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

Yang Jin Im, Ji Hyeon Gong, Hyung Jin Kim, and Jae Nyoung Kim

Department of Chemistry and Institute of Basic Science, Chonnam National University, Kwangju 500-757, Korea

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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. They are widely used in organic synthesis, especially in dehalogenation. There have been reports where DBU or DBN act as a nucleophilic reagent. For example, DBU acts as a nucleophile with 4-halo-3,5-dimethyl-1-nitro-1H-pyrroles, methyl 3,5-dinitrobenzoate and 1,3,5-trinitrobenzene, diethyl maleate, 2-H heptafluorobut-2-ene, 1-halocyclopropane 1,2-di-esters, and 1-bromo-4-benzyloxymono-1,2,3,4-tetrahydrophenanthrene.

The Baylis-Hillman reaction is a well known coupling reaction between aldehydes and activated alkenes, catalyzed by tertiary amines or tertiary phosphines. The reaction with ethyl acrylate serves α-methylene-β-hydroxy esters, which have been transformed to various useful compounds. As continuing projects on the chemical transformation of the Baylis-Hillman adducts, 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. 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 nitro substituted acetates, 1c-d, E-Z mixtures were obtained in various 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. The vinyl protons of ester-substituted E-form products appear.

![Scheme 1](image-url)
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. From the experiment, we conclude that E-form lactam derivatives are generated exclusively from the ester containing Baylis-Hillman acetics and Z-form as the major isomer from the nitrile substituted analogs.

The reaction mechanism is shown in Scheme 1. Nucleophilic substitution of I by DBU or DBN (S=2 type) gave the corresponding cyclic aminal salt II, which was trapped by the acetate anion or a molecule of H₂O present in the reaction mixture, giving the unstable hydroxy- or acetoxy-aminal derivative III subsequently decomposing to the lactam derivatives 2-3 in 64–88% isolated yields. Cleavage of the intermediate III either to 9- (in the case of DBN) or 11-membered ring (in case of DBU) did not occur. Treatment of the Baylis-Hillman adduct instead, of the acetate, with DBU resulted in the decomposition to benzaldehyde, via the retro-Baylis-Hillman reaction.

In conclusion, we have elucidated an anomalous reaction of DBU or DBN with the Baylis-Hillman acetics, 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. 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 (CHCl₃/MeOH/CH₃CN, 9 : 1 : 5) to give analytically pure 2-3. Some representative spectroscopic data of products are listed as follows.

(3,3,3-Trimethyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2a, E): oil IR (CHCl₃) 1639, 1703 cm⁻¹. ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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, 168.28, 176.05.

(3-Isopropyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2b, E): oil IR (CHCl₃) 1637, 1703 cm⁻¹. ¹H NMR (CDCl₃) δ 1.35 (t, J = 7.1 Hz, 3H), 1.61–1.74 (m, 8H), 2.09 (br s, NH, 1H), 2.36 (s, 2H), 2.48–2.52 (m, 2H), 2.63 (t, J = 7.1 Hz, 2H), 3.20–3.22 (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). ¹³C NMR (CDCl₃) 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, 139.25, 142.04, 186.56, 176.07.

(3,3-Dimethyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2c, E): oil IR (CHCl₃) 1633, 2212 cm⁻¹. ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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.

(3,3,3-Trifluoromethyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2d, E): oil IR (CHCl₃) 1630, 2210 cm⁻¹. ¹H NMR (CDCl₃) 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), 7.25–7.77 (m, 5H). ¹³C NMR (CDCl₃) δ 23.11, 27.88, 28.25, 29.55, 36.87, 45.08, 45.33, 49.20, 53.23, 110.35, 118.21, 128.42 (2C), 129.76, 132.16, 143.35, 175.90.

(3,3-Dimethyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2e, E): oil IR (CHCl₃) 1633, 2210 cm⁻¹. ¹H NMR (CDCl₃) δ 1.61–1.74 (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). ¹³C NMR (CDCl₃) 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.

(3,3-Dimethyl-3,4-dihydro-2H-quinolin-2-yl)propylamine[1,4]-2-phenylacrylic acid ethyl ester (2f, E): oil IR (CHCl₃) 1633, 2210 cm⁻¹. ¹H NMR (CDCl₃) 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), 7.24–7.31 (m, 5H), 7.80 (s, 1H).
7.08 (s, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H); 13C NMR (CDCl3) 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, 131.66, 140.87, 144.15, 176.25.

(E)-2-[(E)-2-Oxoyrrolidin-1-yl]-propylamino[methyl]-1-3-phenyloxyacrylic acid ethyl ester (3a, E): oil; IR (CHCl3) 1676.1703 cm⁻¹; 1H NMR (CDCl3) δ 1.35 (t, J = 7.1 Hz, 3H), 1.66-1.71 (m, 2H), 1.93-2.03 (m, 5H), 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), 7.30-7.35 (m, 5H), 7.80 (s, 1H); 13C NMR (CDCl3) δ 14.63, 18.21, 27.88, 31.30, 40.78, 46.07, 47.03, 47.44, 61.18, 128.78, 129.08, 132.82, 131.27, 133.50, 141.79, 168.25, 176.13.

(Z)-2-[(Z)-2-Oxoyrrolidin-1-yl]-propylamino[methyl]-1-3-phenyloxyacrylic acid ethyl ester (3b, Z): oil; IR (CHCl3) 1672, 2210 cm⁻¹; 1H NMR (CDCl3) 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), 7.20-7.30 (m, 6H); 13C NMR (CDCl3) 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, 133.40, 147.52, 176.93.

(Z)-2-[(Z)-2-Oxoyrrolidin-1-yl]-propylamino[methyl]-1-(1,2-dihydroquinoline-3-carboxylic acid ethyl ester) (4): oil; 1H NMR (CDCl3) 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); 13C NMR (CDCl3) δ 14.25, 23.25, 23.78, 28.95, 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-(2-Dichlorophenyl)-1-2-[(Z)-2-oxoyrrolidin-1-yl]-propylamino[methyl]] acrylonitrile (2f, Z): oil; IR (CHCl3) 1652, 2222 cm⁻¹; 1H NMR (CDCl3) δ 1.61-1.79 (m, 8H), 1.96 (br s, NH), 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); 13C NMR (CDCl3) 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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References and Notes

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