

## Hydroxy-assisted catalyst-free Michael addition-dehydroxylation of Baylis–Hillman adducts in poly(ethylene glycol)<sup>☆</sup>

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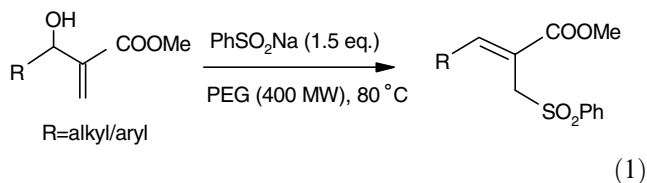
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**Abstract**—Intramolecular hydrogen bonding facilitates nucleophilic addition of sulfones to Baylis–Hillman adducts in a single step to realize the substituted allyl sulfones. The reaction is performed in PEG (400 MW) as solvent, which allows easy solvent recycling. © 2006 Elsevier Ltd. All rights reserved.

Baylis–Hillman adducts have proved to be very useful multifunctional synthons in organic chemistry,<sup>1</sup> especially for the preparation of trisubstituted alkenes.<sup>2</sup> The allylic alcohol functionality is used as a nucleophile acceptor either by converting the hydroxy group into a leaving group (acetate in most cases)<sup>3</sup> or involving Et<sub>3</sub>B as a catalyst or reagent<sup>4</sup> to facilitate hydroxy group departure.



Lately, there has been increased interest in the application of Baylis–Hillman adducts as synthons for bio-active molecule generation.<sup>5</sup> We and several others are engaged in this exercise. Kabalka et al. have reported recently the nucleophilic addition of acetates and sulfones to Baylis–Hillman adducts to realize the substituted allyl acetates and sulfones, and found that the reaction proceeds more efficiently in ionic liquids<sup>6</sup> compared to conventional solvents. However, precondition was that the hydroxy group had been converted into acetate (for

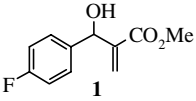
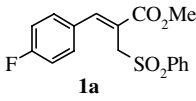
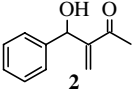
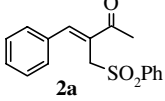
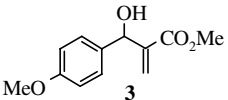
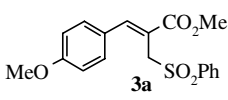
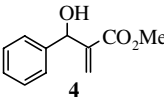
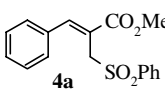
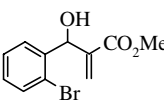
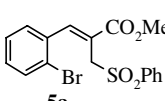
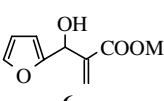
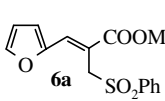
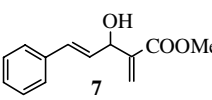
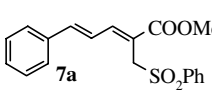
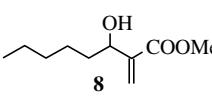
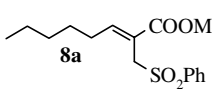
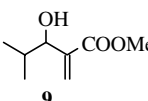
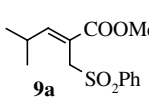
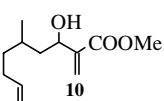
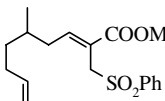
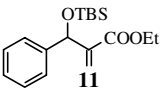
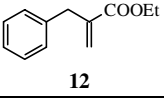
smooth allylic displacement). Herein, we disclose a new protocol in which the Baylis–Hillman adduct (without acetylation) undergoes a smooth and rapid nucleophilic addition of sulfone using sodium phenylsulfinate in PEG (400 MW) (Eq. 1) as a recyclable reaction medium<sup>7</sup> to realize the substituted allyl sulfones.

Firstly the 4-fluorobenzaldehyde-methyl acrylate adduct **1** was subjected to sodium phenylsulfinate in PEG resulting in the clean formation of sulfone ester **1a** (Table 1) in 90% yield in less than 11 h<sup>8</sup> with exclusive (*Z*)-selectivity as evidenced by extensive NMR studies including DQCOSY, NOESY and HSQC experiments.<sup>9</sup> This product is a result not only of the Michael addition of sulfone but also the elimination of hydroxide to generate the  $\alpha,\beta$ -unsaturated ester. A possible reaction mechanism is shown in Scheme 1. No additional reagent or catalyst was needed for the reaction to proceed. To prove the generality, various other Baylis–Hillman adducts were prepared following our own protocol<sup>10</sup> and subjected to Michael reaction-dehydroxylation in one step (see Table 1). The phenyl ketone **2**, 4-methoxyphenyl ester **3**, phenyl ester **4**, 2-bromophenyl ester **5** and furan ester **6** all react to yield products in over 80% yield. The styrene ester **7** and aliphatic substrates **8**, **9** and **10** also reacted in high yields. In all the examples studied, the olefin geometry was found to be *Z* based on the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts and comparison with literature values.<sup>11</sup> To further ascertain the role of –OH group, two substrates viz, the *tert*-butyldimethylsilyl protected acrylate **11** and 2-benzylacrylic acid ethyl ester **12** were subjected to the present protocol

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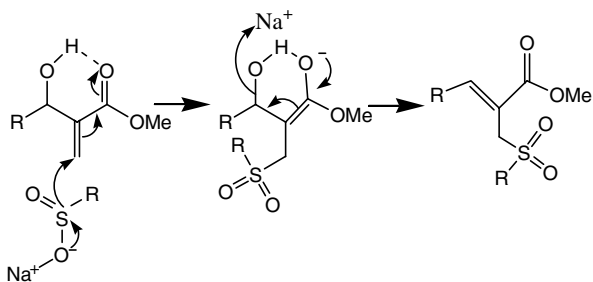
**Table 1.** Hydroxy-assisted catalyst-free Michael addition-dehydroxylation of Baylis–Hillman adducts<sup>12</sup>

Baylis–Hillman adducts	Product	Time (h)	Yield (%) <sup>a</sup>
		11	90
		11.5	92
		12	91
		11	93
		11	90
		12	80
		11	85
		13	85
		13	81
		12	82
	→ No Reaction		
	→ No Reaction		

<sup>a</sup> Isolated yields after chromatography; the products were characterized from spectral data.

but without any success. Thus, the lack of the hydroxy group, or protecting it with a silyl group prevented the nucleophilic addition reaction (Scheme 1).

In summary, the present letter shows that Baylis–Hillman adducts can be subjected to nucleophilic addition in a single step.



**Scheme 1.** Possible reaction mechanism for allylic sulfonylation of Baylis–Hillman adducts.

### Acknowledgements

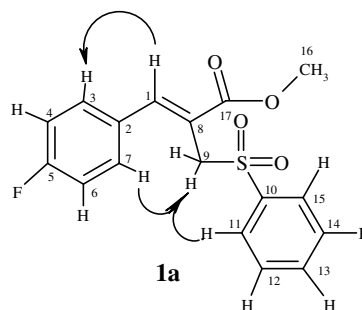
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- The same reaction could be performed with similar yields in absolute EtOH, however, with longer reaction time and without recycling.
- The HSQC and  $^{13}\text{C}$  spectra of **1a** clearly showed the presence of 17 carbons with one methyl, 12 methine and 5 quaternary carbons. The *Z*-stereochemistry of **1a** was assigned on the basis of  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts in comparison with literature values.<sup>11</sup> The structure is supported by NOE cross peaks between H7–H9, H11–H9 and H1–H3. *Spectral data for 1a*:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ );  $\delta$  7.92 (1H, br s, H-1), 7.88 (2H, m, H-11 and H-15), 7.63 (1H, m, H-13), 7.56 (2H, d, H-3 and H-7,  $J = 8.7$  Hz), 7.52 (2H, t, H-12 and H-14,  $J = 7.5$  Hz), 7.09 (2H, dt, H-4 and H-6,  $J = 8.7, 5.4$  Hz), 4.45 (2H, s, H-9), 3.57 (3H, s, H-16);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ );  $\delta$  166.0, 160.2, 139.5, 133.5, 129.5, 129.0, 128.8, 128.6, 128.2, 128.0, 121.0, 55.2, 52.5.



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- Typical experimental procedure: Into a flask purged with  $\text{N}_2$  containing poly(ethylene glycol) (400 MW, 2 g) were added the Baylis–Hillman adduct (1.0 equiv) and sodium phenylsulfinate (1.5 equiv). The reaction mixture was heated at  $80^\circ\text{C}$  for the appropriate time (see Table 1) during which the reaction was monitored by means of TLC. The reaction mixture was extracted with ether ( $4 \times 5$  ml). The combined ether layers were washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Subsequent column chromatography over silica gel gave the product (*Z*)-sulfone in the yields mentioned in Table 1.<sup>8</sup> Spectroscopic data for selected compounds: Compound **4a** (liquid):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  7.95–7.82 (2H, m), 7.62–7.32 (9H, m), 4.40 (2H, s), 3.55 (3H, s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ );  $\delta$  166.8, 146.2, 139.5, 133.6, 129.6, 129.1, 129.0, 128.9, 128.7, 128.5, 121.0, 55.1, 52.2; HRMS

calcd for  $C_{17}H_{17}SO_4$   $[M+H]^+$  317.3855, found 317.3849. Compound **6a** semi-solid:  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.83 (2H, d,  $J = 6.9$  Hz), 7.55–7.40 (5H, m), 6.70 (1H, d,  $J = 1.9$  Hz), 6.40 (1H, d,  $J = 1.9$  Hz), 4.71 (2H, s), 3.58 (3H, s);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  166.2, 158.3, 152.4, 142.8, 138.5, 133.2, 129.6, 126.7, 118.7, 117.2, 111.4, 53.8, 52.1; HRMS calcd for  $C_{15}H_{15}SO_5$   $[M+H]^+$  307.3471,

found 307.3476. Compound **9a** viscous liquid:  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  7.90–7.70 (2H, m), 7.66–7.42 (3H, m), 6.84 (1H, d,  $J = 11.6$  Hz), 4.18 (2H, s), 3.42 (3H, s), 2.82–2.64 (1H, m), 1.04 (6H, d,  $J = 5.5$  Hz);  $^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  166.2, 139.0, 133.6, 128.9, 128.8, 128.7, 128.6, 53.9, 51.9, 28.9, 21.5; HRMS calcd for  $C_{14}H_{19}SO_4$   $[M+H]^+$  283.3684, found 283.3681.