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Double Isocyanide Cyclization: A Synthetic Strategy for Two-Carbon-Tethered Pyrrole/Oxazole Pairs

Yifei Li, Xianxiu Xu,* Jing Tan, Chunyu Xia, Dawei Zhang, and Qun Liu*

Department of Chemistry, Northeast Normal University, Changchun 130024, China

Supporting Information

ABSTRACT: A new strategy for the construction of the compounds with two different heterocycles, linked by a C_2-tether via a domino process involving [5 + 1] annulation, ring-opening, and subsequent double isocyanide cyclization, from the reaction of ethyl isocyanoacetate with divinyl ketones (DVKs) has been developed. The chemoselective fragmentation of the cyclohexanone intermediate is the key for the formation of not only the C_2-tether but also the two different heterocycles.

In recent years several biologically active and natural products were found in the series of C_2-tethered heterocyclic pairs (Figure 1), for example, cyclooroidin (isolated from the Mediterranean sponge *Agelas oroides*),[1a] siphonazoles (isolated from the genus *Herpetosiphon*)[1b] and (*Z*)-2-(1*H*-indol-3-yl)-3-(pyridin-3-yl)acrylonitrile (which was prepared by condensation of 2-(1*H*-indol-3-yl)acetonitrile with nicotinaldehyde and named paprotrain).[1c] The synthesis of siphonazoles was achieved by the use of 4-carbethoxy-5-methyl-2-(phenylsulfonyl)methyloxazole as a conjunctive reagent[2a] or through the construction of two suitable oxazole units followed by their coupling.[2b] The synthesis of cyclooroidin starting from histidine or (±)-longamide B was also reported.[3] In this communication, a new synthetic strategy for the *construction of two different heterocycles (pyrrole and oxazole) connected through a C_2 bridge in a single step* starting from the easily available divinyl ketone derivatives is described (Scheme 1).

Divinyl ketones (DVKs) are typically associated with the Nazarov and related reactions.[4,5] The present study arose from our interest in developing the synthetic potential of α-alkenoyl ketene dithioacetals **1**, the DVKs with terminal gem-dialkylthio substituents (Scheme 1).[5a,6−8] Our previous studies revealed that the reactions of ethyl isocyanoacetate with DVKs **1** under basic conditions can lead to very different products, depending on the nature of the functional group at the 2-position of **1**.[7] For instance, pyrrolizidines and fused oxazolines were synthesized in a single step from DVKs **1** bearing 2-cyano and 2-acyl groups, respectively, through different domino reactions (Scheme 1).[7]

In organic synthesis, the one-pot tandem strategy is used to improve the efficiency of a chemical reaction whereby multiple bonds are formed in a single reaction without the need to isolate intermediates.[5−7,9] Although several methods have been developed for the construction of C_2-tethered heterocyclic pairs,[1c,2,3] to our knowledge, no report has appeared on the synthesis of C_2-tethered heterocyclic pairs from simple acyclic precursors in a single step. The present experiments focused on DVKs **1** (bearing a *N*-(alkyl or aryl)-carbonyl group at the 2-position)[8] showed

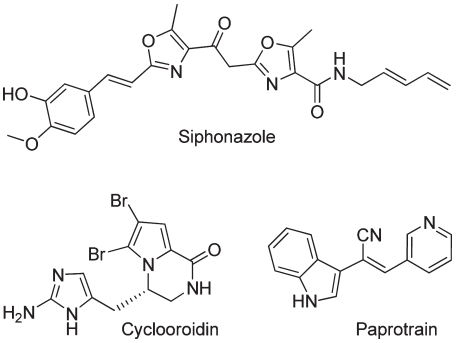
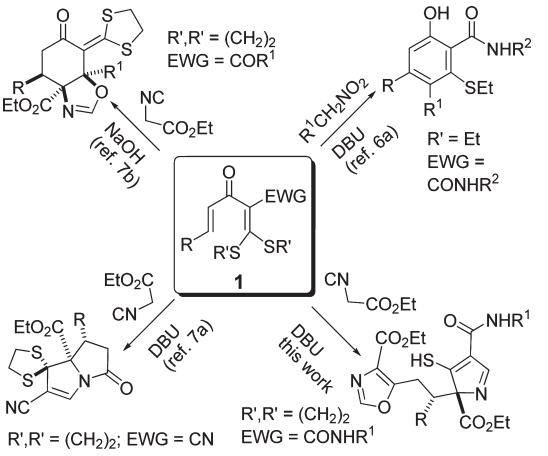


Figure 1. Examples of biologically active and natural products containing C_2-tethered heterocyclic pairs.

Scheme 1. Domino Reactions of DVKs 1 with Nitroalkanes or Ethyl Isocyanoacetate



that the C_2-tethered pyrrole/oxazole pair **2a** could be obtained in 37% isolated yield from the reaction of DVK **1a** (1.0 mmol) with ethyl isocyanoacetate (2.0 mmol) in acetonitrile (5 mL) in the presence of DBU (0.5 mmol; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene) at room temperature for 24 h (Table 1, entry 2). The yield of **2a** was raised to 84% with shorter reaction time (5 h) by increasing the temperature to 80 °C (Table 1, entry 1).[10] In comparison, *t*-BuOK and NaOH were less effective catalysts than DBU (Table 1, entries 5 and 6). Other solvents,

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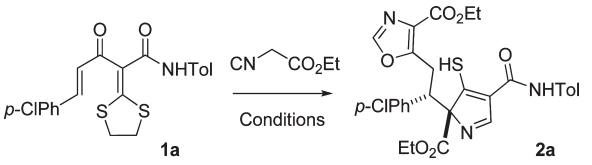
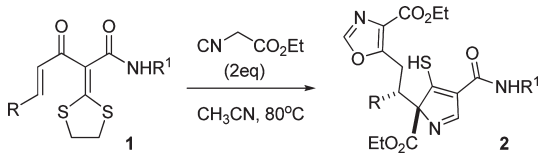
Table 1. Optimization of Reaction Conditions



entry	base (equiv)	solvent	T (°C)	t (h)	yield (%)
1	***DBU (0.5)***	***CH_3CN***	***80***	***5***	***84***
2	DBU (0.5)	CH_3CN	25	24	37[a]
3	DBU (1.0)	CH_3CN	25	6	79
4	DBU (0.3)	CH_3CN	80	5	53[b]
5	*t*-BuOK (0.5)	CH_3CN	80	5	57
6	NaOH (0.5)	CH_3CN	80	5	17[c]
7	DBU (0.5)	THF	reflux	5	63
8	DBU (0.5)	CH_2Cl_2	reflux	5	64

[a] **1a** was recovered in 52% yield. [b] **1a** was recovered in 29% yield. [c] **1a** was recovered in 20% yield.

Table 2. Synthesis of C_2-Tethered Pyrrole/Oxazole Pairs 2



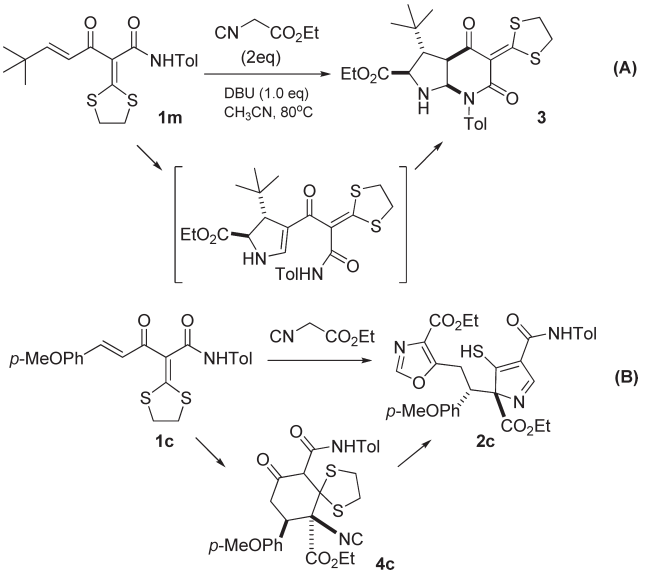
entry	**1**	R	R^1	time (h)	**2**	yield (%)
1	**a**	4-ClPh	4-MePh	5.0	**a**	84
2	**b**	Ph	4-MePh	5.0	**b**	78
3	**c**	4-MeOPh	4-MePh	24.0	**c**	89[a]
4	**d**	3,4-O_2CH_2Ph	4-MePh	10.0	**d**	74
5	**e**	2-Furyl	4-MePh	9.0	**e**	65
6	**f**	4-BrPh	4-MePh	6.0	**f**	72
7	**g**	4-ClPh	3-MePh	6.0	**g**	76
8	**h**	4-ClPh	Ph	5.0	**h**	67
9	**i**	4-ClPh	4-ClPh	6.0	**I**	72
10	**j**	4-ClPh	Me	5.0	**j**	67[b]
11	**k**	Ph	Bn	5.0	**k**	60
12	**l**	4- NO_2Ph	Bn	2.0	**l**	50

[a] 1.0 equiv DBU was used. [b] rt.

such as THF and dichloromethane, gave relatively lower yields of **2a** (Table 1, entries 7 and 8).

Under optimal conditions as in Table 1, entry 1, a series of experiments were performed, and the results are summarized in Table 2. It was proven that the reactions of ethyl isocyanoacetate with DVKs **1** having phenyl (entry 2), electron-rich (entries 3 and 4), electron-deficient (entries 1 and 7−9), aromatic and hetero aromatic R groups (entry 5) can afford the corresponding C_2-tethered pyrrole/oxazole pairs **2a**−**i** in good to high yields with high diastereoselectivity where R^1 = 4-MePh (entries 1−6), 3-MePh (entry 7), Ph (entry 8) or 4-ClPh (entry 9). Similarly,

Scheme 2



the desired pyrrole/oxazole pairs **2j**−**l** were synthesized in good yields from substrates **1j**−**l** bearing an alkyl R^1 group (entries 9−12).[11]

It was found that the reaction of **1m** bearing a bulky *tert*-butyl R group with ethyl isocyanoacetate under optimal conditions for 7 h gave bicyclic aminal **3** in 61% yield with high diastereoselectivity (Scheme 2, A).[10] In addition, the reaction of **1n** bearing a cyclohexanyl R group with ethyl isocyanoacetate gave a complicated mixture. In a separate experiment, highly substituted cyclohexanone **4c** was obtained in 31% yield by quenching the reaction of **1c** at room temperature for 1 h with saturated aqueous NH_4Cl solution (Scheme 2, B).[10,12] It was proven that the reaction of **4c** with ethyl isocyanoacetate (1.2 equiv) in the presence of DBU (50 mol %) in acetonitrile at room temperature for 16 h led to **2c** in 92% yield. These results indicate that cyclohexanone **4** is a key intermediate in the synthesis of C_2-tethered pyrrole/oxazole pairs **2**.

Taken together, the previous[6,7,12−14] and present results (Tables 1, 2 and Scheme 2), a plausible mechanism for the formation of pyrrole/oxazole pairs **2** is proposed in Scheme 3. The overall process may involve: (1) the diastereoselective double Michael addition ([5 + 1] annulation) of ethyl isocyanoacetate to 1,5-dielectrophile **1** under basic conditions to provide cyclohexanone intermediate **4** (Scheme 2, B);[6,12] (2) intramolecular elimination of a thiol group (**4**→**I**)[6] followed by elimination of a thiirane molecule from **I** leading to the thione intermediate **II**;[13] (3) the preferential cleavage of the C−C bond of **II** upon nucleophilic attack by ethyl isocyanoacetate anion (**II**→**III**)[14] followed by double isocyanide cyclization, generating a pyrrole (**III**→**IV**) and a oxazole ring (**IV**→**V**) respectively, to afford C_2-tethered pyrrole/oxazole pairs **2**. The mechanism indicates that insertion of an additional functional group in the molecule of divinyl ketone opens broad possibility for heterocyclization using isocyanoacetates and analogues.[7,15]

In conclusion, we have developed a new strategy for the synthesis of C_2-tethered pyrrole/oxazole pairs in good to high yields under mild reaction conditions from the easily available acyclic substrates. This domino process comprises two [3 + 2] cycloadditions and allows the construction of two different heterocycles

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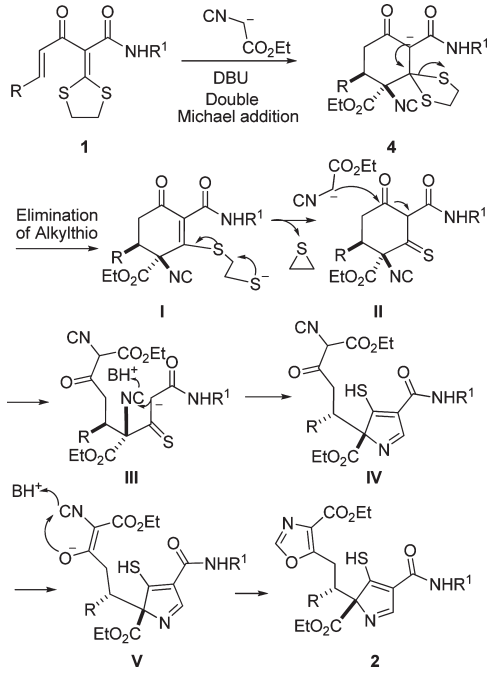
Scheme 3. Proposed Mechanism for the Formation of 2



in a single step. This new strategy involves the formation of four C−C and one C−O bonds in a regio- and diastereoselective manner with the chemoselective fragmentation of the cyclohexanone intermediate as the key. Further studies are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and spectral data for **2a**−**l** and **3** and a cif file of crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
xuxx677@nenu.edu.cn; liuqun@nenu.edu.cn

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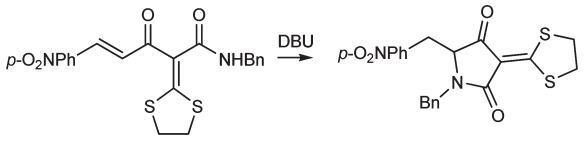
(10) CCDC 801575 (**2a**), CCDC 801574 (**3**), and CCDC 798180 (**4c**: this compound exists in the enol form in the solid state and in organic solvents as determined by NMR spectroscopy: see SI) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ddcd.cam.ac.uk/data_request/cif.

(11) In the reaction of **1l**, a byproduct, formed via intramolecular aza-anti Michael addition was obtained in 24% yield (see ref 8).



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