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PREPARATION OF MONOFLUOROCARBOXYLIC ACIDS USING N,N-DIETHYL-1,1.2.3,3,3-HEXAFLUOROPROPYLAMINE

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SUMMARY

A method is outlined for the preparation of monofluorocarboxylic acids using Ishikawa's reagent, $(C_2H_5)_2NCF_2CHFCF_3$ (PPDA), directly from hydroxyesters, or indirectly from monofluorinated alkylbenzenes, followed by the oxidation of the phenyl ring to a carboxylic acid. The chiral fluorocarboxylic acids, (2S) and (2R)-3-fluoro-2-methylpropionates (>99% ee) and (2S)-2-fluoropropionic acid (55% ee) are prepared as are 3-fluoropropionate and 4-fluorobutyrate.

INTRODUCTION

N,N-diethyl-1,1,2,3,3,3-hexafluoropropylamine (PPDA) was first described [1] as a fluorinating agent by Ishikawa and his colleagues in 1979. The suggested [2a] mnemonic-PPDA- arises as the reagent is prepared from perfluoropropene and diethylamine. Since 1979 the scope of PPDA has been investigated [1,2] and found to be a suitable method for the replacement of alcohols for fluorine as well as the generation of acylfluorides from carboxylic acids. Although not unique in this context [3] the advantages of PPDA lie in its ease of preparation and comparative stability. We were required to prepare a series of monofluorinated carboxylic acids and chose PPDA for the introduction of fluorine. The results and observations are outlined below.

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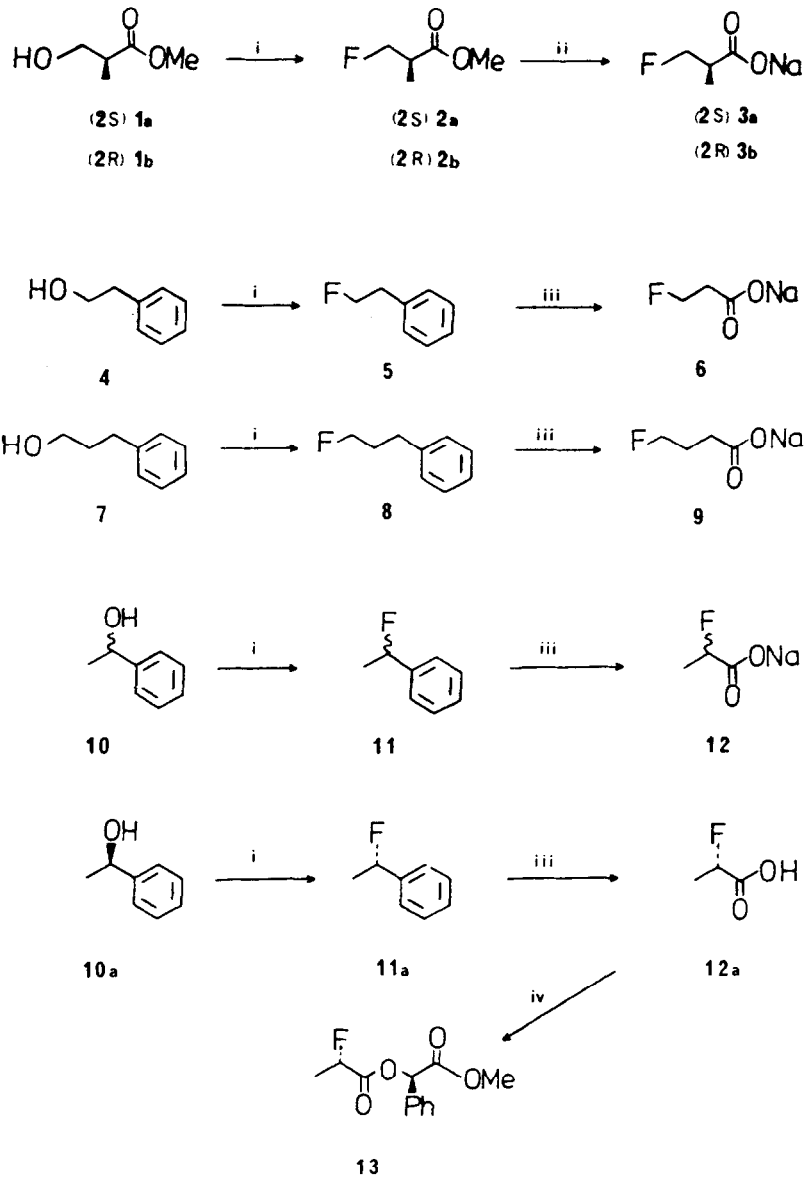
RESULTS AND DISCUSSION

Published accounts [2,4] of treating hydroxyesters with PPDA warn against the concominant formation of 2,3.3,3-tetrafluoropropionate esters. In this study (see Scheme) all the alcohols investigated were converted smoothly to their respective fluorides.

(2S)- and (2R)-3-fluoro-2-methylpropionates (3a) and (3b) were prepared from (2S) and (2R)-methyl-3-hydroxy-2-methylpropionates (1a) and (1b) respectively without loss of stereointegrity. The optical purities (>99% ee) were determined by ^{1}H- and ^{19}F-NMR analysis after acidic ester hydrolysis of (2a) and (2b) and coupling of the free acids to (2R)-(-)-methyl mandelate [5]. The isolated yield (45%) after transformation with PPDA was moderate in this case as the methyl esters (2a) and (2b) had to be separated from N,N-diethyl-2,3,3,3-tetrafluoropropionamide by distillation. In view of this we chose to prepare the remaining monofluorocarboxylic acids via monofluoroalkylbenzenes (5), (8) and (11) as they could be isolated cleanly by silica gel chromatography. In the event (5) and (8) were purified in good yields. Their oxidation with RuO_4 under the conditions described by Sharpless and co-workers [6] afforded 3-fluoropropionate (6) and 4-fluorobutyrate (9) respectively. In the last case treatment of 1-phenylethanol (10) with PPDA gave (11). 1-Fluoroethylbenzene (11) was purified either by chromatography or distillation. Subsequent oxidation of (11) provided 2-fluoropropionate (12). In this study the fluorocarboxylates were all isolated as their sodium salts and it proved essential when preparing (3a), (3b) and (6) to avoid pH conditions above 7.5 as HF elimination resulted in the isolation of sodium acrylates.

Finally (2S)-2-fluoropropionic acid (12a) was prepared from (2R)-1-phenylethanol (10a) via (11a). (11a) Was oxidised and the free acid isolated directly and coupled to (2R)-(-)-methyl mandelate to reveal (13) as the major diastereomer in 55% excess. A shift to lower field of the major diastereomer by 4 Hz, observing the ^{19}F NMR at -185.6 ppm, is consistent [5] with fluorine occupying the 2-pro-R site of (13) and implicating a configurational inversion during fluorination. This study complements a previous stereochemical investigation [7] of this reagent i.e. 74.1% ee for the conversion of (2R)-(-)-ethyl mandelate into (2S)-(+)-2-fluoro-2-phenylacetate. In both cases a loss in stereointegrity is observed and it remains to be determined if this loss



Scheme. i. PPDA, ii. 50% H_2SO_4 then neutralise with dil. NaOH, iii. $RuCl_3$. KIO_4, (CCl_4:MeCN:H_2O; 1:1:3). iv. (2R)-(-)methyl mandelate, DCC. DMAP.

occurs during the fluorination process or arises subsequently from the conditions of the assay procedures. When the sodium salt of (12a) was prepared and then coupled to (2R)-(-)-methyl mandelate via the free acid complete racemisation had occurred implying loss of stereointegrity at pH 7.0.

EXPERIMENTAL

^1H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ or D_2O on Bruker AC250 or Perkin-Elmer 24B NMR spectrometers. Chemical shifts are quoted as δ values relative to TMS (δ = 0) for ^1H NMR and ppm values relative to CF_3CO_2H (-76.5 ppm) for ^{19}F NMR. Kieselgel 60 (230-400 mesh) was used for silica gel chromatography. Petrol refers to petroleum spirit boiling range 40°C-60°C.

Preparation of N,N-diethyl-1,1,2,3,3,3-hexafluoropropyldiethylamine (PPDA)

The reagent was prepared at atmospheric pressure according to the literature procedure [1]. PPDA was distilled directly prior to use.

Preparation of sodium (2S)-3-fluoro-2-methylpropionate (3a)

To a solution of methyl (2S)-3-hydroxy-2-methylpropionate (1a) (3.5 g, 300 mmol) in dichloromethane (20 ml) was added PPDA (17 g, 75 mmol) and the reaction heated under reflux for 18 hours. The solution was quenched at 0°C with water (20 ml) and the yellow oil extracted into dichloromethane. The extract was dried over $MgSO_4$ and the solvent removed at reduced pressure. Distillation afforded (2a) (28°C/14 mmHg) (1.62 g, 13.5 mmol) in 45% yield. ^1H NMR ($CDCl_3$): 1.28 (3H, d, 7 Hz, CH_3), 2.9 (1H, m, CH), 3.7 (3H, s, OCH_3), 4.6 (2H, d.m, 46 Hz, CH_2F); ^{19}F NMR ($CDCl_3$): -217 ppm (d.t 18 Hz, 46 Hz).

(2a) (1.62 g, 13.5 mmol) was stirred vigorously in 50% H_2SO_4 solution (20 ml) for 4 hours. The reaction mixture was lyophilised and the lyophilisate adjusted to pH 7.0 with 0.1 N NaOH solution. The neutral solution was freeze dried providing (3a) (1.2 g, 9.5 mmol) as a white amorphous powder in 70% yield. ^1H NMR (D_2O): 1.25 (3H, d, 6.2 Hz, CH_3), 2.8 (1H, m, CH), 4.7 (2H, d.m, 45 Hz, CH_2F); ^{19}F NMR (D_2O): -217.9 ppm (d.t, 18 Hz, 46.6 Hz).

A portion of (3a) was taken up in water, acidified (50% H_2SO_4) and the free acid extracted into diethyl ether. The acid was treated using an

established procedure [5] with (2R)(-) methyl mandelate to afford only one detectable enantiomer by ^{1}H and ^{19}F NMR analysis (>99% ee).

The preparation of (3b) followed an identical procedure from (2R)-3-hydroxy-2-methylpropionate (1b).

Preparation of sodium 3-fluoropropionate (6)

To a solution of 2-phenylethanol (4) (2 g, 16 mmol) in diethyl ether (30 ml) was added PPDA (5 g, 22 mmol) and the reaction heated under reflux for 2 hours. The reaction mixture was quenched at 0°C with water (20 ml) and extracted into dichloromethane. The extract was dried over $MgSO_4$ and the solvent removed at reduced pressure. The residual oil was purified by silica gel chromatography (100% petrol) to give 2-fluoroethylbenzene (5) (1.8 g, 14.4 mmol) in 90% yield. ^{1}H NMR ($CDCl_3$): 2.85 (2H, d.t, 22 Hz, 6.6 Hz, -C$\underline{H}_2$Ph). 4.46 (2H, d.t, 47 Hz, 6.6 Hz, CH_2F), 7.16 (5H, m); ^{19}F NMR ($CDCl_3$): -216.3 ppm (t.t, 47 Hz, 22 Hz).

(5) (1.8 g, 14.4 mmol) was taken up in a biphasic solution of H_2O:H_3CCN:CCl_4 (3:1:1) (100 ml) and stirred vigorously after addition of KIO_4 (12.5 g, 54 mmol) and $RuCl_3$ (30 mg) for 24 hours. The reaction was filtered and the aqueous layer separated, acidified (50% H_2SO_4) and lyophilised. The lyophilisate was adjusted to pH 7.0 with 0.1 N NaOH and the solution freeze dried providing (6) (0.74 g, 6.5 mmol) as an amorphous white solid in 45% yield. ^{1}H NMR (D_2O): 2.79 (2H, d.t, 29 Hz, 6 Hz, -C$\underline{H}_2$Ph), 4.8 (2H, d.t, 46 Hz, 6 Hz, -CH_2F); ^{19}F NMR (D_2O) -217 ppm (t.t, 46 Hz, 29 Hz).

Preparation of sodium 4-fluorobutyrate (9)

To a solution of 3-phenylpropanol (7) (2 g, 15 mmol) in dichloromethane (25 ml) was added PPDA (4 ml, 20 mmol) and the reaction heated under reflux for 18 hours. The reaction mixture was quenched at 0°C with water (20 ml) and extracted into dichloromethane. The extract was dried over $MgSO_4$ and the solvent removed at reduced pressure. Purification of the residual oil by silica gel chromatography (100% petrol) gave (8) (1.5 g, 12 mmol) as a clear oil in 75% yield. ^{1}H NMR ($CDCl_3$): 2.0 (2H, m, -C$\underline{H}_2CH_2F$), 2.7 (2H, d.t, 6 Hz, 2 Hz, -CH_2Ph), 4.4 (2H, d.t, 46 Hz, 6 Hz, CH_2F), 7.2 (5H, s, Ph); ^{19}F NMR ($CDCl_3$): -216 ppm (t.t, 46 Hz, 24 Hz). (8) (1.5 g, 12 mmol) was treated as above (see preparation of (6) from (5)) to afford (9) (0.79 g, 6.2 mmol) in 52%

yield. ^{1}H NMR (D_2O): 2.0 (4H, m, -CH_2CH_2-), 4.7 (2H, d.t, 45 Hz, 6 Hz, CH_2F); ^{19}F NMR (D_2O): -217 ppm (t.t, 45 Hz, 24 Hz).

Preparation of sodium 2-fluoropropionate (12)

To a solution of 1-phenylethanol (10) (2 g, 16 mmol) in diethyl ether (30 ml) was added PPDA (5 g, 22 mmol) and the solution heated under reflux for 15 hours. The reaction mixture was quenched with water (10 ml) at 0°C and extracted into dichloromethane. The extract was dried over $MgSO_4$ and the solvent removed at reduced pressure to afford a yellow oil. Purification by column chromatography (100% petrol) afforded (11) (0.98 g. 8 mmol) in 50% yield or by distillation in 43% yield (b.p. 48°C/16 mmHg) (46°C/15 mmHg) [3a]. ^{1}H NMR ($CDCl_3$): 1.5 (3H, d.d, 24 Hz, 6 Hz, CH_3), 5.5 (1H, d.q, 48 Hz, 6 Hz, -CHF-), 7.3 (5H, s, Ph); ^{19}F NMR ($CDCl_3$): -167 ppm (d.q, 48 Hz, 24 Hz).

(11) (0.98 g, 8 mmol) was treated as above (see preparation of (6) from (5)) to afford sodium 2-fluoropropionate (12) (0.27 g, 2.4 mmol) in 30% yield. ^{1}H NMR (D_2O): 1.5 (3H, d.d, 24 Hz, 6 Hz, CH_3), 4.9 (1H, d.q. 51 Hz, 6 Hz, -CHF-); ^{19}F NMR (D_2O): -173 ppm (d..q, 51 Hz, 24 Hz).

Preparation of (2S)-2-fluoropropionic acid (12a) and asymmetric analysis

(2S)-1-Fluoroethylbenzene (11a) was prepared from (2R)-(+)-sec-phenylethanol (10a) under the conditions described for the conversion of (10) into (11). Oxidation of (11a) afforded an acidic lyophilisate containing (12a), which was extracted into diethyl ether. The extract was dried over $MgSO_4$ and the solvent removed at reduced pressure. The free acid (13a) was coupled directly to (2R)-(-)-methyl mandelate [5]. The ^{19}F NMR signals at -185.6 ppm clearly indicated diastereomeric mixtures of (13) in the ratio 69:31 (55% ee) with the predominant stereoisomer resonating to lower field by 4 Hz.

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