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Highly Efficient and Eco-friendly Protocol to Functionalized Imidazoles *via* Ring-Opening of α-Nitro Epoxides

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A simple and direct synthesis of functionalized imidazoles from α-nitro-epoxides and amidines was developed. This reaction could proceed smoothly in a highly efficient and eco-friendly manner in moderate to excellent yields. A plausible mechanism has also been proposed.

Imidazoles, an important class of *N*-containing heteroaromatic compounds, are frequently found in various pharmacologically active compounds and natural products.[1] Among them, functionalized imidazoles are privileged core structures used in medicinal chemistry because of their excellent biological effects, such as antitumor, antifungal, antibacterial, antiviral, antiinflammatory and antiarthritic activities.[2] In addition, the utility is also found as fluorescence, agricultural products, dyes and chemsensing.[3]

In light of the importance of imidazoles, a great deal of attention has been given to their organic synthesis. A number of classical methods were established, involving three-component cyclocondensation of a 1,2-diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde and ammonium acetate,[4] metal-catalyzed arylations of prepared imidazole rings,[5] reaction of aryl cyanides with α,α-dilithioarylnitromethanes,[6] cyclization of α-haloketones with amidines,[7] cyclization of nitroolefins with amidines.[8] Despitethese strategies have been greatly improved to be highly valuable for the construction of imidazoles, it is still challenging to find a more attractive protocol to prepare polysubstituted imidazoles with various substituents from simple, readily available building blocks.

Nitroepoxides[9] are an interesting class of compounds with unique chemical reactivities. Exploited as potentially synthons with two vicinal electrophilic centers, nitroepoxides are particularly attractive intermediates and building blocks in organic synthesis.[10]

In view of the special properties of nitroepoxides, we envisioned that this synthon could be employed for the synthesis of polysubstituted imidazoles by simply treated with amidines. An attractive feature of this protocol is that two molecules could be directly assembled into the desired compounds without any transition metal catalysts.

Initially, 2-methyl-2-nitro-3-phenyloxirane, 1.5 equiv. of formamidine acetate and 1.5 equiv. of K_2CO_3 were selected as model reagents to optimize the reaction conditions (Table 1). It was pleased to see that the reaction afforded the desired imidazole **3a** in 36% yield (Table 1, entry 1). Gratifyingly, the yield was notably increased when more equivalents (2 equiv.) of K_2CO_3 were added into the reaction mixture (Table 1, entry 2). However, it did not give a significant change (Table 1, entry 3) while continuously increasing the amount of base (3 equiv.). Further, other inorganic bases (Na_2CO_3, Cs_2CO_3, NaOH and NaOMe) and organic bases (Et_3N and DBU) were also tested for the reaction. It was revealed that NaOMe was the most efficient one (Table 1, entries 4-9). In order to improve the conversion of this reaction, other conditions were also evaluated. Optimization of solvent demonstrated that MeOH (Table 1, entry 9) was superior to other aprotic and protic solvents (Table 1, entries 10-17). Replacing MeOH with other solvents caused either a decrease in the yield (Table 1, entries 10-15 and 17) or failure to obtain the corresponding products (Table 1, entry 16).

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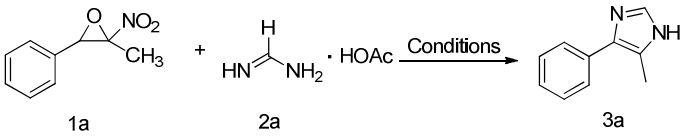
Furthermore, temperature screening showed that room temperature (25 °C) was optimal to obtain the maximum yield of the product (Table 1, entries 18-20). On the basis of the above studies, the optimal reactivity was obtained in MeOH at 25 °C when 2.0 eqiuv. of NaOMe was employed (Table 1, entry 9).

Table 1 Optimization of reaction conditions[a]



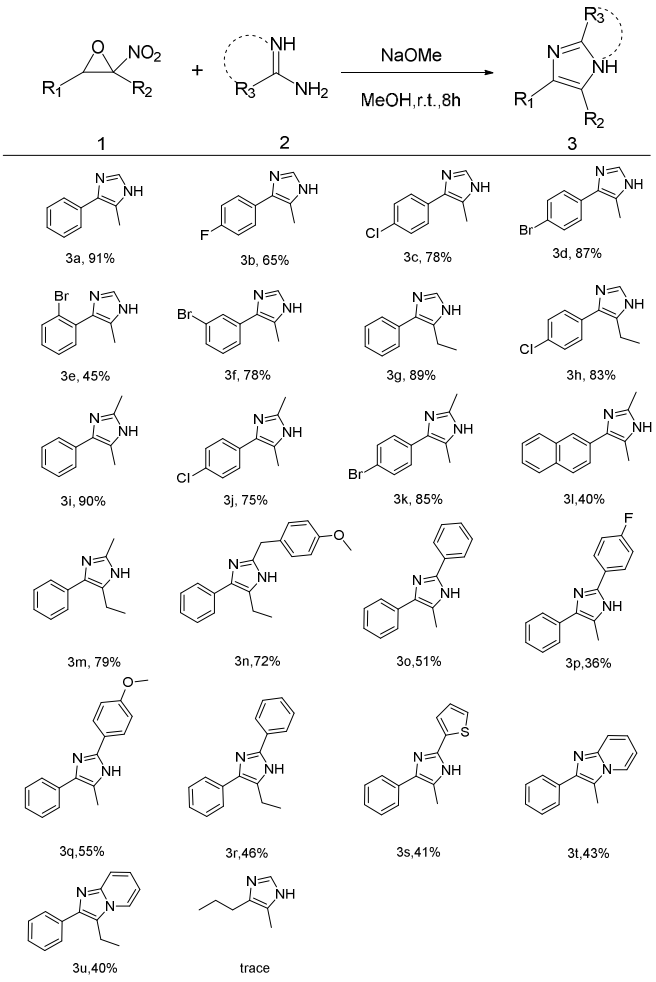
1a 2a 3a

Entry	Base (equiv.)	Solvent	T (^{o}C)	Conversion[b] (%)
1	K_2CO_3(1.5)	MeOH	25	36
2	K_2CO_3(2)	MeOH	25	85
3	K_2CO_3(3)	MeOH	25	85
4	Na_2CO_3(2)	MeOH	25	70
5	Cs_2CO_3(2)	MeOH	25	75
6	NaOH(2)	MeOH	25	21
7	Et_3N(2)	MeOH	25	61
8	DBU(2)	MeOH	25	68
9	**NaOMe(2)**	**MeOH**	**25**	**95(91)**[c]
10	NaOMe(2)	EtOH	25	81
11	NaOMe(2)	IPA	25	67
12	NaOMe(2)	DMF	25	83
13	NaOMe(2)	CH_3CN	25	35
14	NaOMe(2)	THF	25	trace
15	NaOMe(2)	Dioxane	25	trace
16	NaOMe(2)	Toluene	25	n.r.
17	NaOMe(2)	H_2O	25	32
18	NaOMe(2)	MeOH	0	27
19	NaOMe(2)	MeOH	25	95
20[c]	NaOMe(2)	MeOH	50	92

[a] Reaction conditions: mixtures of amidines (0.15 mmol), base (0.2 mmol) and 3 mL of solvent was stirred at 25 ^{o}C for 0.5h, and then nitroepoxide (0.1 mmol) was added, 25 ^{o}C,8h. [b] The conversion rate was determined by HPLC, based on the disappearance of the starting nitroepoxide (1a). [c] Isolated yields. The most successful entry is highlighted in bold.

With the optimized reaction conditions in hand, the scope was examined by coupling a range of nitroepoxides and amidines. As shown in Table 2, the groups at the R_1 and R_2 positions of nitroepoxides 1, either aryl or alkyl substitution, worked well with amidines. It was also found that at the R_1 position, nitroepoxide bearing an *ortho*-brominephenyl group afforded the product **3e** in lower yield than the *meta*- or *para*-brominephenyl substituted nitroepoxides (Table 2, **3f and 3d**). Both aryl and alkyl substitutions at the R_3 position were found compatible in this reaction. However, a lower yield was given when arylsubstitutions were present (**3o** *versus* **3m** and **3n**). Moreover, as shown in Table 2, aryl substituents bearing electron-donating groups at the R_3 position afforded the desired imidazoles in a higher yield than that with electron-withdrawing groups (**3q** *versus* **3p**). Interestingly, the reaction could tolerate when R_3 group was a hetero aryl motif (Table 2, **3s**). Notably, imidazo[1,2-a]pyridine scaffolds could also be constructed when pyridin-2-amine was introduced via this reaction process (Table 2, **3t**, **3u**). The structures of the functionalized imidazoles synthesized in the study were characterized from ^{1}H NMR, ^{13}C NMR spectroscopies and HRMS analysis.

Table 2 Scope of the cyclization reaction of 1 and 2[a,b]



[a] Reaction conditions: mixtures of amidines (0.75 mmol, 1.5 equiv.) , base (1.0 mmol, 2.0 equiv.) and 3 mL of solvent was stirred at 25 ^{o}C for 0.5h, and then nitroepoxide (0.5 mmol, 1.0 equiv.) was added, 25 ^{o}C,8h. [b] Isolated yield.

On the basis of the above experimental results, the following possible mechanism for this reaction was proposed (Scheme 1). In the case of base and amidines **2**, the nitroepoxide **1** would undergo a ring opening to give the intermediate **II**, which continued undergoing an intramolecular nucleophilic addition and elimination of one molecule of H_2O to afford the final product **3**.

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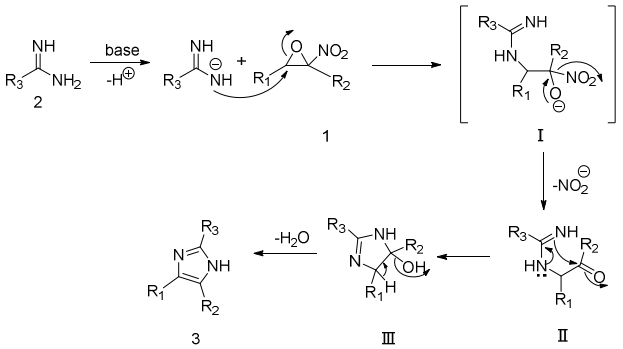
Scheme 1 Proposed Mechanism for the Tandem Reaction



Conclusions

In summary, we have developed a new and mild strategy to prepare functionalized imidazoles. This novel reaction can be realized via a domino process involving a ring-opening of α-nitro epoxides and an intramolecular nucleophilic addition from easily available α-nitro-epoxides and amidines or their analogues. Operational simplicity, mild reaction conditions, and facile substituent variation are all notable aspects of this methodology. This makes it a highly practical approach in the medicinal chemistry.

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