Organic LETTERS

Letter

pubs.acs.org/OrgLett

One-Pot Three-Component Strategy for Functionalized 2-Aminoimidazoles via Ring Opening of α-Nitro Epoxides

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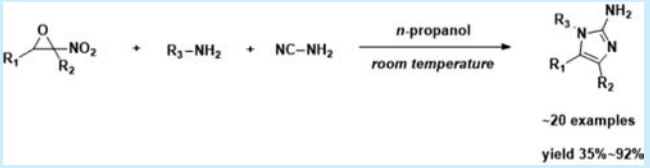
Supporting Information

ABSTRACT: Functionalized 2-aminoimidazole derivatives have been synthesized via a three-component domino reaction of α-nitroepoxides and cyanamide with a series of amines under mild conditions without the need for any additives. This reaction represents a practical process for the facile conversion of α-nitroepoxides to 2-aminoimidazoles via ring opening of epoxides.



The 2-aminoimidazole scaffold is present in a plethora of biological relevant molecules, displaying myriad potentially pharmaceutical properties,[1] such as human β-secretase inhibitors[2] and anticancer activity.[3] In light of the scaffold's importance, a great deal of attention has been given to its organic synthesis. There are a number of established methods for the construction of 2-aminoimidazoles, involving the condensation of α-aminocarbonyl compounds with cyanamide[4a] or the reaction of α-diketones with guanidine followed by reduction,[4b] the functionalization of imidazole derivatives,[5a−f] and the metal-catalyzed hydroamination of acyclic terminally substituted *N*-propargyl guanidines.[5g−j] Although these strategies have been greatly improved for the construction of 2-aminoimidazoles, a more attractive protocol would facilitate the efficient conversion of simple, readily available starting materials in the construction of desired variously substituted 2-aminoimidazole derivatives.

Nitroepoxides[6] comprise an interesting class of compounds with broad and unique chemical reactivity. They are exploited as potentially synthons with two vicinal electrophilic centers.[7] Examples involving in the multicomponent cyclocondensation have been rarely reported. We envisioned that this synthon could be employed for the synthesis of 2-aminoimidazoles by simply treating an amine and cyanamide. These transformations would effect introduction of different groups at the N-1, C-4, and C-5 positions (Figure. 1).

In our initial studies on the synthesis of 2-aminoimidazoles, nitroepoxide **1a** was treated with aniline **2a** and cyanamide **3** in methanol in the presence of 1.0 equiv of NaOMe. Gratifyingly, the reaction afforded the desired 2-aminoimidazole **4a** in 35% yield (Table 1, entry 1). Upon screening of other inorganic bases (K_2CO_3, Cs_2CO_3, and NaOH) and organic bases (Et_3N, DIEA, and DBU), the reaction proceeded less effectively (Table 1, entries 1−7). To our delight, a good yield could be achieved in the absence of base (Table 1, entry 8). However, replacing MeOH with other organic solvents caused either a decrease in the yield (Table 1, entries 9−12, 14, and 16) or failure to obtain the corresponding products (Table 1, entries 13 and 15),

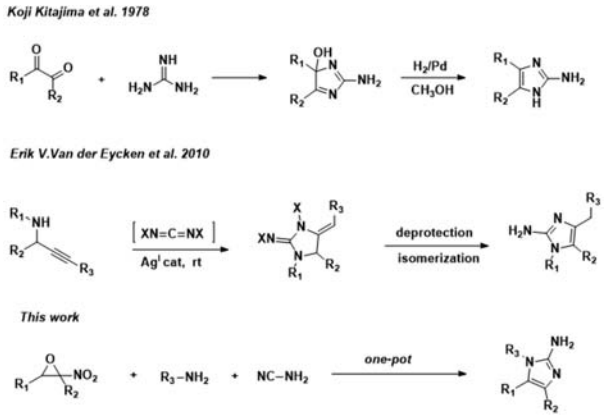


Figure 1. Synthesis of 2-aminoimidazoles via ring opening of nitroepoxides.

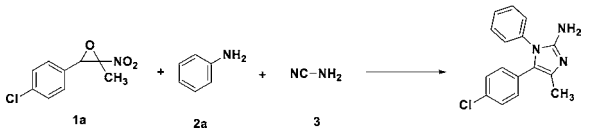
except *n*-propanol (Table 1, entry 17). Among the different temperatures tested, it was indicated that the optimum temperature for this transformation was 25 °C (Table 1, entries 17−19). Furthermore, after reducing the amount of cyanamide to 1 or 3 equiv, the yield of the desired product decreased to 40% or 65%, respectively (Table 1, entries 20−21). Taken together, the optimal reaction conditions included using 5.0 equiv of cyanamide in *n*-propanol at 25 °C without the addition of base.

With the optimized reaction conditions in hand, the scope of this reaction was examined by coupling nitroepoxides **1** and cyanamide **3** with a range of amines **2** (Scheme 1). Gratifyingly, anilines bearing both an electron-donating (Scheme 1, i.e., methyl or methoxy) and electron-withdrawing group (Scheme 1, i.e., fluoro, chloro, or bromo except nitro) were well-tolerated under the reaction conditions. As shown in Scheme 1, substituents bearing electron-donating groups afforded the

Received: January 29, 2015
Published: February 23, 2015

DOI: 10.1021/acs.orglett.5b00289
Org. Lett. 2015, 17, 1157−1159

Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	t (°C)	yield[b] (%)
1	NaOMe	MeOH	25	35
2	K_2CO_3	MeOH	25	12
3	Cs_2CO_3	MeOH	25	8
4	NaOH	MeOH	25	nr
5	Et_3N	MeOH	25	11
6	DIEA	MeOH	25	21
7	DBU	MeOH	25	nr
8	–	MeOH	25	75
9	–	EtOH	25	55
10	–	isopropanol	25	62
11	–	acetone	25	57
12	–	CH_3CN	25	68
13	–	dioxane	25	trace
14	–	THF	25	40
15	–	DMF	25	nr
16	–	H_2O	25	30
17	–	*n*-propanol	25	90
18	–	*n*-propanol	0	27
19	–	*n*-propanol	50	85
20[c]	–	*n*-propanol	25	40
21[d]	–	*n*-propanol	25	65

[a]Unless otherwise specified, reactions were performed using nitroepoxide (0.1 mmol), aniline (0.15 mmol), and cyanamide (0.5 mmol) in various solvents (1.0 mL) at different temperatures in the presence or absence of the base (0.1 mmol) for a period of time. [b]Isolate yield. [c]Reaction was performed using 1.0 equiv of cyanamide. [d]Reaction was performed using 3.0 equiv of cyanamide.

desired 2-aminoimidazoles in a higher yield than that with electron-withdrawing groups. An alkylamine, such as *n*-propanamine, was also tested and resulted in the corresponding product **4l** in a yield of 63%.

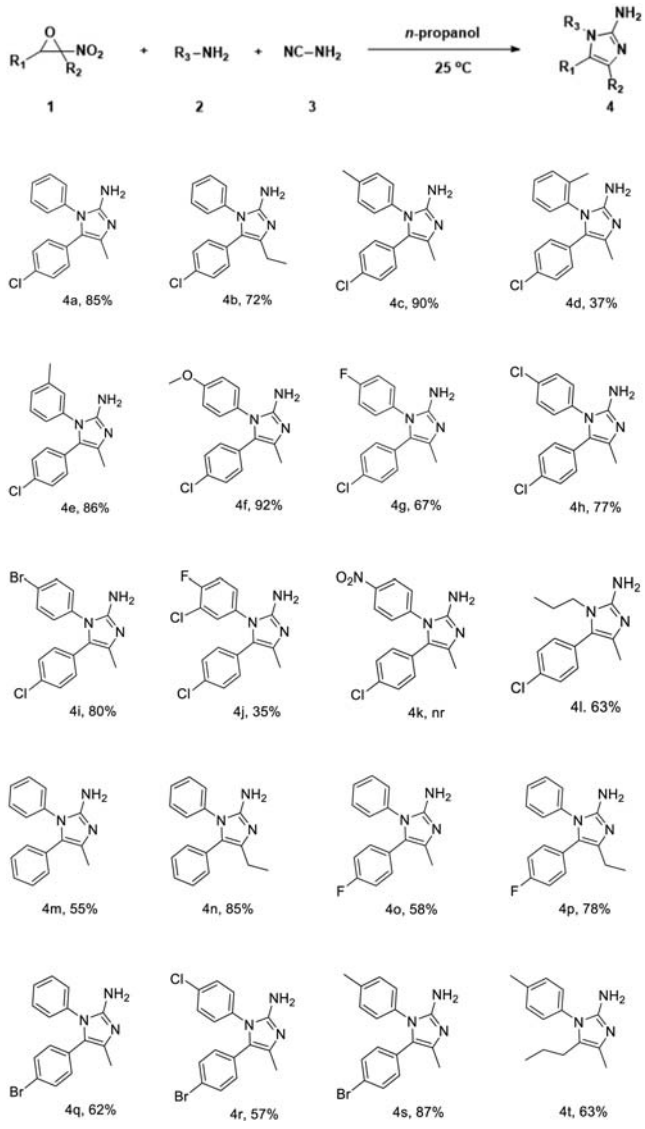
Moreover, the groups at the R_1 and R_2 positions of nitroepoxides **1**, either aryl or alkyl substitution, were compatible in these reaction conditions, giving the corresponding products in good yields (Scheme 1, **4m**–**4t**). Specifically, the desired product **4t** was obtained in 63% yield when 2-methyl-2-nitro-3-propyloxirane was used as the substrate.

The structures of the products synthesized in the current study were characterized from ^{1}H NMR, ^{13}C NMR spectroscopies and HRMS analysis. The structure of compound **4f** was further confirmed by X-ray analysis (Figure 2).

In order to study the proposed mechanism of this reaction, a control reaction was performed (Scheme 2). 4-Methylaniline and cyanamide were treated separately with nitroepoxide. The reaction of **1a** with cyanamide did not result in any adduct formation at room temperature, even when the cyanamide was used in large excess (10 equiv). In contrast, the reaction proceeded effectively to obtain the aminoketone **5** with the addition of 4-methylaniline into the solution of **1a**.

On the basis of our experimental results, a possible reaction mechanism is depicted as follows (Scheme 3). In the case of amine **2**, the nitroepoxide **1** would undergo a ring opening to give the aminoketone **II**. Then, the reaction of aminoketone **II** and cyanamide **3** would give rise to α-aminoimine intermediate **III** by eliminating one molecule of H_2O. Thus, an intramolecular nucleophilic addition of the cyano group and subsequent tautomerization gave the final product **4**.

Scheme 1. Tandem Addition/Cyclization of Nitroepoxide 1, Amine 2, and Cyanamide 3



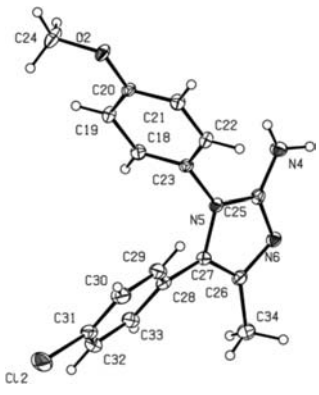
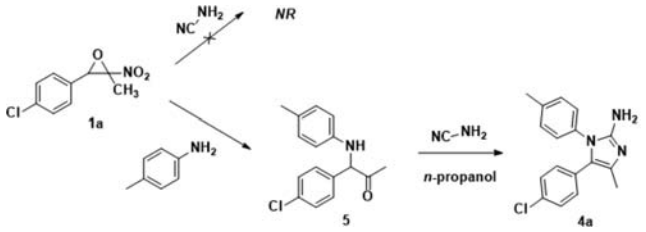


Figure 2. X-ray crystal structure of compound **4f** (CCDC 1042905).

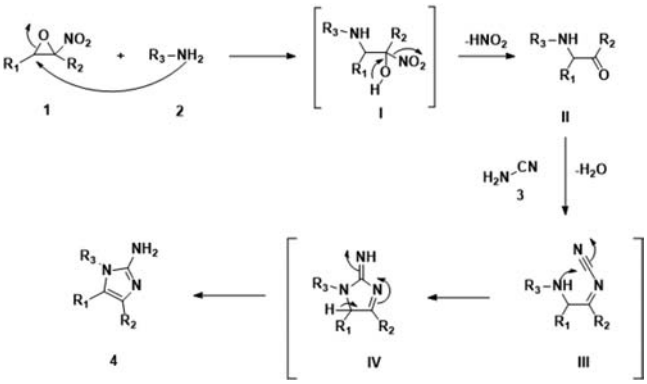
In summary, a novel, one-pot three-component strategy to construct functionalized 2-aminoimidazole derivatives from easily available nitroepoxides and amine was developed. This

DOI: 10.1021/acs.orglett.5b00289
Org. Lett. 2015, 17, 1157–1159

Scheme 2. Control Reactions



Scheme 3. Proposed Mechanism for the Tandem Reaction



reaction was furnished efficiently at room temperature with the advantage of operational simplicity, a satisfactory substrate scope, and no need for any additives. These features render the reaction as a highly practical approach in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and spectra data of the final products. X-ray structure of compound **4f** (CCDC No. 1042905). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported from the National Natural Science Foundation of China (Nos. 81273356 and 81473074), Natural Science Foundation of Zhejiang Province (No. Z2110655), Program for Zhejiang Leading Team of S&T Innovation, and Arthritis & Chronic Pain Research Institute, USA, to Y.Y., and the China Postdoctoral Science Foundation Funded Project (2014M550331), National Natural Science Foundation of China (No. 81402778) to W.C.

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DOI: 10.1021/acs.orglett.5b00289
Org. Lett. 2015, 17, 1157–1159