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A Transition-Metal-Free Synthesis of Multisubstituted Imidazoles

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A novel and simple *t*-BuOLi/I_2-mediated synthesis of 1,2,4-trisubstituted imidazoles was developed without transition-metal added. The transition-metal-free strategy tolerated a range of substrates and provided products in moderate to good yields with 100% regioselectivity.

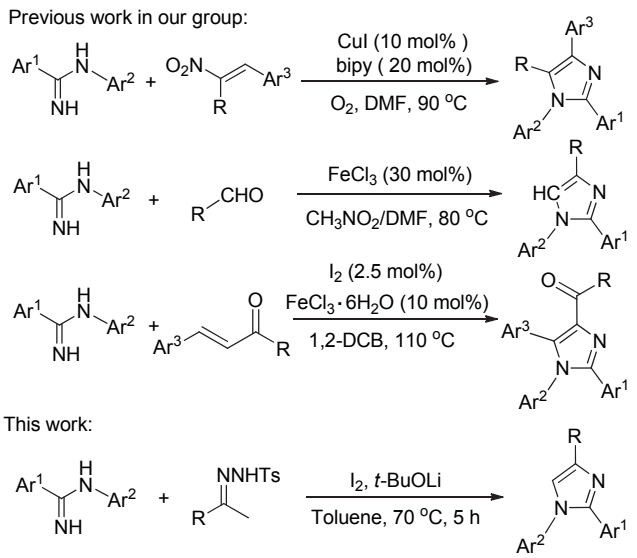
Keywords multisubstituted imidazoles, cyclization, benzamidine, *N*-tosyl-hydrazone, heterocycles

Introduction

Imidazole ring, a key structure among the valuable nitrogen-containing heterocycles,[1-12] is frequently found in numerous natural products, bioactive compounds and agrochemical industries.[13-17] The pharmacological properties of imidazole derivatives, such as antimicrobial,[18,19] antiplasmodium[20] and anti-inflammatory,[21,22] are increasingly remarkable and widely exploited. Besides, its good prospects as the raw materials and ligands in organic synthesis have attracted more and more scientific workers to dedicate to develop complementary strategies and viable alternatives for obtaining multisubstituted imidazoles.[23-27]

Given the importance of imidazole derivatives, a number of transition metals-catalyzed formations of substituted imidazoles have been reported in the literature.[28-31] Although these presented methods are generally efficient, their applications are of great limitation, such as uneasy operation, poor functional group tolerance and high cost of metal catalysts.[32,33] Therefore, there is still a challenge to develop novel synthetic methods for preparation of potentially pharmacologically active imidazole derivatives in terms of operational simplicity and readily available starting materials. Our group[34-37] has been dedicated to investigating the synthesis of imidazole derivatives (Scheme 1). High regioselectivity as it is, but they request a significant amount of expensive metal catalyst. In our continued interest in the synthesis of imidazoles, we herein report a simple and transition-metal-free alternative that can enable the construction of the C—N bond through oxidative transformation[38-42] of readily available benzamidines[43-46] with *N*-tosyl-hydrazones.[47-50]

Scheme 1 Works in our group to gain imidazole derivatives



Experimental

All the reactions were carried out in a round-bottom side arm flask (10 mL). All substrates are easily available. Flash chromatography was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ^{1}H NMR spectra were recorded at 300 MHz and 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 75 MHz and 100 MHz in $CDCl_3$ with using TMS as internal standard. Melting points were determined on a microscopic apparatus without correction. HRMS was performed on an FT-ICRMS mass instrument and measured with electrospray ionization

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(ESI). Copies of ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting Information. Commercially available reagents were used without further purification.

The reactions were carried out in a round-bottom flask reactor (10 mL). **1a** (0.2 mmol), **2a** (0.2 mmol), I_2 (0.2 mmol), *t*-BuOLi (0.4 mmol), and toluene (2.0 mL) were added to the flask with magnetic stirring bar. The resulting mixture was stirred at 70 ℃ for 5 h. After cooling to room temperature, the mixture was filtered and extracted with ethyl acetate (10 mL×3). Then the filtrate was concentrated under reduced pressure in order to get the crude product, which was further purified by silica gel chromatography (petroleum/ethyl acetate, V∶V=15∶1 as eluent) to obtain product **3a**.

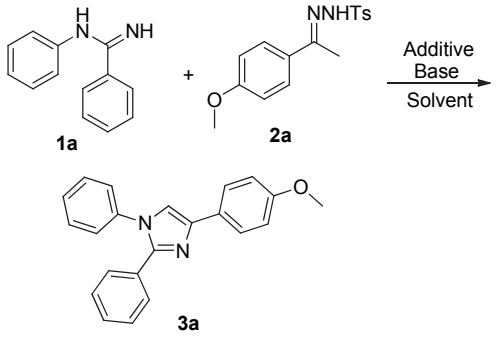
Results and Discussion

In our initial studies, the reaction of *N*-phenyl-benzamidine (**1a**) with 4-methoxyacetophenone *N*-tosyl-hydrazone (**2a**) was chosen as a model reaction for optimizing the reaction conditions. Gratifyingly, the desired product **3a** was obtained in 72% yield in the presence of I_2 (1.0 equiv.) and *t*-BuOLi (2.0 equiv.) in toluene (2.0 mL) at 70 ℃ for 5 h, which indicated that the usage of iodine sources is essential to make the cyclization proceed and to obtain the corresponding products with good yields, as shown in Table 1. Subsequently, we screened the iodine sources and bases. The use of other bases including *t*-BuOK, $CsCO_3$, K_2CO_3 and NaOAc, gave inferior results (Table 1, Entries 2—5), and either increasing or decreasing the amount of *t*-BuOLi did not give a better yield than the use of *t*-BuOLi (2.0 equiv.) (Table 1, Entries 6—8). Furthermore, when other iodine sources including tetrabutylammonium iodide (TBAI), 2-iodoxybenzoic acid (IBX), $PhI(OAc)_2$ or *N*-iodosuccinimide (NIS) were applied, the yield of **3a** dramatically decreased (Table 1, Entries 9—12). With regard to the solvents, CH_3CN, 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and dioxane failed to afford a better result (Table 1, Entries 13—17). Employing the different reaction temperature and reaction time did not provide significant improvements to reaction yields (Table 1, Entries 18—20).

With the optimized reaction conditions in hand, a number of amidine substrates were tested and the results are illustrated in Table 2. Satisfactorily, the transformation was amenable to a series of *N*-substituted amidines affording the corresponding products **3** in moderate to good yields ranging from 52% to 79%. Generally, lower yields were obtained when R^1 or R^2 was electron-withdrawing substituted group (Table 2, Entries 2—4). On the other hand, the cyclization reaction afforded the desired products in higher yields with disubstituted amidines (Table 2, Entries 7 and 10—12) and with electron-donating group at the R^2 position (Table 2, Entries 5 or 9).

Furthermore, *N*-tosyl-hydrazones with different function groups on the aryl ring were tested for this cyclization, and either electron-donating groups (CH_3 and OCH_3) or electron-withdrawing groups (F, Cl and Br) were well compatible with this reaction with yields 54%—72%. Good yields were obtained with electron-withdrawing group at the *para*-position. Moreover, the lower yield of the corresponding product was obtained while the stronger electron-withdrawing group was

Table 1 Screening for optimized conditions[a]



Entry	Base (Dosage/equiv.)	Additive	Temp./℃	Solvent	Yield[b]/%
1	***t*-BuOLi (2.0)**	**I_2**	**70**	**Toluene**	**72**
2	*t*-BuOK (2.0)	I_2	70	Toluene	48
3	$CsCO_3$ (2.0)	I_2	70	Toluene	Trace
4	K_2CO_3 (2.0)	I_2	70	Toluene	Trace
5	NaOAc (2.0)	I_2	70	Toluene	39
6	*t*-BuOLi (1.0)	I_2	70	Toluene	40
7	*t*-BuOLi (1.5)	I_2	70	Toluene	57
8	*t*-BuOLi (2.5)	I_2	70	Toluene	68
9	*t*-BuOLi (2.0)	TBAI	70	Toluene	26
10	*t*-BuOLi (2.0)	IBX	70	Toluene	38
11	*t*-BuOLi (2.0)	$PhI(OAc)_2$	70	Toluene	Nr
12	*t*-BuOLi (2.0)	NIS	70	Toluene	34
13	*t*-BuOLi (2.0)	I_2	70	CH_3CN	56
14	*t*-BuOLi (2.0)	I_2	70	DCE	50
15	*t*-BuOLi (2.0)	I_2	70	DMF	Nr
16	*t*-BuOLi (2.0)	I_2	70	DMSO	Nr
17	*t*-BuOLi (2.0)	I_2	70	Dioxane	Nr
18	*t*-BuOLi (2.0)	I_2	60	Toluene	69
19	*t*-BuOLi (2.0)	I_2	80	Toluene	71
20[c,d]	*t*-BuOLi (2.0)	I_2	70	Toluene	39[c] 72[d]
21[e,f]	*t*-BuOLi (2.0)	I_2	70	Toluene	64[e] 43[f]
22	*t*-BuOLi (2.0)	—	70	Toluene	Nr

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), base, additive (1.0 equiv.), toluene (2.0 mL), 70 ℃ in an oil bath for 5 h, unless otherwise stated. [b] Isolated yields. [c] Reacting for 2.5 h. [d] Reacting for 7 h. [e] Under O_2 atmosphere. [f] Adding 4 Å MS (100 mg).

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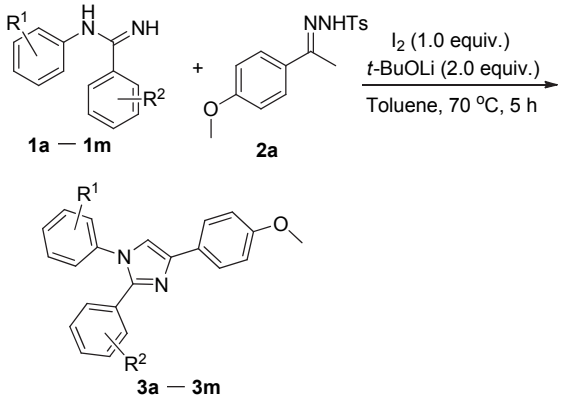
Table 2 Substrate scope of amidine[a]

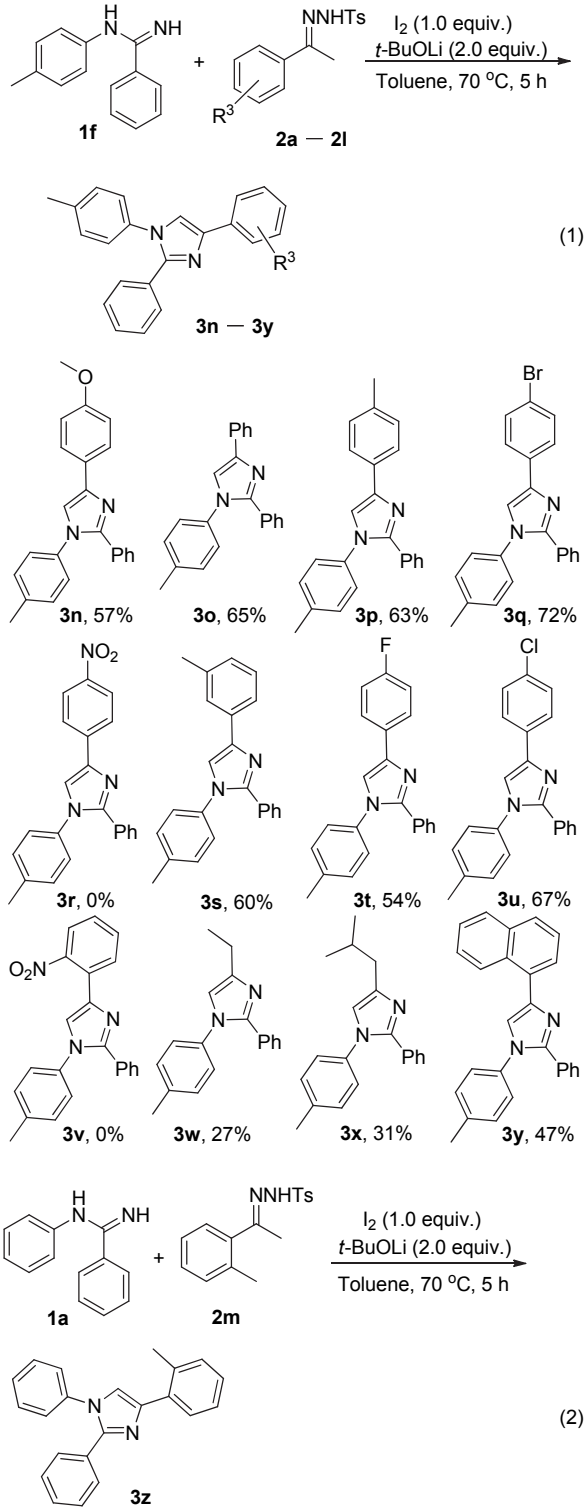


Entry	Compound **1**	R^1, R^2	Product	Yield[b]/%
1	**1a**	H, H	**3a**	72
2	**1b**	3-Cl, H	**3b**	53
3	**1c**	4-Cl, H	**3c**	56
4	**1d**	H, 2-Cl	**3d**	52
5	**1e**	H, 3-ethyl	**3e**	68
6	**1f**	4-CH_3, H	**3f**	57
7	**1g**	4-CH_3, 4-CH_3	**3g**	74
8	**1h**	4-OCH_3, H	**3h**	59
9	**1i**	H, 4-CH_3	**3i**	62
10	**1j**	4-CH_3, 4-OCH_3	**3j**	79
11	**1k**	3-CH_3, 4-Cl	**3k**	60
12	**1l**	4-CH_3, 4-Br	**3l**	66
13	**1m**	2-CH_3, H	**3m**	55

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), *t*-BuOLi (2.0 equiv.), I_2 (1.0 equiv.), toluene (2.0 mL), 70 ℃ in an oil bath for 5 h. [b] Isolated yields.

employed, which indicated that the reaction was more electronic effect sensitive when the C—H amination was undertaken (Eq. 1, **3q**, **3t** and **3u**). The yield was higher with CH_3 at the *para*-position (Eq. 1, **3p**) than that of the *meta*-position (Eq. 1, **3s**), in addition, the use of substrate with bulky aromatic group such as 2'-acetonaphthone *N*-tosyl-hydrazone (**2y**) offered the yield of 47% (Eq. 1, **3y**), which indicated the steric hindrance affected the formation.

Encouragingly, the reaction of aliphatic ketones such as 2-butanone (**2j**) and methyl isobutyl ketone (MIEK, **2k**) proceeded smoothly to produce the desired products 4-ethyl-2-phenyl-1-(*p*-tolyl)-1*H*-imidazole (**3w**) and 4-isobutyl-2-phenyl-1-(*p*-tolyl)-1*H*-imidazole (**3x**) with yield 27% and 31%, respectively (Eq. 1, **3w** and **3x**). Substrate with CH_3 at the *ortho*-position (**2m**) provided an acceptable yield of 62% when reacted with *N*-phenylbenzimidamide (Eq. 2). However, substrates with other groups including 4-nitro- and 2-nitro- did not give satisfying results (Eq. 1, **3r** and **3v**), even prolonging reaction time or increasing temperature, which was probably caused by the strong electron-withdrawing effect.



On the basis of aforementioned results and those reported in the literature,[51-59] a plausible mechanism is proposed, as outlined in the Scheme 3. Firstly, the oxidative iodination of the *N*-tosylhydrazone **2b** affords an iodo-substituted intermediate **B**, which can be subsequently converted to the azoalkene **C**, with a molecular HI leaving at the same time.[51] Then, the intermediate **A**, which can be generated from the substrate amidine **1a**

Scheme 2 Proposed mechanism

releasing a proton on the effect of the base, attatches the azoalkene **C** to generate the diazo compound **D**.[51-56] Subsequent I_2-mediated oxidation of **D** gives the corresponding radical cation **E**. Meanwhile, the N_2 leaves upon heating in the presence of the base. An intramolecular cyclization can undergo to furnish the dihydroimidazole derivative **F**. Further oxidative aromatization of **F** leads to 1,2,4-triphenyl-1*H*-imidazole **3** as the target product.[51,57-58]

Conclusions

In summary, we have developed a transition-metal-free C—N bond formation reaction to synthesize 1,2,4-trisubstituted imidazoles from readily available *N*-phenylbenzamidines and acetophenone *N*-tosyl-hydrazones via oxidative cyclization in the presence of molecular iodine and *t*-BuOLi. The reaction exhibited a tolerance of a range of functional groups to afford alkyl- and aryl-substituted imidazoles in good to high yields. The cyclization reaction followed by intramolecular oxidative amination proceeded smoothly without the need of metal-catalysts or ligands. This is the first report involving the *t*-BuOLi/I_2-mediated intermolecular oxidative amination of *N*-tosyl-hydrazones for the construction of the imidazole derivatives. The method would be helpful for the synthesis of potentially useful imidazole derivatives.

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