Tetrahedron Letters 51 (2010) 6507–6510

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

DABCO catalyzed facile synthesis of highly functionalized pyrazolines from Baylis–Hillman acetates and ethyl diazoacetate

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ARTICLE INFO

Article history:
Received 17 August 2010
Revised 28 September 2010
Accepted 1 October 2010
Available online 8 October 2010

Keywords:
Baylis–Hillman acetates
Ethyl diazoacetate (EDA)
DABCO
Reattack of acetate ion (acetate rearrangement)

ABSTRACT

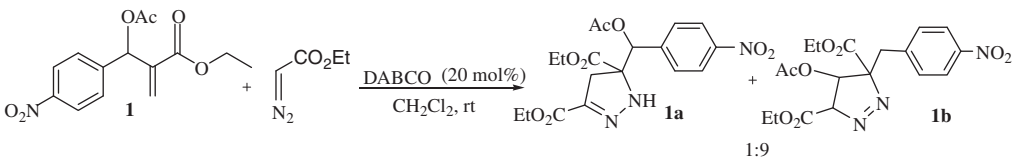
A convenient synthesis of pyrazolines is reported via DABCO mediated reaction of ethyl diazoacetate (EDA) with Baylis–Hillman acetates. The products were obtained in good to excellent yields (70–95%).

Pyrazolines[1] show a wide range of biological activity and play an important role in the pharmaceutical and agrochemical industries. The pyrazolines have been reported to show antidepressant, anticancer, and antibacterial activity.[2] Owing to the high importance of pyrazolines a number of synthetic approaches have been developed.[3] The diazo compounds have been extensively employed as a carbene[4] source, undergo 1,3-dipolar cycloaddition[5] to form five-membered heterocyclic rings, as reagents for carbonyl homologation,[6] and acid esterification.[7]

Over the past few years, we have investigated the Baylis–Hillman reaction[8] and showcased the versatile utility of adducts.[9] Continuing our interest, we conducted a 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reaction between ethyl diazoacetate (EDA) and Baylis–Hillman acetate derived from 4-nitrobenzaldehyde (**1**, Scheme 1) in CH_2Cl_2.

To our delight the reaction proceeded smoothly in 1 h to afford two chromatographically separable products in 1:9 ratio. The products can be rationalized through the DABCO catalyzed cycloaddition of EDA to the olefin of the BH-adduct with a simultaneous rearrangement of –OAc group. Unlike most of the cycloadditions (i.e., concerted) the reaction was thought to proceed through reactive intermediates to afford the products. The products were separated into individual components and their structures identified as regioisomeric pyrazolines **1a** and **1b**, respectively, from the spectral data. Accordingly ^{1}H NMR of **1a** shows the benzylic CH proton at δ 5.83 ppm as a singlet integrating for one proton, NH proton as a singlet at δ 4.02 ppm (D_2O exchangeable), CH_2 protons as AB-doublets at δ 3.68 and at δ 3.13 ppm (J = 19.49 Hz), while **1b** shows a doublet at δ 6.18 ppm (J = 9.35 Hz), a doublet at δ 5.34 ppm (J = 9.35 Hz) and benzylic CH_2 protons as AB-doublets at δ 3.41 and at δ 3.13 ppm (J = 19.49 Hz).

Next, reaction optimization studies were performed between **1** and EDA using different solvents and bases (Table 1). After screening, DABCO was selected as the base and CH_2Cl_2 as the solvent for all further reactions (entry 1, Table 1). The optimum catalyst loading was found to be 20 mol % of DABCO. The ratio of major and minor products remained the same in all the cases. There was no temperature effect on the product distribution or on the rate of



Scheme 1. Reaction of BH acetate derived from 4-nitrobenzaldehyde and EDA under optimal conditions.

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doi:10.1016/j.tetlet.2010.10.006

Table 1
Optimization of reaction conditions

Entry	Base	Solvent	Time (h)	Yield (%)[a]
1	DABCO	CH_2Cl_2	1	95
2	1,8-Diazabicyclo[5,4,0] undec-7-ene	CH_2Cl_2	3	56
3	Imidazole	CH_2Cl_2	2.5	67
4	*N*,*N*-Diisopropylethyl amine	CH_2Cl_2	2	70
5	DABCO	THF	3	75
6	DABCO	MeOH	3	50
7	DABCO	CH_3CN	2	56
8	DABCO	Neat	1	48[b]

[a] The ratio of major and minor products is almost 1:9 ratio in all cases.
[b] Product was isolated along with mixture of undesired products.

the reaction. A blank reaction without a catalyst did not give the desired products.

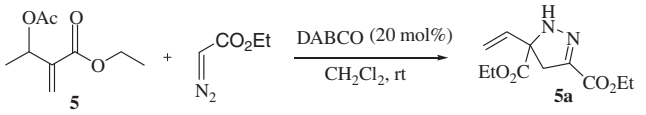
To extend the scope of this methodology, various Baylis–Hillman acetates (**2**–**4**) derived from benzaldehyde, 4-cyanobenzaldehyde, and 4-fluorobenzaldehyde under the standardized conditions afforded the corresponding products (**1a**–**4a**) in minor quantities (8–10%) and their isomeric counterparts (**1b**–**4b**) in excellent yields (Table 2).

But interestingly, when aliphatic Baylis–Hillman acetates were the substrates different products were obtained (Scheme 2). The first example chosen was the Baylis–Hillman acetate (**5**) derived from acetaldehyde under standard reaction conditions.

The product **5a** was obtained in good yield (75%) within 20 min as the only product and it was characterized by its spectral data. For instance, ^{1}H NMR shows olefinic protons as a double doublet at δ 6.01 ppm (J = 10.57, 17.37 Hz), a multiplet at δ 5.40–5.23 ppm, CH_2 protons appeared as AB-doublets at δ 3.53 and at δ 2.94 ppm (J = 17.37 Hz). The reason for this unusual result was explained at a later stage. The relative stereochemistry of the substituents (of the major and minor products) and hence the diastereomeric ratio could not be ascertained from the NMR data.

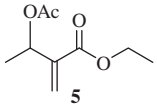
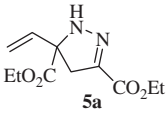
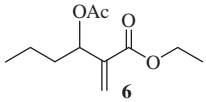
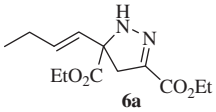
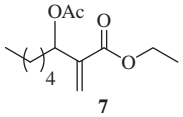
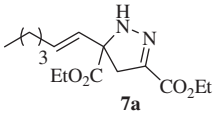
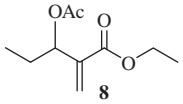
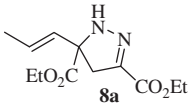
Next, the versatility of this reaction was studied with various aliphatic Baylis–Hillman acetates derived from butyraldehyde, hexanaldehyde, and propionaldehyde as shown in Table 3.

The plausible mechanism is as shown in Scheme 3 (part i). At first the EDA activated by DABCO (triazene intermediate)[10] attacks BH acetate via the Michael addition pathway resulting in intermediate **A** which can isomerise to **B**.[11] Then the reattack of acetate ion on **A** and **B** promotes the cyclization to afford pyrazolines **1a** and



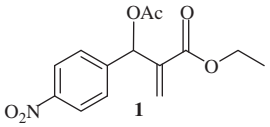
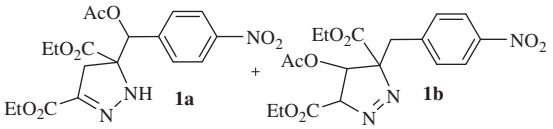
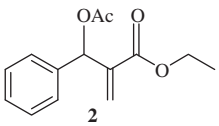
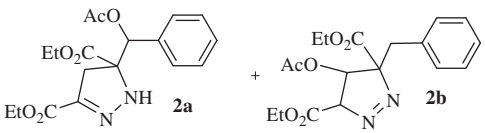
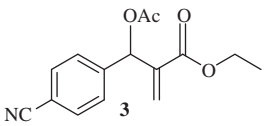
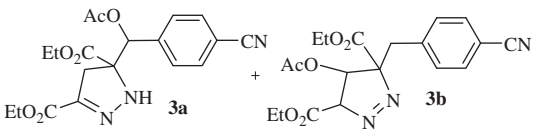
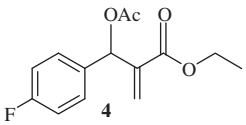
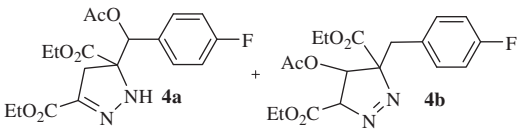
Scheme 2. Reaction of BH acetates derived from acetaldehyde and EDA under optimal conditions.

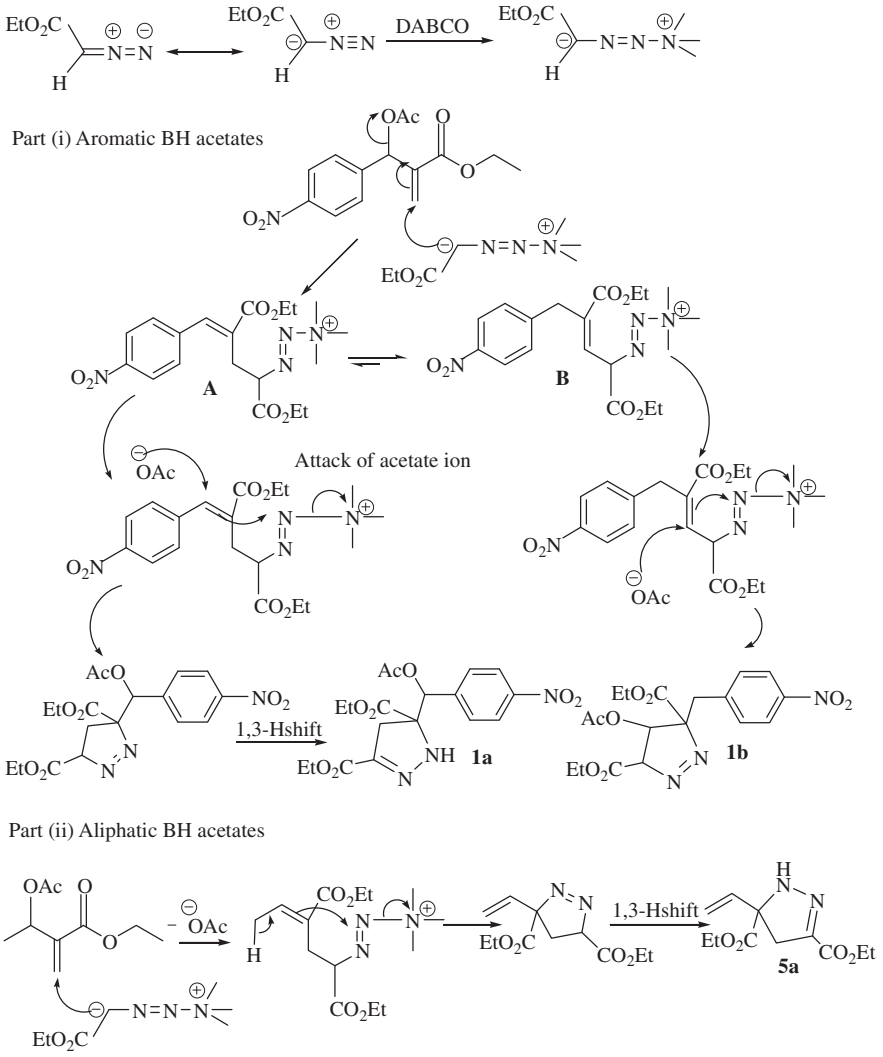
Table 3
Reaction of aliphatic BH acetates with EDA under optimal conditions

Entry	BH acetate	Time (h)	Products	Yield (%)
1	 **5**	0.5	 **5a**	75
2	 **6**	0.6	 **6a**	70
3	 **7**	0.8	 **7a**	71
4	 **8**	0.5	 **8a**	76

1b in 1:9 ratio, respectively. The major products arising from intermediate **B** are sterically more favored. The formation of **5a** (and the related products as in Table 3) can be explained invoking a similar mechanism (Scheme 3, part ii). However, the basic difference is that due to the presence of a γ-proton and its participation in the trapping of the 'acetoxy ion' results in the cyclization followed by 1,3-H shift to afford a 5-vinyl pyrazoline unlike the earlier substrates. Expectedly, we did not obtain a 5-alkenyl pyrazoline product when the acetate of formaldehyde BH-adduct was exposed to the same reaction conditions thus proving the participation of the γ-proton.

Table 2
Reaction of various aromatic BH acetates with EDA under optimal conditions

Entry	BH acetate	Time (h)	Products	Yield (%)
1	 **1**	1	 **1a** + **1b**	10:85
2	 **2**	2	 **2a** + **2b**	9:80
3	 **3**	1.2	 **3a** + **3b**	8:86
4	 **4**	1.5	 **4a** + **4b**	9:86



Scheme 3. Plausible mechanism.

In conclusion, we have demonstrated a new and efficient methodology for the synthesis of pyrazolines.[12,13] The reaction is simple, convenient with lower reaction times, and the starting compounds are easy to prepare, which makes it a useful and attractive process for the preparation of pyrazolines. Overall, a facile synthesis of densely functionalized pyrazolines has been reported.

Acknowledgement

One of the authors (Y.L.P.) thanks UGC, New Delhi for the financial support in the form of a fellowship.

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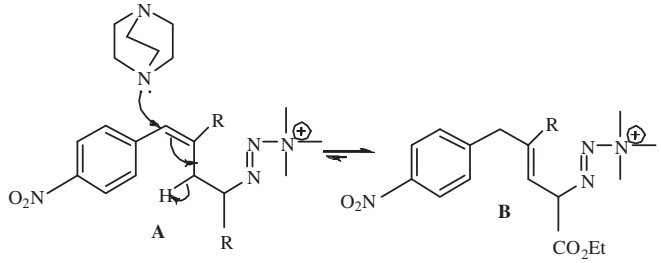
11. The formation of **B** from **A** is preferred due to allylic hydrogen shift which may de induced by DABCO (shown below) that further results in stereochemically favorable major products **1b**–**4b**.



12. *General experimental procedure*: To a solution of EDA (1.0 mmol), and DABCO (0.2 mmol) in CH_2Cl_2 (3.0 mL), Baylis–Hillman acetate (1.0 mmol) was added

and stirred for 0.5–2 h at rt. After completion of the reaction as indicated by TLC, water (5.0 mL) was added and the product was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and purified by column chromatography (silica gel, 60–120 mesh, EtOAc:*n*-hexane, 1:9–2:8) to afford the products.

13. *Spectral data for selected compounds*: Compound **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 2*H*, *J* = 8.57 Hz, Ar–H), 7.47 (d, 2*H*, *J* = 8.57 Hz, Ar–H), 5.83 (s, 1*H*, CH), 4.41–4.19 (m, 4*H*, $2 \times$ O–CH_2), 4.02 (s, 1*H*, NH), 3.68 (d, 1*H*, *J* = 19.49 Hz, H–CH_2), 3.13 (d, 1*H*, *J* = 19.49 Hz, H–CH_2), 2.30 (s, 3*H*, CH_3), 1.35–1.25 (m, 6*H*, $2 \times CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 21.8, 38.5, 62.3, 63.0, 69.4, 72.9, 123.1, 127.8, 143.8, 145.7, 147.8, 160.5, 170.9, 171.4. IR (KBr): 3317, 2986, 1753, 1713, 1653, 1525, 1345, 1261, 1171, 1010, 857 cm^{-1}. ESI-MS: 408 $[M+H]^+$. Anal. Calcd for $C_{18}H_{21}N_3O_8$: C, 53.07, H, 5.20, N, 10.31. Found: 53.09, H, 5.22, N, 10.33. Compound **1b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 2*H*, *J* = 8.57 Hz, Ar–H), 7.46 (d, 2*H*, *J* = 8.57 Hz, Ar–H), 6.18 (d, 1*H*, *J* = 9.35 Hz, CH), 5.34 (d, 1*H*, *J* = 9.35 Hz, CH), 4.32 (q, 2*H*, *J* = 7.40 Hz, O–CH_2), 4.22 (q, 2*H*, *J* = 7.01 Hz, O–CH_2), 3.41 (d, 1*H*, *J* = 19.49 Hz, H–CH_2), 3.24 (d, 1*H*, *J* = 19.49 Hz, H–CH_2), 2.45 (s, 3*H*, CH_3), 1.36 (t, 3*H*, *J* = 7.79 Hz, CH_3), 1.31 (t, 3*H*, *J* = 7.79 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 22.7, 42.6, 61.5, 63.1, 74.8, 75.6, 123.5, 128.6, 129.7, 141.6, 145.2, 160.1, 168.11, 174.3. IR (KBr): 2984, 2931, 1744, 1671, 1524, 1349, 1257, 1093, 755 cm^{-1}. ESI-MS: 408 $[M+H]^+$. Anal. Calcd for $C_{18}H_{21}N_3O_8$: C, 53.07, H, 5.20, N, 10.31. Found: 53.10, H, 5.23, N, 10.28. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 2*H*, *J* = 8.30 Hz, Ar–H), 7.37 (d, 2*H*, *J* = 8.30 Hz, Ar–H), 5.76 (s, 1*H*, CH), 4.38–4.18 (m, 4*H*, $2 \times CH_2$), 3.98 (s, 1*H*, NH), 3.64 (d, 1*H*, *J* = 19.26 Hz, H–CH_2), 3.09 (d, 1*H*, *J* = 19.26 Hz, H–CH_2), 2.28 (s, 3*H*, CH_3), 1.37–1.19 (m, 6*H*, $2 \times CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.4, 38.3, 62.4, 62.9, 69.7, 73.2, 112.5, 118.6, 127.6, 128.7, 132.0, 132.2, 142.1, 145.6, 160.0, 170.9, 171.3. IR (KBr): 3339, 2896, 2932, 2229, 1750, 1710, 1520, 1335, 1261, 1171, 1010, 856 cm^{-1}. ESI-MS: 410 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}N_3O_6$: C, 58.91, H, 5.46, N, 10.85. Found: 58.94, H, 5.43, N, 10.88. Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 2*H*, *J* = 8.05 Hz, Ar–H), 7.39 (d, 2*H*, *J* = 8.48 Hz, Ar–H), 6.16 (d, 1*H*, *J* = 9.33 Hz, CH), 5.24 (d, 1*H*, *J* = 9.33 Hz), 4.32 (q, 2*H*, *J* = 7.20 Hz, O–CH_2), 4.26 (q, 2*H*, *J* = 7.20 Hz, O–CH_2), 3.40 (d, 1*H*, *J* = 19.50 Hz, H–CH_2), 3.22 (d, 1*H*, *J* = 19.10 Hz, H–CH_2), 2.46 (s, 3*H*, CH_3), 1.39–1.25 (m, 6*H*, $2 \times CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.8, 22.5, 42.2, 62.1, 62.8, 74.5, 77.1, 112.1, 118.1, 128.3, 131.9, 143.2, 145.4, 160.0, 168.0, 173.9. IR (KBr): 2983, 2928, 2229, 1742, 1678, 1255, 1094, 756 cm^{-1}. ESI-MS: 410 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}N_3O_6$: C, 58.91, H, 5.46, N, 10.85. Found: 58.89, H, 5.48, N, 10.88. Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 1*H*, NH), 6.01 (dd, 1*H*, *J* = 10.57, 17.37 Hz, olefinic), 5.40–5.23 (m, 2*H*, olefinic), 4.30–4.19 (m, 4*H*, $2 \times$ O–CH_2) 3.53 (d, 1*H*, *J* = 17.37 Hz, H–CH_2), 2.94 (d, 1*H*, *J* = 17.37 Hz, H–CH_2), 1.37–1.20 (m, 6*H*, $2 \times CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.1, 41.0, 61.2, 62.3, 74.4, 116.9, 135.6, 142.3, 161.9, 172.1. IR (KBr): 3435, 2981, 2934, 1713, 1654, 1255, 1086, 1047, 714 cm^{-1}. ESI-MS: 263 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99, H, 6.71, N, 11.66. Found: 54.96, H, 6.69, N, 11.64. Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1*H*, NH), 5.82–5.71 (m, 1*H*, olefinic), 5.63–5.53 (m, 1*H*, olefinic), 4.32–4.18 (m, 4*H*, O–CH_2), 3.56 (d, 1*H*, *J* = 17.75 Hz, H–CH_2), 2.87 (d, 1*H*, *J* = 17.75 Hz, H–CH_2), 2.13–2.02 (m, 2*H*, CH_2), 1.40–1.23 (m, 6*H*, $2 \times CH_3$), 1.00 (t, 3*H*, *J* = 7.55 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ13.0, 14.03, 14.2, 25.4, 41.2, 61.2, 62.2, 74.2, 126.8, 135.0, 142.2, 162.2, 172.6. IR (KBr): 3350, 2964, 2926, 1735, 1706, 1243, 1118, 1032, 751 cm^{-1}. ESI-MS: 269 $[M+H]^+$. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.16; H, 7.55; N, 10.41.