ORGANIC LETTERS

2008
Vol. 10, No. 1
13−16

Facile Access to Pyrazolines via Domino Reaction of the Huisgen Zwitterions with Aziridines

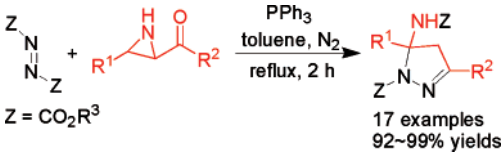
Sun-Liang Cui, Jing Wang, and Yan-Guang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

orgwyg@zju.edu.cn

Received September 24, 2007

ABSTRACT



A novel, efficient, and general domino reaction of 2-acylaziridines with the Huisgen zwitterions to furnish 2-pyrazoline rings is described. A possible mechanism for the domino sequence is proposed.

2-Pyrazolines are a medicinally important class of heterocyclic small molecules that have shown potential bioactivity in numerous screening tests.[1] A number of compounds containing the pyrazoline core have been examined for antidepressant activity through screening against monoamine oxidases,[2] treatment of obesity as cannabinoid-1 antagonists,[3] antiviral activity against the West Nile virus,[4] and multidrug resistance modulators in tumor cells.[5] Pyrazolines are also synthetically useful scaffolds in organic chemistry.[6] The 1,3-dipolar cycloaddition reaction is a classical and widely used method for the construction of 2-pyrazolines.[7]

Triphenylphosphine and dialkyl azodicarboxylates were utilized as the redox couple for the formation of Huisgen zwitterion,[8] which plays an important role in the Mitsunobu reaction.[9] Recently, it was reported that the Huisgen zwitterion reacted with carbonyl compounds to afford various products.[10] Very recently, Nair and co-workers used this zwitterion to synthesize *N*,*N*-dicarboethoxy monohydrazones,

(1) (a) Manyem, S.; Sibi, M. P.; Lushington, G. H.; Neuenswander, B.; Schoenen, F.; Aube, J. *J. Comb. Chem.* **2007**, *9*, 20−28. (b) Schreiber, S. L. *Nat. Chem. Biol.* **2005**, *1*, 64−66. (c) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472−482. (d) Camacho, M. E.; Leon, J.; Entrena, A.; Velasco, G.; Carrion, M. D.; Escames, G.; Vivo, A.; Acuna-Castroviejo, D.; Gallo, M. A.; Espinosa, A. *J. Med. Chem.* **2004**, *47*, 5641−5650. (e) Camacho, E.; Leon, J.; Carrion, A.; Entrena, A.; Escames, G.; Khaldy, H.; Acuna-Castroviejo, D.; Gallo, M. A.; Espinosa, A. *J. Med. Chem.* **2002**, *45*, 263−274.

(2) (a) Chimenti, F.; Bolasco, A.; Manna, F.; Secci, D.; Chimenti, P.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B.; Cirilli, R.; La Torre, F. *J. Med. Chem.* **2004**, *47*, 2071−2074. (b) Rajendra Prasad, Y.; Lakshmana Rao, A.; Prasoona, L.; Murali, K.; Ravi Kumar, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030−5034.

(3) Lange, J. H. M.; van Stuivenberg, H. H.; Veerman, W.; Wals, H. C.; Stork, B.; Coolen, H. K. A. C.; McCreary, A. C.; Adolfs, T. J. P.; Kruse, C. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4794−4798.

(4) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.-Y.; Ferguson, D. M. *J. Med. Chem.* **2006**, *49*, 2127−2137.

(5) Manna, F.; Chimenti, F.; Fioravanti, R.; Bolasco, A.; Secci, D.; Chimenti, P.; Ferlini, C.; Scambia, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4632−4635.

(6) (a) Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4265−4267. (b) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955−3957. (c) Ruano, J. L. G.; de Diego, S. A. A.; Martín, M. R.; Torrente, E.; Castro, A. M. M. *Org. Lett.* **2004**, *6*, 4945−4948.

(7) (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174−2175. (b) Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 11279−11282. (c) Chen, Y.; Lam, Y. L.; Lai, Y. H. *Org. Lett.* **2003**, *5*, 1067−1069. (d) Simovic, D.; Di, M.; Marks, V.; Chatfield, D. C.; Rein, K. S. *J. Org. Chem.* **2007**, *72*, 650−653. (e) Mish, M.; Guerra-Martinez, F.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379−8380. (f) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253−1256.

(8) (a) Huisgen, R. In *The Adventure Playground of Mechanisms and Novel Reactions*: *Profiles, Pathways and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1994; p 62. (b) Huisgen, R.; Blaschke, H.; Brunn, E. *Tetrahedron Lett.* **1966**, *7*, 405. (c) Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 513- 515.

(9) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughs, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127−164. (c) Prakash, G. K. S.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4933−4936.

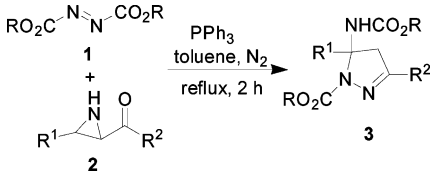
(10) Otte, R. D.; Sakata, T.; Guzei, I. A.; Lee, D. *Org. Lett.* **2005**, *7*, 495−498.

10.1021/ol7022888 CCC: $40.75
Published on Web 12/07/2007

dihydro-1,2,3-benzoxadiazoles, and functionalized pyrazole, pyrazoline, as well as pyrazolopyridazine derivatives.[11] Inspired by these works and as a part of our continuing program on development of domino reactions,[12] we are interested in the domino reaction of Huisgen zwitterion with 2-acylaziridines. We anticipated that the in situ generated Huisgen zwitterion could be intercepted by the carbonyl group of 2-acylaziridine, followed by an intramolecular domino process to construct a class of 2-pyrazolines.

In our initial investigations, we found that diethyl azodicarboxylate (**1a**) reacted with triphenylphosphine and 2-acylaziridine **2a** to yield quantitatively pyrazoline **3aa** when the reaction was performed in toluene and refluxed for 2 h (Table 1, entry 1). Benzene also worked effectively as the solvent, affording **3aa** in 95% yield (see the Supporting Information).

Table 1. Synthesis of Pyrazolines via Domino Reaction of Huisgen Zwitterions with Aziridines[a]



entry	R^1	R^2	R	product	yield (%)[b]
1	C_6H_5	C_6H_5	Et	**3aa**	99
2	C_6H_5	C_6H_5	*i*-Pr	**3ab**	98
3	C_6H_5	C_6H_5	*t*-Bu	**3ac**	98
4	3,4-$Me_2C_6H_3$	C_6H_5	Et	**3ba**	98
5	3,4-$Me_2C_6H_3$	C_6H_5	*i*-Pr	**3bb**	96
6	4-ClC_6H_4	C_6H_5	Et	**3ca**	95
7	4-ClC_6H_4	C_6H_5	*i*-Pr	**3cb**	94
8	2-furyl	C_6H_5	Et	**3da**	92
9	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	Et	**3ea**	98
10	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	*i*-Pr	**3eb**	98
11	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	*t*-Bu	**3ec**	97
12	3,4-$(OCH_2O)C_6H_3$	2-ClC_6H_4	*i*-Pr	**3fa**	95[c]
13	2-naphthyl	2-ClC_6H_4	*i*-Pr	**3ga**	98
14	2-naphthyl	2-ClC_6H_4	*t*-Bu	**3gb**	98
15	C_6H_5	3-$O_2NC_6H_4$	Et	**3ha**	99
16	C_6H_5	3-$O_2NC_6H_4$	*i*-Pr	**3hb**	98
17	C_6H_5	3-$O_2NC_6H_4$	*t*-Bu	**3hc**	98

[a] Reaction conditions: dialkyl azodicarboxylate **1** (1.3 mmol), aziridine **2** (1 mmol), PPh_3 (1.3 mmol), toluene, reflux, 2 h. [b] Isolated yields refer to aziridines. [c] Reaction was performed at rt for 8 h.

With suitable reaction conditions in hand, we next focused our attention on exploring the scope using a variety of aziridines **2** (Table 1, entries 2−17), which were easily synthesized from the corresponding chalcones according to a previous report by Shi.[13] In all of our cases, both the electron-donating and electron-withdrawing group substituted aziridines **2** reacted with the zwitterions to give the corresponding pyrazolines **3** in excellent yields, exhibiting a remarkable efficiency.

The two hydrogen atoms at the CH_2 group of the pyrazoline ring determined by ^1H NMR spectrum resonate as two doublets displaying ^1H resonance signals at about 3.39 and 4.49 ppm, respectively, and their coupling constants exceed 17 Hz.[14] The structure of **3ha** was firmly established by X-ray analysis (Figure 1).

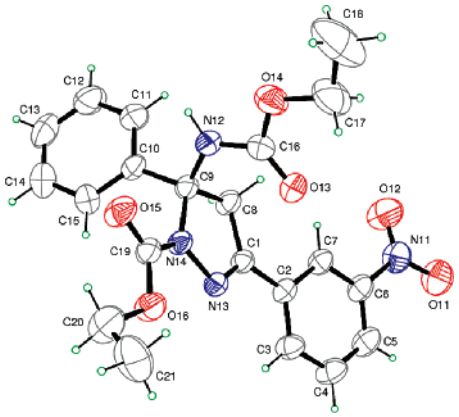
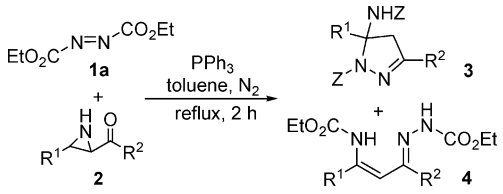


Figure 1. Crystal structure of **3ha**.

It is interesting that the reaction of **1a** with aziridine **2g** or **2i** afforded pyrazoline **3gc** or **3ia** along with hydrazone **4a** or **4b**, respectively (Table 2). We also found that products

Table 2. Synthesis of Pyrazolines **3** and Hydrazones **4**[a]



entry	R^1/R^2	product/yield (%)[b]
1	2-naphthyl/2-ClPh (**2g**)	**3gc**/35 + **4a**/60
2	4-PhC_6H_4/2-MePh (**2i**)	**3ia**/31 + **4b**/65

[a] Reaction conditions: aziridine (1 mmol), dialkyl azodicarboxylate (1.3 mmol), PPh_3 (1.3 mmol), toluene, reflux, 2 h. [b] Isolated yields refer to aziridines.

3 and **4** were stable in toluene and could not transform each other even in the presence of PPh_3 and **1a** under reflux conditions. The structure **4a** was unambiguously confirmed by crystal X-ray analysis (see the Supporting Information).

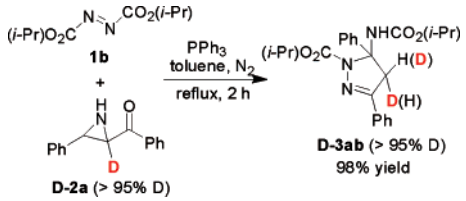
(11) (a) Nair, V.; Biju, A. T.; Abhilash, K. G.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2121−2123. (b) Nair, V.; Biju, A. T.; Vinod, A. U.; Suresh, E. *Org. Lett.* **2005**, *7*, 5139−5142. (c) Nair, V.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213−2216. (d) Nair, V.; Mathew, S. C.; Biju, A. T.; Suresh, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2070−2073.

(12) (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517−4520. (b) Wang, Y. G.; Cui, S. L.; Lin, X. F. *Org. Lett.* **2006**, *8*, 1241−1244. (c) Cui, S. L.; Lin. X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866−2869. (d) Cui, S. L.; Wang, J.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2007**, *72*, 7779−7782.

(13) Shen, Y. M.; Zhao, M. X.; Xu, J. X.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005−8008.

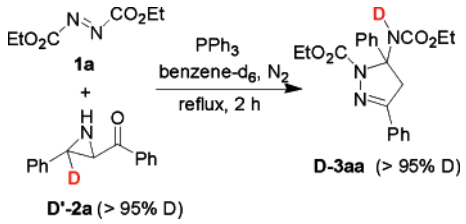
To view insight into the reaction mechanism, we conducted two deuterium-labeling experiments, i.e., the reaction of deuterated aziridine **D-2a** (>95% D) with **1b** (Scheme 1)

Scheme 1. The Deuterium-Labeling Experiment A



and the reaction of deuterated aziridine **D′-2a** (>95% D) with **1a** (Scheme 2). In the first case, we isolated the

Scheme 2. The Deuterium-Labeling Experiment B



deuterated product **D-3ab** (>95% D) in 98% yield. In the second case, we obtained the deuterated product **D-3aa** (>95% D) in quantitative conversion.[15]

On the basis of these results we depicted our current working hypothesis in Scheme 3. The formation of a strained five-membered ring can be rationalized as being initiated by the combination of PPh_3 and diethyl azodicarboxylate **1** to Huisgen zwitterion **A**. **A** undergoes addition to the carbonyl group of 2-acylaziridine **2** to form **B**, which subsequently cyclizes to **C**. Then the resulting **C** decomposes to triphenylphosphine oxide and the oxadiazoline **D**,[16] followed by an intramolecular addition reaction to **E** and a subsequent proton migration to **F**. The high strained fusion ring **F** expands to **G** and then opens to **H**. Two possibilities for the next steps remain. One possibility is that **H** undergoes an intramolecular Michael-type addition to afford pyrazoline **3** (path a). The other possibility is the formation of **4** via a proton migration (path b).

The utility of the domino reaction of Huisgen zwitterions with aziridines for facile access to pyrazolines was immediately realized in an ideal transformation to pyrazoles. As shown in Table 3, the pyrazolines **3** underwent elimination to afford pyrazoles **5** or **6** in excellent yields.

In conclusion, we have developed a novel and general domino reaction of 2-acylaziridines with the Huisgen zwitterions to furnish pyrazoline rings in excellent yields. A possible mechanism for the domino sequence is proposed, and the evidence has been established by isolation of some byproducts and the deuterium-labeling experiments. Furthermore, the resulting pyrazolines could be easily converted to pyrazoles. Therefore, the present methodology extends promise for a convenient synthetic protocol for the preparation of pyrazoline and pyrazole compounds.

Scheme 3. Proposed Mechanism for the Formation of Pyrazolines **3** and Hydrazones **4**

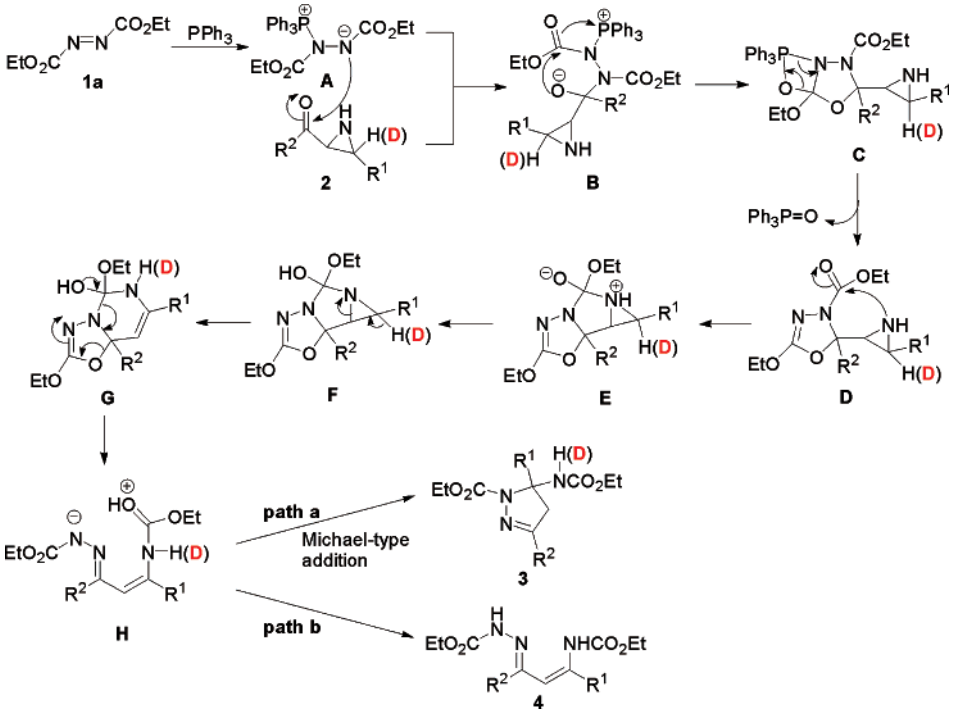
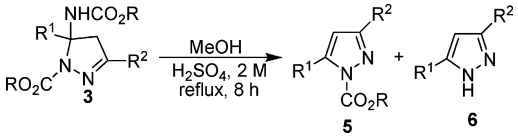


Table 3. Synthesis of Pyrazoles from Pyrazolines **3**[a]



				product/yield (%)[b]	
entry	R^1	R^2	R	**5**	**6**
1	4-ClC_6H_4	Ph	Et	**5a**/91	
2	3,4-$(OCH_2O)C_6H_3$	2-ClC_6H_4	*i*-Pr	**5b**/85	
3	2-naphthyl	2-ClC_6H_4	*i*-Pr	**5c**/83	
4	Ph	3-$O_2NC_6H_4$	*t*-Bu		**6a**/90

[a] Reaction conditions: **3** (0.5 mmol), 2 M H_2SO_4 (1.5 mmol), MeOH (5 mL), reflux, 8 h. [b] Yields refer to **3**.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20672093) and the 973 Project of Ministry of Science and Technology (No. 2002CB 713808).

Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^1H and ^{13}C NMR spectra for all products, and crystallographic information files (CIF) for compounds **3ha** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7022888

(14) For similar details of the ^1H NMR spectrum of the methylene group of the strained pyrazoline ring scaffold, see ref 7.

(15) The reaction was performed in benzene-d_6. After the reaction was completed, the resulting solution containing **D**-**3aa** was directly subjected to ^1H NMR analysis.

(16) We have isolated the resulting triphenylphosphine oxide as a byproduct. For similar domino processes, see ref 11.