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FLUORINATION OF HYDROXYESTERS WITH N,N-DIETHYL-1,1,2,3,3,3-HEXAFLUORO PROPYLAMINE

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SUMMARY

The reaction of 1,1,2,3,3,3-hexafluoropropyldiethylamine (PPDA) with hydroxy esters having Ph-C(H)(OH)-groups gave their corresponding secondary fluorides. Fluorination of (R)-(-)-mandelic acid ethylester ($[\alpha]_D^{29}$ -106.46) gave ethyl (S)-(+)-2-fluoro-2-phenyl acetate ($[\alpha]_D^{29}$ +6.57). The value of the enantiomeric excess (% ee) was 74.1. The reaction mechanism of the fluorination by PPDA is suggested to be the S_N2 type.

INTRODUCTION

Fluorinated compounds have been widely utilized in biochemical and industrial investigations [1]. 2-Chloro-1,1,2-trifluorotriethanolamine (FAR) [2] and (diethylamino)-sulfur trifluoride (DAST) [3] are useful fluorinating reagents for various alcohols. Recently, we reported that 1,1,2,3,3,3-hexafluoropropyl-diethylamine (PPDA) is useful as a fluorinating reagent for some fatty alcohols [4] and various diols [5,6]. However, the reactions of various hydroxy-esters with PPDA have not been studied in detail. On examination of this reaction, we found that the corresponding fluoro-esters are obtained from hydroxy esters and PPDA.

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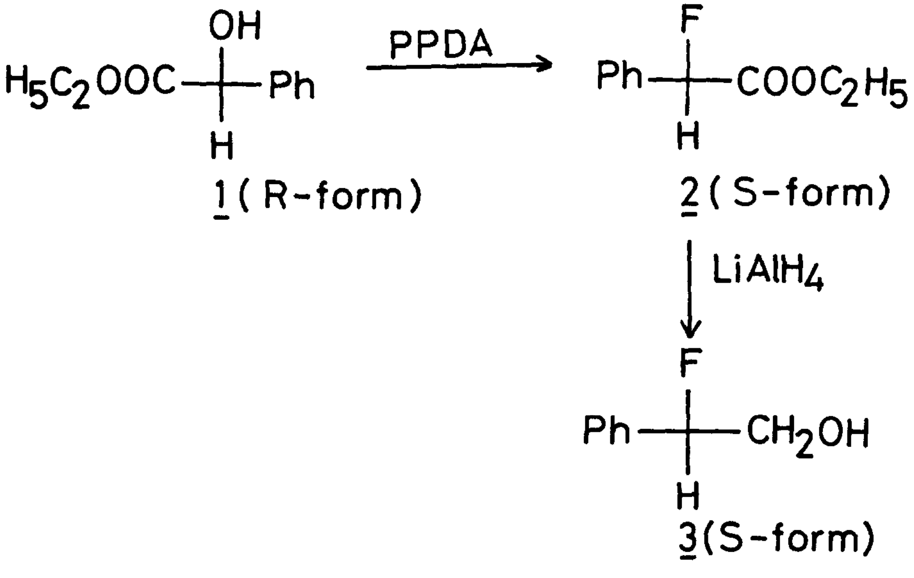
RESULTS AND DISCUSSION

It is known that PPDA is a useful fluorination reagent for saturated primary alcohols [4] and various diols [5,6]. However, the reactions of PPDA and most secondary alcohols give the corresponding fluorides in low yields only. Side reactions such as dehydration, isomerisation and dimerisation of alcohols are apt to occur.

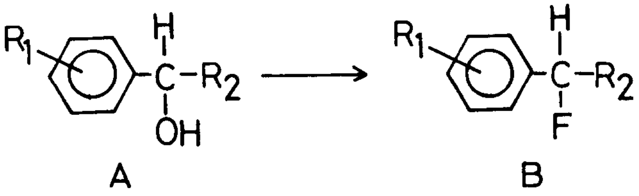
The present paper describes the reactions of various hydroxy esters containing a PhC(H)(OH)- group with PPDA to give the corresponding secondary fluorides. For example, from the reaction of PPDA with ethyl mandelate 1, ethyl 2-fluorophenylacetate 2 was obtained in 66% yield. The results are listed in Table I.



The preparation of optically active secondary fluorine compounds is not well known. Fluorination of (R)-(-)-mandelic acid ethylester 1 ($[\alpha]_D^{29}$ -106.46) gave ethyl (S)-(+)-2-fluoro-2-phenyl acetate 2 ($[\alpha]_D^{29}$ +6.57). The

TABLE 1

Fluorination of Hydroxyesters with PPDA



Compound (A)		Compound (B)[a] Boiling Point(°C/mmHg)[b] (Yield %)[c]	^{19}F NMR $-CH\underline{F}-$ δ(ppm), J_{HF} Hz
R_1	R_2		
H	$-COOC_2H_5$	117-118°/22mmHg (66.5)	+97.8 (d, J_{HF}=47.6 Hz)
H	$-CH_2COOC_2H_5$	132.5-134°/24mmHg (75.5)	+92.0 (d,d,d J_{FH}=39.5, J_{FHvic}=15.0, J_{FHvic}=24.8)
H	$-\overset{CH_3}{\overset{\vert}{C}}HCOOC_2H_5$	136-138°/24mmHg (75.0)	+88.5 (d,d, J_{HF}38.5, J_{FHvic}=8.5) +105.5 (d,d, J_{HF}=38.5, d J_{FHvic}=17.9)[d]
H	$-\overset{CH_2CH_3}{\overset{\vert}{C}}HCOOC_2H_5$	130-134°/20mmHg (60.0)	+104.5 (dd, J_{HF}=44, J_{FHvic}=13.0)
H	$-\overset{CH_2CH_2CH_3}{\overset{\vert}{C}}HCOOC_2H_5$	c[f] (62.0)	+87.0 (d,d, J_{HF}=46, J_{FHvic}=9.2)
H	$-\overset{CH_2CH_2CH_2CH_3}{\overset{\vert}{C}}HCOOC_2H_5$	144-145°/20mmHg (70.0)	+86.25 (d,d, J_{HF}=47, J_{FHvic}=10 Hz) +98.5 (d,d, J_{HF}=47, J_{FHvic}=14.5)[e]

(Continued overleaf)

TABLE I (Cont.)

Compound (A)		Compound (B)[a] Boiling Point(°C/mmHg)[b] (Yield %)[c]	^{19}F NMR -CHF- δ(ppm) J_{HF} Hz
R_1	R_2		
H	$-\overset{CH_2CH_2CH_2CH_2CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (67.5)	+87.5 (d,d, J_{HF}=46, J_{FHvic}=9.4)
o-CH_3	$-\overset{CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (70.4)	+105.5 (d,d J_{HF}=45.6, J_{FHvic}=9.2)
m-CH_3	$-\overset{CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (75.2)	+95.0 (d,d J_{HF}=45.2, J_{FHvic}=8.6)
p-CH_3	$-\overset{CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (63.2)	+85.5 (d,d J_{HF}=45.0, J_{FHvic}=8.0)
o-CH_3	$-\overset{CH_2-CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (73.6)	+97.5 (d, J_{HF}=44.0)
p-CH_3CH_2	$-\overset{CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	130°/15mmHg (60.2)	+89.0 (d, J_{HF}=44.4)
iso-C_3H_7	$-\overset{CH_3}{\overset{\mid}{C}}H-COOC_2H_5$	C^f (52.3)	+90.0 (d, J_{HF}=42.0)

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[a] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.30 %, H ± 0.04 %.

[b] These fluorides were isolated by reduced distillation with a spinning band column.

[c] The yield was calculated as isolated yield.

[d,e] These two signals may be due to diastereomers (50:50).

[f] These compounds were separated by liquid chromatography with silica gel column using n-hexane containing 1 % ethyl acetate as the solvent. All these compounds were liquid.

optical purity of 2 was determined by ^{19}F NMR after the conversion of the alcohol 3 to its diastereomeric esters by optically active (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (R)(MTPA). The enantiomeric excess (%ee) was 74.1. The ratio of (S)(3)-(R)(MTPA) and (R)(3)-(R)(MTPA) is expected to be 87:13. This suggests that fluorination by PPDA involves a S_N2 reaction pathway.

EXPERIMENTAL

The reaction products were analyzed by GLC on a Shimadzu Model GC-3BF Chromatograph using a 3m x 3mm column of 15% Silicone DC 200 on 60-80 mesh Celite 545. ^{1}H NMR and ^{19}F NMR spectra were obtained using $CDCl_3$ as a solvent on a Hitachi Model R-24 spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a TMS internal standard (^{1}H NMR), and ppm values relative to an external CF_3COOH (^{19}F NMR)(positive values upfield). IR spectra were obtained on a JASCO Model IR-G infrared spectrophotometer. Hydroxy esters were prepared by Reformatsky reaction.

Ethyl R(-)-Mandelate 1.

Compound 1 showed $[\alpha]_D^{29}$ -106.46 (c=2.54, CH_3OH).

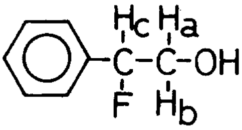
Reaction of Ethyl R(-)-Mandelate 1 with PPDA

A solution of PPDA (6.0 g, 26.9mmol) in CH_2Cl_2 (10 ml) was added dropwise into a solution of 1 (1.5 g, 8.3 mmol) in CH_2Cl_2 (20 mL) at room temperature. After stirring for 2 hr, the reaction mixture was left overnight. It was poured into water and an oily product was extracted with diisopropylether. The extract was washed with water, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was distilled with a small spinning type column to give the following fractions: (i) 85-91.5°C/22mmHg, 3.0g; (ii) 91.5-117°C/22mmHg, 1.0g; (iii) 117-118°C/22mmHg, 1.3g. Analysis of fraction (i) indicated that it was a mixture of N,N-diethyl-2,3,3,3-tetrafluoropropioamide (90 %) and ethyl (S)(+)-2-fluorophenylacetate 2 (10 %). Fraction (ii) was a mixture of the amide (40 %) and fluoro ester 2 (60 %). Fraction (iii) was a mixture of the amide (5 %) and fluoro ester 2 (95 %). These compositions were determined by gas chromatography. [Shimadzu GC-3BF, column Silicone DC 200 (15 %) on Celite 545 (3 m), temperature 160°C, carrier gas N_2, 40 mL min^{-1}.] Fraction (iii)(1.3 g) was chromatographed on a silica gel column (30.0 g) and eluted with n-hexane containing 1 % ethylacetate. Elution gave 1.0 g of pure ethyl (S)(+)-2-fluorophenylacetate 2 (yield 66 %). IR (cm^{-1}): 1740, 1210, 1060, 720, 700; ^1H NMR: 1.24 (3H, t, J=7.4 Hz, CH_3-), 4.20 (2H, q, J=7.4 Hz, $-OC\underline{H}_2CH_3$), 5.63 (1H, d, J=47.6 Hz, -CHF), 7.35 (5H, s, C_6H_5-); ^{19}F NMR: +97.8 ppm (d,J_{HF}=47.6 Hz); $[\alpha]_D^{29}$ +6.57, c= 2.90, CH_3OH. A mixture (0.15 g) of fluoride 2 and N,N-diethyl-2,3,3,3-tetrafluoropropioamide was obtained using n-hexane containing 3 % ethyl acetate as eluent. Analysis: Found: C, 65.90; H, 6.070; F 10.01 %. $C_{10}H_{11}FO_2$ requires C, 65.92; H, 6.085; F, 10.43 %.

Other hydroxy esters were treated with PPDA in the same manner, and the results are listed in Table I.

2-Fluoro-2-phenylethylalcohol 3

A solution of fluoride 2 (1.0 g, 7.1 mmol) in dry diethyl ether (20 mL) was added dropwise to a suspension of lithium aluminium hydride (0.25 g, 6.58 mmol) in dry diethyl ether (30 mL) at 0^oC. After stirring for 4 hr, the reaction mixture was decomposed with water and then diluted sulfuric acid. A diethylether extract of the reaction mixture was washed with water, dried over anhydrous sodium sulfate, and the residue was distilled to give 0.50 g of 2-fluoro-2-phenylethyl alcohol 3; b. p. at 90 - 94^oC / 14 mmHg. IR (cm^{-1}): 3150, 1040, 750, 700; ^1H NMR: 3.10 (1H, s, OH), 3.87 (2H, dd, J_{HaF}=23.0 Hz, J_{HaHc}=7.0 Hz, $-CHF-C\underline{H}_2-$), 5.55 (1H, dt, J_{HcF}=47.0 Hz, J_{HcHa}= 7.0 Hz, $-C\underline{H}F-CH_2$), 7.32 (5H, s, C_6H_5); ^{19}F NMR: +104 ppm (ddd, J_{FHc}=47.0 Hz, J_{FHa}=23.0 Hz, J_{FHb}=19.0 Hz); $[\alpha]_D^{29}$=+1.13, c=1.36, CH_3OH.



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Determination of Enantiomeric Composition of 2-Fluoro-2-phenylethyl Alcohol 3

A mixture of 3 and (R)(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA) [7] in pyridine solution was stirred overnight. It was decomposed with water and dilute hydrochloric acid. A diethylether extract of the reaction mixture was treated in the reported way [7] to give diastereomeric esters by optically active (R)-(+)-MTPA. The optical purity, 74.1 %ee was determined by ^{19}F NMR.

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