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Lipase mediated preparation of the enantiomers of 3,3,3-trifluoro-2-methylpropanoic acid

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Abstract—The preparation of both enantiomers of 3,3,3-trifluoro-2-methylpropanoic acid by a lipase mediated kinetic resolution of the racemate is described.

1. Introduction

Compounds containing the trifluoromethyl group have and continue to play an important role as fine chemical constituents contributing to the development of pharmaceutical, agrochemical and materials products.[1] Many of these are nonchiral aryl CF_3 and OCF_3 containing compounds, however there has been the recent emergence of commercial products carrying the CF_3 group at a stereogenic centre.[2] The number of available starting materials in this category is few and methods for preparing compounds with the CF_3 at a stereogenic centre are limited.[3] Herein we report the lipase mediated resolution of 3,3,3-trifluoro-2-methylpropanoic acid **1**. The only reported preparation of enantioenriched **1** was achieved by hydrogenation of 2-(trifluoromethyl)acrylic acid with H_2 in the presence of Ru-(*R*)-BINAP catalyst. However product **1** was not isolated and characterized, but directly transformed into (2*S*)-3,3,3-trifluoro-2-methyl-1-propanol (ee 80%).[4] Some α-trifluoromethylated carboxylic acids have been obtained in optically active form (unknown stereochemistry) by enzymatic hydrolysis of their esters using the PS lipase in an aqueous medium,[5] yet the resolution of **1** has not been described. We have been exploring the resolution of fluorinated esters in dry organic solvents[6] and in this program decided to address the resolution of **1** by esterification using the *Candida rugosa* lipase[†](CRL) in hexane. This was an attractive method as it allowed us to test the ability of such enzymes to distinguish directly between the CH_3 and CF_3 groups. Previous analyses and studies in asymmetric syntheses suggest a significant difference in the steric influence of a CH_3 and CF_3 group,[7] with an estimate that the CF_3 approximates the size of an isopropyl group.[8] It is somewhat surprising that this has not been explored in this system before. Herein we have successfully resolved each of the enantiomers in high enantiomeric excess.

2. Results and discussion

Ethyl 3,3,3-trifluoro-2-methylpropanoate **2** was prepared in two steps by the reaction of diethyl 2-methylmalonate **3** with sodium hydride and dibromo(difluoro)methane followed by a fluorination–decarboxylation process.[9] Alkaline hydrolysis of the resultant ester proved unsuccessful leading to conversion of the CF_3 group to a carboxylate with the generation of 2-methylmalonate.[10] However acidic hydrolysis gave the desired 3,3,3-trifluoro-2-methylpropanoic acid,[11] **1** as illustrated in Scheme 1.

Lipase mediated kinetic resolution of **1** via enantioselective esterification with 1-decanol in hexane gave decyl ester **5**. When this reaction was stopped after 4 h

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[†] Lipase from *Candida rugosa,* Type VII (CRL) was purchased from the Sigma Chemical Co. and had a specific activity of 1140 U mg-1 solid. The lipase was used 'straight from the bottle'.

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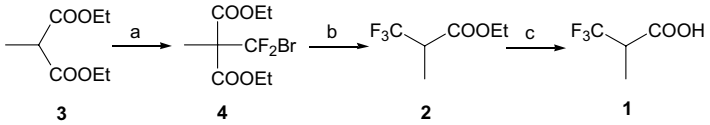
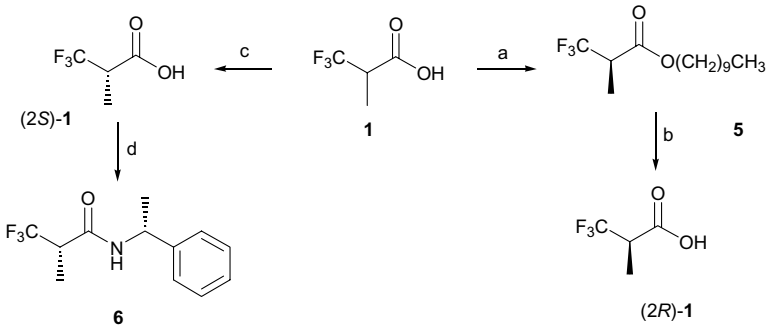


Scheme 1. Reagents and conditions: (a) NaH, CF_2Br_2, THF, 48%; (b) KF, DMSO, 170 °C, 91%; (c) HCl, 1,4-dioxane, reflux, 61%.



Scheme 2. Reagents and conditions: (a) CRL, 1-decanol (2 equiv), hexane, 37 °C, 4 h; (b) HCl, 1,4-dioxane, reflux; (c) CRL, 1-decanol (2 equiv), hexane, 37 °C, 20 h; (d) *N*-methylmorpholine, ClCOOMe, (1*R*)-1-phenylethanamine, THF, −10 °C, 90%.

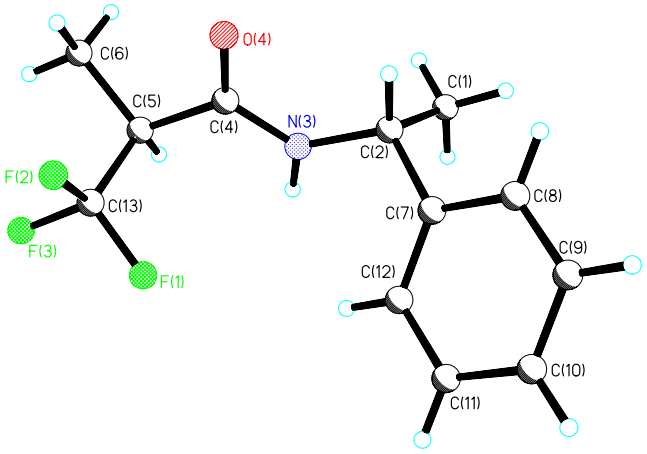
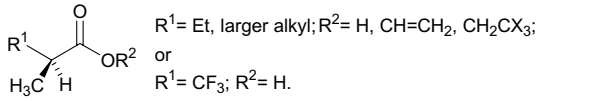


Figure 1. X-ray derived structure of (2*S*)-3,3,3-trifluoro-2-methyl-*N*-[(1*R*)-1-phenyl]-propanamide **6**.[‡]

and **5** was hydrolyzed, enantiomerically enriched **1** was obtained[12] ee 90%, 36%, $[\alpha]_D^{19} < +1$ (*c* 1.12, MeOH) as shown in Scheme 2. Longer reaction times (20 h) gave the other enantiomer of **1** recovered as the unreacted and enantiomerically pure acid[13] {ee >98%, 74%, $[\alpha]_D^{19} = -0.8$ (*c* 1.23, MeOH)}, Scheme 2.[§]

To determine the absolute configuration of the recovered **1**, amide **6** {$[\alpha]_D^{25} = +88.7$ (*c* 0.345, $CHCl_3$)} was prepared[14,15] by reaction with (1*R*)-1-phenylethylamine, (Scheme 2). X-ray diffraction analysis of a single crystal of amide **6** showed an (*S*)-configuration on the acid derived moiety (Fig. 1) and therefore a lipase preference for enantiomer (2*R*)-**1**.

The stereochemical outcome of the CRL catalyzed kinetic resolution follows the pattern of reactivity of 2-methylalkanoic acids.[16] The faster reacting enantiomers have a stereochemistry as shown in Scheme 3, a configurational preference that is persistent through enzymatic hydrolysis, esterification or transesterification reactions with this lipase.



Scheme 3. The stereochemistry of the faster reacting enantiomer with CRL.

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[‡] The crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236631.

[§] The ee values of the enantiomers of **1** were determined by GC–MS using a chiral β-DEX 120 (Supelco) column (30 m × 250 μm, film thickness 0.25 μm). Temp 75 °C hold 20 min, then at 10 °C min^{-1} to 100 °C, hold 11 min, ret. time 29.5 min (*R*), 30.15 min (*S*).

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11. 3,3,3-Trifluoro-2-methylpropanoic acid, **1**:**2** (16.1 g, 9.7 mmol) was dissolved in 1,4-dioxane (100 cm^3) and HCl (36%, 70 cm^3) added. The mixture was heated under reflux for 15 h, cooled and DCM (200 cm^3) then added. The two phases were separated and the aqueous was extracted into DCM (3×100 cm^3). The combined organic extracts were washed with aq $NaHCO_3$ (0.8 M, 3×100 cm^3). The aqueous phase was acidified (conc. HCl), the product isolated by extraction into diethyl ether (3×100 cm^3), drying over $MgSO_4$ and removal of the solvent under reduced pressure. Distillation (80 °C/20 mm Hg) gave **1** as a colourless liquid (8.205 g, 61%). MS (CI): *m/z* = 143.0316 $[M+H]^+$ $C_4H_6O_2F_3$ requires 143.0320. IR (film) 2923, 2853, 2689, 1701 (CO), 1471, 1327, 1083, 1043, 965, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$; Me_4Si): δ 9.9 (br s, 1H), 3.33–3.18 (m, 1H), 1.47 (d, 3H, J = 7.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$; $CFCl_3$): δ −70.5 (d, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 124.7 (q, J = 279 Hz), 44.4 (q, J = 29 Hz), 11.0. MS (EI): *m/z* (rel int.) = 142 $[M]^+$ (1), 125 (30), 122 $[M-F]^+$ (20), 102 (35), 78 (70), 77 (100), 69 $[CF_3]^+$ (20), 45 (35).
12. (2*R*)-3,3,3-Trifluoro-2-methylpropanoic acid, (2*R*)-**1**: 1-Decanol (6.708 g, 42.38 mmol) and **1** (3.009 g, 21.19 mmol) were dissolved in hexane (200 cm^3). The CRL (7.5 g) was added and the mixture shaken at 250 rpm/37 °C for 4 h. The reaction was terminated by the addition of $MgSO_4$ (5 g) and the mixture filtered. The solid was washed with diethyl ether (3×15 cm^3), the solvent removed under reduced pressure and the residue dissolved in diethyl ether (50 cm^3). The solution was washed with aq $NaHCO_3$ (0.8 M, 3×40 cm^3), the solvent removed from the organic phase and the residue hydrolyzed (HCl in 1,4-dioxane). Similar work-up as for the racemic acid afforded (2*R*)-**1** (541 mg, 36%, ee 90%), $[\alpha]_D^{19} < +1$ (*c* 1.12, MeOH).
13. (2*S*)-3,3,3-Trifluoro-2-methylpropanoic acid, (2*S*)-**1**: 1-Decanol (6.708 g, 42.38 mmol) and **1** (3.009 g, 21.19 mmol) were dissolved in hexane (200 cm^3). The CRL (7.5 g) was added and the mixture shaken at 250 rpm/37 °C for 20 h. The reaction was terminated by the addition of $MgSO_4$ (5 g) and the mixture filtered. The solid was washed with diethyl ether (3×15 cm^3), the solvent removed under reduced pressure and the residue dissolved in diethyl ether (50 cm^3). The unreacted acid was isolated by extraction with aq $NaHCO_3$ (0.8 M, 3×40 cm^3), acidification and extraction into diethyl ether (3×20 cm^3). Drying and solvent removal gave (2*S*)-**1** (1.111 g, 74%, ee >98%). $[\alpha]_D^{19} = -0.8$ (*c* 1.23, MeOH).
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15. (2*S*)-3,3,3-Trifluoro-2-methyl-*N*-[(1*R*)-1-phenyl]-propanamide, **6**: (2*S*)-**1** (ee >98%, 106 mg, 0.746 mmol) was dissolved in dry THF (12 cm^3) and cooled to −10 °C under nitrogen. 4-Methylmorpholine (81 mg, 0.8 mmol) and methyl chloridocarbonate (75 mg, 0.8 mmol) were added and after 1 min of stirring (1*R*)-1-phenylethanamine (113 mg, 0.93 mmol) then added. The solution was stirred at −5 to −10 °C for 40 min and then an aqueous solution of citric acid (5%, 150 cm^3) added. The mixture was extracted with ethyl acetate (3×40 cm^3), the organic phase washed with aqueous solution of sodium hydrogen carbonate (1 M, 3×20 cm^3), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue (de 98%) was purified using silica gel column chromatography to give the major diastereomer as a white solid (de 100%, 165 mg, 90%) mp 138.5–139 °C (from hexane). $[\alpha]_D^{25} = +88.7$ (*c* 0.345, $CHCl_3$). MS (CI): *m/z* = 246.1107 $[M+H]^+$ $C_{12}H_{15}OF_3N$ requires 246.1107. IR (KBr) 3308, 3093, 2987, 2972, 1651 (CO), 1560, 1268, 1239, 1175, 1125, 1006, 754, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$; Me_4Si): δ 7.38–7.25 (m, 5H), 5.9 (br s, 1H), 5.19–5.09 (m, 1H), 3.09–2.93 (m, 1H), 1.51 (d, 3H, J = 6.8 Hz), 1.39 (d, 3H, J = 7.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$; $CFCl_3$): δ −69.9 (d, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 142.4, 128.8, 127.6, 126.0, 125.6 (q, J = 280 Hz), 49.2, 46.3 (q, J = 28 Hz), 21.5, 11.0. MS (EI): *m/z* (rel int.) = 245 $[M]^+$ (60), 230 $[M-Me]^+$ (50), 120 (20), 106 (100), 105 (40), 77 (30). MS (ESI): *m/z* = 244 $[M-H]^-$.
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