

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

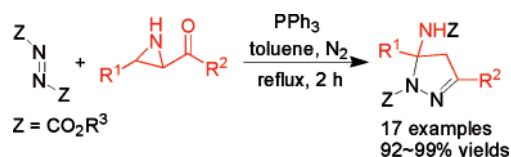
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ABSTRACT



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,

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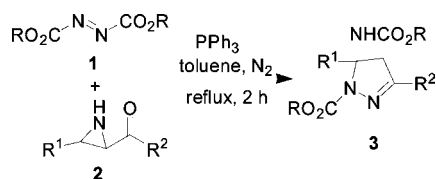
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dihydro-1,2,3-benzoxadiazoles, and functionalized pyrazole, pyrazoline, as well as pyrazolopyridazine derivatives.¹¹ Inspired by these works and as a part of our continuing program on development of domino reactions,¹² we are interested in the domino 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 ₆ H ₅	C ₆ H ₅	Et	3aa	99
2	C ₆ H ₅	C ₆ H ₅	<i>i</i> -Pr	3ab	98
3	C ₆ H ₅	C ₆ H ₅	<i>t</i> -Bu	3ac	98
4	3,4-Me ₂ C ₆ H ₃	C ₆ H ₅	Et	3ba	98
5	3,4-Me ₂ C ₆ H ₃	C ₆ H ₅	<i>i</i> -Pr	3bb	96
6	4-ClC ₆ H ₄	C ₆ H ₅	Et	3ca	95
7	4-ClC ₆ H ₄	C ₆ H ₅	<i>i</i> -Pr	3cb	94
8	2-furyl	C ₆ H ₅	Et	3da	92
9	4-O ₂ NC ₆ H ₄	4-MeOC ₆ H ₄	Et	3ea	98
10	4-O ₂ NC ₆ H ₄	4-MeOC ₆ H ₄	<i>i</i> -Pr	3eb	98
11	4-O ₂ NC ₆ H ₄	4-MeOC ₆ H ₄	<i>t</i> -Bu	3ec	97
12	3,4-(OCH ₂ O)C ₆ H ₃	2-ClC ₆ H ₄	<i>i</i> -Pr	3fa	95 ^c
13	2-naphthyl	2-ClC ₆ H ₄	<i>i</i> -Pr	3ga	98
14	2-naphthyl	2-ClC ₆ H ₄	<i>t</i> -Bu	3gb	98
15	C ₆ H ₅	3-O ₂ NC ₆ H ₄	Et	3ha	99
16	C ₆ H ₅	3-O ₂ NC ₆ H ₄	<i>i</i> -Pr	3hb	98
17	C ₆ H ₅	3-O ₂ NC ₆ H ₄	<i>t</i> -Bu	3hc	98

^a Reaction conditions: dialkyl azodicarboxylate **1** (1.3 mmol), aziridine **2** (1 mmol), PPh₃ (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

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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 CH₂ 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).

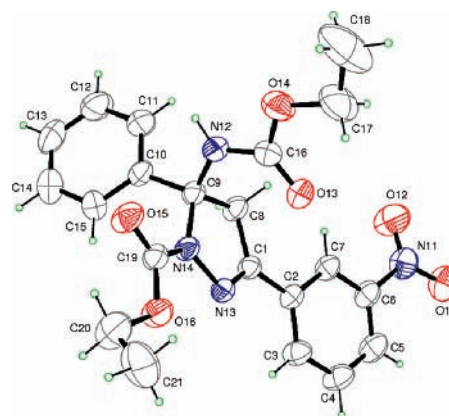
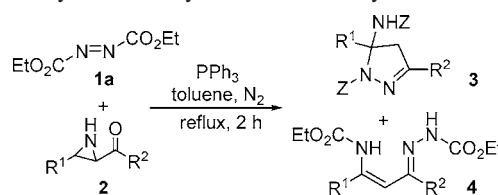


Figure 1. Crystal structure of **3ha**.

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 ₆ H ₄ /2-MePh (2i)	3ia /31 + 4b /65

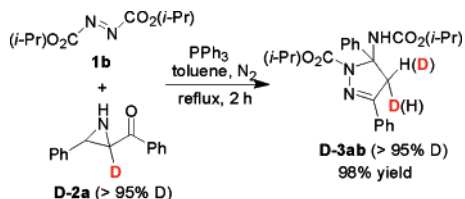
^a Reaction conditions: aziridine (1 mmol), dialkyl azodicarboxylate (1.3 mmol), PPh₃ (1.3 mmol), toluene, reflux, 2 h. ^b Isolated yields refer to aziridines.

3 and **4** were stable in toluene; and could not transform each other even in the presence of PPh₃ and **1a** under reflux conditions. The structure **4a** was unambiguously confirmed by crystal X-ray analysis (see the Supporting Information).

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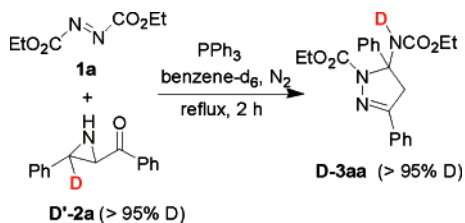
To view insight into the reaction mechanism, we conducted two deuterium-labeling experiments, i.e., the reaction of deuterated aziridine **D-2a** (>95% D) with **1b** (Scheme 1)

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**

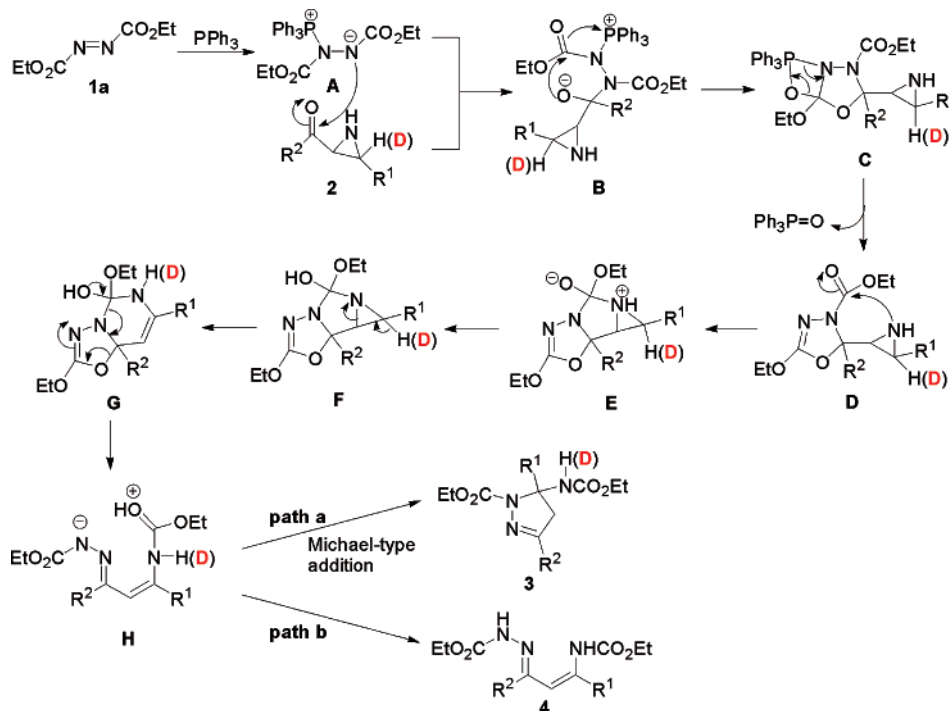
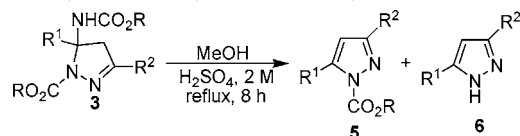


Table 3. Synthesis of Pyrazoles from Pyrazolines **3**^a



entry	R ¹	R ²	R	product/yield (%) ^b	
				5	6
1	4-ClC ₆ H ₄	Ph	Et	5a /91	
2	3,4-(OCH ₂ O)C ₆ H ₃	2-ClC ₆ H ₄	<i>i</i> -Pr	5b /85	
3	2-naphthyl	2-ClC ₆ H ₄	<i>i</i> -Pr	5c /83	
4	Ph	3-O ₂ NC ₆ H ₄	<i>t</i> -Bu		6a /90

^a Reaction conditions: **3** (0.5 mmol), 2 M H₂SO₄ (1.5 mmol), MeOH (5 mL), reflux, 8 h. ^b Yields refer to **3**.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ¹H and ¹³C 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>.

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(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.