Facile Synthesis of 4-Hydroxy-(*E*)-2-alkenoic Esters from Aldehydes

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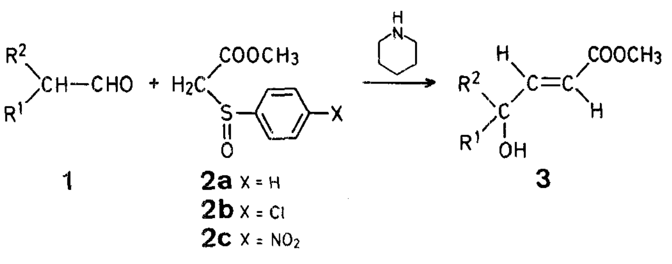
The skeleton of 4-hydroxy-(*E*)-2-alkenoic esters (**3**) is found in many naturally occurring compounds[1,2]. We have previously reported that the condensation of methyl phenylsulfinylacetate (**2a**) with aldehydes (**1**) in the presence of a catalytic amount of piperidine yields 2-phenylsulfinyl-2-alkenoic esters[3]. We have now found that compounds **3** are easily obtained from aldehydes **1** and methyl arylsulfinylacetates **2** using excess piperidine via Knoevenagel reaction, C=C double-bond shift, [2,3]-sigmatropic rearrangement, and hydrolysis by a one-step procedure[4]. When methyl 4-chloro- (**2b**) or methyl 4-nitrophenylsulfinylacetate (**2c**) are used in place of **2a**, compounds **3** are obtained in better yields because the competitive self-condensation of aldehydes **1** scarcely occurs.



The present method has the following advantages: the reagents are readily available; the procedure is simple, e.g., inert atmosphere and dry solvents are not required; the reaction conditions are mild; and the reaction can be performed with a wide range of aldehydes. A limitation of the method is that ketones fail to react with compounds **2**.

Methyl 4-Chlorophenylsulfinylacetate (2b):

Methyl (4-Chlorophenylthio)-acetate: Sodium (11.5 g, 0.5 mol) is dissolved in methanol (250 ml). To this solution is added, with stirring, a solution of 4-chlorobenzenethiol (72.3 g, 0.5 mol) in methanol (100 ml) and a solution of methyl chloroacetate (54.3 g, 0.5 mol) in methanol (50 ml) at room temperature. The resultant mixture is refluxed for 1 h, then distilled in vacuo to give the ester as a colorless liquid; yield: 99.5 g (92%); b.p. 118 °C/1.2 torr.

Methyl 4-Chlorophenylsulfinylacetate (**2b**): A 30% hydrogen peroxide solution (51.0 g, 0.45 mol) is added dropwise to a stirred solution of methyl (4-chlorophenylthio)-acetate (97.5 g, 0.45 mol) in acetic acid (200 ml) at 10 °C. Stirring is continued at room temperature overnight and the solvent then removed in vacuo to give **2b** as a colorless solid; yield: 94.2 g (90%); m.p. 58–59 °C (ethanol/hexane 1/1).

M.S.: $m/e = 232$ (Ref.[5], $m/e = 232$).

Methyl 4-Hydroxy-(*E*)-2-hexenoate (3a); Typical Procedure:

A solution of butanal (**1a**; 2.0 g, 24 mmol) in acetonitrile (10 ml) is added, over a period of 1 h, to a stirred solution of methyl 4-chlorophenylsulfinylacetate (**2b**; 4.7 g, 20 mol) and piperidine (2.0 g, 24 mmol) in acetonitrile (40 ml) at room temperature and stirring is continued for a further 2 h. Acetonitrile and piperidine are then removed in vacuo and product **3a** is isolated by distillation in vacuo or by column chromatography on silica gel (chloroform); yield: 2.4 g (83%); b.p. 81–83 °C/0.3 torr.

When the above procedure is carried out using compounds **2a** or **2c** in place of **2b** the yield of product **3a** is 74% or 85%, respectively.

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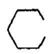
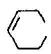
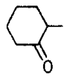
Table 1. 4-Hydroxy-(*E*)-2-alkenoic Ester (**3**) prepared

3	R[1]	R[2]	Reaction Conditions time/temperature	Yield[a] [%]	b.p. [°C]/ torr	Lit. Data or Molecular formula[b]
a	C_2H_5	H	r.t./3 h	83	81–83°/0.3	$C_7H_{12}O_3$ (144.2)
b	n-C_4H_9	H	r.t./3 h	84	90–95°/0.3	$C_9H_{16}O_3$ (172.2)
c	n-C_5H_{11}	H	r.t./3 h	76	105–111°/0.2	$C_{10}H_{18}O_3$ (186.2)
d	n-C_6H_{13}	H	r.t./3 h	80	125–130°/0.3	$C_{11}H_{20}O_3$ (200.3)
			r.t./3 h[c]	82[c]		
e	CH_3	CH_3	r.t./3 days	66	80–84°/0.3	120°/1[6]
			r.t./1 h + reflux/2 h	64		
f	n-C_4H_9	C_2H_5	r.t./1 h + reflux/10 h	73	130–135°/0.3	$C_{11}H_{20}O_3$ (200.3)
g			r.t./1 h + reflux/2 h	72	110–116°/0.6	$C_{10}H_{16}O_3$ (184.2)
h			r.t./1 h + reflux/2 h	72	113–116°/0.2	$C_{10}H_{14}O_3$ (182.2)
i	 $-CH_2-$	H	r.t./1 day	67	106–110°/0.1	$C_{12}H_{18}O_4$ (226.3)

[a] Yield of isolated product based on **2b**.
[b] Satisfactory microanalyses obtained: C, ±0.28; H, ±0.21.
[c] Mol. ratio used, **2b** : **1d** : piperidine = 1.2 : 1.0 : 1.2; yield based on **1d**.

Table 2. I.R.- and [1]H-N.M.R.-Spectral Data of Compounds **3**

3	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	1720	0.94 (t, 3 H, J=7 Hz); 1.4–1.8 (m, 2 H); 2.7 (br. s, 1 H); 3.69 (s, 3 H); 4.1–4.3 (m, 1 H); 5.97 (dd, 1 H, J=16 Hz, 2 Hz); 6.94 (dd, 1 H, J=16 Hz, 4 Hz)
b	1720	0.8–1.0 (m, 3 H); 1.1–1.7 (m, 6 H); 2.6 (br. s, 1 H); 3.69 (s, 3 H); 4.1–4.3 (m, 1 H); 5.99 (dd, 1 H, J=16 Hz, 1 Hz); 6.97 (dd, 1 H, J=16 Hz, 4 Hz)
c	1720	0.8–1.0 (m, 3 H); 1.1–1.7 (m, 8 H); 3.0 (br. s, 1 H); 3.67 (s, 3 H); 4.1–4.3 (m, 1 H); 5.97 (dd, 1 H, J=16 Hz, 1 Hz); 6.94 (dd, 1 H, J=16 Hz, 4 Hz)
d	1720	0.8–1.0 (m, 3 H); 1.1–1.7 (m, 10 H); 3.0 (br. s, 1 H); 3.68 (s, 3 H); 4.1–4.3 (m, 1 H); 5.95 (dd, 1 H, J=16 Hz, 1 Hz); 6.95 (dd, 1 H, J=16 Hz, 4 Hz)
e	1720	1.31 (s, 6 H); 2.8 (br. s, 1 H); 3.67 (s, 3 H); 5.88 (d, 1 H, J=16 Hz); 6.92 (d, 1 H, J=16 Hz)
f	1720	0.7–1.0 (m, 6 H); 1.1–1.7 (m, 8 H); 2.5 (br. s, 1 H); 3.68 (s, 3 H); 5.84 (d, 1 H, J=16 Hz); 6.73 (d, 1 H, J=16 Hz)
g	1720	1.2–2.5 (m, 11 H); 3.70 (s, 3 H); 5.96 (d, 1 H, J=16 Hz); 6.98 (d, 1 H, J=16 Hz)
h	1720	1.3–2.4 (m, 7 H); 3.74 (s, 3 H); 5.6–5.8 (m, 2 H); 6.09 (d, 1 H, J=16 Hz); 7.04 (d, 1 H, J=16 Hz)
i	1710, 1720	1.4–2.9 (m, 12 H); 3.70 (s, 3 H); 5.0 (br. s, 1 H); 5.98 (dd, 1 H, J=16 Hz, 2 Hz); 6.96 (dd, 1 H, J=16 Hz, 5 Hz)

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