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The use of acetylenic aldehydes in Baylis–Hillman reactions: synthesis of versatile allyl propargyl alcohols☆

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Abstract—The utility of acetylenic aldehydes in Baylis–Hillman reactions giving allyl propargyl alcohols in moderate to good yields is reported. © 2003 Elsevier Science Ltd. All rights reserved.

Chiral propargyl and allyl propargyl alcohols are important intermediates for the synthesis of hydroxylated fatty acids,[1] natural products such as alkaloids,[2] pyrethroids,[3] avenaciolide,[4] steroids,[5] pheromones,[6] vitamin E,[7] and prostaglandins,[8] and biologically active prostacyclin mimetics.[9] The Baylis–Hillman reaction of an acetylenic carbonyl compound with an activated alkene could be utilized for the formation of allyl propargyl alcohols. However, acetylenic compounds have less frequently been used in Baylis–Hillman reactions. For instance, the reaction of 3-butyn-2-one[10] with ethyl acrylate in the presence of DABCO did not provide the expected Baylis–Hillman adduct, but resulted in self condensation to form a divinyl ether. However, prop-2-yn-1-al and 1-phenylprop-2-yn-1-one have been used in the chalcogen Baylis–Hillman reaction.[11] In continuation of our work on chiral allyl propargyl alcohols[12] and Baylis–Hillman reactions,[13] herein a study on the use of acetylenic aldehydes for the synthesis of allyl propargyl alcohols by Baylis–Hillman reactions is reported (Eq. (1)). It is interesting to note that tertiary hydroxy esters[14] which form an important part of the structures of many natural products such as *S*-oxybutynin, may be accessed from these adducts.

(1)

All the primary alkynyl alcohols, the precursors of the acetylenic aldehydes used in this study, were synthesized from the commercially available terminal alkynes by reported procedures.[15] For example, phenyl acetylene on reaction with EtMgBr under Grignard conditions followed by treatment with formaldehyde gave the corresponding primary alkynyl alcohol. The alkynyl alcohol thus obtained on oxidation with iodoxybenzoic acid (IBX) provided 3-phenyl-2-propynal **1** in 90% yield, which was subjected to a Baylis–Hillman reaction with ethyl acrylate **4** in the presence of DABCO (0.5 equiv.) in THF at room temperature. The reaction gave only a moderate yield of the adduct **7a** in 45% yield after two days, but the same reaction was completed within 15 h in DMSO in the presence of 50 mol% of DABCO giving a 74% yield of the product **7a**. Subsequently, the aldehyde **1** when treated with methyl vinyl ketone **5** and 1,2:5,6-di-*O*-isopropylidene-3-*O*-acrylate-α-D-glucopentoaldo-1,4-furanose **6** in DMSO afforded the corresponding Baylis–Hillman adducts **7b** and **7c** in good yields (Scheme 1, Table 1).

This method was then extended to other acetylenic aldehydes such as 2-nonynal **2** and 5-benzyloxy-2-pentynal **3** to provide the desired products **8a**–**c**, and **9a**–**c**, respectively (Table 1). To increase the scope of this methodology for realizing the synthesis of chiral allyl propargyl alcohols, this reaction was performed using **6** as a chiral acrylate. The diastereoselectivity observed in the adducts **7c**, **8c** and **9c** corresponded to 30, 44 and 24% *de*'s, respectively, as determined by ^{1}H NMR. The absolute stereochemistry at the newly created center of the major isomer was assigned based on our earlier report,[13] which describes the use of the same chiral acrylate **6** for asymmetric Baylis–Hillman reactions

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Keywords: chiral allyl propargyl alcohols; acetylenic aldehydes; Baylis–Hillman reactions; DABCO and chiral acrylates.

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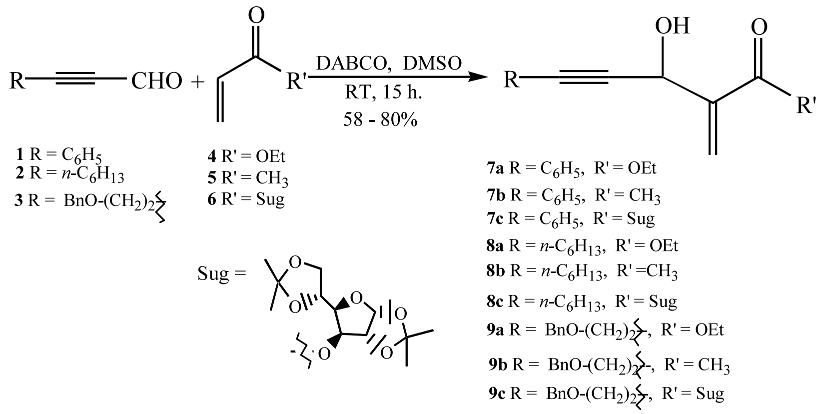

Scheme 1.

Table 1. Baylis–Hillman reaction of acetylenic aldehydes with activated alkenes[16,17]

S. No.	Acetylenic aldehyde	Activated alkene	Yield[a] (%)
1	**1**	**4**	**7a**, 74
2	**2**	**4**	**8a**, 80
3	**3**	**4**	**9a**, 75
4	**1**	**5**	**7b**, 67
5	**2**	**5**	**8b**, 59
6	**3**	**5**	**9b**, 61
7	**1**	**6**	**7c**, 58 (30% *de*)[b]
8	**2**	**6**	**8c**, 64 (44% *de*)[b]
9	**3**	**6**	**9c**, 72 (24% *de*)[b]

[a] Yields of isolated products.

[b] As determined by ^{1}H NMR.

with aromatic aldehydes. It is pertinent to mention that the earlier study resulted in establishing the stereochemistry as *R* by chemical correlation with an independently synthesized optically pure compound. Similarly, the absolute stereochemistry at the newly created center of the major isomer of all adducts obtained in the present study was assigned as (*R*)-**7c**, (*R*)-**8c** and (*R*)-**9c**.

In conclusion, it has successfully been demonstrated that acetylenic aldehydes can be used in Baylis–Hillman reactions for the synthesis of allyl propargyl alcohols. The asymmetric version of this reaction using other chiral acrylates is currently under investigation.

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16. *General experimental procedure*: To the acetylenic aldehyde (1 mmol) in DMSO (1 mL), DABCO (0.5 mmol) and activated alkene (1.2 mmol) were added and the reaction mixture stirred for 15 h at room temperature. Then the reaction mixture was partitioned between ether (3×15 mL) and water (25 mL), the collected organic layer

was washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc:hexane, 1:9) to afford adducts **7a**–**c**, **8a**–**c** and **9a**–**c** in 58–80% yield.

17. *Spectral data for selected compounds*: **7a**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.50–7.40 (m, 2H, Ar-H), 7.38–7.25 (m, 3H, Ar-H), 6.34 (s, 1H, olefinic), 6.18 (s, 1H, olefinic), 5.39 (s, 1H, allylic), 4.30 (q, 2H, $J=7.5$ Hz, -CH_2-), 3.12 (br. s, 1H, -OH), 1.40 (t, 3H, $J=7.5$ Hz, -CH_3); FABMS: m/z 229 (M^+-1). Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03, H, 6.13. Found: C, 73.15, H, 6.08. **7b**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.48–7.29 (m, 5H, Ar-H), 6.80 (s, 1H, olefinic), 6.00 (s, 1H, olefinic), 5.62 (s, 1H, allylic), 2.38 (s, 3H, -CH_3); FABMS: m/z 202 (M^++2). Anal. calcd for $C_{13}H_{12}O_2$: C, 77.98, H, 6.04. Found: C, 77.87, H, 6.06. **7c**. $[\alpha]_D=-20.73$ (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.52–7.24 (m, 5H, Ar-H), 6.37 (s, 0.65H, olefinic), 6.35 (s, 0.35H, olefinic), 6.24 (s, 0.65H, olefinic), 6.08 (s, 0.35H, olefinic), 5.80 (d, 1H, $J=4.2$ Hz, H-1), 5.42 (s, 0.65H, allylic), 5.27 (s, 0.35H, allylic), 5.24 (d, 1H, $J=2.5$ Hz, H-3), 4.58 (d, 0.65H, $J=4.2$ Hz, H-2), 4.54 (d, 0.35H, $J=4.2$ Hz, H-2), 4.24–4.16 (m, 2H, H-4, 5), 4.08–3.94 (m, 2H, H-6,6′), 1.50 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.24 (s, 6H, 2×CH_3); FABMS: m/z 444 (M^+). Anal. calcd for $C_{24}H_{28}O_8$: C, 64.85, H, 6.35. Found: C, 64.79, H, 6.27.