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Preparation of Methyl 2-Arylpropanoates by the Reaction of 2-Hydroxypropiophenone Dimethyl Acetals with Sulfuryl Chloride in the Presence of an Amide or a Weak Base

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Treatment of 2-hydroxypropiophenone dimethyl acetals [p-$\mathrm{RC_6H_4C(OMe)_2CH(OH)Me}$] (**1**; R=H, *i*-Bu, OMe, Ph, Br) with sulfuryl chloride in the presence of an amide or a weak base affords methyl 2-arylpropanoates (**2**) in good to excellent yields via 1,2-aryl migration of **1**. The hydrolysis of **2** leads to the corresponding acids, some of which are pharmaceutically important compounds having nonsteroidal anti-inflammatory and analgesic activities. The aryl migration proceeds stereospecifically with complete inversion of configuration at the β-carbon atom.

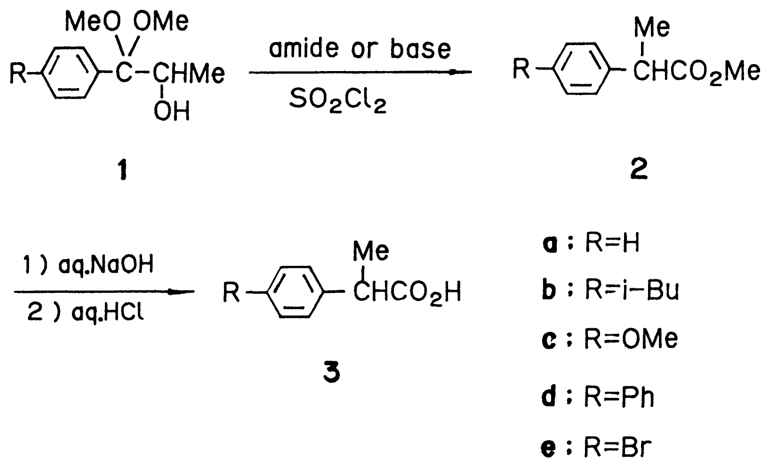
It has been known that 2-arylpropanoic acids are useful medical drugs having antipyretic action or nonsteroidal antiinflammatory activity[1,2] Some of these acids are required to be optically active. Many preparative methods for optically active or inactive 2-arylpropanoic acids have so far been developed. Among them, methods using 1,2-aryl migration in alkyl aryl ketones and their derivatives have proven to be very useful;[3] alkyl esters of 2-arylpropanoic acids were obtained by direct oxidation of alkyl aryl ketones in alcohols with thallium(III) nitrate trihydrate,[4–7] (diacetoxyiodo) benzene,[8] iodine-silver nitrate[7] and also by treatment of enamines with diphenyl phosphorazidate.[9] Further, the same compounds were produced as well from aryl 1-haloalkyl ketones or their acetals either by treating them with silver salts[10,11] or Lewis acids,[12,13] or by heating them in protic polar solvents in the absence of metal catalysts.[14] Recently, we also disclosed several new methods for the synthesis of 2-arylpropanoic acid alkyl esters from aryl 1-haloalkyl ketones and related substances.[15–18]

Tsuchihashi et al.[19–21] reported that a base-promoted rearrangement of chiral acetals of 1-aryl-2-sulfonyloxy-1-alkanones proceeds with a complete inversion of the configuration to afford optically active 2-arylalkanoic acids.

We report here a new and facile one-pot preparative method of methyl 2-arylpropanoates from 2-hydroxypropiophenone dimethyl acetals by using sulfuryl chloride in the presence of an amide or a weak base.

Results and Discussion

The reaction was generally carried out by adding sulfuryl chloride to a mixture of 1-aryl-1,1-dimethoxy-2-propanol (**1**) and weak bases or amides in dichloromethane at −50—0 °C. The resulting mixture was stirred for 1—3 h at the same temperature. The main product was methyl 2-arylpropanoate (**2**) and its alkaline hydrolysis afforded the corresponding acid **3** (Scheme 1). Typical results are summarized in Table 1. In these reactions pyridine, diisopropylamine or potassium acetate was found to be effective as a base. *N,N*-Dimethylformamide (DMF) worked as solvent as well as a base and, thus, the treatment of **1** with sulfuryl chloride in this solvent resulted in a high yield formation of **2**. The yield of the rearranged product is satisfactory at lower



Scheme 1.

reaction temperatures, and generally high when the substituent R is an electron-releasing group such as isobutyl, methoxyl, or phenyl. This tendency is similar to that observed in thallium(III) nitrate-mediated[16)] and silver salt-mediated[11)] synthesis of alkyl 2-arylpropanoates from aryl 1-haloethyl ketones. The treatment of **1b** in DMF with thionyl chloride instead of sulfuryl chloride at 20 °C for 3 h afforded the expected **2b** in only 17% yield, 2-chloro-4′-isobutylpropiophenone being the main product (47%). The rearrangement did not occur with thionyl bromide or seleninyl chloride ($SeOCl_2$) in pyridine. From the viewpoint of industrial applications of this preparative method, experiments involving the combinational use of sulfur dioxide and halogen gas instead of sulfuryl chloride were also carried out. The reaction proceeded using SO_2–Cl_2, which was revealed to be more economical. Typical results are shown in Table 2. When sulfur dioxide and bromine were used, the yield of **2b** was low, while the rearrangement hardly occurred with a combination of sulfur dioxide and iodine.

Table 1. Preparation of **2** from **1**[a)]

Compound	Base or amide	Reaction condition		Yield of **2**[b)]
		Temp/°C	Time/h	%
1a	Pyridine	−50	3	55
1b	Pyridine	−50	3	86
1b	Pyridine	0	1	73
1b	$(i\text{-Pr})_2NH$[d)]	0	3	72[c)]
1b	$i\text{-PrNH}_2$[d)]	0	3	61[c)]
1b	AcOK[d)]	0	3	64
1b	DMF[e)]	−50	3	84
1b	DMF[e)]	0	3	86[c)]
1c	Pyridine	−50	3	85
1d	Pyridine	−50	3	87
1e	Pyridine	−50	3	54

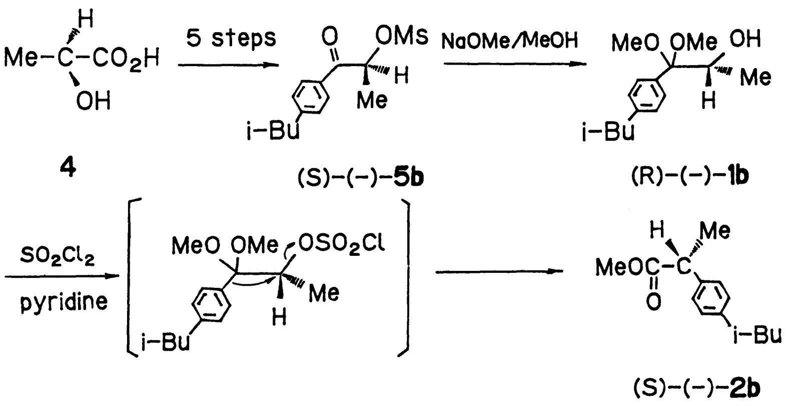
a) Carried out using **1** (5 mmol), SO_2Cl_2 (7.5 mmol), and a base or an amide (12.5 ml) in dichloromethane (12.5 ml). b) Isolated yield by column chromatography. c) Determined by GLC analysis. d) 10 mmol. e) DMF was used as the solvent (12.5 ml).

Next, the stereochemistry of this rearrangement was investigated using optically active (*R*)-(−)-1-(4-isobutylphenyl)-1,1-dimethoxy-2-propanol [(*R*)-(−)-**1b**] derived from (*S*)-(−)-1-(4-isobutylphenyl)-2-methylsulfonyloxy-1-propanone [(*S*)-(−)-**5b**] which in turn was synthesized from L-(+)-lactic acid (**4**) via 5 steps by the known methods[21)] (Scheme 2, see Experimental section). Compound (*R*)-(−)-**1b** was obtained in 91% chemical yield by treating optical pure (*S*)-(−)-**5b** with sodium methoxide in methanol at room temperature for 1 h. This procedure is known to proceed with an inversion of the configuration at asymmetric carbon.[22,23)] Thus, the stereochemistry of (*R*)-(−)-**1b** should be that shown in Scheme 2. The optical purity of (*R*)-(−)-**1b** was estimated to be 74% ee by NMR measurement using a chiral shift reagent, $Eu(hfc)_3$, indicating the occurrence of a slight racemization under this acetalization condition. A treatment of (*R*)-(−)-**1b**, thus obtained, with sulfuryl chloride in pyridine at −50 °C afforded (*S*)-(−)-**2b** of 74% ee. The result clearly shows that the rearrangement of (*R*)-(−)-

Table 2. Preparation of **2b** from **1b** Using Halogen, Sulfur Dioxide, and Base[a)]

Base	Halogen	Yield of **2b**[b)] %
Et_3N	Cl_2	95 (88)[d)]
Et_3N	Cl_2[c)]	93
Pyridine	Cl_2	94
Pyridine	Br_2	48
Pyridine	I_2	Trace
$i\text{-PrNH}_2$	Cl_2	75
Et_2NH	Cl_2	52

a) Carried out using **1b** (10 mmol), base (15 mmol), sulfur dioxide (15 mmol), halogen (15 mmol), and dichloromethane (61 ml) at −50 °C for 3 h. b) Determined by GLC analysis. c) 10 mmol. d) Isolated yield.



Scheme 2.

1b to (*S*)-(−)-**2b** proceeded with a complete inversion of the configuration at the β-carbon atom (Scheme 2). This new and economical method for the preparation of an optically active 2-arylalkanoic acid is industrially important.

Experimental

^{1}H NMR spectra were recorded with a JEOL FX-90Q (90 MHz) instrument on solutions in $CDCl_3$ with Me_4Si as an internal standard. GLC analyses were carried out with a Shimadzu 4CMPF apparatus by using DEGS (2%) on Gas Chrom Q (3 mm×1.5 m) and OV-101 (0.24 mm×30 m) columns (N_2 as carrier gas). IR spectra were recorded with a Shimadzu IR-435 spectrometer. Melting points were determined with Yanagimoto MP micro melting-point determination apparatus and were uncorrected. Optical rotations were measured on a Union PM-201 automatic polarimeter.

All organic and inorganic materials were commercial products of the purest grade. 1-Aryl-1,1-dimethoxy-2-propanols (**1**) were prepared by the literature method[19] from methanol, sodium methoxide, and 2-halopropiophenone.

Rearrangement of 1 to Methyl 2-Arylpropanoates (2). A typical example is as follows. To the solution of **1b** (1.26 g, 5 mmol) in pyridine (12.5 ml) and dichloromethane (12.5 ml) was added sulfuryl chloride (1.01 g, 7.5 mmol) at −50 °C under stirring. After the mixture was stirred for 3 h at the same temperature, saturated aqueous $NaHCO_3$ (25 ml) was added and then an aqueous layer was extracted with chloroform (3×75 ml). The extract was dried over $MgSO_4$ and the solvent was removed by evaporation under reduced pressure. The resulting oily residue was purified by column chromatography on SiO_2 [hexane–ethyl acetate (30:1) as eluent] to give **2b** (0.95 g, yield 86%) as a pale yellow oil.

An experiment using isopropylamine, diisopropylamine or potassium acetate as a base was carried out in a 1/5-fold scale and **2b** was analyzed by GLC using triphenylmethane as an internal standard [2% DEGS on Gas Chrom Q, (3 mm×1.5 m) column at 100→200 °C (5 °C min^{-1})]. The yield of **2a**, **2c**, **2d**, and **2e** was determined by GLC on OV-101 (0.24 mm×30 m) column [at 120→260 °C (4 °C min^{-1})] using an internal standard: pentamethylbenzene for **2a** and **2c**, and biphenyl for **2d** and **2e**.

Experiments using $SOCl_2$/DMF, $SOBr_2$/pyridine, and $SeOCl_2$/pyridine were similarly carried out.

Alkaline hydrolysis of **2** to **3** was carried out as previously reported.[15—17]

Rearrangement of 1b with Sulfur Dioxide and Halogen. To a solution of **1b** (10 mmol) in dichloromethane (40 ml) were added an amine (15 mmol) and a solution of sulfur dioxide (0.96 g, 15 mmol) in dichloromethane (7 ml) successively, and the resulting mixture was cooled down to −50 °C. To the mixture was added dropwise a solution of halogen (15 mmol) in dichloromethane (14 ml) and the mixture was stirred at −50 °C for 3 h. After a similar treatment as above, **2b** in the extract was analyzed by GLC and isolated by column chromatography in a pure form (as described above).

Synthesis of (*R*)-(−)-1-(4-Isobutylphenyl)-1,1-dimethoxy-2-propanol [(*R*)-(−)-1b]. (a) (−)-Ethyl L-Lactate (6). A solution of L-(+)-lactic acid (**4**, 89.2 g, 0.99 mol) and concentrated sulfuric acid (8.93 g, 91 mmol) in ethanol (893 ml) was refluxed for 2 h. After it had been cooled down, the mixture was neutralized to pH 5.2 with saturated aqueous $NaHCO_3$. Evaporation of the solvent left an oily residue which was distilled to give **6**; bp 78.5 °C/43 Torr (1 Torr=133.322 Pa) (67.3 g, 57 mmol, 57.5% yield); $[\alpha]_D^{19}$ −10.7° (neat) [lit,[24] $[\alpha]_D^{19}$ −11.26° (neat)]; Found: C, 76.05; H, 9.13%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%. ^{1}H NMR ($CDCl_3$) δ=1.30 (3H, t), 1.42 (3H, d), 3.32 (1H, s), 4.1—4.4 (3H, m).

(b) (−)-Ethyl (*S*)-2-(Methylsulfonyloxy) propanoate (7). To a solution of **6** (64.7 g, 548 mmol) in dichloromethane (110 ml) was added methylsulfonyl chloride (81.6 g, 712 mmol) at −20 °C, then pyridine (52.0 g, 657 mmol) was added dropwise at −15—−20 °C for 1 h. After the mixture was stirred at −15 °C for 3 h, it was quenched with water (137 ml), neutralized to pH 4.7 with 3 mol dm^{-3} sodium hydroxide (190 ml), and extracted with dichloromethane (356 ml). The organic layer was washed with brine (685 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and an only residue was distilled in vacuo to give **7**; bp 106 °C/2.5 Torr (74.1 g, 378 mmol, 68.9% yield, lit,[21] bp 97—102 °C/2 Torr); $[\alpha]_D^{22}$ −52.3 °C (*c* 1.00, $CHCl_3$) [lit,[21] $[\alpha]_D^{19}$ −50.55 (*c* 1.00, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ=1.29 (3H, t), 1.58 (3H, d), 3.11 (3H, s), 4.22 (2H, q), 5.06 (1H, q).

(c) (*S*)-(−)-2-(Methylsulfonyloxy)propionic Acid (8). A solution of potassium hydroxide (25 g, 446 mmol) in water (250 ml) was slowly added to **7** (72.8 g, 371 mmol) at 5—10 °C during 1 h. The mixture was stirred at 10—15 °C for 3 h, then acidified to pH 1.0 with concentrated hydrochloric acid (35 ml), and extracted with ethyl acetate (3×450 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crystalline residue was suspended with hexane (180 ml) and filtered to give crude **8**; mp 69 °C (55.1 g, 328 mmol, 88.4% yield, lit,[21] mp 65—72 °C); $[\alpha]_D^{22}$ −53.9° (*c* 1.00, $CHCl_3$) [lit, [21] $[\alpha]_D^{22}$ −49.8° (*c* 1.00, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ=1.68 (3H, d), 3.12 (3H, s), 5.15 (1H, q), 9.10 (1H, br s).

(d) (*S*)-(−)-2-(Methylsulfonyloxy)propionyl Chloride (9). A mixture of **8** (55.1 g, 328 mmol) and thionyl chloride (78 g, 656 mmol) was refluxed for 4 h. The mixture was distilled in vacuo to give **9**; bp 91—93 °C/2 Torr (52.9 g, 283 mmol, 86.4% yield, lit,[21] bp 70—74 °C/1.5 Torr); ^{1}H NMR ($CDCl_3$) δ=1.75 (3H, d), 3.17 (3H, s), 5.28 (1H, q).

(e) (*S*)-(−)-1-(4-Isobutylphenyl)-2-methylsulfonyloxy-1-propanone [(*S*)-(−)-5b]. To a solution of isobutylbenzene (20.1 g, 150 mmol) and **9** (18.7 g, 100 mmol) in nitromethane (100 ml) was added iron(III) chloride (17.8 g, 110 mmol) at 5—10 °C. The mixture was stirred at room temperature for 4 h, then quenched with water (200 ml), and extracted with ethyl acetate (2×100 ml). The organic layer was washed with brine (200 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to leave an oily residue which was purified by column chromatography on SiO_2 [hexane–ethyl acetate (30:1—4:1) as eluent] to give (*S*)-(−)-**5b**; mp 82.5 °C (15.0 g, 52.9 mmol) 52.9% yield, lit,[21] mp 81—82 °C), $[\alpha]_D^{24}$ −52.53° (*c* 1.00, $CHCl_3$) [lit,[21] $[\alpha]_D^{24}$ −52.48° (*c* 1.00, $CHCl_3$)], IR (KBr disk) 2960, 1697, 1609, 1240, 1180, 1023, and 745 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ=0.90 (6H, d), 1.63 (3H, d) 1.6—2.1 (1H, m), 2.53 (2H, d), 3.10 (3H, s), 6.00 (1H, q), 7.23 (2H, d), 7.83 (2H, d).

(f) (*R*)-(−)-1b. To a solution of (*S*)-(−)-**5b** (10.0 g, 35 mmol) in methanol (70 ml) was added a solution of sodium methoxide (3.78 g, 70 mmol) in methanol (47 ml) at room temperature and the mixture was stirred for 1 h. After water (300 ml) and ethyl acetate (100 ml) were added to the mixture, two layers were separated and the aqueous layer was then extracted with ethyl acetate (100 ml). The combined organic layers were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left an oily residue which was distilled in vacuo to give (*R*)-(−)-**1b**; bp 97—100 °C/0.2 Torr (8.07 g, 32 mmol, 91.4% yield); $[\alpha]_D^{21}$ −1.64 °C (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.89 (6H, d), 0.97 (3H, d), 1.6—2.1 (1H, m), 2.35 (1H, br. s), 2.45 (2H, d), 3.20 (3H, s), 3.36 (3H, s), 3.95—4.20 (1H, m), 7.08 (2H, d), 7.34 (2H, d); when the signal at δ=3.36 of methoxy group was determined in the presence of 5 mol% of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [Eu(hfc)$_3$], this signal was separated into two signals at δ=3.93 and 4.03. From the integration value of these signals, the ratio of (−)-form/(+)-form was determined to be 87/13 (74±2% ee).

(−)-Methyl (*S*)-2-(4-Isobutylphenyl) propanoate [(*S*)-(−)-2b]. To a solution of (*R*)-(−)-**1b** (5.0 g. 19.8 mmol), pyridine (3.13 g, 39.6 mmol), and dichloromethane (3.96 ml) was added sulfuryl chloride (4.01 g, 29.7 mmol) at −50 °C for 10 min. The mixture was stirred at the same temperature for 3 h and then quenched with saturated aqueous $NaHCO_3$ (50 ml). The resulting mixture was added with water (100 ml) and chloroform (100 ml). The two layers were separated and the aqueous layer was extracted with chloroform (100 ml). The combined organic layers were washed with brine (100 ml) and dried ($MgSO_4$). Evaporation of the solvent left a light-yellow oil which was subjected to column chromatography on SiO_2 [hexane–ethyl acetate (10:1—5:1) as eluent] to give (*S*)-(−)-**2b**; bp 85—86 °C/0.3 Torr (3.46 g, 15.7 mmol, 79.3% yield); $[\alpha]_D^{23}$ −48.4° (*c* 1.00, $CHCl_3$) lit,21) $[\alpha]_D^{23}$ −56.2° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.09 (6H, d), 1.47 (3H, d), 1.6—2.1 (1H, m), 2.44 (2H, d), 3.63 (3H, s), 3.68 (1H, q), 7.05 (2H, d), 7.18 (2H, d); when the signal at δ=3.63 of ester methyl group was determined in the presence of 80 mol% of Eu(hfc)$_3$, this signal was separated into two signals at δ=5.68 and 5.74. From the integration value of these signals, the ratio of (−)-form/(+)-form was determined to be 87/13 (74±2% ee).

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