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Facile synthesis of novel tetrasubstituted 1-pyrazolines from Baylis–Hillman adducts and acyl diazomethanes ☆

Hongbao Sun [a,†], Xiaoyan Wang [b,†], Miao Zhan [a], Jie Liu [a,*], Yongmei Xie [a,*]

[a] State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China
[b] Analytical & Testing Center, Sichuan University, Chengdu 610064, China

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ABSTRACT

An efficient method for the regioselective synthesis of potentially biologically active tetrasubstituted 1-pyrazolines has been achieved via a 1,3-dipolar cycloaddition reaction. A range of tetrasubstituted 1-pyrazolines bearing one Boc group and two ester groups were obtained in high yields (up to 99%). The structure and relative stereochemistry of cycloadducts were confirmed by NMR spectra and single crystal X-ray diffraction. The possible mechanism was proposed and the major *Z*-cycloadducts as a single diastereomer could be separated from each other by chromatography.

Pyrazolines are heterocyclic compounds of five membered unsaturated ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. These nitrogen heterocycles and their derivatives are versatile synthetic blocks, frequent structural skeleton of natural products, or potential drug molecules.[1] Many of them showed a broad spectrum of biological activities such as analgesic,[2] anti-inflammatory,[3] antipyretic,[4] antiarrhythmic,[4] antidepressant,[5] anticonvulsant,[6] antioxidant,[7] antihypertensive,[8] antidiabetic,[4,9] antimicrobial,[10] and anticancer activities.[11] In addition, these heterocycles were also widely used as dyestuffs,[12] analytical reagents,[13] and agrochemicals.[14] Because of these diverse properties, synthesis of pyrazolines and pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry. Currently, a variety of synthetic methods for the preparation of these compounds were reported. In general, the synthesis of pyrazolines by the so-called [3+2] atom fragments has been relatively well investigated. In this method, β-diketones or their derivatives (the three-atom fragment) are condensed with hydrazine or its derivatives (the two-atom fragment) to close a five-membered ring.[12,13,15,16] The second strategy is the classical 1,3-dipolar cycloaddition (1,3-DC) reaction of diazoalkanes or nitrile imines, and the usual dipolarophiles for this purpose are alkynes,[17] alkyne equivalents,[18] or alkenes.[19] Despite these successes, the design and synthesis of new complex pyrazoline derivatives possessing biological activities are still a challenge and have become a much attempted research endeavor. So far, the synthesis of functionalized 2-pyrazoline by 1,3-DC reactions between nitrile imines and alkene has been extensive investigated.[19,20] However, only a few references for preparation of polysubstituted 1-pyrazoline by the 1,3-DC reaction were found.[21] To the best of our knowledge, the Baylis–Hillman adduct is a structural motif and is often found in bioactive molecules. The use of such olefin as dipolarophiles in 1,3-DC reaction for the production of new pyrazoline derivatives with biological interest is not very extensive. As a part of our own interest in cycloaddition reactions, we report herein the efficient synthesis of novel tetrasubstituted 1-pyrazolines via 1,3-dipolar cycloaddition of Baylis–Hillman adducts and acyl diazomethanes.

Initially, we chose methyl α-benzyl-α-diazoacetate **1a** and the Baylis–Hillman adduct derived from 4-nitrobenzaldehyde **2a** as model substrates for establishing the feasibility of the strategy and the optimal reaction conditions. A variety of Lewis bases were first screened as catalysts for the reaction. After the mixture of **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (20 mol %, such as DABCO, Ph_3P, Et_3N, and DBU) in dichloromethane (1.0 mL) being stirred at 25 °C for 24 h, tetrasubstituted 1-pyrazoline **3a** was obtained in a low yield (Table 1, entries 1–4). However, in another parallel experiment, a blank reaction without a catalyst gave the desired

* Corresponding authors. Tel./fax: +86 028 85503817 (J.L.); tel.: +86 028 85411508; fax: +86 028 85412316 (Y.X.).
E-mail addresses: liujie2011@scu.edu.cn (J. Liu), xieym@scu.edu.cn (Y. Xie).
† These authors contributed equally.

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Table 1
Optimization of reaction conditions to yield compound **3a**[a]

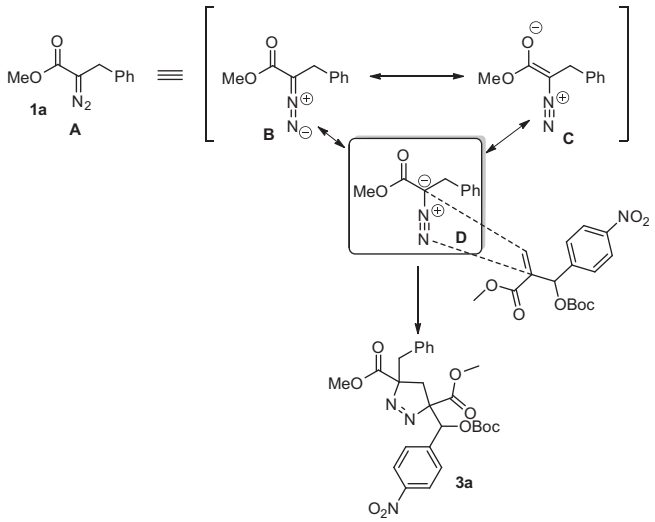
Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	DABCO	CH_2Cl_2	25	32
2	Ph_3P	CH_2Cl_2	25	Trace
3	Et_3N	CH_2Cl_2	25	35
4	DBU	CH_2Cl_2	25	13
5	—	CH_2Cl_2	25	38
6	—	THF	25	54
7	—	Toluene	25	47
8	—	CH_3CN	25	52
9	—	$CHCl_3$	25	51
10	—	CH_3OH	25	75
11	—	EtOH	25	66
12	—	*n*-PrOH	25	78
13	—	*i*-PrOH	25	89
14	—	*n*-BuOH	25	66
15	—	*i*-BuOH	25	58
16	—	*i*-PrOH	35	99
17	—	*i*-PrOH	65	98
18	—	*i*-PrOH	−20	Trace

[a] The reaction was carried out in 0.1 mmol scale in solvent (1.0 mL) at 25 °C for 24 h, and the ratio of **1a**/**2a**/catalyst is 1:1:0.2.
[b] Isolated yield based on Baylis–Hillman adduct.

product with equivalent yield (Table 1, entry 5). This result indicated that catalyst may not play a role, even led to a lower reaction activity. Considering the easy nature of the above process, the reaction will not need the catalyst.

The structure of cycloadduct **3a** was confirmed through spectroscopic analysis. We were pleased to see that the reaction afforded the adduct **3a** as a single regioisomer (Scheme 1). As shown in Scheme 1, from the resonance structure B, C, D of the diazo group it is obvious that the carbon, to which the diazo group is attached, has a partial negative charge. Electrophiles usually attack at the carbon atom, while the terminal nitrogen of the diazo group is attacked by nucleophiles. Therefore, **3a** was exclusively formed according to the regulations obtained from previous reports on the 1,3-dipolar addition of acyl diazomethanes with alkenes.[21b–d]

Next, the diastereoselectivity of the reaction and relative configurations of the stereogenic centers of the cycloadduct **3a** were also determined by NMR spectra and single crystal X-ray analysis. Based on the chemical shifts and coupling constants of the aliphatic protons in proton NMR (Fig. 1), the adduct **3a** is a mixture of different diastereomers. Thus, methyl α-benzyl-α-diazoacetate



Scheme 1. 1,3-Dipolar cycloaddition reaction for synthesis of tetrasubstituted 1-pyrazoline **3a**.

1a cycloaddition to the Baylis–Hillman adduct **2a** is completely regioselective but yielded a mixture of diastereomers (**3aa**, **3ab,** and **3ac**). The exact ratio of diastereomers has been determined by comparing the integral values of aliphatic protons in crude reaction mixture, especially, methoxyl protons (diastereoselectivity 66:26:8). Only **3aa** as a single diastereomer could be separated from each other by chromatography and the rest of cycloadducts (**3ab**, **3ac**) yielded an inseparable diastereomeric mixture. In Figure 1, the proton NMR spectra of **3aa**, **3ab,** and **3ac** indicating the aliphatic and methoxyl protons are shown. Among the aliphatic protons, Ha is the most deshielded one due to its proximity to oxygen and the phenyl moiety and it appeared at around 6.4 ppm in three isomers as a singlet. The methylene protons of the benzyl (Hb and Hc) in three isomers resonated relatively up field (3.14–3.52 ppm) with a J = 14.0 Hz. The methylene protons of the pyrazoline ring (Hd and He) exhibited AB doublets at δ 2.60 and at δ 1.72 ppm (J = 13.6 Hz). In addition, the HMBC spectra confirmed that the connectivities of these protons to the carbons were in accord with the assigned structures. The stereochemical outcome of the cycloaddition was determined by single crystal X-ray analysis of the cycloadduct **3aa** (Fig. 2).[22] The X-ray structure of the product **3aa** reflects that the cycloaddition proceeds via two models (Scheme 2).

To improve the yield, efforts were made to optimize other reaction parameters including solvents and reaction temperatures. Different solvents including THF, toluene, CH_3CN, $CHCl_3$, CH_3OH, and EtOH were investigated and the results are listed in Table 1 (entries 6–11). To our delight, the reaction in methanol led to the desired product in a yield of 75% (Table 1, entry 10), while ethanol as solvent gave the product in only 66% yield (Table 1, entry 11). In general, reactions carried out in protic solvents were better yielding than those in aprotic solvents. Further improvement was achieved by employing *i*-PrOH as solvent and the tetrasubstituted 1-pyrazoline **3a** was obtained in 89% yield (Table 1, entry 13).

Temperature influenced the rate of the reaction, but had no obvious effect on the diastereoselectivity. Reducing the reaction temperature resulted in a low reactivity (Table 1, entry 18), while conducting the reaction at 35 °C provided the best results (Table 1, entry 16). Based on the comprehensive consideration of reaction temperature and yield, the optimal reaction conditions were established as shown in Table 1, entry 16. The ratio of three diastereomers remained the same in all the cases.

Having the optimized conditions in hand, the scope of Baylis–Hillman adducts was examined by using methyl α-benzyl-α-diazoacetate **1a** as 1,3-dipole. The results are shown in Table 2. Although the diastereoselectivities of these reactions were low, it did not effect on the formation of products in higher yields during the course of reaction. A variety of Baylis–Hillman adducts proved to be excellent dipolarophiles for this reaction, and provided the corresponding tetrasubstituted 1-pyrazolines in good yields (up to 99%). Substituents on aryl groups influenced slightly the yields. (Table 2, entries 1–10). Generally, Baylis–Hillman adducts derived from 4-substituted benzaldehyde gave higher yields than those derived from 2-substituted and 3-substituted benzaldehyde. Baylis–Hillman adducts with electron-donating groups and with electron-withdrawing groups all gave good yields. However, the diastereoselectivities of the reaction were affected by the position of substituents at the aromatic ring. The 2-Br substituted Baylis–Hillman adduct yielded four diastereomers (diastereoselectivity 25:25:25:25) (Table 2, entry 10) and the diastereomers could not be separated. Naphthyl and heterocyclic substituents participated in smooth cycloaddition reactions in 97% and 89% yield, respectively (Table 2, entries 11, 12). It is worthwhile to note that the Baylis–Hillman adduct derived from cinnamaldehyde was examined and was transformed with a yield of 81% (Table 2, entry 13). Moreover, changing the methyl ester group of the Baylis–Hillman adduct to