Nucleophilic Behaviour of DBU and DBN toward Acetylated Baylis-Hillman Adducts

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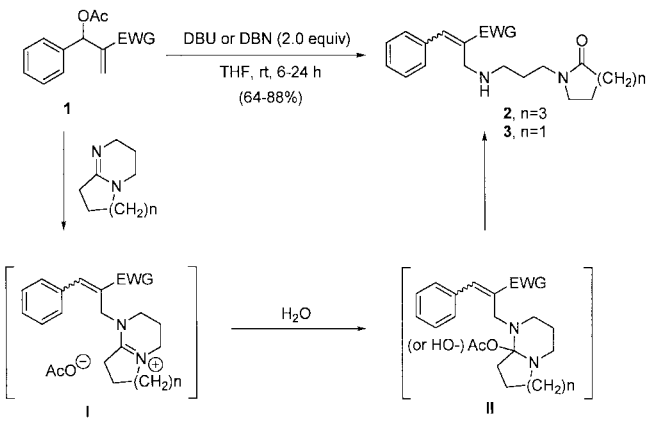
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) are known as non-nucleophilic, sterically hindered, strong tertiary amine bases.[1] They are widely used in organic synthesis, especially in dehydrohalogenation.[1] There have been reports where DBU or DBN act as a nucleophilic reagent.[2] For example, DBU acts as a nucleophile with 4-halo-3,5-dimethyl-1-nitro-1H-pyrazoles,[2a] methyl 3,5-dinitrobenzoate and 1,3,5-trinitrobenzene,[2b] diethyl maleate,[2c] 2-H heptafluorobut-2-ene,[2d] 1-halocyclopropane 1,2-diesters,[2e] and 1-bromo-4-benzoyloxy-imino-1,2,3,4-tetrahydrophenanthrene.[2f]

The Baylis-Hillman reaction is a well known coupling reaction between aldehydes and activated alkenes, catalyzed by tertiary amines or tertiary phosphines.[3-5] The reaction with ethyl acrylate serves α-methylene-β-hydroxy esters, which have been transformed to various useful compounds.[4,5]

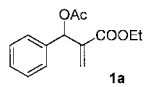
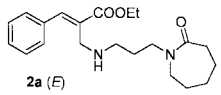
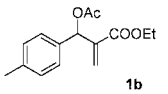
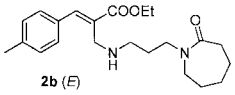
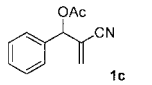
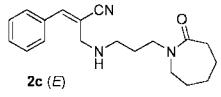
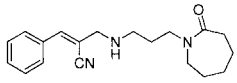
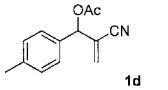
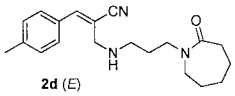
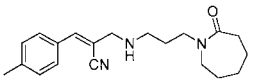
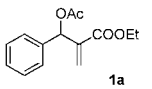
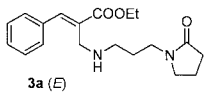
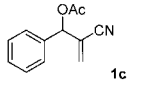
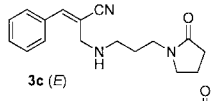
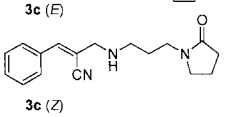
As continuing projects on the chemical transformation of the Baylis-Hillman adducts,[5] we have focused recently on the synthesis of 2-substituted naphthalenes from the Baylis-Hillman acetates **1** and primary nitroalkanes in the presence of a base.[6] During our study we found that ε-caprolactam derivatives were isolated in moderate yields when we used DBU as a base. We have investigated the reaction of various Baylis-Hillman acetates **1** with DBU and DBN and report here the results.

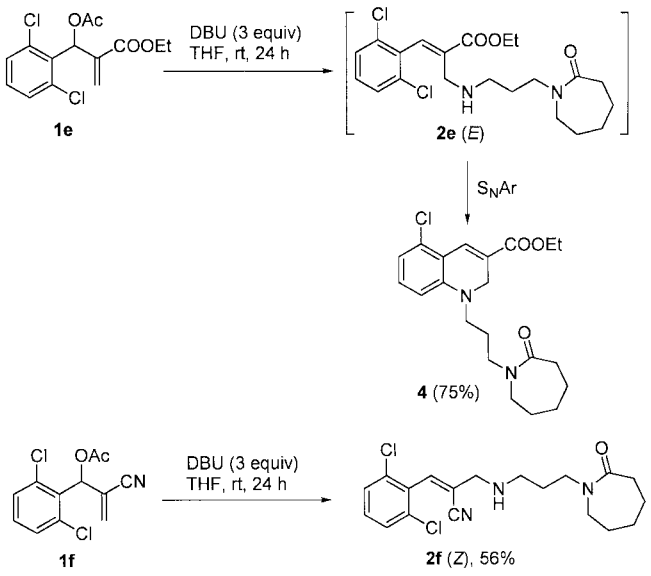
As shown in Scheme 1 and in Table 1, the reaction of **1a** and DBU (2 equiv) in tetrahydrofuran afforded ε-caprolactam derivative **2a** in 88% isolated yield. Similarly, the reaction of **1a** and DBN gave the γ-butyrolactam derivative **3a** in 73% isolated yield. The geometry of the double bonds of **2a** and **3a** is *E*-form. When we used the Baylis-Hillman acetates, **1a-b**, derived from ethyl acrylate, only *E*-isomer was obtained (entries 1, 2 and 5 in Table 1), whereas in cases of nitrile substituted acetates, **1c-d**, *E-Z* mixtures were obtained in variable ratios (entries 3, 4, and 6). The assignment of the stereochemistry was based on the chemical shift data of vinyl protons as indicated in our previous report.[5b,5d-e] The vinyl protons of ester-substituted *E*-form products appear



Scheme 1

Table 1. The reaction of Baylis-Hillman acetates 1 and DBU or DBN

Entry	Acetates (1)	Conditions	Products (**2-3**)	Yield (%)
1	 **1a**	DBU, THF rt, 24 h	 **2a** (*E*)	88
2	 **1b**	DBU, THF rt, 6 h	 **2b** (*E*)	81
3	 **1c**	DBU, THF rt, 15 h	 **2c** (*E*)	18
			 **2c** (*Z*)	46
4	 **1d**	DBU, THF rt, 24 h	 **2d** (*E*)	23
			 **2d** (*Z*)	46
5	 **1a**	DBN, THF rt, 20 h	 **3a** (*E*)	73
6	 **1c**	DBN, THF rt, 6 h	 **3c** (*E*)	23
			 **3c** (*Z*)	58



Scheme 2

around 7.77-7.80 ppm as a singlet. For the nitrile-substituted products, the vinyl protons of *Z*-form appeared around 7.08-7.13 ppm, whereas *E*-form was 7.20-7.44 ppm. To confirm the assignment of *E*:*Z* stereochemistry definitively, we examined the reaction with **1e** and **1f** as shown in Scheme 2. As expected, 1,2-dihydroquinoline derivative **4** was obtained from **1e** in 75% yield *via* the plausible intermediate (*E*)-**2e** under similar reaction conditions. From the reaction of **1f** and DBU we obtained (*Z*)-**2f** (56%) as the major product.[8] From the experiment, we conclude that *E*-form lactam derivatives are generated exclusively from the ester containing Baylis-Hillman acetates and *Z*-form as the major isomer from the nitrile substituted analogs.

The reaction mechanism is shown in Scheme 1. Nucleophilic substitution of **1** by DBU or DBN (S_N2' type) gave the corresponding cyclic amidinium salt **I**, which was trapped by the acetate anion or a molecule of H_2O present in the reaction mixture, giving the unstable hydroxy- or acetoxy-aminal derivative **II**-subsequently decomposing to the lactam derivatives **2-3** in 64-88% isolated yields. Cleavage of the intermediate **II** either to 9- (in the case of DBN) or 11-membered ring (in the case of DBU) did not occur.[2a,7] Treatment of the Baylis-Hillman adduct itself, instead of the acetate, with DBU resulted in the decomposition to benzaldehyde, *via* the retro-Baylis-Hillman reaction.[3]

In conclusion, we have elucidated an anomalous reaction of DBU or DBN with the Baylis-Hillman acetates, which forms the lactam derivatives.

Experimental Section

All materials and solvents were of reagent grade as received from commercial sources. Baylis-Hillman adducts were prepared as reported.[3,4] Acetylation of the Baylis-Hillman adducts was carried out with acetic anhydride and catalytic amounts of 4-(dimethylamino)pyridine.

General procedure for the preparation of 2-3: To a stirred solution of **1** (1 mmol) in THF (4 mL) was added slowly a solution of DBU or DBN (2 mmol) in THF (1 mL) at room temperature. After being stirred for the time given in Table 1, solvent was removed under reduced pressure and the residue was separated by column chromatography ($CHCl_3$/MeOH/EtOAc, 9 : 1 : 5) to give analytically pure **2-3**. Some representative spectroscopic data of products are listed as follows.

(*E*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-phenylacrylic acid ethyl ester (**2a**. *E*): oil; IR ($CHCl_3$) 1639, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 1.61-1.73 (m, 8H), 2.09 (br s, NH, 1H), 2.50-2.52 (m, 2H), 2.62 (t, J = 7.0 Hz, 2H), 3.30-3.33 (m, 2H), 3.42 (t, J = 7.0 Hz, 2H), 3.58 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 7.31-7.50 (m, 5H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.68, 23.81, 28.73, 29.05, 30.34, 37.61, 46.13, 46.46, 47.07, 49.92, 61.27, 128.83, 129.11, 129.88, 131.37, 135.59, 141.87, 168.38, 176.05.

(*E*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-*p*-tolylacrylic acid ethyl ester (**2b**. *E*): oil; IR ($CHCl_3$) 1637, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 1.61-1.74 (m, 8H), 2.09 (br s, NH, 1H), 2.36 (s, 3H), 2.48-2.52 (m, 2H), 2.63 (t, J = 7.1 Hz, 2H), 3.30-3.33 (m, 2H), 3.43 (t, J = 7.1 Hz, 2H), 3.58 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.78, 21.79, 23.90, 28.84, 29.15, 30.43, 37.70, 46.28, 46.57, 47.19, 50.00, 61.24, 129.66, 130.07, 130.61, 132.82, 139.35, 142.04, 168.56, 176.07.

(*E*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-phenylacrylonitrile (**2c**. *E*): oil; IR ($CHCl_3$) 1633, 2212 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62-1.73 (m, 8H), 1.92 (br s, NH, 1H), 2.48-2.52 (m, 2H), 2.62 (t, J = 6.6 Hz, 2H), 3.31-3.34 (m, 2H), 3.44 (t, J = 6.9 Hz, 2H), 3.60 (s, 2H), 7.31-7.44 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 23.34, 28.17, 28.51, 29.83, 37.12, 45.68, 45.97, 47.21, 49.44, 115.51, 119.87, 128.57, 129.29, 129.42, 133.59, 145.44, 175.73.

(*Z*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-phenylacrylonitrile (**2c**. *Z*): oil; IR ($CHCl_3$) 1630, 2210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61-1.74 (m, 8H), 2.00 (br s, NH, 1H), 2.48-2.51 (m, 2H), 2.63 (t, J = 6.6 Hz, 2H), 3.31-3.34 (m, 2H), 3.46 (t, J = 6.9 Hz, 2H), 3.54 (s, 2H), 7.13 (s, 1H), 7.35-7.77 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.11, 27.88, 28.28, 29.55, 36.87, 45.08, 45.33, 49.20, 53.23, 110.35, 118.21, 128.42 (2C), 129.76, 133.16, 143.35, 175.52.

(*E*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-*p*-tolylacrylonitrile (**2d**. *E*): oil; IR ($CHCl_3$) 1633, 2210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62-1.75 (m, 8H), 2.00 (br s, NH, 1H), 2.38 (s, 3H), 2.49-2.52 (m, 2H), 2.62 (t, J = 6.6 Hz, 2H), 3.31-3.34 (m, 2H), 3.44 (t, J = 7.0 Hz, 2H), 3.60 (s, 2H), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.39, 23.45, 28.25, 28.60, 29.96, 37.22, 45.75, 46.05, 47.36, 49.54, 114.41, 120.27, 129.42, 129.54, 130.91, 139.98, 145.66, 175.90.

(*Z*)-2-{[3-(2-Oxoazepan-1-yl)propylamino]methyl}-3-*p*-tolylacrylonitrile (**2d**. *Z*): oil; IR ($CHCl_3$) 1630, 2208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61-1.76 (m, 8H), 2.14 (br s, NH, 1H), 2.36 (s, 3H), 2.47-2.51 (m, 2H), 2.62 (t, J = 6.6 Hz, 2H), 3.31-3.34 (m, 2H), 3.45 (t, J = 6.8 Hz, 2H), 3.52 (s, 2H),

7.08 (s, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.79, 23.78, 28.49, 28.93, 30.25, 37.52, 45.64, 45.94, 49.85, 53.95, 109.51, 119.17, 129.14, 129.80, 131.06, 140.87, 144.15, 176.25.

(*E*)-2-{[3-(2-Oxopyrrolidin-1-yl)propylamino]methyl}-3-phenylacrylic acid ethyl ester (**3a**, *E*): oil; IR ($CHCl_3$) 1676, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 1.66-1.71 (m, 2H), 1.93-2.03 (m, 3H), 2.35 (t, J = 8.1 Hz, 2H), 2.61 (t, J = 7.1 Hz, 2H), 3.31-3.36 (m, 4H), 3.57 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 7.30-7.50 (m, 5H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.63, 18.21, 27.88, 31.30, 40.78, 46.07, 47.03, 47.44, 61.18, 128.78, 129.08, 129.82, 131.27, 135.50, 141.79, 168.25, 175.13.

(*E*)-2-{[3-(2-Oxopyrrolidin-1-yl)propylamino]methyl}-3-phenylacrylonitrile (**3c**, *E*): oil; IR ($CHCl_3$) 1672, 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65-1.74 (m, 2H), 1.88 (brs, NH, 1H), 1.95-2.05 (m, 2H), 2.37 (t, J = 8.1 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 3.32-3.39 (m, 4H), 3.60 (s, 2H), 7.30-7.44 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 19.70, 29.26, 32.78, 41.99, 47.85, 48.97, 49.04, 117.20, 121.77, 130.53, 131.24, 131.44, 135.40, 147.52, 176.93.

(*Z*)-2-{[3-(2-Oxopyrrolidin-1-yl)propylamino]methyl}-3-phenylacrylonitrile (**3c**, *Z*): oil; IR ($CHCl_3$) 1672, 2214 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68-1.77 (m, 2H), 1.93-2.03 (m, 3H), 2.34 (t, J = 8.1 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 3.36 (t, J = 6.8 Hz, 4H), 3.53 (s, 2H), 7.12 (s, 1H), 7.37-7.77 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.21, 27.72, 31.30, 40.40, 45.74, 47.49, 53.89, 110.85, 118.89, 129.12 (2C), 130.52, 133.74, 144.14, 175.40.

5-Chloro-1-[3-(2-oxoazepan-1-yl)propyl]-1,2-dihydroquinoline-3-carboxylic acid ethyl ester (**4**): oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6.9 Hz, 3H), 1.65-1.88 (m, 8H), 2.51-2.55 (m, 2H), 3.23 (t, J = 7.5 Hz, 2H), 3.34-3.37 (m, 2H), 3.44 (t, J = 7.2 Hz, 2H), 4.24-4.31 (m, 4H), 6.40 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.25, 23.35, 23.78, 28.68, 29.85, 37.16, 45.99, 48.11, 48.24, 49.64, 60.67, 108.98, 117.30, 118.07, 121.87, 131.32, 131.76, 134.43, 147.50, 165.23, 175.75.

(*Z*)-3-(2,6-Dichlorophenyl)-2-{[3-(2-oxoazepan-1-yl)propylamino]methyl} acrylonitrile (**2f**, *Z*): oil; IR ($CHCl_3$) 1633, 2222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61-1.79 (m, 8H), 1.96 (br s, NH, 1H), 2.50-2.54 (m, 2H), 2.70 (t, J = 6.6 Hz, 2H), 3.33-3.37 (m, 2H), 3.48 (t, J = 6.9 Hz, 2H), 3.63 (d, J = 1.5 Hz, 2H), 7.13 (s, 1H), 7.22-7.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 23.41, 28.20, 28.56, 29.90, 37.17, 45.27, 45.67, 49.53, 52.11, 116.48, 120.89, 128.13, 130.17, 132.25, 134.22, 138.69, 175.86.

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8. The corresponding 1,2-dihydroquinoline derivative might be formed from the corresponding **2f**-*E*. However, we cannot isolate it in pure state.