ORGANIC LETTERS

2011
Vol. 13, No. 24
6362–6365

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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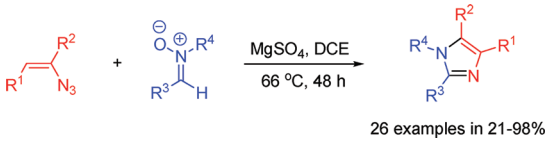
Received September 30, 2011

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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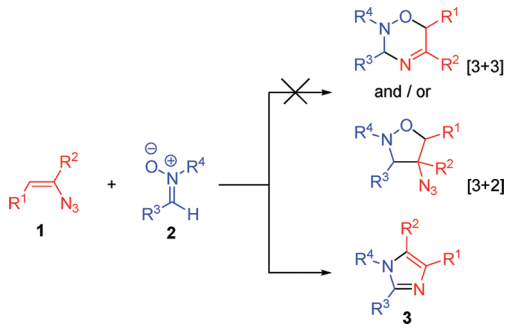
10.1021/ol202650z
Published on Web 11/09/2011

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]

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



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.

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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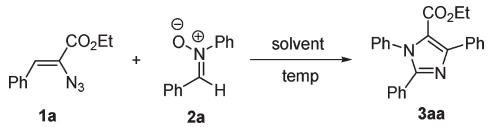
Table 1. Optimization of Reaction Conditions[a]



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).

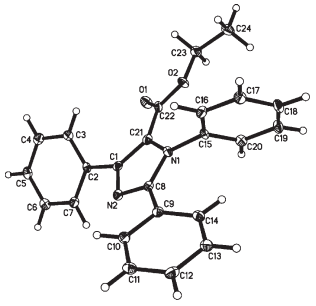
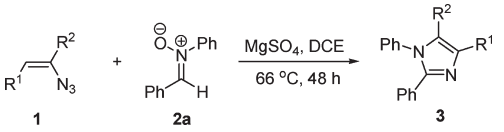


Figure 1. ORTEP drawing of **3aa**.

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).

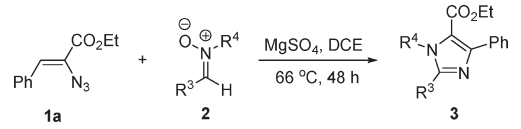
Further studies revealed that the reactions of a variety of nitrones **2** with 2-azido acrylate **1a** also proceeded smoothly to give the corresponding products **3ab**−**al** in 21−98% yields (Table 3, entries 1−11). It should be noted that substrate **2i** with methyl substituted at the 2-position 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).

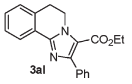
To understand the mechanism of the domino process, 2*H*-azirine **4**[26] prepared by thermolysis of 2-azido acrylate **1e** was used instead of **1e** to perform the reaction (Scheme 2). We found that it did not follow the same reaction as **1e**, and we did not obtain the desired imidazole product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

(26) For synthesis of 2*H*-azirine, see: (a) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 205. (b) Knittel, D. *Synthesis* **1985**, 186. (c) Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189. (d) Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 299.

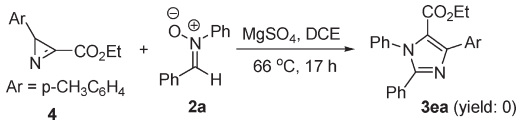
Table 3. Reactions of 2-Azido Acrylate **1a** with Several Nitrones **2**[a]



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.

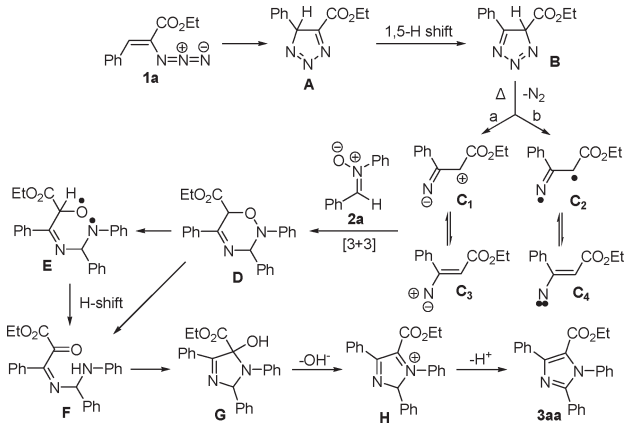
Scheme 2. Reaction of 2*H*-Azirine **4** and Nitrone **2a**



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.

Acknowledgment. We thank the starter grant from Zhejiang University of Technology (56710108007), the Science and Technology Project of Zhejiang Province (Y201121893), the National Natural Science Foundation of China (No. 21006095), and the Natural Science Foundation of Zhejiang Province (Y4100680) for financial support. Dr. Xiaoliang Xu (College of Chemical Engineering and Materials, Zhejiang University of Technology) are kindly acknowledged for helpful discussions. Manuscript revision by Dr. Ding Du at China Pharmaceutical University is also gratefully acknowledged.

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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