One-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles by a tandem three-component reaction of hydroxylamines, aldehydes and 2-azido acrylates

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Abstract

The reaction of nitrones, formed in situ by reaction of hydroxylamines and aldehydes, with 2-azido acrylates results in the formation of 1,2,4,5-tetrasubstituted imidazoles has been developed. This three-component reaction allows for the formation of a diverse array of imidazole derivatives with moderate to excellent yields.

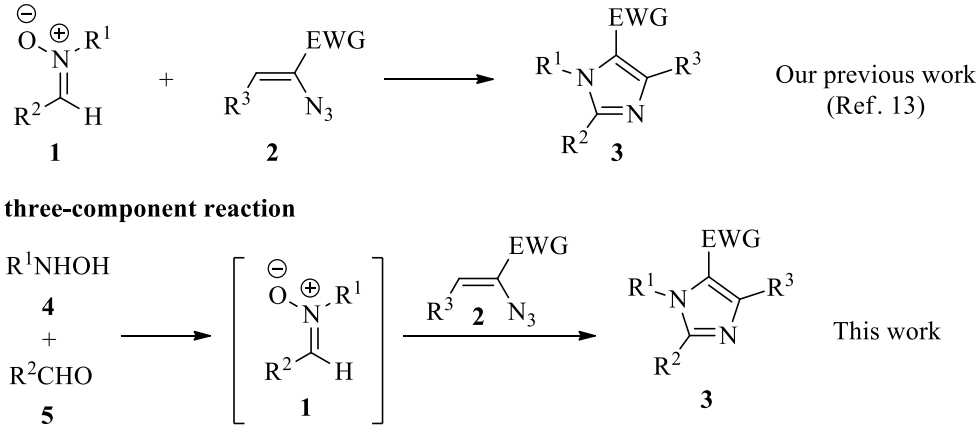
Keywords: Hydroxylamines, aldehydes, 2-azido acrylates, multicomponent reactions, imidazoles

Introduction

Multicomponent reactions (MCRs) forming heterocyclic compounds are powerful tools in the drug-discovery process as they can offer expedient synthesis of libraries of druglike compounds in a single operation.[1] The imidazole ring represents one of the most ubiquitous heterocyclic motifs found in naturally occurring molecules.[2] Whereas the unsubstituted parent compound serves as a nucleophilic catalyst or corrosion inhibitor, its derivatives exhibit variable biological activities such as anti-inflammatory,[3] anti-bacterial,[4] anti-mycotic,[5] antiallergic,[6] analgesic,[7] as well as cytostatic[8] activity. The biological importance of the imidazole moiety has made it a common structure in many drug candidates. It stands to reason that simple methods for the formation of imidazoles from readily available materials would be most welcomed by the synthetic community.

2-Azido acrylates are versatile building blocks in organic synthesis. In recent years, much attention has been focused toward applying 2-azido acrylates as a pivotal three-atom synthon for the formation of diverse nitrogen-containing heterocycles.[9-12] Recently, we have reported a

domino reaction between nitrones **1** and 2-azido acrylates **2** to yield 1,2,4,5-tetrasubstituted imidazoles **3** (Scheme 1).[13] While many nitrones are readily available and stable, some are difficult to prepare or are unstable due to oligomerization. During efforts to address this, it occurred to us that the nitrone could be prepared in situ from the reaction of a hydroxylamine and an aldehyde, avoiding the isolation or handling of the nitrone at all. In this full paper, we report our efforts and success in developing an effective one-pot three-component reaction of hydroxylamines **4**, aldehydes **5**, and 2-azido acrylates **1** for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **3** (Scheme 1).

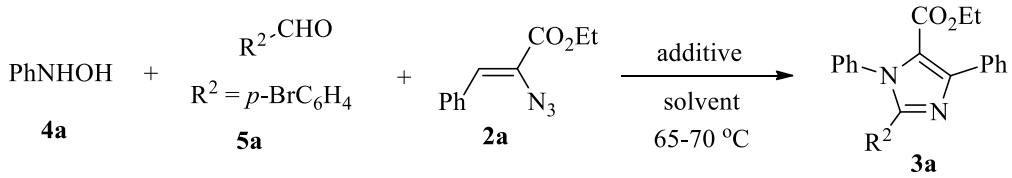


Scheme 1. Preparation of 1,2,4,5-tetrasubstituted imidazoles.

Results and Discussion

From previous work, it was thought that anhydrous $MgSO_4$ would be helpful in the formation of both nitrones **1** and imidazoles **3**.[13] The first experiment was set up as follows: hydroxylamine **4a** (3.0 equiv), *p*-Bromobenzaldehyde **5a** (3.0 equiv), and anhydrous $MgSO_4$ (4.0 equiv) were combined and stirred overnight in DCE at room temperature. After the nitrone **1a** was formed completely, 2-azido acrylate **2a** (1.0 equiv) was added, and the reaction mixture was stirred at 65-70 °C for 72 h. This afforded **3a** in 60% isolated yield (Table 1, entry 1). Solvent screening showed that CH_3CN was the best one for this transformation (Table 1, entries 2-8). Further investigation indicated that 58% yield of **3a** was obtained if the three components were mixed at once in contrast to the 78% yield obtained upon premixing the hydroxylamine and the aldehyde prior to addition of the 2-azido acrylate (Table 1, entries 5 and 9). We assumed that the 2-azido acrylates might be somewhat labile or have effect on the formation of nitrones. It was found that **3a** was obtained in similar yield (74%) by the using of anhydrous $CaCl_2$ as an additive, while anhydrous Na_2SO_4 resulted in only 28% yield (Table 1, entries 11 and 12). We chose the optimized conditions as in entry 5, Table 1 for further investigation.

Table 1. Optimization of reaction conditions[a]

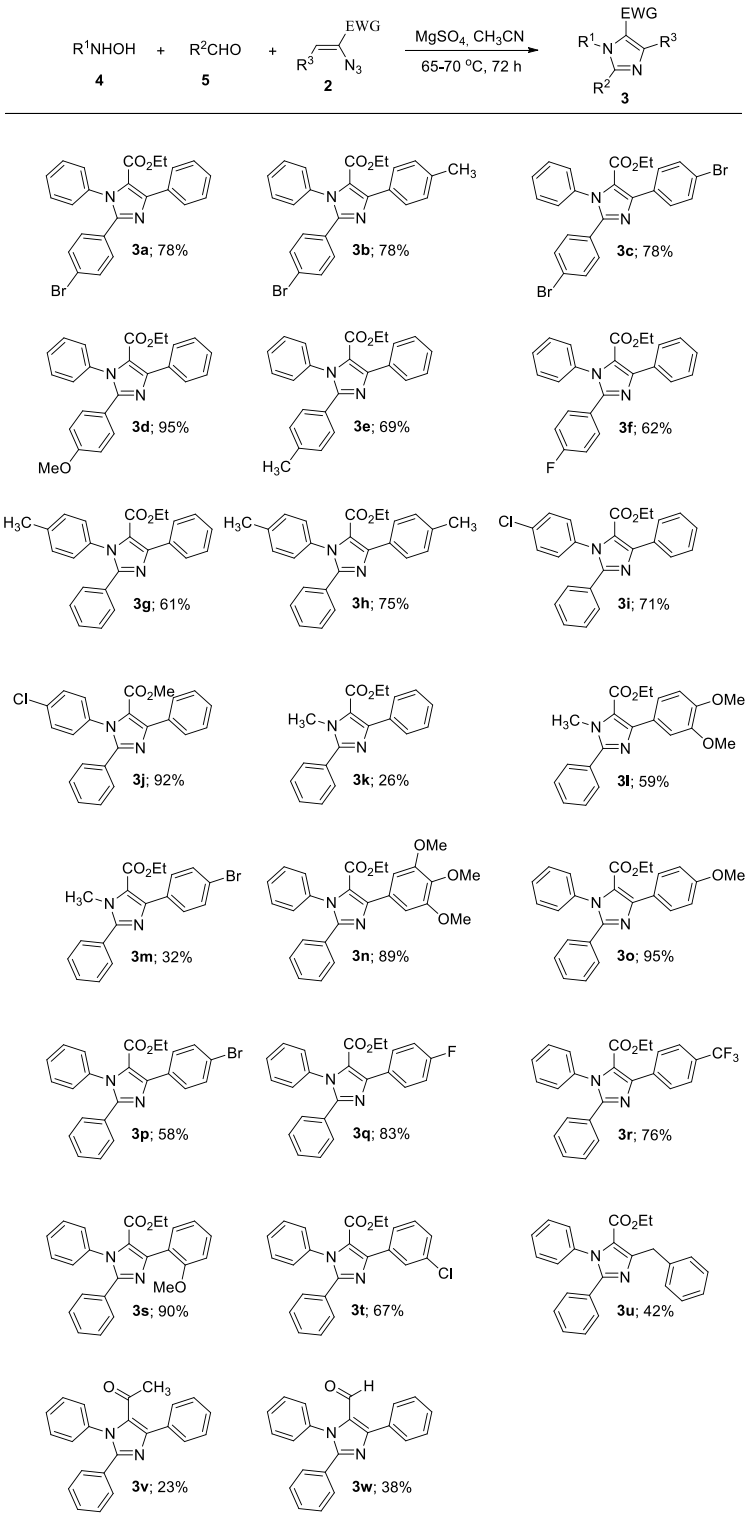


Entry	Solvent	Additive	Time (h)	Yield (%)[b]
1	DCE	$MgSO_4$	72	60
2	toluene	$MgSO_4$	72	<20
3	$CHCl_3$	$MgSO_4$	72	22
4	EtOAc	$MgSO_4$	72	37
5	**CH_3CN**	**$MgSO_4$**	**72**	**78**
6	DMSO	$MgSO_4$	72	28
7	DMF	$MgSO_4$	72	39
8	EtOH	$MgSO_4$	72	48
9[c]	CH_3CN	$MgSO_4$	72	58
10	CH_3CN	$MgSO_4$	48	72
11	CH_3CN	$CaCl_2$	72	74
12	CH_3CN	Na_2SO_4	72	28

[a]Conditions: **4a** (0.90 mmol, 3.0 equiv), **5a** (0.90 mmol, 3.0 equiv), an additive (150 mg), 10.0 mL of solvent, r.t. overnight, then **2a** (0.30 mmol, 1.0 equiv), 65-70 °C, Ar. [b]Yields isolated by column chromatography on silica gel. [c]The three components were mixed and stirred overnight at r.t. before heated.

With the optimal reaction conditions established, the scope and limitations of this three-component coupling process were next examined using various hydroxylamines, aldehydes, and 2-azido acrylates precursors. As depicted in Scheme 2, aromatic aldehydes gave good yields in the three-component reaction. Benzaldehydes with electron-donating groups reacted smoothly, while substitution of electron-withdrawing groups on the benzene ring decreased the reactivity. However, no desired product was obtained for *n*-butylaldehyde, probably due to the intrinsic instability of such nitrone. The scope of the reaction was then investigated on hydroxylamine derivatives. Both aryl hydroxylamines and *N*-methylhydroxylamine hydrochloride (3.0 equiv of Et_3N was used) seem to be well tolerated in the reaction; however, aryl hydroxylamines produce far more satisfactory results than *N*-methylhydroxylamine hydrochloride (which gave generally poor results). The reaction could tolerate aromatic substituted 2-azido acrylates with various steric and electronic properties. With respect to the substituent effect of the aryl ring of 2-azido acrylates, the electron-rich ones provided a slightly better yield than the electron-deficient ones. For benzyl-substituted 2-azido acrylate, the corresponding imidazole product **3u** was obtained in 42% yield, which is similar to our previous reports.[13] Instead of α-ethoxycarbonyl-substituted

vinyl azides, the reaction of vinyl azide bearing an acetyl or a formyl group at the α-position gave the desired products with lower yields.



Scheme 2. 1,2,4,5-Tetrasubstituted imidazoles prepared by three-component reaction.

Conclusions

In summary, we have developed a one-pot three-component reaction of hydroxylamines, aldehydes, and 2-azido acrylates, which afforded moderate to excellent yields of highly substituted imidazoles. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

Experimental Section

General. The ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 500 MHz spectrometer instruments in $CDCl_3$. The chemical shifts (δ) were measured in ppm and with the solvents as references (For $CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. All solvents were obtained from commercial sources and were purified according to standard procedures. Column chromatography was performed on silica gel (100-200 or 200-300 mesh) using petroleum ether and ethyl acetate as eluent. Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm). Melting points were uncorrected. The starting material **2**[10a,14] and **4**[15] were prepared according to literature methods. The imidazoles **3a**, **3d**, **3e**, **3g**, **3i**, **3k**, **3n-w** are known compounds and all spectroscopic data were in agreement with the literature.[13]

General procedure for the synthesis of 3

Hydroxylamines **4** (0.90 mmol), aldehydes **5** (0.90 mmol), and anhydrous $MgSO_4$ (150 mg), were dissolved in dry CH_3CN (10 mL) and stirred overnight. 2-azido acrylates **2** (0.30 mmol) were added under an argon atmosphere, and the mixture was heated to 65-70 °C for 72 h. After cooling to room temperature and being diluted with H_2O (20 mL), the product was extracted with EtOAc (10 mL × 3). The combined extracts were washed with H_2O (20 mL × 2) and brine (20 mL), dried over Na_2SO_4 and concentrated to a residue. The residue was purified on silica gel chromatography (ethyl acetate/petroleum ether) to afford imidazoles **3**.

Ethyl 2-(4-bromophenyl)-1-phenyl-4-p-tolyl-1*H*-imidazole-5-carboxylate (3b). White solid, mp 106-108 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.51-7.44 (m, 3 H), 7.40-7.35 (m, 2 H), 7.31-7.22 (m, 6 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 2.41 (s, 3 H), 0.97 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 148.6, 148.3, 138.2, 137.7, 131.9, 131.4, 130.8, 130.6, 129.4, 129.2, 129.1, 128.5, 128.3, 128.0, 123.6, 121.9, 60.6, 21.4, 13.6; MS (ESI): m/z $(M+H)^+$: 461.1; HRMS (ESI) Calcd for $C_{25}H_{22}BrN_2O_2$ $(M+H)^+$: 461.0859; Found: 461.0861.

Ethyl 2,4-bis(4-bromophenyl)-1-phenyl-1*H*-imidazole-5-carboxylate (3c). White solid, mp 194-195 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, *J* = 8.5 Hz, 2 H), 7.58 (d, *J* = 8.5 Hz, 2 H), 7.52-7.44 (m, 3 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.32-7.23 (m, 4 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 0.97 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.1, 148.8, 147.0, 137.6, 132.8, 131.4,

131.1, 131.0, 130.5, 129.2, 128.3, 127.9, 123.8, 122.6, 122.2, 60.7, 13.6; MS (ESI): m/z $(M+H)^+$: 525.0; HRMS (ESI) Calcd for $C_{24}H_{19}Br_2N_2O_2$ $(M+H)^+$: 524.9813; Found: 524.9818.

Ethyl 2-(4-fluorophenyl)-1,4-diphenyl-1*H*-imidazole-5-carboxylate (3f). White solid, mp 119-120 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (d, *J* = 7.0 Hz, 2 H), 7.48-7.36 (m, 8 H), 7.33-7.28 (m, 2 H), 6.92 (t, *J* = 9.0 Hz, 2 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 0.96 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.0, 162.0, 160.3, 148.9, 148.1, 137.7, 133.9, 131.1, 131.0, 129.4, 129.1, 129.0, 128.2, 128.0, 127.7, 125.8, 121.8, 115.3, 115.2, 60.5, 13.5; MS (ESI): m/z $(M+H)^+$: 387.2; HRMS (ESI) Calcd for $C_{24}H_{20}FN_2O_2$ $(M+H)^+$: 387.1509; Found: 387.1516.

Ethyl 2-phenyl-1,4-dip-tolyl-1*H*-imidazole-5-carboxylate (3h). White solid, mp 127-128 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 7.0 Hz, 2 H), 7.31-7.16 (m, 9 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 6 H), 1.01 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6, 149.8, 148.1, 138.8, 137.9, 135.3, 131.2, 129.8, 129.6, 129.4, 129.2, 128.9, 128.5, 128.1, 127.8, 121.6, 60.5, 21.4, 21.3, 13.7; MS (ESI): m/z $(M+H)^+$: 397.2; HRMS (ESI) Calcd for $C_{26}H_{25}N_2O_2$ $(M+H)^+$: 397.1916; Found: 397.1923.

Methyl 1-(4-chlorophenyl)-2,4-diphenyl-1*H*-imidazole-5-carboxylate (3j). White solid, mp 157-158 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, *J* = 7.0 Hz, 2 H), 7.48-7.38 (m, 7 H), 7.34-7.22 (m, 5 H), 3.60 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.8, 150.3, 148.6, 136.2, 134.9, 133.9, 129.4, 129.3, 129.2, 129.2, 128.4, 128.3, 127.9, 121.3, 51.4; MS (ESI): m/z $(M+H)^+$: 389.1; HRMS (ESI) Calcd for $C_{23}H_{18}ClN_2O_2$ $(M+H)^+$: 389.1057; Found: 389.1066.

Ethyl 4-(3,4-dimethoxyphenyl)-1-methyl-2-phenyl-1*H*-imidazole-5-carboxylate (3l). White solid, mp 115-116 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67-7.64 (m, 2 H), 7.52-7.44 (m, 3 H), 7.32-7.27 (m, 2 H), 6.89 (d, *J* = 9.0 Hz, 1 H), 4.27 (q, *J* = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.91 (s, 6 H), 1.24 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.3, 151.3, 149.0, 148.6, 148.1, 129.8, 129.6, 128.6, 127.3, 122.6, 111.9, 113.0, 110.3, 60.6, 55.9, 35.1, 14.1; MS (ESI): m/z $(M+H)^+$: 367.2; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O_4$ $(M+H)^+$: 367.1658; Found: 367.1658.

Ethyl 4-(4-bromophenyl)-1-methyl-2-phenyl-1*H*-imidazole-5-carboxylate (3m). White solid, mp 106-107 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67-7.62 (m, 2 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 7.50-7.46 (m, 3 H), 4.27 (q, *J* = 7.0 Hz, 2 H), 3.93 (s, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.0, 151.6, 147.5, 133.6, 131.4, 130.7, 129.7, 129.5, 128.7, 122.2, 120.3, 60.7, 35.1, 14.0; MS (ESI): m/z $(M+H)^+$: 385.1; HRMS (ESI) Calcd for $C_{19}H_{18}BrN_2O_2$ $(M+H)^+$: 385.0552; Found: 385.0547.

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