A Convenient Synthesis of the (E)-Monoacetates of 2-Alkylidenepropane-1,3-diols

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The authors dedicate this article to Professor E. J. Corey at Harvard University on the occasion of his 80th birthday.

Abstract: Various kinds of 3-substituted (E)-2-(hydroxymethyl)prop-2-enyl acetates were conveniently obtained in excellent yields by the regiospecific acetylation of 2-alkylidene propan-1,3-diols with 10 equivalents of vinyl acetate in the presence of 50% w/w porcine pancreatic lipase (PPL) type II; the starting materials or (Z)-monoacetate or diacetate byproducts were generally not present.

Key words: (E)-monoacetates, acetylation, diols, regioselectivity, lipase

The development of highly selective acetylation reactions is an attractive research field because the acetyl group, as one of the most popular protecting groups, plays an important role in organic synthesis.1 Enzymatic acetylation using lipase and vinyl acetate is an excellent methodology, and many papers have reported the enantioselective acetylation of racemic alcohols in the presence of lipase.2 In the case of the unique highly regioselective acetylation of 2-benzylidene propan-1,3-diols using several kinds of lipases reported by Takabe and co-workers,3 diacetates and (Z)-monoacetates were obtained as byproducts in all cases, and 1 equivalent of vinyl acetate had to be used to avoid the production of the diacetates. We recently developed and reported in a preliminary communication the preparation of 3-substituted (E)-2-(hydroxymethyl)prop-2-enyl acetates by the regiospecific acetylation of 2-alkylidene propan-1,3-diols with vinyl acetate using 50% w/w porcine pancreatic lipase (PPL) type II,4 and the preparation of 3-substituted (Z)-2-(hydroxymethyl)prop-2-enyl acetates by the highly regioselective hydrolysis of 2-alkylidene-1,3-propylene diacetates using 100% w/w PPL type II.5 Herein, we report the details of a regiospecific acetylation of 2-alkylidene propan-1,3-diols with vinyl acetate using 50% w/w PPL type II.

2-Alkylidene propan-1,3-diols 2 were easily prepared in 20–62% yield from diethyl 2-alkylidene malonates 1, which can be obtained from the Knoevenagel condensation of the corresponding aldehydes with diethyl malonate,6 by reduction using diisobutylaluminum hydride (DIBAL-H) (Table 1).7

Table 1 Preparation of 2-Alkylidenepropane-1,3-diols 2 from Diethyl 2-Alkylidene Malonates 1

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Yield (%)</th>
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<td>13</td>
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<td>2</td>
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* All reactions were carried out with diethyl 2-alkylidene malonate 1 (1 equiv) and DIBAL-H (4.5 equiv) in toluene at –30 °C.

In a preliminary investigation, the reaction of 2-benzylidene propan-1,3-diol (2a)8 with vinyl acetate in the presence of 50% w/w PPL in 1,4-dioxane afforded the corresponding E-isomer 3a as the sole product in 95% yield, as indicated in Table 2, entry 1. The overacetylated product and the Z-isomer were not detected in the 1H NMR spectroscopic analysis of the crude product. We examined the regioselective acetylation of 2-benzylidene propan-1,3-diols substituted on the benzene ring by electron-donating or electron-withdrawing groups. The results from the acetylation of various substituted 2-benzylidene propan-1,3-diols 2b–h and that of 2-alkylidene derivative 2i with vinyl acetate in the presence of 50% w/w PPL in 1,4-dioxane are collated in Table 2. We selected methoxy and methyl substituents as representative electron-donating groups (entries 2 and 5–8, respec-
respectively), trifluoromethyl and chloro substituents as electron-donating groups (entries 3 and 4, respectively), and 2-(3-phenylpropyldiene)propane-1,3-diol (2i) for the reaction of an aliphatic species (entry 9). Fortunately, all para-monosubstituted 2-benzylidenepropane-1,3-diols 2b–e reacted under the above conditions to afford the corresponding (E)-monoacetylated products 3b–e in excellent yields with complete regioselectivity. High regioselectivity was also observed in the reactions of the more-hindered substrates 2f and 2g containing methyl groups at the meta- and ortho-positions of the benzene ring (entries 6 and 7, respectively). 2-(2,4,6-Trimethylbenzylidene)propane-1,3-diol (2h) was a poor substrate for acetylation using PPL, probably because of the steric hindrance of the ortho-substituents on the benzene ring, and its corresponding (E)-monoacetate 3h was obtained in only 30% yield (entry 8). The reaction of 2-(3-phenylpropyldiene)propane-1,3-diol (2i) (entry 9) afforded the (E)-monoacetate with lower regioselectivity than that observed for the reactions of substituted 2-benzylidenepropane-1,3-diols 2a–h. Although the corresponding E-isomer 3i was obtained in 80% yield, Z-isomer 4i and diacetate 5i were produced as byproducts in 5 and 6% yield, respectively (Figure 1). In addition to the above reactions, polycyclic and heterocyclic aromatic diols 2j–m were converted into the corresponding E-monoacetates 3j–m with high regioselectivity (entries 10 and 11–13, respectively); however, the reaction of polycyclic diol 2j containing a 2-naphthyl group gave a lower yield because of steric hindrance similar to that mentioned above for entry 8.

The structure of monoacetate 3b was determined as the E-isomer by nuclear Overhauser effect spectroscopy (NOESY) (Figure 2). A NOESY relationship was observed between the aromatic and the methylene protons adjacent to the hydroxy group. All the other monoacetates 3a and 3c–m were also determined to be the E-isomers by NOESY analysis.

### Table 2: E-Acetylation of 2-Alkylidenepropane-1,3-diols 2 in the Presence of Porcine Pancreatic Lipase

<table>
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<th>Entry</th>
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<th>Time (h)</th>
<th>Product 3</th>
<th>Yield (%)</th>
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- All reactions were carried out with 2-alkylidenepropane-1,3-diol 2 (1 equiv), vinyl acetate (10 equiv), and 50% w/w PPL in 1,4-dioxane (3 mL) at r.t.
- Starting material 2h was recovered in 61% yield.
- Starting material 2i was recovered in 4% yield, and Z-isomer 4i and diacetate 5i were obtained in 5 and 6% yield, respectively.
- Starting material 2j was recovered in 37% yield.
- Starting material 2k was recovered in 14% yield.

In summary, PPL works efficiently as a catalyst in the regiospecific acetylation of 2-alkylidenepropane-1,3-diols. Although a large excess of vinyl acetate (10 equiv) was used in the reaction, the corresponding (E)-monoacetates were generally obtained as the sole products in high yields without overacetylation. 3-Substituted (E)-2-(hydroxy-ethyl)prop-2-yl acetates are potentially useful intermediates in organic synthesis and may be used as building blocks in the syntheses of natural products. Using our procedure, it is possible to prepare various kinds of (E)-monoacetates.

The 1H NMR spectra were measured with a Bruker Ultrashield 400 Plus (400 MHz) spectrometer, with TMS as an internal standard. 13C NMR spectroscopy was performed on a Bruker Ultrashield 400 Plus (100 MHz) spectrometer, with TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. For TLC, Merck precoated TLC plates (silica gel 60 F_{254}, Art 5715) were used. Porcine pancreatic lipase type II was commercially available from Sigma.

Diethyl 2-(4-Trifluoromethyl)benzylidene|malonate (1c); Typical Procedure
A clear, colorless solution of 4-trifluoromethylbenzaldehyde (4.00 mL, 30.0 mmol, 1.00 equiv), diethyl malonate (4.76 mL, 31.5 mmol, 1.05 equiv), and benzoic acid (403 mg, 3.30 mmol, 0.11 equiv) in benzene (15 mL) was stirred at 120 °C for 17 h using a Dean–Stark trap. The mixture was then diluted with EtOAc (200 mL), washed with sat. NaHCO3 (100 mL) and sat. NaCl (100 mL), and dried (anhdy MgSO4). The crude product was chromatographed (silica gel, EtOAc–hexane, 1:10) to afford 1c. Yield: 8.99 g (95%); colorless plate crystals; mp 49–50 °C.

1H NMR (400 MHz, CDCl3): δ = 2.18 (s, 3 H, CH3), 2.59 (br s, 1 H, OH), 2.67 (t, J = 4.8 Hz, 2 H, CH2), 6.87 (s, 1 H, =CH), 7.17 (s, 2 H, ArH-5).
13C NMR (100 MHz, CDCl3): δ = 20.3, 20.9, 60.8, 66.1, 127.6, 128.0, 132.2, 135.9, 136.5, 139.8.

2-(4-Chlorobenzylidene)propane-1,3-diol (2d)
Colorless powder; mp 61–62 °C.
1H NMR (400 MHz, CDCl3): δ = 2.23 (s, 3 H, CH3), 3.05 (br s, 1 H, OH), 3.15 (br s, 1 H, OH), 4.29 (2 s, H, CH2), 4.39 (2 s, H, CH2), 6.62 (1 H, =CH), 7.12–7.20 (m, 3 H, ArH), 7.18 (t, J = 8.0 Hz, 1 H, ArH-5).
13C NMR (100 MHz, CDCl3): δ = 19.9, 60.5, 66.9, 125.6, 128.0, 129.8, 129.9, 134.3, 139.2.

2-(2,4,6-Trimethylbenzylidene)propane-1,3-diol (2f)
Colorless powder; mp 88–89 °C.
1H NMR (400 MHz, CDCl3): δ = 2.30 (s, 3 H, CH3), 3.50 (br s, 1 H, OH), 3.63 (br s, 1 H, OH), 4.31 (s, 2 H, CH2), 4.37 (s, 2 H, CH2), 6.55 (1 H, =CH), 7.01–7.05 (m, 3 H, ArH), 7.18 (t, J = 8.0 Hz, 1 H, ArH-5).
13C NMR (100 MHz, CDCl3): δ = 121.4, 60.1, 66.9, 125.9, 128.1, 129.5, 136.1, 137.8, 141.0.

2-(2-Methylbenzylidene)propane-1,3-diol (2g)
Colorless oil.
1H NMR (400 MHz, CDCl3): δ = 2.11 (s, 6 H, 2 CH3), 2.25 (s, 3 H, CH3), 2.93 (br s, 1 H, OH), 4.29 (2 s, H, CH2), 4.39 (2 s, H, CH2), 6.62 (1 H, =CH), 7.12–7.20 (m, 4 H, ArH).
13C NMR (100 MHz, CDCl3): δ = 128.0, 132.2, 135.9, 136.5, 139.8.

2-(3-Phenylpropylidene)propane-1,3-diol (2i)
Date: 2008, No. 17, 2695–2700 © Thieme Stuttgart · New York
2-(2-Naphthylmethylene)propane-1,3-diol (2j)
Colorless oil.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{12}H_{14}O_2: 237.0941; found: 237.0938.

(2)-2-(Hydroxymerthyl)-3-phenylprop-2-enyl Acetate (3a)
Colorless oil.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{12}H_{14}O_2: 237.0941; found: 237.0938.

(2)-2-(Hydroxymerthyl)-3-(4-trifluoromethylnyl)phenylprop-2-enyl Acetate (3c)
Colorless oil.


(2)-3-(4-Chlorophenyl)-2-(hydroxymerthyl)prop-2-enyl Acetate (3d)
Colorless oil.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{15}H_{13}ClO_3: 263.0445; found: 263.0488.

(2)-2-(Hydroxymerthyl)-3-(4-methoxyphenyl)prop-2-enyl Acetate (3b)
Typical Procedure

A pale-yellow suspension of 2-(4-methoxybenzylidene)propane-1,3-diol (2h) (194 mg, 1.00 mmol, 1.00 equiv), vinyl acetate (0.92 mL, 10.0 mmol, 1.00 equiv), and 50% w/w PPL (97 mg) in 1,4-dioxane (3 mL) was stirred at r.t. for 23 h. Then, the resulting suspension was diluted with EtOAc (10 mL) and dried (anhyd MgSO_4). The mixture was filtered, and the filtrate was evaporated. The crude product was chromatographed (silica gel, EtOAc–hexane, 2:3) to afford 3b. Yield: 222 mg (94%); colorless oil.

(2)-2-(Hydroxymerthyl)-3-(3-toly)prop-2-enyl Acetate (3f)
Colorless oil.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{14}H_{16}O_{3}: 243.0992; found: 243.1003.

(E)-2-(Hydroxymethyl)-3-(2-toly1)prop-2-enyl Acetate (3g)
Colorless oil.

1H NMR (400 MHz, CDCl3): δ = 2.12 (s, 6 H, 2 CH3), 2.06 (s, 3 H, COCH3), 2.44 (q, J = 7.5 Hz, 2 H, CH2CH3), 2.69 (t, J = 7.5 Hz, 2 H, CH2Ph), 4.00 (s, 2 H, CH2OH), 4.59 (s, 2 H, CH2OAc), 5.67 (t, J = 7.5 Hz, 1 H, =CH), 7.15–7.21 (m, 3 H, ArH), 7.26–7.30 (m, 2 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 20.9, 29.3, 35.4, 58.1, 66.8, 126.0, 128.3, 128.5, 132.4, 134.4, 141.1, 171.2.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{14}H_{16}O_{3}: 243.1003; found: 243.1003.

(Z)-2-(Hydroxymethyl)-5-phenylpent-2-enyl Acetate (4)
Colorless oil.

1H NMR (400 MHz, CDCl3): δ = 2.04 (s, 3 H, COCH3), 2.19 (br s, 1 H, OH), 2.46 (q, J = 7.5 Hz, 2 H, CH2CH3), 2.69 (s, 2 H, CH2OH), 4.61 (s, 2 H, CH2OAc), 5.74 (t, J = 7.4 Hz, 1 H, =CH), 7.15–7.20 (m, 3 H, ArH), 7.25–7.30 (m, 2 H, ArH).

13C NMR (100 MHz, CDCl3): δ = 20.9, 29.5, 35.6, 60.1, 65.6, 126.0, 128.3, 128.4, 132.2, 143.3, 171.3.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{15}H_{19}O_{4}: 257.1107; found: 257.1107.

1H NMR (400 MHz, CDCl3): δ = 2.12 (s, 3 H, COCH3), 2.30 (br s, 1 H, OH), 4.55 (s, 2 H, CH2OH), 4.78 (s, 2 H, CH2OAc), 6.38 (d, J = 3.4 Hz, 1 H, ArH=3), 6.40 (s, 1 H, =CH), 6.43 (dd, J = 1.8, 3.4 Hz, 1 H, ArH=4), 7.44 (d, J = 1.8 Hz, 1 H, ArH=5).

13C NMR (100 MHz, CDCl3): δ = 21.0, 60.0, 67.1, 111.6, 111.8, 119.2, 133.5, 142.9, 151.3, 171.2.

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{15}H_{19}O_{4}: 257.1107; found: 257.1107.

Hydroxymethyl)-3-(2-thienyl)prop-2-enyl Acetate (3l)
Colorless oil.

(E)-2-(Hydroxymethyl)-3-(2-thienyl)prop-2-enyl Acetate (3l)

HRMS (ESI-TOF): m/z [M + Na]+ calcd for C_{15}H_{19}O_{4}: 257.1107; found: 257.1107.

References


