Nucleophilic Addition of 4-Hydroxycoumarin to Baylis–Hillman Acetate Adducts

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Abstract: The exploration of 4-hydroxycoumarin for nucleophilic addition on to Baylis–Hillman acetate adducts has been described for the first time. The reactions of various Baylis–Hillman acetate adducts were examined with 4-hydroxycoumarins in the presence of base to produce the corresponding 3-substituted 4-hydroxycoumarins in good yields.

Key words: Baylis–Hillman adduct, hydroxycoumarin, nucleophilic addition, 3-substituted coumarin, potassium carbonate

The Baylis–Hillman adducts (the products of Baylis–Hillman reactions) are multifunctional allylic alcohol derivatives that serve as extremely handy building blocks in organic synthesis.[1–7] In particular, Baylis–Hillman (BH) acetate adducts have received considerable attention in recent times, which undergo a variety of nucleophilic addition reactions often with good control of regioselectivity/stereoselectivity. Thus far, a number of substitution/addition reactions using various nucleophiles have been explored.[1,6,8,9] However, to the best of our knowledge 4-hydroxycoumarins have not been explored as nucleophiles in the addition reactions of BH acetate adducts. This addition reaction provides an easy access to 3-substituted 4-hydroxycoumarins, which are valuable derivatives in medicinal chemistry and for diversity oriented organic synthesis.[10–13]

In continuation of our work on BH acetate adducts,[14] herein, we report on the nucleophilic addition of 4-hydroxycoumarins on BH acetate adducts to produce the 3-substituted 4-hydroxycoumarins **3** for the first time (Scheme 1).

The initial reaction of BH acetate adduct **1a** with 4-hydroxycoumarin (**2a**) in the presence of potassium carbonate in anhydrous DMF at 75 °C afforded the corresponding 3-substituted 4-hydroxycoumarin **3a**. The reaction was complete in three hours to give the product in 92% yield with exclusive *E*-selectivity (Table 1, entry 1). The reaction did not proceed either at room temperature or in the absence of base. The stereochemistry of the product was established based on extensive 2D NMR studies including NOESY, DQFCOSY, and TOCSY experiments.

The *E*-stereochemistry of **3a** was assigned on the basis of ^{1}H and ^{13}C NMR chemical shifts in comparison with literature values.[15] The structure was supported by NOE cross peaks between H_a–H_b, H_a–H_i, H_e–H_g, and H_f–H_g (Figure 1).

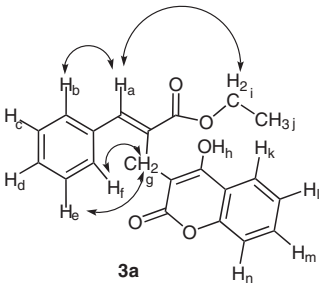
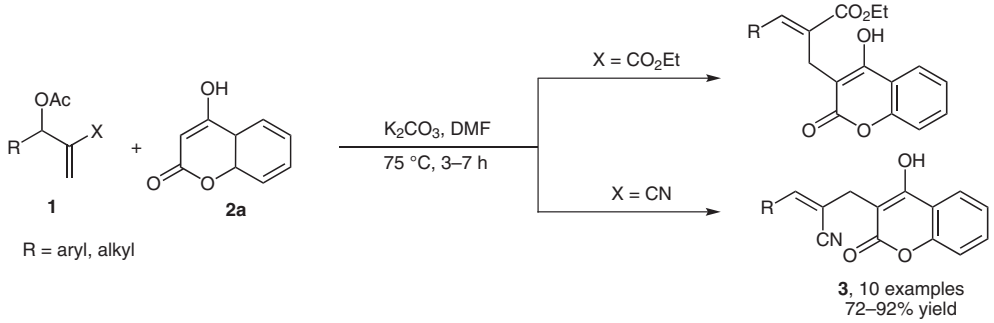


Figure 1 NOE cross-peak assignments for **3a**



Scheme 1

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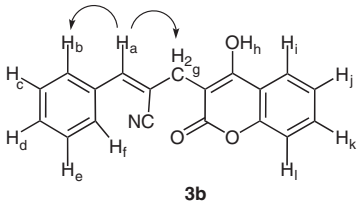
A second example employed **1b**, derived from benzaldehyde and acrylonitrile, with 4-hydroxycoumarin (**2a**) was also proceeded to give **3b** in good yield (82%) with exclusive *Z*-selectivity (entry 2). The structure of **3b** was supported by NOE cross peaks between H_a-H_b and H_a-H_g (Figure 2).



3b

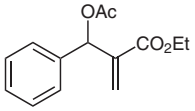
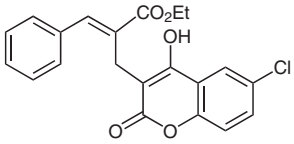
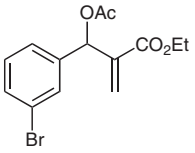
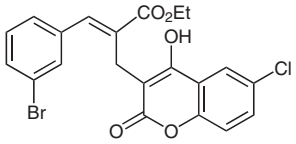
Figure 2 NOE cross-peak assignments for **3b**

To demonstrate the efficiency and scope, we applied the present method to a variety of BH acetate adducts derived from aromatic as well as aliphatic aldehydes and ethyl acrylate or acrylonitrile. The results indicated that the reactions proceeded well in DMF at 75 °C to give the corresponding substituted coumarins **3c–j** in good yields (Table 1). The reactions of BH adducts with ester group **1c–g** gave the *E*-isomers selectively (entries 3–8) while the BH adduct with nitrile group **1h** gave the *Z*-isomer predominantly (entry 8). Finally, the reactions of **1a** and **1c** with 7-chloro-4-hydroxycoumarin were also successful to provide the corresponding substituted coumarins **3i** and **3j**, respectively (entries 9 and 10), useful structural motifs for diversity, in good yields.

Table 1 Addition of 4-Hydroxycoumarin (**2a**) to BH Acetate Adducts[a]

Entry	BH acetate adduct	Time (h)	Product	Yield (%)[b]
1	**1a**	3.5	**3a**	92
2	**1b**	4	**3b**	82
3	**1c**	3.5	**3c**	85
4	**1d**	6	**3d**	72
5	**1e**	5	**3e**	89
6	**1f**	6	**3f**	73
7	**1g**	6	**3g**	78
8	**1h**	4	**3h**	82

Table 1 Addition of 4-Hydroxycoumarin (**2a**) to BH Acetate Adducts[a] (continued)

Entry	BH acetate adduct	Time (h)	Product	Yield (%)[b]
9[c]	**1a** 	3.5	**3i** 	86
10[c]	**1c** 	3.5	**3j** 	91

[a] Reaction conditions: K_2CO_3, DMF, 75 °C.
[b] Isolated yields.
[c] 7-Chloro-4-hydroxycoumarin (**2b**) was used as the nucleophile.

In conclusion, we have demonstrated first examples of a nucleophilic addition reaction of 4-hydroxycoumarins with Baylis–Hillman acetate adducts affording an efficient method to synthesize 3-substituted 4-hydroxycoumarins. This reaction should be useful due to the wide utility of these compounds in organic synthesis.

The chemicals such as 4-hydroxycoumarins, aldehydes used for the preparation of Baylis–Hillman adduct, and other reagents/catalysts were purchased from Aldrich and used as received. DMF was distilled over CaH_2. IR spectra were recorded on a Perkin-Elmer 683 spectrometer. ^{1}H (200 MHz, 300 MHz, and 600 MHz) and ^{13}C NMR (150 MHz and 50 MHz) spectra of samples in $CDCl_3$ were recorded on a Bruker Avance spectrometer. Chemical shifts are reported in ppm with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL mass spectrometer.

Nucleophilic Addition of 4-Hydroxycoumarins to Baylis–Hillman Acetate Adducts; General Procedure

To a stirred solution of the appropriate Baylis–Hillman acetate adduct **1** (1 mmol) in anhyd DMF (2 mL) was added K_2CO_3 (414 mg, 3 mmol) followed by the respective 4-hydroxycoumarin (0.95 mmol) and the mixture was stirred at 75 °C for the given time (Table 1). After completion of the reaction (monitored by TLC), the mixture was diluted with H_2O (3 mL). The product was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated under vacuum and the crude product was purified by column chromatography (eluent: hexanes–EtOAc) to afford the corresponding product.

3a

Colorless solid; mp 144.2–145.2 °C.

IR (KBr): 3403, 2925, 1706, 1657, 1620, 752 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.5 (s, 1 H, H_h), 7.92 (dd, $J_{H,H}$ = 8.0, 1.6 Hz, 1 H, H_k), 7.90 (s, 1 H, H_a), 7.69 (d, $J_{H,H}$ = 7.5 Hz, 2 H, H_f, H_b), 7.49 (m, 1 H, H_m), 7.47 (m, 1 H, H_d), 7.45 (m, 1 H, H_e), 7.39 (m, 1 H, H_c), 7.26 (dd, $J_{H,H}$ = 8.0, 7.0 Hz, 1 H, H_l), 7.23 (d, $J_{H,H}$ = 8.1 Hz, 1 H, H_n), 4.33 (q, $J_{H,H}$ = 7.1 Hz, 2 H, H_i), 3.81 (s, 2 H, H_g), 1.37 (t, $J_{H,H}$ = 7.1 Hz, 3 H, H_j).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.3, 163.5, 162.2, 152.5, 143.9, 135.0, 131.7, 129.5, 129.0, 128.4, 128.2, 123.8, 123.6, 116.7, 116.2, 102.9, 62.6, 22.6, 14.1.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}O_5$ + Na (M + Na)$^+$: 373.1051; found: 373.1055 and 351.1242.

3b

Off-white solid; mp 191.3–193.3 °C.

IR (KBr): 3227, 2925, 2210, 1669, 1632, 761 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$ + DMSO-d_6): δ = 11.1 (br s, 1 H, H_h), 8.02 (dd, $J_{H,H}$ = 8.0, 1.5 Hz, 1 H, H_i), 7.71 (d, $J_{H,H}$ = 8.2 Hz, 2 H, H_b, H_f), 7.54 (ddd, $J_{H,H}$ = 9.7, 7.2, 1.5 Hz, 1 H, H_k), 7.36 (m, 3 H, H_c, H_d, H_e), 7.33 (m, 1 H, H_l), 7.30 (m, 1 H, H_j), 7.14 (s, 1 H, H_a), 3.78 (d, $J_{H,H}$ = 1.4 Hz, 2 H, H_g).

^{13}C NMR (150 MHz, $CDCl_3$ + DMSO-d_6): δ = 163.6, 162.3, 152.8, 144.1, 133.8, 131.9, 129.8, 129.3, 128.7, 123.7, 123.6, 119.3, 116.6, 116.3, 108.1, 100.4, 22.6.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{13}NO_3$ + Na (M + Na)$^+$: 326.0793; found: 326.0790.

3c

Pale yellow solid; mp 131.0–131.8 °C.

IR (KBr): 3248, 2924, 1715, 1672, 1610, 1201, 759 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.4 (s, 1 H), 7.91 (d, *J* = 7.34 Hz, 1 H), 7.80 (s, 2 H), 7.69 (d, *J* = 7.34 Hz, 1 H), 7.48 (t, *J* = 7.34 Hz, 2 H), 7.37–7.20 (m, 3 H), 4.33 (q, *J* = 7.34 Hz, 2 H), 3.74 (s, 2 H), 1.38 (t, *J* = 7.34 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 163.6, 162.5, 152.7, 142.1, 137.2, 132.4, 132.0, 130.1, 129.8, 128.2, 124.0, 123.9, 122.6, 116.8, 116.4, 102.7, 62.9, 22.9, 14.2.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}BrO_5$ (M + H)$^+$: 429.0337; found: 429.0332.

3d

Off-white solid; mp 156.6–157.6 °C.

IR (KBr): 3081, 2925, 1710, 1672, 1618, 1100, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.4 (s, 1 H), 8.4 (s, 1 H), 8.25 (dd, *J* = 1.51, 8.30 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 7.92 (m, 2 H), 7.64 (t, *J* = 8.3 Hz, 1 H), 7.50 (dt, *J* = 1.51, 8.30 Hz, 1 H), 7.32–7.20 (m, 2 H), 4.36 (q, *J* = 6.79 Hz, 2 H), 3.74 (s, 2 H), 1.39 (t, *J* = 6.79 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 162.3, 154.0, 148.0, 140.8, 137.0, 135.2, 131.9, 130.9, 129.4, 124.2, 123.8, 123.4, 116.2, 116.4, 102.0, 63.0, 22.5, 14.0.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{17}NO_7$ + Na (M+ Na)$^+$: 418.0337; found: 418.0880.

3e
Pale yellow solid; mp 107–108 °C.

IR (KBr): 3423, 2923, 1708, 1657, 1604, 1261, 1174, 1091, 1028, 751 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 7.92 (d, *J* = 7.5 Hz, 1 H), 7.8 (m, 3 H), 7.5 (m, 1 H), 7.25 (m, 2 H), 6.94 (m, 2 H), 4.38 (q, *J* = 6.7 Hz, 2 H), 3.86 (s, 5 H), 1.38 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 164.0, 162.7, 160.6, 152.7, 143.8, 132.2, 131.8, 127.4, 125.8, 124.0, 123.8, 117.0, 116.3, 114.1, 103.1, 62.7, 55.5, 23.0, 14.3.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{21}O_6$ $(M + H)^+$: 381.1338; found: 381.1330.

3f
Pale yellow sticky liquid.

IR (KBr): 3422, 2925, 1734, 1667, 1618, 1166, 1030, 749 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.75 (s, 1 H), 7.9 (d, *J* = 8.3 Hz, 1 H), 7.8 (s, 1 H), 7.6 (s, 1 H), 7.5 (m, 1 H), 7.3 (m, 3 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.9 (d, *J* = 8.5 Hz, 1 H), 4.15 (q, *J* = 7.5 Hz, 2 H), 3.8 (s, 2 H), 2.1 (s, 3 H), 1.35 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 164.0, 162.7, 160.6, 152.7, 143.8, 132.2, 131.8, 127.4, 125.8, 124.0, 123.8, 117.0, 116.3, 114.1, 103.1, 55.5, 23.0, 14.3.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{20}O_7$ + Na $(M + Na)^+$: 431.1106; found: 431.1096.

3g
Pale yellow solid; mp 92–93 °C.

IR (KBr): 3415, 2925, 1707, 1661, 1621, 1306, 1107, 756 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 10.9 (s, 1 H), 7.88 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.48 (m, 1 H), 7.30–7.02 (m, 8 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 3.5 (s, 2 H), 3.02 (q, *J* = 7.0 Hz, 2 H), 2.79 (t, *J* = 7.0 Hz, 2 H), 1.34 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.3, 164.0, 162.4, 152.8, 148.4, 141.3, 131.8, 128.7, 128.5, 126.2, 124.0, 123.8, 116.9, 116.3, 103.0, 62.6, 35.0, 31.3, 22.1, 14.2.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{23}O_5$ $(M + H)^+$: 379.1545; found: 379.1544.

3h
Off-white solid; mp 202–204 °C.

IR (KBr): 3193, 2924, 2209, 1672, 1629, 1109, 763 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 7.99 (m, 1 H), 7.69 (m, 2 H), 7.6–7.2 (m, 5 H), 7.14 (s, 1 H), 3.74 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ = 163.5, 162.5, 152.8, 144.1, 143.2, 134.2, 132.7, 131.9, 130.7, 130.4, 129.6, 127.5, 124.0, 123.6, 116.6, 116.3, 111.9, 100.0, 24.4.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{12}N_2O_5$ + Na (M + Na)$^+$: 371.0643; found: 371.0637.

3i
Colorless solid; mp 167.8–169.8 °C.

IR (KBr): 3415, 2929, 1716, 1663, 1622, 1265, 761 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 10.7 (br s, 1 H), 7.9 (m, 2 H), 7.65 (m, 2 H), 7.55–7.35 (m, 4 H), 7.20–7.12 (m, 1 H), 4.3 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 2 H), 1.4 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5, 163.1, 161.3, 151.1, 144.4, 135.1, 131.8, 129.7, 129.3, 129.2, 128.7, 128.2, 123.6, 118.1, 117.8, 104.0, 62.9, 22.9, 14.3.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}ClO_5$ $(M + H)^+$: 385.0842; found: 385.0845.

LCMS: *m*/*z* = 385 $(M + H)^+$.

3j
Colorless solid; mp 144.2–146.2 °C.

IR (KBr): 3248, 2928, 1715, 1666, 1622, 1260, 756 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 10.6 (br s, 1 H), 7.95 (m, 3 H), 7.62 (m, 1 H), 7.55–7.21 (m, 4 H), 4.3 (q, *J* = 7.0 Hz, 2 H), 3.75 (s, 2 H), 1.4 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 161.4, 151.1, 142.5, 137.1, 132.4, 132.1, 131.9, 130.2, 129.5, 129.4, 128.1, 123.6, 122.7, 118.0, 117.9, 103.6, 63.1, 22.9, 14.2.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{16}BrClO_5$ + Na $(M + Na)^+$: 484.9767; found: 484.9764.

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