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Zinc mediated propenylation of Baylis–Hillman acetates☆

P. Srihari,* Ashutosh Pratap Singh, A. K. Basak and J. S. Yadav

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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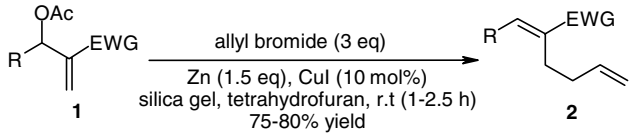
Abstract—Allyl bromide efficiently reacts with Baylis–Hillman acetates in the presence of zinc and copper iodide resulting in substituted 1,5-dienes.

The Baylis–Hillman reaction is an important C–C bond forming reaction that affords multifunctional synthetic intermediates. It has been well documented and numerous applications of the derived acetates have been described.[1] Organic intermediates possessing a terminal olefin moiety play an important role as essential handles for synthetic organic chemists to construct targets[2] as exemplified by their utilization in reactions such as olefin metathesis. Towards this direction, the addition of allyl bromide is a straightforward reaction for the preparation of terminal olefins and is generally achieved by addition, viz. Grignard reactions[3] or allylations in the presence of various metals/metallic salts[4] or through Lewis acid catalyzed allyltrimethylsilane[5] or allyltributyltin addition[6] to carbonyl compounds, acetals, imines or electrophilic carbons, including α,β-unsaturated compounds involving 1,2- or 1,4-additions.

The addition of alkyl and aryl groups to Baylis–Hillman adducts is a recent development for new scaffold synthesis.[7] Surprisingly, however, simple addition of allyl bromide (1-bromo-2-propene) is not successful under established reaction conditions. In continuation of our studies on utilizing Baylis–Hillman acetates for addition reactions,[8] herein, we disclose a modified protocol for creating new C–C bonds between 1-bromo-2-propene and various Baylis–Hillman acetates that results in 1,5-diene derivatives.

Initially, we expected that a 1,4-addition would be achieved by simple addition of allyl bromide to a mixture of Baylis–Hillman acetate in the presence of zinc (1.5 mmol) and copper iodide (10 mol %) in THF, but surprisingly, there was no reaction. However, when the reaction was repeated in the presence of silica gel, a significant change in the TLC was observed. Within 2 h the starting material was completely consumed leading to a single spot that was characterized as the allylated product by spectroscopic analysis (see Scheme 1).

Encouraged by this result, several other Baylis–Hillman acetates were studied to determine the scope of the reaction. Adducts possessing aryl groups bearing electron withdrawing and electron donating moieties responded well affording 75–80% yields. Also, aliphatic substrates (**1h**–**j**) were found to yield the expected products in good yields (Table 1). However, when Baylis–Hillman acetates containing nitriles were subjected to this protocol, the reaction led to diminished yields (~5–10%) of the desired product along with unwanted side reactions and complete consumption of the starting material.[9] Other bromides such as crotyl bromide, benzyl bromide and propargyl bromide did not yield the expected products under the present conditions.



EWG = CO_2Me, CO_2Et
R = Ar, ethyl, propenyl, *n*-pentyl

Scheme 1.

Keywords: Baylis–Hillman acetates; Allyl bromide; Metathesis; Allyl trimethylsilane; 1,5-Diene.
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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: srihari@iict.res.in

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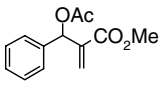
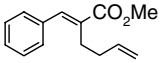
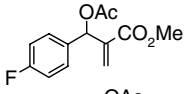
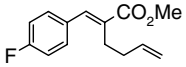
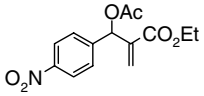
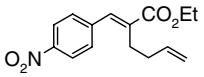
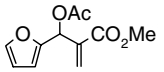
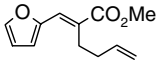
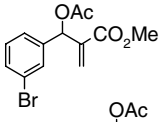
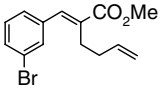
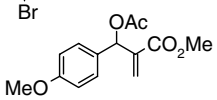
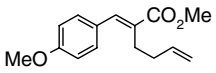
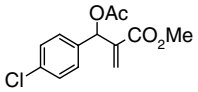
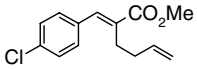
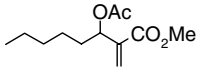
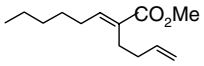
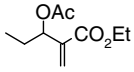
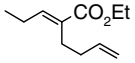
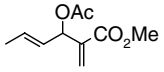
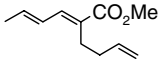
Table 1. Allylation of Baylis–Hillman (BH) acetates

Entry	BH acetate **1**	Product[a] **2**	Time (h)	Yield[b] (%)‘	*E*/*Z*[c] (%)
a			2.0	75	95:5
b			1.5	77	78:22
c			2.5	78	89:11
d			1.5	77	68:32
e			2.0	80	91:9
f			2.5	79	91:9
g			1.0	80	90:10
h			1.5	80	80:20
i			1.5	75	82:18
j			1.5	78	78:22

[a] All products were characterized by IR, ^{1}H, ^{13}C NMR and mass spectroscopy.
[b] Isolated and unoptimized yields.
[c] Ratio was determined based on LCMS analysis.

Mechanistically, it is assumed that silica gel activates the zinc metal to form allyl zinc bromide, which in the presence of a catalytic amount of copper iodide takes part in allylic S_N2 substitution. However, no further efforts were made to study the exact mechanism. The geometry of the major isomer was assigned based on NOE studies of the representative examples **2b** and **2e**, where a strong NOE was observed between the benzylic proton and the methoxy group of the carboxylic ester (see Fig. 1).

In conclusion, an efficient procedure for propenylation of Baylis–Hillman acetates in the presence of allyl bromide, zinc, copper iodide and silica gel is described. The resulting 1,5-dienes may find further use in synthetic chemistry. Further work on the applications of these 1,5-dienes is in progress.

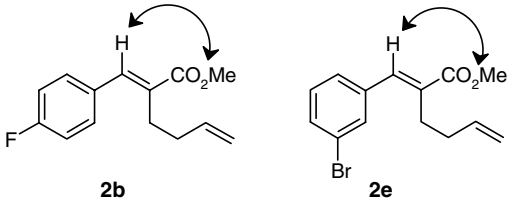


Figure 1.

General procedure. A mixture of zinc (1.5 mmol), CuI (0.1 mmol) and silica gel (400 mesh, 200 mg) was stirred for 10 min before the addition of allyl bromide (3 mmol). The resulting mixture was stirred at room temperature for 15 min before adding a solution of Baylis–Hillman acetate (1 mmol) in anhydrous THF (5 mL). After stirring for the specified time mentioned in the Table, THF was evaporated and the crude mixture was purified by column chromatography.[10]

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9. No attempts were made to characterize the byproducts formed when the nitrile-containing compounds were used.
10. Spectroscopic data for the products *(E)-Methyl 2-benzylidenehex-5-enoate* (**2a**). Liquid. IR (neat): ν 3076, 2922, 2851, 1952, 1636, 1494, 1374, 1258, 1128, 1084, 913, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.18–2.27 (m, 2H), 2.51–2.59 (m, 2H), 3.80 (s, 3H), 4.94–4.87 (m, 2H), 5.68–5.82 (m, 1H), 7.25–7.40 (m, 5H), 7.64 (s, 1H). EIMS *m/z* (%) 216 (M^+, 10), 186 (20), 176 (20), 158 (15), 142 (30), 130 (30), 116 (100), 92 (60), 69 (50), 55 (60), 41 (95). Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.64; H, 7.50. *(E)-Methyl 2-(4-fluorobenzylidene)hex-5-enoate* (**2b**). Liquid. IR (neat): ν 3075, 2927, 1716, 1640, 1508, 1435, 1369, 1228, 1126, 1019, 915, 830 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.20–2.36 (m, 2H), 2.53–2.65 (m, 2H), 3.81 (s, 3H), 4.92–5.10 (m, 2H), 5.69–5.93 (m, 1H), 6.99–7.12 (m, 2H), 7.28–7.38 (m, 2H), 7.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.10, 33.38, 52.19, 115.49, 116.06, 131.28, 132.00, 132.82, 137.75, 138.45, 161.23, 168.51. EIMS *m/z* (%) 234 (M^+, 10), 168 (20), 154 (30), 140 (100), 81 (20), 69 (40), 55 (35), 41 (50). Anal. Calcd. for $C_{14}H_{15}FO_2$: C, 71.78; H, 6.45. Found: C, 70.96; H, 6.79. *(E)-Ethyl 2-(4-nitrobenzylidene)hex-5-enoate* (**2c**). Liquid. IR (neat): ν 2923, 2853, 1706, 1641, 1461, 1238, 1130, 1045, 928, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, $J = 6.8$ Hz), 2.22–2.39 (m, 2H), 2.50–2.69 (m, 2H), 4.30 (q, 2H, $J = 6.8$ Hz), 4.90–5.32 (m, 2H), 5.45–6.04 (m, 1H), 7.50 (d, 2H, $J = 8.5$ Hz), 7.66 (s, 1H), 8.28 (d, 2H, $J = 8.5$ Hz). EIMS *m/z* (%) 275 (M^+, 10), 205 (7), 169 (20), 155 (40), 141 (100), 116 (10), 98 (8), 69 (20), 55 (40). *(E)-Methyl 2-(furan-2-ylmethylene)hex-5-enoate* (**2d**). Liquid IR (neat): ν 3076, 2948, 2851, 1709, 1634, 1551, 1434, 1367, 1261, 1128, 1086, 915, 746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.15–2.35 (m, 2H), 2.74–2.87 (m, 2H), 3.78 (s, 3H), 4.90–5.22 (m, 2H), 5.60–6.02 (m, 1H), 6.45 (dd, 1H, $J = 1.5$, 3.1 Hz), 6.58 (d, 1H, $J = 3.1$ Hz), 7.38 (s, 1H), 7.51 (s, 1H). EIMS *m/z* (%) 206 (M^+, 40), 175 (20), 165 (60), 111 (20), 105 (20), 91 (15), 77 (25), 55 (45), 41 (100). Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.77; H, 6.58. *(E)-Methyl 2-(3-bromobenzylidene)hex-5-enoate* (**2e**). Liquid. IR (neat): ν 2924, 2853, 1727, 1595, 1461, 1378, 1269, 1124, 1073, 914, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.27–2.38 (m, 2H), 2.58–2.64 (m, 2H), 3.84 (s, 3H), 4.99–5.34 (m, 2H), 5.76–5.90 (m, 1H), 7.25–7.29 (m, 2H), 7.43–7.49 (m, 1H), 7.53(s, 1H), 7.59 (s, 1H). EIMS *m/z* (%) 295 (M^++1, 10), 204 (50), 173 (60), 144 (70), 114 (68), 70 (60), 42 (100). Anal. Calcd. for $C_{14}H_{15}BrO_2$: C, 56.97; H, 5.12. Found C, 56.89; H, 5.08. *(E)-Methyl 2-(4-methoxybenzylidene)hex-5-enoate* (**2f**). Liquid. IR (neat): ν 3074, 2950, 2841, 1707, 1605, 1510, 1437, 1303, 1253, 1128, 1032, 912, 828, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25–2.44 (m, 2H), 2.45–2.65 (m, 2H), 3.82 (s, 3H), 3.86 (s, 3H) 4.90–5.05 (m, 2H), 5.73–5.95 (m, 1H), 6.92 (d, 2H, $J = 8.3$ Hz), 7.35 (d, 2H, $J = 8.3$ Hz), 7.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 32.0, 51.8, 55.2, 114.8, 114.0, 128.0, 129.6, 133.6, 133.7, 137.8, 159.8, 169.0. EIMS *m/z* (%) 246 (M^+ 15), 205 (60), 151 (10), 146 (100), 131 (20), 115 (25), 103 (30) 77 (30), 59 (25), 41 (30). Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found C, 73.20; H, 7.30. *(E)-Methyl 2-(4-chlorobenzylidene)hex-5-enoate* (**2g**). Liquid IR (neat): ν 2922, 2852, 1725, 1638, 1490, 1091, 1089, 913, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25–2.35 (m, 2H), 2.36–2.53 (m, 2H), 3.65 (s, 3H), 4.85–5.15 (m, 2H), 5.63–5.90 (m, 1H), 7.13 (d, 2H, $J = 8.0$ Hz), 7.30 (d, 2H, $J = 8.0$), 7.50 (s, 1H). LCMS *m/z* (251, M^++1). *(E)-Methyl 2-(but-3-enyl) oct-2-enoate* (**2h**). Liquid. IR (neat): ν 2925, 2854, 1716, 1638, 1458, 1260, 1089, 1021, 913, 805 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 0.92 (t, 3H, $J = 6.8$ Hz), 1.20–1.55 (m, 6H), 2.05–2.24 (m, 4H), 2.25–2.45 (m, 2H), 3.74 (s, 3H), 4.87– 5.12 (m, 2H), 5.63–5.90 (m, 1H), 6.72 (t, 1H, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 29.0, 31.5, 22.4, 28.4, 28.5, 32.3, 51.4, 114.7, 131.3, 138.0, 143.4, 168.2. LCMS *m/z* (233, M^++Na). *(E)-Ethyl 2-propylidenehex-5-enoate* (**2i**). Liquid IR (neat): ν 2924, 2852, 1739, 1641, 1460, 1371, 1235, 1091, 1021, 913, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.5$ Hz), 1.07 (t, 3H, $J = 6.8$ Hz), 2.02–2.08 (m, 2H), 2.13–2.23 (m, 2H), 2.33–2.42 (m, 2H), 4.20 (q, 2H, $J = 6.8$ Hz) 4.87–5.20 (m, 2H), 5.70–5.88 (m, 1H), 6.71 (t, 1H, $J = 7.3$ Hz). EIMS *m/z* (%) 183 (M^++1, 5), 167 (10), 155 (25), 141 (80), 125 (5), 111 (10), 97 (50), 83 (60), 71 (80) 57 (98), 43 (100). *(2E,4E)-Methyl 2-(but-3-enyl)hexa-2,4-dienoate* (**2j**). Liquid IR (neat): ν 2926, 2859, 1706, 1634, 1490, 1354, 1244, 1097, 1080, 937, 725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (d, 3H, $J = 6.8$ Hz), 2.19–2.30 (m, 2H), 2.38–2.56 (m, 2H), 3.81 (s, 3H), 4.99–5.12 (m, 2H), 5.77–6.22 (m, 2H), 6.41 (d, 1H, $J = 11.1$ Hz), 7.03–7.26 (m, 1H). LCMS *m/z* (180, M^+).