand, different ketones of either electron-poor or electron-rich groups resulted in the targets in good yields. All the ketones containing halogen substituents (fluoro-, chloro- and bromo-) or some electron-donating groups including phenyl-, methoxyl- and methyl- reacted smoothly with **1a**, and good yields ranged from 69% to 96% (Table 3, Entries 1-15). In particular, the substrates with trifluoromethyl (**2h**) was also well tolerated giving 50% yield (Table 3, Entry 7). Moreover, the substrate with a methoxy group at the *ortho*-position afforded the corresponding product **3q** in the yield of 79% (Table 3, Entry 6), which indicated that the reaction may be insensitive to steric hindrance. Additionally, the catalytic system was also applicable for 2-acetonaphthone and 6-methoxy-2-acetonaphthone under optimized condition offering 88% and 86% yield, respectively (Table 3, Entries 11 and 12).

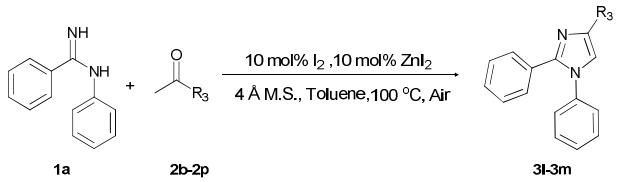
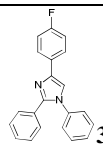
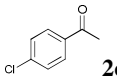
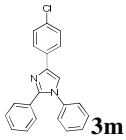
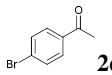
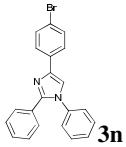
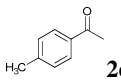
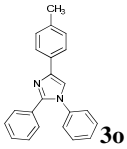
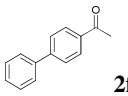
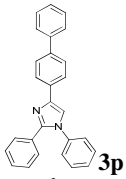
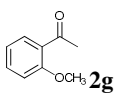
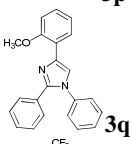
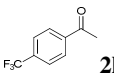
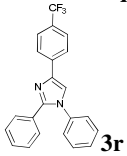
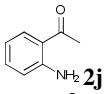
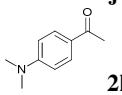
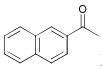
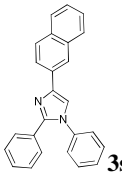
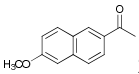
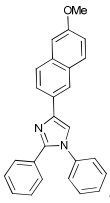
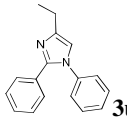
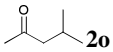
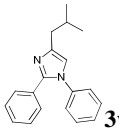


Table 3. Substrate Scope of Ketones[a]

Entry	R_3	Product	Yield (%)[b]
1	 **2b**	 **3l**	69
2	 **2c**	 **3m**	84
3	 **2d**	 **3n**	96
4	 **2e**	 **3o**	77
5	 **2f**	 **3p**	89
6	 **2g**	 **3q**	79
7	 **2h**	 **3r**	50

8	 **2i**	-	Nr
9	 **2j**	-	Nr
10	 **2k**	-	Nr
11	 **2l**	 **3s**	88
12	 **2m**	 **3t**	86
13	 **2n**	 **3u**	93
14	 **2o**	 **3v**	95
15	 **2p**	-	Nr

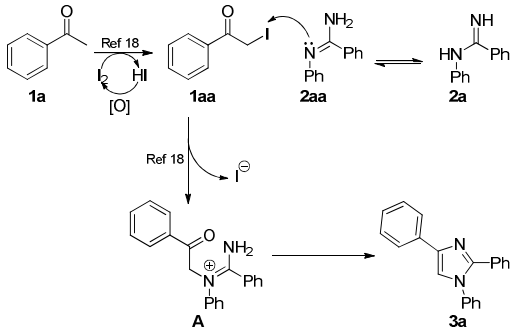
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), 4 Å M.S. (1.0 equiv.), ZnI_2 (10%), PhMe (2.0 mL), 100 °C, 5 h. [b]Isolated yields.

Notably, the reactions of 2-butanone and methyl isobutyl ketone with amidine successfully proceeded to generate the desired products, and the yields were 93% and 95%, respectively (Table 3, Entries 13 and 14). Unfortunately, the reactions failed to give ideal results when substrates with 2-nitro, 4-amino or 4-dimethylamino were applied to this cycloaddition reaction, as well as 1-(pyridin-2-yl)ethanone (Table 3, Entries 8-10 and 15), which might because the nitrogen atom effected the formation of reaction intermediates.

Scheme 1. Reaction carried out under optimized condition and TEMPO.

To gain a further sight of the reaction, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2.0 equiv.) was added to the system, and the reaction provided an excellent yield of 84%, which eliminated radical processes.

On the basis of aforementioned information[18] and above results, a proposed mechanism for this I_2-catalyzed C-H/N-H oxidative cyclization is illustrated in Scheme 2. The Ortoleva-King reaction promoted by Lewis acid was the key step for this reaction. Initially, acetophenone **1a** converted into α-iodoketone **1aa** in the presence of I_2, with a molecular HI released. Then, intermediate **2aa**, which could be tautomerized from amidine **2a**, reacted with α-iodoketone **1aa** to form the intermediate **A**. Simultaneously, with a molecular H_2O released, the subsequent intramolecular cyclization of the intermediate **A** afforded the desired product **3a**.



Scheme 2. Proposed mechanism

In summary, we have illustrated a convenient and direct synthetic route to contribute imidazole derivatives from the amidines and ketones in the presence of air, using I_2 as the catalyst and ZnI_2 as the Lewis acid. The regioselective diamination reaction was carried out through sp^3 C–H bond oxidation, tolerating a wide range of functional groups such as fluoro-, chloro-, bromo-, methoxyl-, phenyl- and alkyl-, which afforded the corresponding imidazole scaffolds in good to excellent yields.

Acknowledgments
We are sincerely grateful to the project sponsored by the National Science Foundation of P. R. China (No. 21372102 and 21403256).

Experimental

General remarks:

All reagents were commercially available and used as is without further purification. ^{1}H NMR spectra were recorded on 300 or 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 75 or 100 MHz in $CDCl_3$ using TMS as internal standard. Melting points were determined on a microscopic apparatus. Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. HRMS was performed on an FT-ICRMS mass instrument and measured with electrospray ionization (ESI). Copies of all desired products ^{1}H NMR and ^{13}C NMR spectra are provided. Commercially available reagents and solvents were used without further purification.

General procedure for the synthesis of 1,2,4-triphenyl-imidazole (3a):

All the reactions were carried out in a reaction vessel (10 mL), *N*-phenylbenzamidine (**1a**, 0.2 mmol), acetophenone (**2a**, 0.2 mmol), I_2 (10 mol%), ZnI_2 (10 mol%), 4 Å M.S. (1.0 equiv.), and PhMe (2.0 mL) were successfully mixed in the flask with a magnetic stir bar and reacted at 100 °C for 5 h in the presence of air. Then the mixture was removed from oil bath and cooled to temperature. The mixture was filtered and washed with ethyl acetate (3 × 50 mL)and the crude product was obtained by concentrating under reduced pressure. Finally, product **3a** was isolated as a yellow oil by silica gel chromatography (petroleum ether /ethyl acetate=10/1 as eluent). The remaining substituted imidazoles were prepared in similar manner.

Notes and references

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