Acrylamide in the Baylis-Hillman Reaction: Expanded Reaction Scope and the Unexpected Superiority of DABCO Over More Basic Tertiary Amine Catalysts

*Cornelia Faltin, Eimear M. Fleming and Stephen J. Connon**

Department of Chemistry, Trinity College Dublin, Dublin 2, Ireland.

connons@tcd.ie

Table of Contents

1.0 General	S3
2.0 Experimental details	S3
2.1 Kinetic studies on the hydroalkoxylation reaction (Table 1)	S3
2.2 Baylis-Hillman reaction involving acrylamide and various aldehydes	S4
2.3 Characterisation data for Baylis-Hillman adducts	S5
2-[Hydroxy(2-nitrophenyl)methyl]acrylamide (13)	S5
2-[Hydroxy(4-chlorophenyl)methyl]acrylamide (14)	S5
2-[Hydroxy(phenyl)methyl]acrylamide (4)	
S6	
2-[Hydroxy(2-naphthyl)methyl]acrylamide (15)	S6
2-[Hydroxy(4-methylphenyl)methyl]acrylamide (16)	S6
2-[Hydroxy(2-methylphenyl)methyl]acrylamide (17)	S7
2-[Hydroxy(2-methoxyphenyl)methyl]acrylamide (6)	S7
3.0 ¹H NMR Spectra	S8
2-[Hydroxy(2-nitrophenyl)methyl]acrylamide (13)	S8
2-[Hydroxy(4-chlorophenyl)methyl]acrylamide (14)	S8
2-[Hydroxy(phenyl)methyl]acrylamide (4)	
S9	
2-[Hydroxy(2-naphthyl)methyl]acrylamide (15)	S9
2-[Hydroxy(4-methylphenyl)methyl]acrylamide (16)	S10
2-[Hydroxy(2-methylphenyl)methyl]acrylamide (17)	S10
2-[Hydroxy(2-methoxyphenyl)methyl]acrylamide (6)	S11
Hydromethoxylation product (3a)	S11
Hydromethoxylation product (3a) – ¹³ C NMR and DEPT 135 spectra	S12

4.0 References**1.0 General**

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in CDCl₃ referenced relative to residual CHCl₃ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by either UV irradiation or KMnO₄ staining. Acrylamide, 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), quinuclidine, tri-*n*-butylphosphine, triethylamine (TEA), diisopropylethylamine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were obtained from commercial sources and used as received. DABCO could be recrystallised/sublimed before use, however this had no observable beneficial effect on reaction rates/yields. All liquid aldehydes, anisole and reaction solvents were distilled before use. *o*-Nitrobenzaldehyde was recrystallised from hexane prior to use.

2. Experimental Details**2.1 Kinetic studies on the hydroalkoxylation reaction (Table 1)**

A 1 mL vial equipped with a septum and a small stirring bar under Ar (balloon) was charged with a solution of the amine catalyst (1.0 mmol) and acrylamide (1.0 mmol) in MeOH (500 μ L). To this was added anisole (27 μ L, 0.25 mmol) *via* syringe (as an internal standard). Samples were taken periodically and analysed by ¹H NMR spectroscopy. Two sample *pseudo* 1st order rate plots are shown below for the hydromethoxylation reaction promoted by quinuclidine. The results are averaged to give the value shown in Table 1 (entry 4).

Note: For hydroalkoxylation reactions involving Bu_3P , the methanolic solvent was subjected to three freeze-thaw vacuum cycles before reaction.

2.2 Baylis-Hillman reaction involving acrylamide and various aldehydes

Procedure using condition set A: A 1 mL reaction vessel equipped with a stirring bar was charged with acrylamide (142 mg, 2.0 mmol), DABCO (224 mg, 2.0 mmol) and phenol (47 mg, 0.5 mmol). Note: If the aldehyde component is a solid it is added at this stage. The vessel was fitted with a septum, gently flushed with Ar gas and fitted with an Ar balloon. A $^t\text{BuOH}/\text{H}_2\text{O}$ solvent mixture (120 μL) and the aldehyde (3.0 mmol) were then added *via* syringe. The resulting homogeneous mixture was stirred at 55 $^\circ\text{C}$ for the time indicated in Table 3 and allowed to cool. Column chromatography of the reaction mixture (95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) yielded the required Baylis-Hillman adducts.

Procedure using condition set B: A 1 mL reaction vessel equipped with a stirring bar was charged with acrylamide (142 mg, 2.0 mmol), DABCO (224 mg, 2.0 mmol) and phenol (188 mg, 2.0 mmol). Note: If the aldehyde component is a solid it is added at this stage. The vessel was fitted with a septum, gently flushed with Ar gas and fitted with an Ar balloon. The aldehyde (3.0 mmol) was then added *via* syringe. The resulting mixture was heated to 55 °C (whereupon it became homogeneous) and stirred at this temperature for the time indicated in Table 3 and then allowed to cool. Column chromatography of the reaction mixtures (95:5 CH₂Cl₂/MeOH) yielded the required Baylis-Hillman adducts.

2.3 Characterisation data for Baylis-Hillman adducts¹

2-[Hydroxy(2-nitrophenyl)methyl]acrylamide (13)

Spectral data consistent with that reported in the literature²

M.p. 136-138 °C; IR (film) 3446, 3215, 2925, 1666, 1523 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.48 (s, 1H), 5.89 (s, 1H), 5.94 (d, 1H, J = 5.5 Hz), 6.05 (d, 1H, J = 5.5 Hz), 7.02 (s, 1H), 7.48 (t, 1H, J = 7.5 Hz), 7.57 (m, 2H), 7.65 (t, 1H, J = 7.5 Hz), 7.84 (d, 1H, J = 8.0 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 65.7, 118.3, 123.8, 128.3, 128.9, 132.8, 137.3, 146.2, 148.5, 168.1; HRMS (EI) *m/z* (MH⁺) calcd for C₁₀H₁₁N₂O₄ 223.0719, found 223.0712; Anal. Calcd for C₁₀H₁₀N₂O₄ C, 54.05; H, 4.54; N, 12.61. Found C, 53.85; H, 4.50; N, 12.37.

2-[Hydroxy(4-chlorophenyl)methyl]acrylamide (14)

M.p. 132-134 °C; IR (film) 3338, 3203, 2885, 1662, 1624, 1596, 1490 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.49 (d, 1H, J = 4.5 Hz), 5.62 (s, 1H), 5.78 (d, 1H, J = 4.5 Hz), 5.81 (s, 1H), 7.01 (s, 1H), 7.30 (d, 2H, J = 8.6 Hz), 7.35 (d, 2H, J = 8.6 Hz), 7.47 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 70.3, 117.6, 127.9, 128.6, 131.4, 142.4, 147.1, 168.5; HRMS (EI) *m/z* calcd for C₁₀H₁₀ClNO₂ 211.0400,

found 211.0412; Anal. Calcd for $C_{10}H_{10}ClNO_2$ C, 56.75; H, 4.76; N, 6.62. Found C, 56.48; H, 4.72; N, 6.45.

2-[Hydroxy(phenyl)methyl]acrylamide (4)

Spectral data consistent with that reported in the literature³

M.p. 97-99 °C; IR (film) 3331, 3212, 3031, 1665, 1626, 1594 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 5.49 (d, 1H, J = 4.5 Hz), 5.60 (s, 1H), 5.69 (d, 1H, J = 4.5 Hz), 5.79 (s, 1H), 6.98 (s, 1H), 7.22 (m, 1H), 7.30 (m, 4H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 71.1, 117.4, 126.7, 126.9, 127.9, 143.3, 147.5, 168.7; HRMS (EI) m/z calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0788; Anal. Calcd for $C_{10}H_{11}NO_2$ C, 67.78; H, 6.26; N, 7.90. Found C, 67.29; H, 6.23; N, 7.77.

2-[Hydroxy(2-naphthyl)methyl]acrylamide (15)

M.p. 132-134 °C; IR (film) 3332, 3212, 3056, 2973, 1665, 1626, 1597 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 1H), 5.44 (bs, 1H), 5.59 (s, 1H), 5.76 (s, 1H), 6.01 (s, 1H), 6.21 (bs, 1H), 7.49 (m, 3H), 7.84 (m, 3H) 7.91 (s, 1H); HRMS (EI) m/z calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0943; Anal. Calcd for $C_{14}H_{13}NO_2$ C, 73.99; H, 5.77; N, 6.16. Found C, 73.43; H, 5.67; N, 6.12.

2-[Hydroxy(4-methylphenyl)methyl]acrylamide (16)

M.p. 113-115 °C; IR (film) 3332, 3212, 2921, 1665, 1627, 1594 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6) δ 2.27 (s, 3H), 5.45 (d, 1H, J = 5.0 Hz), 5.58 (s, 1H), 5.60 (d, 1H, J = 5.0 Hz), 5.77 (s, 1H), 6.96 (s, 1H), 7.09 (d, 2H, J = 7.6 Hz), 7.17 (d, 2H, J = 7.6 Hz), 7.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 20.7, 70.9, 117.1, 126.7, 128.4, 136.0, 140.2, 147.6, 168.1; Anal. Calcd for $C_{11}H_{13}NO_2$ C, 69.09; H, 6.85; N, 7.32. Found C, 69.03; H, 6.84; N, 7.58.

2-[Hydroxy(2-methylphenyl)methyl]acrylamide (17)

M.p. 133-135 °C; IR (film) 3337, 3208, 2971, 1664, 1629, 1594 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.31 (s, 3H) 5.42 (d, 1H, $J = 4.0$ Hz), 5.44 (s, 1H), 5.66 (d, 1H, $J = 4.0$ Hz), 5.78 (s, 1H), 6.97 (s, 1H), 7.12 (m, 3H), 7.24 (m, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 23.5, 72.4, 122.0, 130.2, 131.3, 131.7, 134.7, 140.4, 145.7, 152.1, 168.3; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ 191.0946, found 191.0945.

2-[Hydroxy(2-methoxyphenyl)methyl]acrylamide (6)

M.p. 164-166 °C; IR (film) 3331, 3209, 2938, 1665, 1628, 1600, 1589 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.75 (s, 3H) 5.30 (s, 1H), 5.38 (s, 1H), 5.75 (s, 1H), 5.78 (s, 1H), 6.93 (m, 3H), 7.21 (m, 2H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 55.4, 65.0, 110.7, 117.9, 120.0, 127.2, 128.3, 130.9, 147.0, 156.3, 169.0; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_3$ 207.0895, found 207.0891; Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_3$ C, 63.76; H, 6.32; N, 6.76. Found C, 63.51; H, 6.41; N, 6.53.

3.0 ^1H NMR Spectra of selected Baylis-Hillman adducts and the addition product 3a

(Spectra obtained in DMSO- d_6 solvent unless otherwise stated)

test ☐

¹H, ¹³C and DEPT-135 spectra included⁴

□

Hydromethoxylation of acrylamide in MeOH catalysed by DMAP ($t = 1.16\text{h}$ - anisole added as an internal standard) showing signals assigned to ammonium intermediate **A**.

References

1. We would like to thank Prof. S. Blechert, Technische Universitaet Berlin, for HRMS and elemental analysis data.
2. Yu, C.; Hu, L. *J. Org. Chem.*, **2002**, 67, 219.
3. Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, 68, 692.

-
4. Dabi, S.; Zilkha, A. *Eur. Polym. J.* **1977**, *13*, 545