Efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate†

Jian-Wu Xie,*[a,b] Zheng Wang,[a] Wei-Jun Yang,[a] Li-Chun Kong[a] and Dong-Cheng Xu[a]

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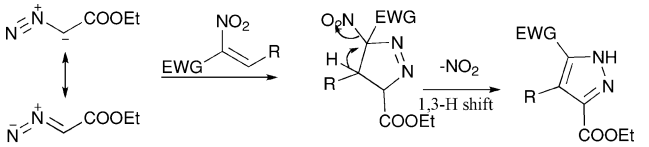
The one-pot synthesis of multisubstituted pyrazole derivatives was achieved *via* catalyst-free 1,3-dipolar cycloaddition of ethyl diazoacetate and nitroalkenes as the key step and elimination of the leaving group (NO_2 or Br) followed by intramolecular proton transfer with satisfactory yields.

Pyrazoles and their derivatives which are present in a plethora of natural and synthetic compounds are of considerable interest as they possess a wide range of biological properties.[1] Pyrazoles are also efficient coordinating ligands in synthesis.[2] Thus, a variety of methods are known in the literature for the synthesis of pyrazoles,[3] which include reaction between hydrazines and 1,3-difunctional substrates (*e.g.* 1,3-dicarbonyl compounds,[4] or ynones[5]) and 1,3-dipolar cycloaddition of diazo compounds to alkenes and alkynes using Lewis acid as catalyst.[6,7] Although the 1,3-dipolar cycloaddition of electron-rich diazo compounds to alkenes is known, to the best our knowledge, catalyst-free intermolecular 1,3-dipolar cycloaddition of electron-deficient diazo compounds with electron-deficient alkenes has rarely been reported. Thus, a straightforward and "greener" approach to pyrazoles is interesting. Herein, we report an efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate for the first time.

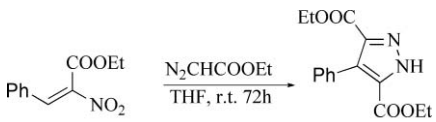
The 1,3-dipolar cycloaddition reactions have been employed as one of the most powerful synthetic tools to provide a variety of five membered carbocycles as well as heterocycles.[8] To accelerate these types of reactions, one possible solution to the problem is to lower the LUMO of the dipolarophiles, *e.g.* by a Lewis acid.[9] However, this often resulted in the decomposition of the diazocarbonyl compounds, leading to various well known competing side reactions.[10] The use of readily available electron-rich ethyl diazoacetate as dipole is well-known. On the other hand, the electron-poor nitroalkene is a good dipolarophile with a good leave group NO_2. We envisioned that the new one-pot reactions would be possible between nitroalkenes and ethyl diazoacetate, as outlined in Scheme 1, giving pyrazoles with multiple substitutions.

The initial investigation started with the reaction of ethyl diazoacetate and α-carbethoxy-1- nitrostyrene **1a** (Scheme 2). First, we tested several bases (for example $NaOC_2H_5$, NaOH) for their



EWG = Electron Withdrawing Group

Scheme 1 Proposed one-pot tandem reaction of nitroalkenes with ethyl diazoacetate.



1a **2a**

Scheme 2 1,3-Dipolar cycloaddition of α-carbethoxy-1- nitrostyrene **1a** to ethyl diazoacetate.

application in these highly sensitive 1,3-dipolar cycloadditions. But all the 1,3-dipolar cycloadditions yielded varying mixtures, no main product was observed. To our delight, further optimization experiments revealed a clean 1, 3-dipolar cycloaddition in the absence of any catalyst after 72h at room temperature in THF and the cycloaddition product **2a** was isolated in moderate yield (61% yield). As could have been expected, the pyrazole is formed in a one-pot tandem reaction *via* 1, 3-dipolar cycloaddition and spontaneous elimination of the nitro group.

Under the above optimized conditions, these findings could be extended to the application of various other α-carbethoxy-1-nitrostyrenes **1a-1g**. And the 1,3-dipolar cycloaddition of α-carbethoxy-1-nitrostyrenes **1** to ethyl diazoacetate proceeded smoothly to afford the pyrazoles **2a-2g** as single regioisomers. The reaction's scope proved to be quite broad with respect to the α-carbethoxy-1-nitrostyrenes. Good yields were obtained in the reactions of electron-withdrawing substituents on the aryl ring of α-carbethoxy-1-nitrostyrenes **1** with ethyl diazoacetate (Table 1). In addition, an electron-donating substituent on the aryl ring of α-carbethoxy-1-nitrostyrenes **1** substrates tended to decrease their reactivity (Table 1, entry 5). Good yields were also obtained for heteroaryl-substituted substrates **1f** (entry 6). The high regioselectivity observed in these 1,3-dipolar cycloadditions is in keeping with previous literature reports involving cycloadditions onto electron poor olefins.[11] This can be explained by both the steric interaction of the substituents of the reactants and the atomic orbital coefficients of the HOMO (ethyl diazoacetate)-LUMO (nitroalkene) favored interaction expected for this type of cycloaddition.[7a,12]

Coumarins are important heterocycles widely present in natural products exhibiting a broad range of biological and therapeutic

[a]*Department of Chemistry and Life Science, Zhejiang Normal University, Jinhua, 321004, China*
[b]*Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, Zhejiang Normal University, Jinhua, 321004, China. E-mail: xiejw@zjnu.cn; Fax: +86 579 82282610*

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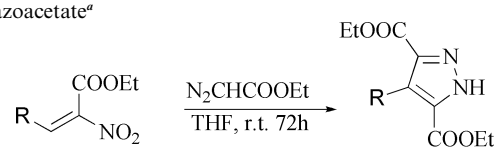
Table 1 1,3-Dipolar cycloaddition of α-carbethoxy-1-nitrostyrenes (**1**) to ethyl diazoacetate[a]

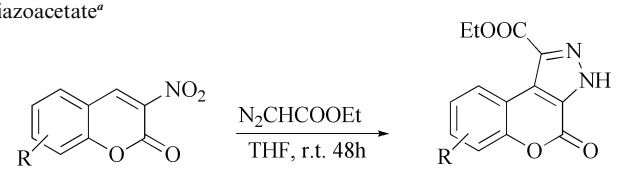


1 **2**

Entry	1	R	Yield[b] (%)
1	**1a**	C_6H_5	61 (**2a**)
2	**1b**	*m*-ClC_6H_4	75 (**2b**)
3	**1c**	*p*-BrC_6H_4	65 (**2c**)
4	**1d**	*m*-$CH_3OC_6H_4$	69 (**2d**)
5	**1e**	*p*-$CH_3C_6H_4$	59 (**2e**)
6	**1f**	2-furanyl	51 (**2f**)
7	**1g**	*p*-biphenyl	48 (**2g**)

[a] All the reactions were performed with α-carbethoxy-1-nitrostyrene **1** (0.5 mmol, 1 equiv.) and ethyl diazoacetate (2.5 mmol, 5 equiv.) and were stirred at room temperature in THF (2 ml) for 72h. [b] Isolated yields.

Table 2 1,3-Dipolar cycloaddition of 3-nitrocoumarins to ethyl diazoacetate[a]



3 **4**

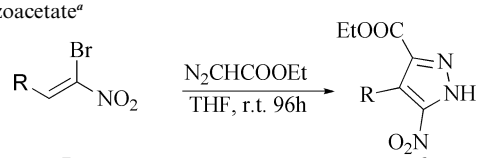
Entry	3	R	Yield[b] (%)
1	**3a**	H	86 (**4a**)
2	**3b**	5-F	89 (**4b**)
3	**3c**	5-Cl	91 (**4c**)
4	**3d**	5-Br	82 (**4d**)
5	**3e**	4-MeO	71 (**4e**)

[a] All the reactions were performed with 3-nitrocoumarins **3** (0.5 mmol, 1 equiv.) and ethyl diazoacetate (2.5 mmol, 5 equiv.) and were stirred at room temperature in THF (2 ml) for 48h. [b] Isolated yields.

activities and have been the subject intensive research.[13,14] Having succeeded in synthesizing pyrazoles **2**, we considered that the incorporation of a pyrazole heterocyclic unit into coumarins might provide new compounds that have important biological and pharmaceutical activities. Thus, we turned our attention to the possible synthesis of pyrazoles using 3-nitrocoumarins **3** as dipolarophiles. To our delight, the 1,3-dipolar cycloaddition of 3-nitrocoumarins **3** to ethyl diazoacetate proceeded smoothly in THF at room temperature. The corresponding 1,3-dipolar cycloaddition products were isolated with high yields as single regioisomers. Table 2 shows that 3-nitrocoumarins with electron-withdrawing substituents provided the cycloadducts benzopyrano[3,4-c]pyrazoles **4b-4d** in excellent yields (82-91%, entries 2-4). On the contrary, 3-nitrocoumarins with electron-donating substituents resulted in a slight decrease in yield (71%, entry 5).

Nitroalkenes **1** and **3** were the cycloaddition partners with ethyl diazoacetate in the above cases. However, the pyrazole formation involved elimination of the nitro group, a synthetically and biologically useful functionality. Therefore, it was felt that the nitro group could be retained in the pyrazole moiety, provided the nitroalkene

Table 3 1,3-Dipolar cycloaddition of acyclic α-bromo-α-nitroalkenes to ethyl diazoacetate[a]

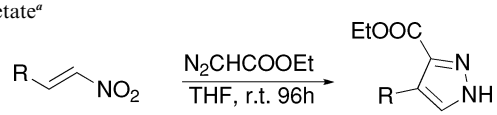


5 **6**

Entry	5	R	Yield[b] (%)
1	**5a**	C_6H_5	35 (**6a**)
2	**5b**	*p*-ClC_6H_4	49 (**6b**)
3	**5c**	*p*-BrC_6H_4	42 (**6c**)

[a] All the reactions were performed with α-bromo-α- nitroalkenes **5** (0.5 mmol, 1 equiv.) and ethyl diazoacetate (2.5 mmol, 5 equiv.) and were stirred at room temperature in THF (2 ml) for 96h. [b] Isolated yields.

Table 4 1,3-Dipolar cycloaddition of acyclic nitroalkenes to ethyl diazoacetate[a]



7 **8**

Entry	7	R	Yield[b] (%)
1	**7a**	C_6H_5	31 (91)[c] (**8a**)
2	**7b**	*p*-ClC_6H_4	43 (95)[c] (**8b**)
3	**7c**	*p*-$MeOC_6H_4$	29 (90)[c] (**8c**)
4	**7d**	2-furanyl	26 (88)[c] (**8d**)

[a] All the reactions were performed with nitrostyrene **7** (0.5 mmol, 1 equiv.) and ethyl diazoacetate (2.5 mmol, 5 equiv.) and were stirred at room temperature in THF (2 ml) for 96h. [b] Isolated yields. [c] Yields in bracket based on recovered **7**.

possesses an α-substituent which is a better leaving group than the nitro group. This was realized by taking α-bromonitroalkenes **5** as cycloaddition partners with ethyl diazoacetate (Table 3). Nitropyrazole **6** was the only product isolated when **5** was reacted with ethyl diazoacetate (entries 1-3).

During our ongoing studies of the one-pot tandem reaction, the simple nitroolefins **7a** exhibited low reactivity. The 1,3-dipolar cycloaddition of nitroalkene **7a** to ethyl diazoacetate proceeded with a clean product **8a** while the yield was low (Table 4, entry 1) under the same conditions as above. A few nitroolefins derivatives **7a-7c** with different substitutions were investigated. The electronic effect was very marginal and low yield was achieved (entries 1-4).

In conclusion, an efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate has been investigated. The one-pot reaction can proceed smoothly under mild conditions and provides pure pyrazole derivatives in moderate to excellent yield. The reaction's scope proved to be quite broad. Notably, we incorporated a pyrazole heterocyclic unit into coumarins and provided substituted benzopyrano[3,4-c]pyrazole that might have important biological and pharmaceutical activities in the future. This novel methodology should be of great interest for natural product synthesis because of the mild reaction conditions.

Acknowledgements

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