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Novel protocol for the generation of β-branched Baylis–Hillman adducts from ethyl sorbate and aryl aldehydes☆

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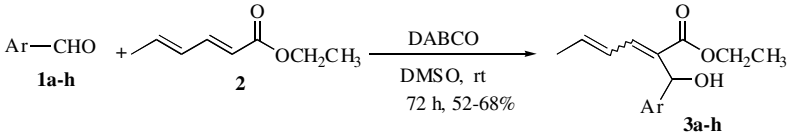
Abstract—A novel protocol for the generation of β-branched Baylis–Hillman adducts in moderate yields (52–68%) as *E*/*Z* mixtures from commercially available dienoates such as ethyl sorbate and aryl aldehydes catalyzed by DABCO in DMSO is reported.

The construction of C–C bonds is an important task in the field of synthetic organic chemistry.[1] The Baylis–Hillman reaction is recognized as a versatile and economically favourable C–C bond forming reaction for generating multifunctional adducts[2] as useful synthons.[3] Because synthesis of multi-functionalized alkenes is an important goal in organic chemistry,[4] Lewis acid catalyzed β-halo Baylis–Hillman adducts[5] gained prominence and were synthesized from propargylic acids or ketones and aldehydes, but less importance has been attached to β,β-disubstituted[6] or β-branched adducts. As part of our continued interest in the Baylis–Hillman reaction,[7] herein we describe a practical protocol for the preparation of β-branched adducts for the first time using the commercially available dienoate, ethyl sorbate, as a Michael acceptor and various aldehydes in the presence of DABCO in DMSO at room temperature (Eq. 1).

To optimize the reaction conditions, **1a** was treated with **2** in DMSO, sulfolane, 1,4-dioxane/H_2O (1:1), dimethylformamide, tetrahydrofuran, and in the presence of a variety of bases such as DABCO, DBU, DMAP, Et_3N and *N*-ethyl diisopropylamine. The optimum results were obtained when the reaction was conducted in DMSO and catalyzed by DABCO to afford adduct **3a** (65%) at ambient temperature in 72 h. The adduct **3a** was isolated as an *E*/*Z* mixture presumably because of free rotation prior to elimination of DABCO in the product-forming step. The scope of this reaction was extended when aryl aldehydes **1b–h** were reacted with **2** under optimized reaction conditions to afford adducts **3b–h**, respectively, in moderate yields (Table 1).[8] The yields of all the products are reported as the combined yield of both geometrical isomers. However, an attempt to extrapolate the protocol to less reactive aldehydes was not fruitful.



(1)

Keywords: Ethyl sorbate; β-Branched adducts; DABCO; DMSO; *E*/*Z* mixture.
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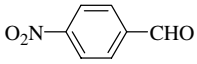
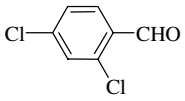
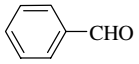
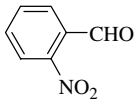
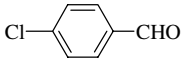
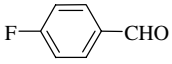
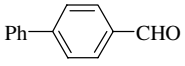
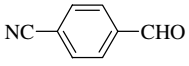
Table 1. Baylis–Hillman reaction of various aryl aldehydes with ethyl sorbate catalyzed by DABCO in DMSO at room temperature[a]

Entry	Aldehyde	Product[b]	Yield[c]	*E*,*E*/*E*,*Z*[d]
1		**3a**	65	65/35
2		**3b**	68	70/30
3		**3c**	66	70/30
4		**3d**	61	65/35
5		**3e**	64	70/30
6		**3f**	54	70/30
7		**3g**	52	70/30
8		**3h**	65	70/30

[a] All the reactions were conducted as described in the general experimental procedure in the reference section.
[b] All the products were thoroughly characterized from their spectral data.
[c] Isolated yields are for the mixture of geometrical isomers.
[d] *E*,*E*/*E*,*Z* ratio was determined based on the ^{1}H NMR spectra.

The major product was unambiguously proved to be an *E*,*E*-isomer from NMR studies. In all cases, the olefinic proton signals for *E*,*Z* and *E*,*E* isomers were clearly distinguishable in their ^{1}H NMR spectra, with all the olefinic protons for the *E*,*E*-isomer resonating relatively downfield compared with the *E*,*Z*-isomer.[9] The geometry of the diene system was proved conclusively using separated pure isomers. For instance, the major isomer of **3a** was proved to be *E*,*E* based on a strong NOE between the benzylic proton and H_γ, as well as between H_β and H_δ which means that the propenyl chain and the α-hydroxy benzyl moiety are in a cis-orientation (Fig. 1). The minor isomer did not show these effects. However, the separation of the *E*/*Z* mixtures present in all the adducts by chromatography was not an easy task. Hence, the major isomer in all other adduct mixtures were assigned as *E*,*E* by analogy and the ratios were determined by the relative integration of the clearly distinguishable protons.

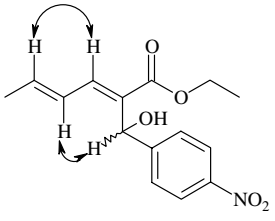
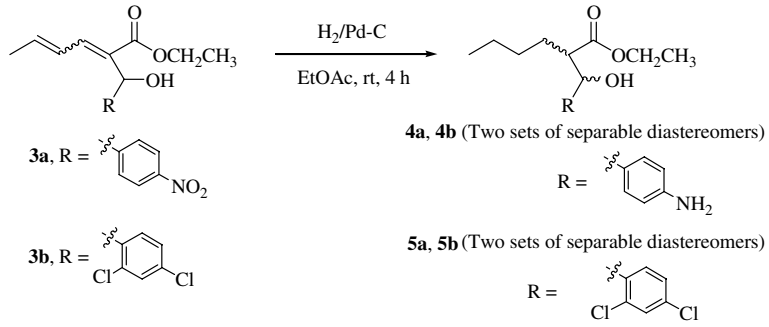


Figure 1. Diagramatic representation of the NOEs of compound **3a**.

Additionally, the point of attachment was proved unambiguously by a chemical method (Scheme 1). Thus, **3a** and **3b** were subjected to exhaustive reduction (Pd–C/H_2/EtOAc/rt) to afford two sets of separable diastereomers **4a**, **4b** (84%, 1:1) and **5a**, **5b** (81%, 1:1), respectively, in good yields. ^{1}H NMR analysis of each compound revealed that in **4a**, H_α appeared at δ 2.60 and the benzylic proton at δ 4.73 integrating for one proton each; while the same protons appeared at δ 2.62 and at δ 4.62 for compound **4b**.[10] Similarly, the ^{1}H NMR spectrum of **5a** revealed the H_α proton at δ 2.78 and the benzylic proton at δ 5.32; correspondingly, its diastereomer **5b** showed the same protons at δ 2.80 and δ 5.20, respectively.[10] Though these experiments do not predict the initial site of attack of DABCO onto the dienoate, nevertheless they unambiguously prove the site of aldol reaction of the dienoate (α-carbon) and the aldehydes. Subsequent elimination of DABCO regenerates the olefin to afford β-branched Baylis–Hillman adducts.

In summary, an efficient yet simple protocol for ready access to β-branched Baylis–Hillman adducts using ethyl sorbate as the Michael acceptor is reported for the first time. The resulting adducts may find broad utility in the synthesis of bioactive compounds.



Scheme 1.

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References and notes

1. (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vols. 1–9; (b) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408–5412; (c) Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206–3210.
2. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.
3. (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670; (b) Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318; (c) Wori, M.; Kuroda, S.; Dekura, F. *J. Am. Chem. Soc.* **1999**, *121*, 5591–5592.
4. Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821–5822.
5. (a) Taniguchi, M.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 4767–4770; (b) Li, G.; Wei, H.-X.; Gao, J. J.; Johnson, J. *Synth. Commun.* **2002**, *32*, 1765–1773; (c) Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Pare, P. W. *Tetrahedron* **2004**, *60*, 10233–10237.
6. Li, G.; Sun Hee, K.; Wei, H.-X. *Tetrahedron* **2000**, *56*, 719–723.
7. (a) Radha Krishna, P.; Raja Sekhar, E.; Kannan, V. *Tetrahedron Lett.* **2003**, *44*, 4973–4975; (b) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888–890; (c) Radha Krishna, P.; Manjuvani, A.; Kannan, V.; Sharma, G. V. M. *Tetrahedron Lett.* **2004**, *45*, 1183–1185; (d) Radha Krishna, P.; Narsingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773–4775; (e) Radha Krishna, P.; Krishna Rao Lopinti; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 7847–7850; (f) Radha Krishna, P.; Rachna Sachwani; Kannan, V. *Chem. Commun.* **2004**, 2580–2581.
8. General experimental procedure: To a mixture of ethyl sorbate (1.0 mmol) and DABCO (1.0 mmol) in DMSO (3 mL), aldehyde (1.0 mmol) was added and the mixture stirred at room temperature for 72 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl acetate (20 mL), washed sequentially with water (1×10 mL), brine (2×10 mL), concentrated and dried (Na_2SO_4). The residue was purified by chromatography on silica gel (60–120 mesh, *n*-hexane/EtOAc, 9:1) to give the corresponding adduct.

   Spectral data for selected compounds. Compound **3a**: yellow syrup; *E*,*E*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.18 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.54 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.39 (d, 1H, $J = 11.7$ Hz, H_β), 6.57 (ddq, 1H, $J = 13.8$, 11.7, 1.6 Hz, H_γ), 6.38 (dq, 1H, $J = 13.8$, 7.0 Hz, H_δ), 5.85 (d, 1H, $J = 10.5$ Hz, benzylic), 4.22 (d, 1H, $J = 10.5$ Hz, –OH), 4.15 (m, 2H, $-OCH_2$), 1.95 (dd, 3H, $J = 7.0$, 1.6 Hz, CH_3), 1.24 (t, 3H, $J = 7.0$ Hz, CH_3); IR (neat) ν 3440, 2986, 1701, 1640, 1530, 1320, 820 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 166.8, 150, 140.32, 140.2, 135.04, 126.2, 125, 123.5, 123, 60.94, 60.12, 19.7, 13.8; FABMS: m/z 292 (M^++1); Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88. Found: C, 61.81; H, 5.85; *E*,*Z*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 8.20 (d, 2H, $J = 8.9$ Hz, Ar-H), 7.52 (d, 2H, $J = 8.9$ Hz, Ar-H), 7.08 (m, 1H, H_β), 6.60–6.04 (m, 2H, H_γ, H_δ), 5.45 (d, 1H, $J = 7.4$ Hz, benzylic), 4.20 (m, 2H, $-OCH_2$), 3.25 (d, 1H, $J = 7.4$ Hz, –OH), 1.90 (d, 3H, $J = 7.4$ Hz, CH_3), 1.31 (t, 3H, $J = 7.4$ Hz, CH_3); Compound **3b**: light yellow syrup; *E*,*E*-Isomer: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.58 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.30–7.25 (m, 2H, Ar-H), 7.18 (d, 1H, $J = 11.4$ Hz, H_β), 6.63 (dist. t, 1H $J = 14.35$ Hz, H_γ), 6.62 (m, 1H, H_δ), 5.90 (d, 1H, $J = 9.8$, benzylic) 4.20 (m, 2H, $-OCH_2$), 3.98 (d, 1H, $J = 9.8$ Hz, –OH), 1.92 (d, 3H, $J = 6.8$ Hz, $-CH_3$), 1.25 (t, 3H, $J = 6.8$ Hz, $-CH_3$); IR (neat) ν 3447, 2980, 1698, 1639, 1593, 1465, and 1234; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 167.6, 141.4, 138.2, 133.0, 132.8, 129.3, 129.0, 127.0, 126.7, 126.2, 123.2, 67.4, 60.8, 29.5, 13.5; FABMS: m/z 315 (M^++1); Anal. Calcd for $C_{15}H_{16}Cl_2O_3$: C, 57.16; H, 5.12. Found: C, 57.10; H, 5.09; *E*,*Z*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.50 (d, 1H, $J = 8.3$ Hz), 7.30–7.25 (m, 2H), 7.05 (m, 1H), 6.38 (d, 1H, $J = 10.5$ Hz, H_γ), 6.00 (m, 1H, H_δ), 5.80 (d, 1H, $J = 4.5$ Hz, benzylic), 4.20 (m, 2H, $-OCH_2$), 3.08 (d, 1H, $J = 4.5$ Hz, –OH), 1.85 (d, 3H, $J = 9.0$ Hz, CH_3), 1.25 (t, 3H, $J = 6.8$ Hz, CH_3).
9. (a) Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Pare, P. W. *Tetrahedron* **2004**, *60*, 10233–10237; (b) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377–2379.
10. Compound **4a**: yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.10 (d, 2H, $J = 9.06$ Hz), 6.60 (d, 2H, $J = 8.30$ Hz), 4.73 (d, 1H, $J = 6.04$ Hz), 4.05 (q, 2H, $J = 7.5$, 14.35 Hz), 2.60 (dt, 1H, $J = 6.04$, 8.3 Hz), 1.40–1.05 (m, 9H), 0.85 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 167.0, 145.5, 128.0, 126.0, 115.0, 71.0, 61.2, 50.5, 29.5, 29.2, 22.1, 14.0, 13.4; Compound **4b**: yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.10 (d, 2H, $J = 9.06$ Hz), 6.60 (d, 2H, $J = 8.30$ Hz), 4.62 (d, 1H, $J = 8.3$ Hz), 4.15 (q, 2H, $J = 6.79$, 14.35 Hz), 2.62 (dt, 1H, $J = 3.77$, 7.55 Hz), 1.40–1.05 (m, 9H), 0.85 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 167.0,

145.0, 128.5, 125.8, 115.2, 70.5, 61.2, 50.0, 29.5, 28.8, 21.8, 13.9, 13.2; Compound **5a**: light yellow syrup; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.60 (d, 1H, $J = 8.17$ Hz), 7.3 (m, 2H), 5.32 (br s, 1H), 4.20 (m, 2H), 3.48 (d, 1H, $J = 1.48$ Hz, –OH), 2.78 (dt, 1H, $J = 6.04$, 9.06 Hz), 1.44–1.00 (m, 9H), 0.90 (t, 3H, $J = 6.68$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 168.0, 133.8, 131.8, 129.5, 129.2, 127.2, 126.8, 70.0, 61.0, 50.0, 29.4, 29.0, 22.0, 14.0, 13.5; Compound **5b**: light yellow syrup; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.60 (d, 1H, $J = 8.17$ Hz), 7.30 (m, 2H), 5.20 (br s, 1H), 4.20 (m, 2H), 3.48 (d, 1H, $J = 1.48$ Hz, –OH), 2.80 (dt, 1H, $J = 3.71$, 6.68 Hz), 1.44–1.00 (m, 9H), 0.90 (t, 3H, $J = 6.68$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 168.0, 133.8, 132.6, 129.0, 128.5, 127.0, 126.4, 71.0, 61.0, 50.5, 29.6, 29.0, 22.0, 14.0, 13.5.