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Catalyst-Free Preparation of 1,2,4,5-Tetrasubstituted Imidazoles from a Novel Unexpected Domino Reaction of 2-Azido Acrylates and Nitrones

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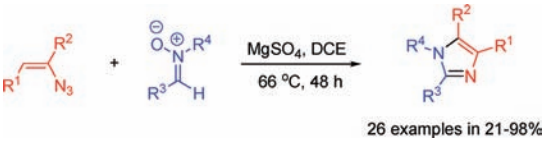
ABSTRACT



A highly efficient and convenient method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles from readily accessible 2-azido acrylates and nitrones has been developed. This reaction proceeded under mild conditions without the assistance of any metal, acid, or base.

Imidazoles are an important class of N-heterocycles that are finding many diverse applications,[1] with examples including drug cores (e.g., angiotensin II inhibitors,[2a] antiinflammatory,[2b] and anticancer[2c] agents), natural products,[3] conjugated and functional polymers,[4] coordination complexes,[5] important ligands in metalloenzymes,[6] precursors of stable carbene ligands,[7] and ionic liquids.[8] This versatile applicability highlights the importance of access to efficient synthetic routes to prepare imidazole derivatives.[9] Traditional methods[1] for imidazole core synthesis include cyclocondensation reactions between α-diketones, α-haloketones (or their derivatives), and formamide (Bredereck synthesis);[10] the reaction of α-diketones with aldehydes and ammonia (Debus–Radziszewski reaction);[11] the reaction of α-haloketones with amidines;[12] and the base-promoted reaction of *p*-tosylmethyl isocyanide and aldimines or imidoyl chlorides (van Leusen reaction).[13] However, many of these reaction conditions require the use of a strong base or high

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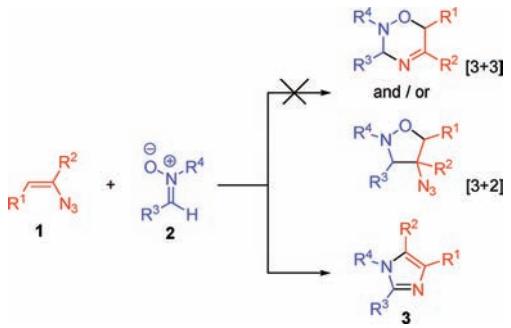
temperature or produce acids as byproducts. As such, a range of new synthetic routes,[9] including stepwise substitution reactions on simple imidazoles,[14] and catalytic cyclizations from acyclic precursors,[15] have been developed, many of which can provide easy access to these products. However, there are still some limitations associated with these methods, such as use of corresponding imidazoles as a starting material; inaccessible synthetic precursors; and hazardous, toxic, special, and often expensive reagent or transition-metal catalysts. Thus, the discovery of new, direct, and general synthetic routes to such heterocycles remains a formidable challenge.

As remarkably versatile intermediates in modern organic synthesis, azides participate in a wide range of reactions that construct new carbon−nitrogen or nitrogen−heteroatom bonds.[16] Recently, much attention has been focused toward applying 2-azido acrylates as a pivotal three-atom synthon for the formation of diverse nitrogen-containing heterocycles including indoles, pyridines, pyrroles, isoquinolines, 1,2,4-triazolines, pyrrolo[1,2-α]-pyrazines, and pyrazoles, which have been synthesized with the assistance of meal salt,[17] triphenylphosphine,[18] or base.[19] Inspired by these results and with the interest of developing a new type of [3 + 3] cycloaddition of nitrones,[20] we investigated the reaction of 2-azido acrylates **1** and nitrones **2**. Quite surprisingly, instead of the anticipated [3 + 3] cycloaddition products and/or the possible [3 + 2] cycloaddition[21] side products, we observed an unexpected domino process leading to 1,2,4,5-tetrasubstituted imidazoles **3** under catalyst-free conditions (Scheme 1). To the best of our knowledge, only a few one-step, noncatalytic reactions which produce highly substituted imidazoles have been reported.[9,22] Herein, we wish to report our recent results.

Scheme 1. A Domino Process Leading to 1,2,4,5-Tetrasubstituted Imidazoles **3**



Initially, we examined the reaction of 2-azido acrylate **1a** (1.0 equiv) with nitrone **2a** (1.5 equiv) in 1,2-dichloroethane (DCE) at 50 °C for 24 h and obtained the imidazole **3aa** in 23% yield together with the recovery of 51% of **1a** (Table 1, entry 1). Further screening of the solvents, reaction temperature, and time (entries 2−16) established the optimal reaction conditions: 3.0 equiv of **2a** and use of anhydrous $MgSO_4$ (4.0 equiv) as an additive in DCE at 66 °C for 48 h with 96% yield of **3aa** (entry 11). The structure of **3aa** was established by spectroscopic analysis and further confirmed by single-crystal X-ray analysis (Figure 1).[23]

Since 2-azido acrylates[24] and nitrones[25] are readily available, the domino approach to imidazoles is highly appealing. We, therefore, extended the substrate scope to various 2-azido acrylates **1** and nitrones **2** using the optimized conditions. As presented in Table 2, various substituted 2-azido acrylates **1** with nitrone **2a** worked well

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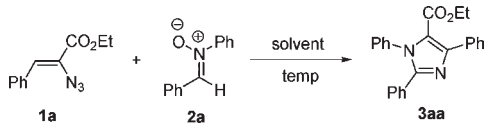
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	conversion (%)[b]	yield (%)[c]
1	DCE	50	24	49	23
2	DCE	60	36	75	66
3	EtOAc	60	36	73	65
4	THF	60	36	83	55
5	DMF	60	36	67	58
6	DCE	66	24	80	67
7[d]	DCE	80	24	29	22
8	DCE	66	36	82	77
9	DCE	66	48	88	83
10[e]	DCE	66	48	>95	87
11[e,f]	**DCE**	**66**	**48**	**>95**	**96**
12[e,f]	DCE	70	48	>95	93
13[e,f]	DCE	83	17	>95	44
14[e,g]	DCE	66	48	>95	37
15[e,h]	DCE	66	48	>95	71
16[e,i]	DCE	66	48	>95	<20

[a] Reaction conditions, unless otherwise stated: 2-azido acrylate **1a** (0.30 mmol, 1.0 equiv), nitrone **2a** (0.45 mmol, 1.5 equiv), 5.0 mL of solvent, Ar atmosphere. [b] Determined by recovered **1a**. [c] Isolated yields based on **1a**. [d] Nitrone **2a** was consumed. [e] 3.0 equiv of **2a** was added. [f] Anhydrous $MgSO_4$ (150 mg) was added as an additive. [g] 4 Å molecular sieves (150 mg) was added as an additive. [h] Anhydrous $MgSO_4$ (50 mg). [i] Anhydrous $MgSO_4$ (200 mg).

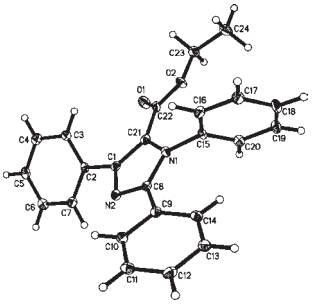
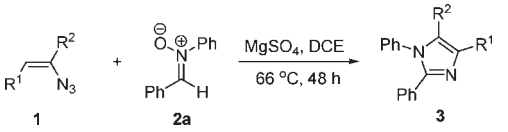


Figure 1. ORTEP drawing of **3aa**.

to provide the corresponding 1,2,4,5-tetrasubstituted imidazoles **3** in moderate to excellent yields. The reaction could tolerate aromatic substituted 2-azido acrylates with various steric and electronic properties (entries 1−11). Notably, excellent yields of imidazoles were obtained for both **1b** bearing a strong electron-donating group (entry 2) and **1h** bearing a strong electron-withdrawing group (entry 8). The retarding effect of sterics on the reaction is illustrated in entry

Table 2. Reactions of Various 2-Azido Acrylates **1** with Nitrones **2a**[a]



entry	**1**	R^1	R^2	product **3**	yield (%)[b]
1	**1a**	C_6H_5	CO_2Et	**3aa**	96
2	**1b**	3,4,5-tri-$MeOC_6H_2$	CO_2Et	**3ba**	98
3	**1c**	3,4-di-$MeOC_6H_3$	CO_2Et	**3ca**	98
4	**1d**	*p*-$MeOC_6H_4$	CO_2Et	**3da**	95
5	**1e**	*p*-$CH_3C_6H_4$	CO_2Et	**3ea**	95
6	**1f**	*p*-BrC_6H_4	CO_2Et	**3fa**	91
7	**1g**	*p*-FC_6H_4	CO_2Et	**3ga**	90
8	**1h**	*p*-$CF_3C_6H_4$	CO_2Et	**3ha**	91
9	**1i**	*o*-$MeOC_6H_4$	CO_2Et	**3ia**	83
10	**1j**	*m*-MeC_6H_4	CO_2Et	**3ja**	96
11	**1k**	*m*-ClC_6H_4	CO_2Et	**3ka**	98
12	**1l**	$C_6H_5CH_2$	CO_2Et	**3la**	41
13	**1m**	C_6H_5	CO_2Me	**3ma**	97
14	**1n**	C_6H_5	COMe	**3na**	98
15	**1o**	C_6H_5	CHO	**3oa**	88
16[c,d]	**1p**	H	C_6H_5	**3pa**	0

[a] Reaction conditions, unless otherwise stated: 2-azido acrylates **1** (0.30 mmol, 1.0 equiv), nitrone **2a** (0.90 mmol, 3.0 equiv), anhydrous $MgSO_4$ (150 mg), DCE (5.0 mL) at 66 °C, Ar atmosphere. [b] Isolated yields based on **1**. [c] 2-Azido acrylate **1P** was consumed. [d] Reaction was carried out at 40 and 66 °C respectively.

9 where ortho substituents on the aryl ring gave a slightly reduced yield (83%), compared to entry 4 (95%). For alkyl substituted 2-azido acrylate **1l**, the corresponding imidazole product **3la** was obtained in 41% yield (entry 12). Instead of 2-azido acrylates, both 3-azido but-3-en-2-one **1n** and 2-azido acrylaldehyde **1o** worked well to give the corresponding products in 98% and 88% yields (entries 14 and 15). However, when α-azidostyrene **1p** was subjected to reaction conditions, no imidazole formation was observed (entry 16).

Further studies revealed that the reactions of a variety of nitrones **2** with 2-azido acrylate **1a** also proceeded smoothly to give the corresponding products **3ab**−**al** in 21−98% yields (Table 3, entries 1−11). It should be noted that substrate **2i** with methyl substituted at the 2-position on the aryl ring gave the desired product **3ai** in 84% yield (entry 8). When applied to the cyclic nitrone **2l**, the reaction also proceeded smoothly to give the corresponding imidazole derivative **3al** in 21% yield under identical reaction conditions (entry 11).

To understand the mechanism of the domino process, 2*H*-azirine **4**[26] prepared by thermolysis of 2-azido acrylate **1e** was used instead of **1e** to perform the reaction (Scheme 2). We found that it did not follow the same reaction as **1e**, and we did not obtain the desired imidazole product **3ea**. These

(25) For synthesis of nitrones, see: (a) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (b) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (c) Beckmann, E. *Justus Liebigs Ann. Chem.* **1909**, *365*, 201. (d) Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.

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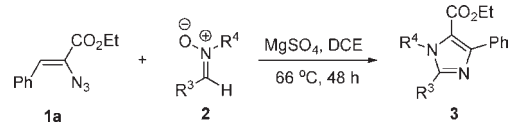
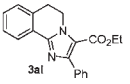
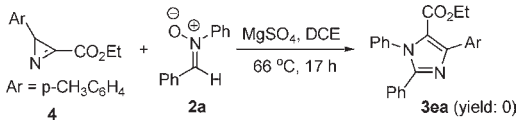
Table 3. Reactions of 2-Azido Acrylate **1a** with Several Nitrones **2**[a]



entry	2	R^3	R^4	product 3	yield (%)[b]
1	**2b**	*p*-$MeOC_6H_4$	C_6H_5	**3ab**	98%
2	**2c**	*p*-$CH_3C_6H_4$	C_6H_5	**3ac**	92%
3	**2d**	*p*-BrC_6H_4	C_6H_5	**3ad**	80%
4	**2e**	2-furyl	C_6H_5	**3ae**	96%
5	**2f**	C_6H_5	*p*-ClC_6H_4	**3af**	94%
6	**2g**	C_6H_5	*m*-ClC_6H_4	**3ag**	94%
7	**2h**	C_6H_5	*p*-$CH_3C_6H_4$	**3ah**	98%
8	**2i**	C_6H_5	*o*-$CH_3C_6H_4$	**3ai**	84%
9	**2j**	C_6H_5	CH_3	**3aj**	91%
10[c]	**2k**	C_6H_5	$C_6H_5CH_2$	**3ak**	46%
11					21%

[a] Reaction conditions: 2-azido acrylate **1a** (0.30 mmol, 1.0 equiv), nitrones **2** (0.90 mmol, 3.0 equiv), anhydrous $MgSO_4$ (150 mg), DCE (5.0 mL) at 66 °C, Ar atmosphere. [b] Isolated yields based on **1a**. [c] After 57 h.

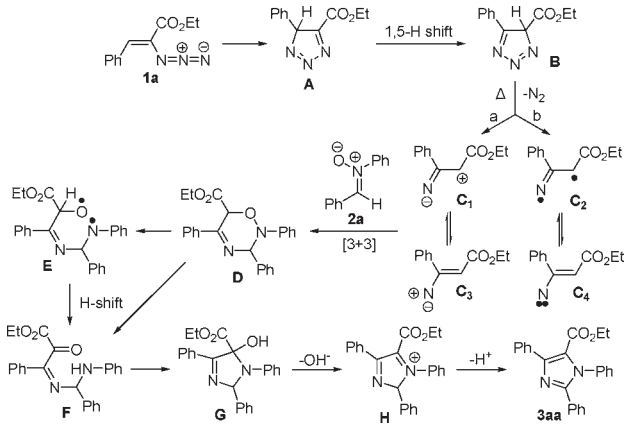
Scheme 2. Reaction of 2*H*-Azirine **4** and Nitrone **2a**



results suggest that the present reaction does not undergo the 2*H*-azirine intermediate. Further investigation implied that the reaction might go on via free radical species, which was supported by the case that no imidazole product **3aa** was obtained with the addition of a radical-trapping compound, 2,6-di-*tert*-butyl-4-methylphenol (1.0 equiv), in the domino reaction of 2-azido acrylate **1a** and nitrone **2a**.

On the basis of these results, a tentative mechanism for the domino reaction is proposed in Scheme 3. Initially, intramolecular cyclization of 2-azido acrylate **1a** takes place to form a triazoline **A**,[27] which undergoes 1,5-hydrogen shift processes to give a triazoline **B**. The zwitterionic intermediate $\mathbf{C_1}$[28] (path a) or biradical intermediate $\mathbf{C_2}$[29] (path b) is in situ generated from the triazoline intermediate **B** by thermal elimination of dinitrogen. The intermediate $\mathbf{C_1}$ presumably exists in one resonance form $\mathbf{C_3}$. The intermediate $\mathbf{C_2}$ might also stand in one

Scheme 3. A Plausible Mechanism for the Formation of **3aa**



resonance form $\mathbf{C_4}$. It is believed that the key intermediate **C** undergoes a former [3 + 3] cycloaddition with nitrone **2a** via the zwitterionic pathway or the two-electron processes, giving intermediate **D** with high regioselectivity. Then, the intermediate **D** undergoes a thermally induced homolytic cleavage of the N−O bond,[30] followed by the hydrogen shift resulting in the formation of 5-amino ketomalonate **F**. **D** might also directly convert to **F**. The intermediate **G** is readily obtained via an intramolecular cyclization through nucleophilic addition of the amino nitrogen to the carbonyl group. Finally, dehydration of intermediate **G** would afford the desired product **3aa**. Further investigation into the mechanism is currently underway.

In conclusion, we have developed a new and efficient strategy to prepare highly substituted imidazoles in moderate to excellent yields. This reaction was realized through a novel domino process from readily available 2-azido acrylates and nitrones. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

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Supporting Information Available. Detailed description of experimental procedures, ^1H and ^{13}C NMR spectra of the compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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