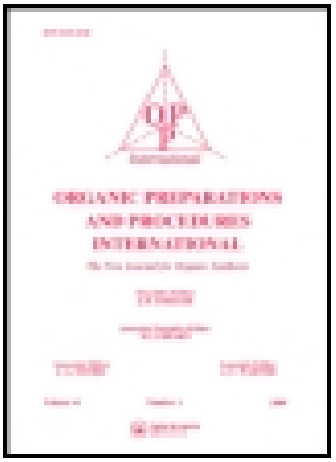

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AN IMPROVED PROCEDURE FOR THE ETHERIFICATION OF α-HYDROXY ACID DERIVATIVES

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AN IMPROVED PROCEDURE FOR THE ETHERIFICATION OF α-HYDROXY ACID DERIVATIVES

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(04/14/04)

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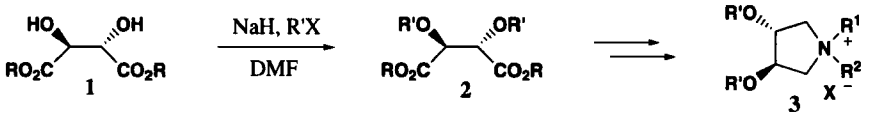
Ethers of chiral hydroxy carboxylic esters and their derivatives are having wide synthetic applications both as chiral building blocks for the synthesis of biologically important molecules[1] as well as in the synthesis of novel chiral phase-transfer catalysts such as **3**.[2] Our interest in the preparation of diverse non-flexible chiral phase-transfer catalysts as shown in *Scheme 1*, led us to synthesize various tartrate ethers. In order to prepare benzyl ethers of **1a,**



a) R = Et, R' = Bn; b) R = ^{i}Pr, R' = Bn; c) ^{i}Pr, R' = Me; d) R = ^{i}Pr, R' = Bu; e) R = ^{i}Pr, R' = allyl; f) R = ^{i}Pr, R' = 2-Bromomethylnaphthalene

Scheme 1

Seebach *et al* used[3] thallium ethoxide to convert the oxygen function into thallium (II) alkoxide followed by the addition of benzyl bromide at 50°C for 50 hrs to afford **2a** in good yields. They also reported the formation of other ethers of **1a** in moderate to good yields (68-95%). However, both toxicity and cost limit the use of thallium ethoxide for large scale preparations. Prior to the use of thallium ethoxide, there was no single efficient method to obtain various ethers of α-hydroxy esters. The classical method[4] using Ag_2O/alkyl halide gives satisfactory results, albeit only with reactive alkylating agents such as dimethyl sulfate and methyl iodide. When NaH is used, **2a** is obtained in low yields.[1] Yamamoto and co-workers[5] utilized NaH as base and a combination of tetrabutylammonium iodide and expensive crown ethers as phase-transfer catalysts in tetrahydrofuran and obtained moderate yield (76%) of product **2a**. The main hurdle in using simple conventional methods such as NaH/alkylating agent is the high rate of ester hydrolysis and possible racemization at high temperature. The use of diisopropyl esters of tartaric acid, which are more stable than the diethyl ester, may circumvent this problem as was shown by Liu[1d] and Schreiber.[1b] Starting with **1b**, they obtained **2b** in moderate yields (53-60%) utilizing NaH and tetrabutylammonium iodide as phase-transfer catalyst. We now report a method for the preparation of ethers of hydroxy esters using NaH as a base in dimethylformamide. The reaction is carried out at 0°C under inert atmosphere using NaH as a 60% suspension in mineral oil. The reaction proceeds rapidly with excellent yields, especially in the case of *O*-benzylation of diiso-

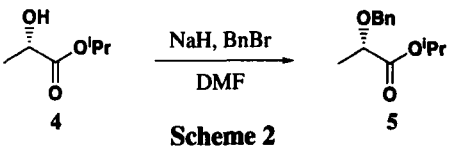
propyl tartrate with benzyl bromide. The product was easily purified by recrystallization from hexane (92% yield). In case of *O*-dibenzylated diisopropyl tartrate, the ester was further reduced

Table 1. Yields, mp., bp. and rotation of Compounds **2** and **5**

Cmpd	Time (hrs)	Yield (%)	mp. (°C)	*Lit.* mp. (°C)	$[\alpha]_D^{20}$	*Lit.* $[\alpha]_D^{20}$
2b	0.5	92	79.0-80.0[a]	79.5-80.5[b]	+62.4[c]	62.3[c]
2c	0.7	85	46.5-47.5[a]	-[d]	+69.3[e]	N. A.
2d	5.0	79	(175-178)[f]	-[g]	+53.3[h]	N. A.
2e	1.5	86	-[j]	N. A.	+55.6[i]	+55.8[i]
2f	1.0	83	-[j]	-[k]	+137.9[l]	N. A.
5	0.5	94	(215-217)[f]	-[m]	-53.0[n]	N. A.

a) from *n*-hexane; b) from *n*-hexane and ethyl acetate; c) (*c* 2, ethyl acetate); d) not reported, *Anal.* Calcd for $C_{12}H_{22}O_6$: C, 54.76; H, 8.78; O, 36.46. Found: C, 54.95; H, 8.45; O, 36.60; e) (*c* 1, $CHCl_3$); f) bp.; g) *Anal.* Calcd for $C_{18}H_{34}O_6$: C, 62.31; H, 10.01; O, 27.68. Found: C, 62.40; H, 9.89; O, 27.71; h) (*c* 0.7, $CHCl_3$); i) (*c* 0.66, $CHCl_3$); j) oil; k) *Anal.* Calcd for $C_{32}H_{34}O_6$: C, 74.53; H, 6.73; O,18.74. Found: C, 74.69; H, 6.66; O,18.65; l) (*c* 1, $CHCl_3$); m) *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; O, 21.60. Found: C, 70.10; H, 8.21; O, 21.68; n) (*c* 1.25, $CHCl_3$)

to give the pure diol in 97% yield under the reported conditions[6] and no further purification was required. This method works equally well for a wide variety of alkylating agents. However, the reaction was somewhat slow in the case of long chain alkylating agents, such as butyl iodide, requiring 5 hrs for completion. This method works well for the *O*-alkylation of other α-hydroxy acid esters. *O*-Benzylation of isopropyl lactate gave product **5** in 94% yield (*Scheme 2*). The reaction proceeds without racemization in all the cases; this was confirmed by measuring the optical rotations of the products.



4 5

Scheme 2

In conclusion, we have developed an efficient method for the O-alkylation of α-hydroxyl esters. The advantages of this new method are its possible applications for a wide variety of alkylating agents, milder reaction conditions, operational simplicity, higher yields and the possibility of using in large scale.

EXPERIMENTAL SECTION

All starting materials were obtained from commercial suppliers. Dimethylformamide was dried over 4A° molecular sieves. Melting points are uncorrected. ^1H spectra were determined at 300 MHz Bruker Advance spectrometer with chemical shifts in ppm and tetramethylsilane as internal standard J values are given in Hz. Infrared absorption spectra were recorded on Nicolet Impact

410 spectrometer; the frequencies in the IR spectra are reportedin cm^{-1}. Mass spectra data were recorded on Finnigan-MAT LCMS spectrometer with atmospheric pressure ionization mode. Elemental analysis was recorded on Elementa Vario EL. Optical rotations were measured on Rudolph Autopol. TLC was performed on plates pre-coated (0.25 mm) with silica gel 60, Merck F-254. Column chromatography was carried out with silica gel Merck 60 (80-230 mesh).

Table 2. IR, ^{1}H NMR and mass spectra of Compounds **2** and **5**.

Cmpd	IR (cm^{-1})	^{1}H NMR	MS
2b	3468, 3051, 2987, 2905, 1749, 1605, 1499, 1452, 1386, 1270, 1107, 992	1.16 (d, 6H, J = 6.23, $(C\underline{H}_3)_2CH$), 1.24 (d, 6H, J = 6.18, $(C\underline{H}_3)_2CH$), 4.40 (s, 2H, CH), 4.47 (d, 2H, J = 11.7, $C\underline{H}_2Ph$), 4.84 (d, 2H, J = 11.8, $C\underline{H}_2Ph$), 5.04 (m, 2H, $(CH_3)_2C\underline{H}OR$), 7.25-7.30 (m, 10H, Ph)	414 (M^+, 21), 181 (100)
2c	2995, 2955, 2900, 2833, 1755, 1455, 1374, 1277, 1108,	1.30 (d, 12H, J = 2.90, $2(C\underline{H}_3)_2CH$), 3.45 (s, 6H, OCH_3), 4.18 (s, 2H, CH), 5.16 (m, 2H, $(CH_3)_2C\underline{H}OR$)	262 (M^+, 100), 220 (35), 178 (40)
2d	2960, 2929, 2878, 1756, 1730, 1458, 1369, 1272, 1166, 1105, 1015	0.88 (t, 6H, J = 7.32, $O(CH_2)_3C\underline{H}_3$, 1.27-1.37 (m, 16H, $(C\underline{H}_3)_2CH$, $O(CH_2)_2C\underline{H}_2CH_3$), 1.51-1.58 (m, 4H, $OCH_2C\underline{H}_2CH_2CH_3$), 3.30 (q, 2H, J = 8.97, $OCH_2C\underline{H}_2CH_2CH_3$), 3.75 (q, 2H, J = 6.58, $OCH_2C\underline{H}_2CH_2CH_3$), 4.27 (s, 2H, CH), 5.10 (m, 2H, $(CH_3)_2C\underline{H}OR$)	346 (M^+, 100), 304 (60), 262 (65)
2e	3074, 2982, 2937, 2878, 1755, 1723, 1646, 1456, 1426, 1375, 1329, 1273, 1204, 1104, 1037	1.28 (d, 12H, J = 5.79, $(C\underline{H}_3)_2CH$), 3.90-3.97 (dd, 2H, J = 6.48, 5.87, OCH_2), 4.28-4.32 (dd, 2H, J = 4.87, 7.56, OCH_2), 4.35 (s, 2H, CH), 5.07-5.32 (m, 6H, $CH=C\underline{H}_2$, $(CH_3)_2C\underline{H}$), 5.81-5.90 (m, 2H, $C\underline{H}=CH_2$)	314 (M^+, 100), 272 (30), 230 (40)
2f	3048, 2980, 2929, 1748, 1729, 1598, 1511, 1466, 1374, 1273, 1148, 1100	0.80 (d, 6H, J = 6.15, $(C\underline{H}_3)_2CH$), 1.10 (d, 6H, J = 6.09, $(C\underline{H}_3)_2CH$), 4.39 (s, 2H, CH), 4.71 (m, 2H, $(CH_3)_2C\underline{H}OR$), 4.83 (d, 2H, J = 11.85, $C\underline{H}_2Ar$), 5.32 (d, 2H, J = 11.83, $C\underline{H}_2Ar$), 7.31-7.76 (m, 12 H, Ar-H), 8.16 (d, 2H, J = 7.71, Ar-H)	373 (M^+-141 24), 281 (100)
5	2982, 2937, 2875, 1744, 1497, 1455, 1374, 1275, 1204, 1146, 1106, 1064	1.26 (dd, 6H, J1 = 3.00, J2 = 3.22, $(C\underline{H}_3)_2CH$), 1.41 (d, 3H, J = 6.85, $CHC\underline{H}_3$), 4.02 (q, 1H, J = 6.84, $C\underline{H}CH_3$), 4.43 (d, H, J = 11.58, $OC\underline{H}Ph$), 4.68 (d, H, J = 11.58, $OC\underline{H}Ph$), 5.09 (m, 1H, $(CH_3)_2C\underline{H}OR$), 7.24-7.37 (m, 5H, Ph)	222 (M^+, 100)

General Procedure for the Preparation of Ethers.- To a suspension of sodium hydride (3.32 g, 83.2 mmol) in dimethylformamide (150 mL) at 0°C under an argon atmosphere was added a solution of diisopropyl (L)-tartrate (10.0 g, 42.7 mmol) in dimethylformamide (25 mL) over a period of 15 min while the temperature was maintained below 5°C. After stirring for 1 hr at 5°C, the mixture was cooled to –5°C, and the alkyl halide (85.4 mmol) was added slowly over a period of 15 min. The mixture was stirred at 0°C for 30 min and allowed to warm to room temperature (20°C) and stirred for additional time (See *Table 1*). The reaction mixture was

poured into crushed ice (200 g) and extracted with three portions of ether (150 mL x 3). The combined organic extract was dried over magnesium sulfate and concentrated under vacuum to give the crude products. The crude products were purified through column chromatography; wherever possible the product was recrystallized from hexane.

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FACILE BECKMANN REARRANGEMENT OF KETOXIMES MEDIATED BY YTTRIUM TRIFLATE

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(06/01/04)

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The Beckmann rearrangement of ketoximes to the corresponding amide is a common method in organic chemistry and is a topic of current interest.[1] The rearrangement proceeds through *anti*-migration and is usually stereospecific.[2] Generally, this reaction requires an excess amount of a strong protic acid, such as conc. sulfuric or phosphoric acid which can lead a large