NJC

LETTER

View Article Online
View Journal

Cite this: DOI: 10.1039/c5nj00910c

Received (in Montpellier, France)
13th April 2015,
Accepted 21st April 2015

DOI: 10.1039/c5nj00910c

www.rsc.org/njc

I_2-Catalyzed diamination of acetyl-compounds for the synthesis of multi-substituted imidazoles†

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An expedient and straightforward synthetic route to 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 in 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 the 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, and biological and pharmaceutical industries. As a privileged structural motif, its pharmacological properties, including antitumoral,[8] antimicrobial[9] and antiinflammatory,[10] are widely exploited and utilized. In addition, its photophysical properties have 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 chemistry.[12,13]

Given the importance as they are, diverse transition metal catalyzed direct C–N formation reactions via the cleavage of C–H/N–H have 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 is dedicated to the efficient synthesis of multi-substituted imidazoles via metal-catalyzed oxidative processes.[16] In recent times, we have reported the 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 which is environmentally friendly and atom economical, we first reported a novel and efficient I_2-catalyzed synthesis of tri-substituted imidazoles *via* the oxidative activation of C–H and N–H bonds from amidines and ketones. It showed several advantages compared to our previous methods, such as the use of an inexpensive and environmentally friendly catalyst, ligand-free conditions, and ease of operation, and did not need a 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 a catalyst were investigated.

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). Continuous increase of temperature failed to enhance the product yield substantially when the temperature reached 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%).

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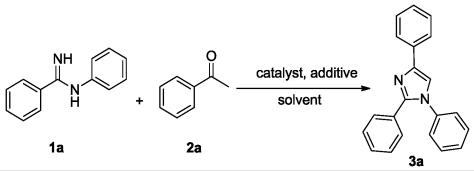
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5nj00910c

Table 1 Optimization of reaction conditions[a]

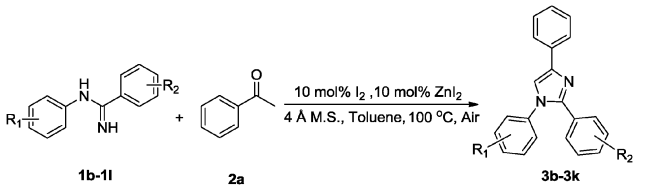


1a 2a 3a

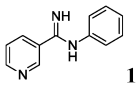
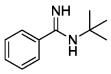
Entry	I_2 (%)	Lewis acid (%)	Additive (1.0 equiv.)	Solvent	T (°C)	Yield[b] (%)
1	10	—	—	Ph–Me	80	48
2	10	—	—	NMP	80	Trace
3	10	—	—	DMSO	80	Trace
4	10	—	—	Ph–Cl	80	41
5	10	—	—	DMF	80	31
6	10	—	—	EtOH	80	38
7	10	—	—	CH_3CN	80	22
8	10	ZnI_2 (0.1)	—	Ph–Me	80	56
9	10	ZnI_2 (0.1)	—	Ph–Me	100	63
10	10	ZnI_2 (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 the nitrogen atmosphere. [g] Reaction was carried out under the oxygen atmosphere. Nr = No reaction.

Table 2 Substrate scope of amidine[a]



1b-1l 2a 3b-3k

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.

Furthermore, 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 the reaction time would decrease the yield, and an increase in the reaction time did not show a better result (Table 1, entry 16). When the reaction was carried out under nitrogen and oxygen atmospheres, the yield of the reaction under the nitrogen atmosphere was apparently lower, which proved that O_2 in the air played a vital role in the process (Table 1, entry 18).

With the optimized conditions in hand, we set out to investigate the reactivities 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 electron-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 effects. The substrate *N*-phenylnicotinimidamide with the 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).

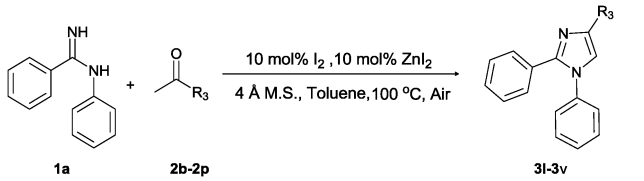
On the other hand, different ketones of either electron-poor or electron-rich groups resulted in the targets in good yields. All the ketones containing halogen substituents (fluoro-, chloro- and bromo-) or some electron-donating groups including phenyl, methoxyl and methyl reacted smoothly with **1a**, and good yields ranged from 69% to 96% (Table 3, entries 1–15). In particular, the substrates with trifluoromethyl (**2h**) were also well tolerated giving a 50% yield (Table 3, entry 7). Moreover, the substrate with a methoxy group at the *ortho*-position afforded the corresponding product **3q** in 79% yield (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 conditions offering 88% and 86% yields, respectively (Table 3, entries 11 and 12).

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 be because the nitrogen atom effected the formation of reaction intermediates.

To gain a further insight into 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 (Scheme 1).

On the basis of the aforementioned information[18] and the 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 the Lewis acid was the key step for this reaction. Initially, acetophenone **1a** was converted into α-iodoketone **1aa** in the presence of I_2, with release of

Table 3 Substrate scope of ketones[a]



1a 2b-2p 3l-3v

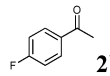
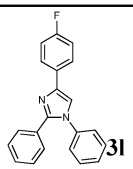
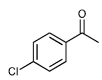
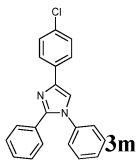
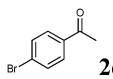
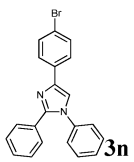
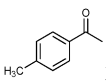
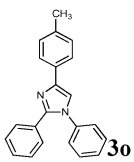
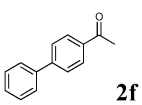
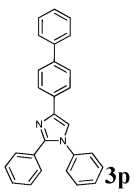
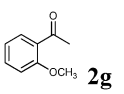
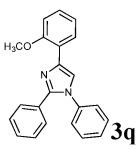
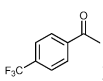
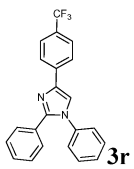
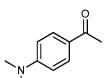
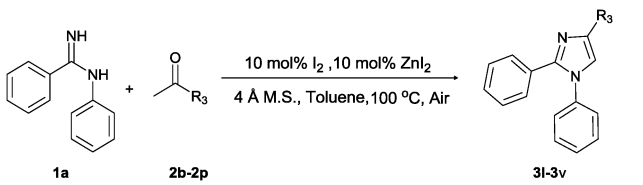
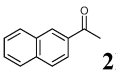
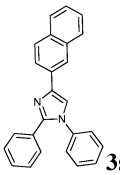
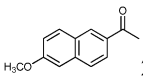
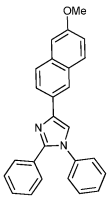
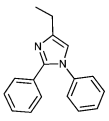
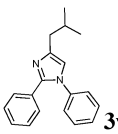
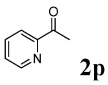
Entry	R_3	Product	Yield[b] (%)
1	 2b	 3l	69
2	 2c	 3m	84
3	 2d	 3n	96
4	 2e	 3o	77
5	 2f	 3p	89
6	 2g	 3q	79
7	 2h	 3r	50
8	 2i	—	Nr
9	 2j	—	Nr
10	 2k	—	Nr

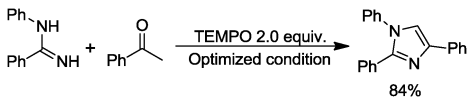
Table 3 (*continued*)



1a 2b-2p 3l-3v

Entry	R_3	Product	Yield[b] (%)
11	 2l	 3s	88
12	 2m	 3t	86
13	 2n	 3u	93
14	 2o	 3v	95
15	 2p	—	Nr

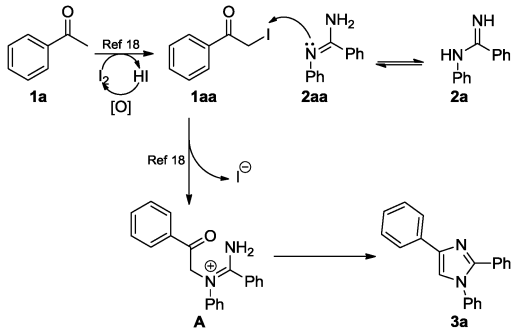
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (10%), 4 Å M.S. (1.0 equiv.), ZnI_2 (10%), PhMe (2.0 mL), 100 °C, 5 h. [b] Isolated yields.



Scheme 1 Reaction carried out under optimized conditions and TEMPO.

molecular HI. Then, intermediate **2aa**, which could be tautomerized from amidine **2a**, reacted with α-iodoketone **1aa** to form the intermediate **A**. Simultaneously, with release of molecular H_2O, the subsequent intramolecular cyclization of the intermediate **A** afforded the desired product **3a**.

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.



Scheme 2 Proposed mechanism.

Experimental

General remarks

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

General procedure for the synthesis of 1,2,4-triphenylimidazole (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 using a magnetic stir bar and reacted at 100 °C for 5 h in the presence of air. Then the mixture was removed from the oil bath and cooled to room 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 the eluent). The remaining substituted imidazoles were prepared in a similar manner.

Acknowledgements

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

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