A Convenient Benzylation Procedure for β-Hydroxy Esters

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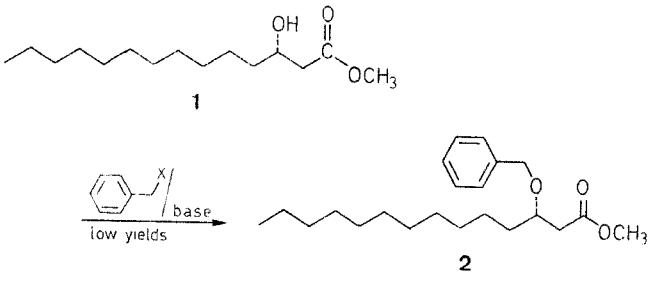
Benzylation of β-hydroxy esters, containing primary and secondary alcohol functions, with benzyl 2,2,2-trichloroacetimidate gives the corresponding benzyl ethers in good yield. In the case of chiral substrates no racemisation is observed.

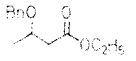
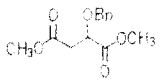
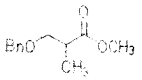
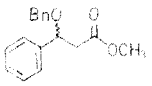
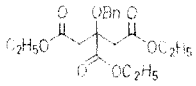
For the preparation of the optically pure benzylated β-hydroxy ester **2**, which was needed as a starting material connected with other work, we planned to transform the hydroxy function of **1** to an ether group with a benzyl halogenide. However, by applying different methods reported in the literature, we did not obtain the ether **2** in any reasonable yield. Moreover, partial racemisation at C-3 was observed.



A solution to the problem was found using the acid-catalysed procedure developed by Iversen and Bundle,[1,2] which is well known in carbohydrate chemistry,[2-4] but was never applied for the preparation of β-benzyloxy esters.

Treatment of **1** with the commercially available benzyl 2,2,2-trichloroacetimidate (**3**) in the presence of a catalytic amount of trifluoromethanesulfonic acid furnished the ether **2** in 79% yield. For analytical control of the enantiomeric purity of **2**, the

Table 1. Benzyl Ethers **2**, **4**–**8** Prepared

Product[a]	Reaction Time (h)	Yield (%)	e.e. (%) (starting material)	e.e. (%) (hydrogenolysed product)	b.p. (°C)/mbar[b]	Molecular Formula[c] or Lit. Data
2	3	79	100[d]	100[d]	–	$C_{22}H_{36}O_3$ (348.5)
4 	0.5	63	96.6	96.6[e]	140/15	$C_{13}H_{18}O_3$ (222.3)
5 	0.5	60	99.7	99.7[e]	100/0.13	$C_{13}H_{16}O_5$ (252.3)
6 	0.5	76	≥95	≥95[e,f]	100/15	$C_{12}H_{16}O_3$ (208.3)
7 	0.5	71[g]	–	–	125/15	$C_{17}H_{18}O_3$ (270.3)
8 	2.5	5	–	–	110/0.13	$C_{19}H_{26}O_7$ (366.4)

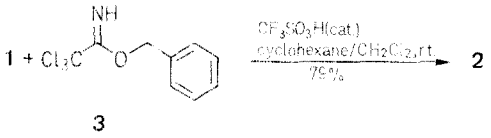
[a] Bn = Benzyl.
[b] Kugelrohr distillation.
[c] Satisfactory microanalyses obtained: C ±0.3, H ±0.18 (Exception: **2**, no microanalysis, because the product could not be distilled without decomposition).
[d] Analysed by ^{1}H-NMR spectroscopy in the presence of Eu(tfc)$_3$.
[e] GC-analysis after esterification with Mosher's reagent.
[f] No base-line separation, but an amount of less than 5% of the diastereomer could be detected in a test mixture.
[g] As by-product methyl cinnamate was isolated in 8% yield.

Table 2. Spectroscopic Data of the Benzyl Ethers **2**, **4**–**6**, **8**

Product	$[\alpha]_D^{20}$ ($CHCl_3$, c)[a]	IR (Film)[b] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[a] δ(ppm)	MS[c] m/e (rel. int. %)
2	+3.5° (1.08)	1741, 1196, 1095, 734, 697	0.88 (m, 3H); 1.7–1.2 (m, 20H); 2.55 (ABX, 2H, J = 14.0, 7.3, 5.4 Hz); 3.68 (s, 3H); 3.88 (m, 1H); 4.54 (s, 2H); 7.3 (m, 5H)	348 (M^+, 1); 242 (28); 107 (36); 91 (100)
4	+19.9° (1.0)	1736, 1187, 1092, 738, 697	1.25 (t + d, 6H); 2.53 (ABX, 2H, J = 15, 7.3, 5.8 Hz); 4.07 (m, 1H); 4.13 (q, 2H, J = 7.0 Hz); 4.54 (AB, 2H, J = 11.5 Hz); 7.3 (m, 5H)	116 (44); 91 (100)
5	−72.6° (1.6)	1741, 1280, 1169, 1123, 741, 699	2.81 (m, 2H); 3.69 (s, 3H); 3.77 (s, 3H); 4.05 (m, 1H); 4.65 (AB, 2H, J = 11.5 Hz); 7.35 (m, 5H)	146 (22); 114 (42); 91 (100)
6	−11.6° (1.0)	1739, 1200, 1100, 739, 698	1.18 (d, 3H, J = 7.2 Hz); 2.79 (m, 1H); 3.57 (ABX, 2H, J = 9.1, 7.3, 5.9 Hz); 3.69 (s, 3H); 4.52 (s, 2H); 7.3 (m, 5H)	208 (M^+, 1); 107 (44); 91 (100)
8	–	1738, 1281, 1183, 739, 697	1.26 (m, 9H); 3.16 (AB, 4H, J = 15.5 Hz); 4.13 (q, 4H, J = 7.0 Hz); 4.26 (q, 2H, J = 7.0 Hz); 4.57 (s, 2H); 7.3 (m, 5H)	293 (6); 260 (10); 214 (24); 140 (20); 91 (100)

[a] Recorded on a Bruker AC 250 instrument.
[b] Recorded on a Nicolet 7199 FT-IR spectrophotometer.
[c] Recorded on a MS 9-ZAB Kratos and Vacuum Generators, Data System SS 200 Finnigan MAT.
[d] Recorded on a Perkin-Elmer 241 instrument.

ether was cleaved by hydrogenolysis providing alcohol **1** again. No trace of the *R*-enantiomer could be detected by ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent Eu(tfc)$_3$.



Using the same methodology ethers **4–8** (Tables 1 and 2) were prepared. The enantiomeric purity of products **4–6** (Table 1) was checked by hydrogenolysis followed by esterification with Mosher's reagent. It was unequivocally shown by GC-analysis that under the reaction conditions no racemisation had occurred.

From the results displayed in Table 1 it is concluded that applying the present procedure, primary and secondary hydroxy groups at C-3 of a carboxylic ester are benzylated in good yields. However, tertiary alcohols seem to react sluggishly (cf. *8*) probably due to steric reasons.

The present method of benzylation of *β*-hydroxy esters making use of a commercially available reagent and mild reaction conditions has evident advantages over classical methods. Moreover, we should like to point out that the reagent **3** may be recycled from trichloroacetamide,[2,6] which is formed as a by-product.

Benzyl Ethers 2, 4–8; General Procedure:
To a stirred solution of the appropriate *β*-hydroxy ester (15 mmol) and benzyl 2,2,2-trichloroacetimidate (**3**; 4.54 g, 18 mmol) in a mixture of cyclohexane (20 ml) and dichloromethane (10 ml) is added under an argon atmosphere, trifluoromethanesulfonic acid (0.2 ml). Within 5 min, the temperature rises from room temperature to about 38 °C. The mixture is then stirred until the starting material has completely reacted (Table 1) as monitored by TLC (mobile phase: *n*-hexane/ethyl acetate, 9:1). The crystalline trichloroacetamide is removed by filtration and the filtrate washed with aqueous saturated solution of sodium hydrogen carbonate (50 ml) and water (50 ml). The organic layer after being dried with sodium sulfate is evaporated. Finally, the residue is purified by chromatography on silica gel using hexane/ether (suitable mixture) as eluent and subsequently (with the exception of **2**) by Kugelrohr distillation (Table 1).

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