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Laboratory Scale Preparation of 4,4,5,5,5-Pentafluoropentan-1-thiol: An Important Chain of Anti-Breast Cancer Agents

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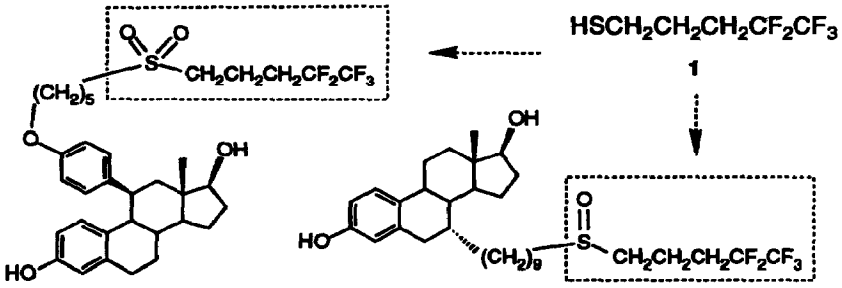
Abstract: Quantitative free radical addition of perfluoroethyl iodide to propargyl alcohol in the presence of sodium hydrosulfite gave E/Z-2-iodo-4,4,5,5,5-pentafluoro-2-penten-1-ols, which were converted to 4,4,5,5,5-pentafluoropentan-1-ol in one step in excellent yield by catalytic hydrogenation over platinum oxide in the presence of triethylamine. 4,4,5,5,5-Pentafluoropentan-1-thiol was obtained in good yield *via* modified Mitsunobu reaction of the alcohol.

Importance of fluorinated compounds as therapeutic agents is well documented. Recently, introduction of a 4,4,5,5,5-Pentafluoropentan-1-thiol (1) moiety in the side chain of estradiol significantly increased its antiestrogenic potency. The antiestrogens RU 58 688[1] and ICI 182,780[2] are good examples of the above indicated application.

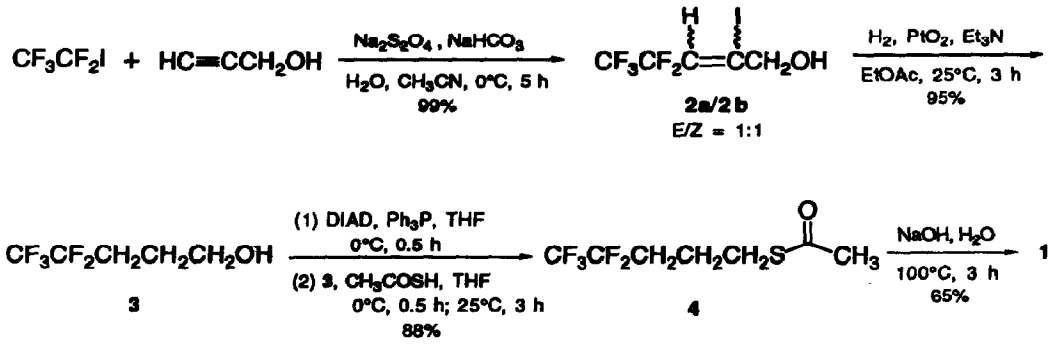


RU 58 688 ICI 182,780

Despite the interest of this chain, there is a lack of general methods to prepare thiol 1. Herein, we describe a simple and relatively straight forward synthesis of 4,4,5,5,5-Pentafluoropentan-1-thiol from perfluoroethyl iodide.

Scheme 1 outlines our approach: the key steps of this approach are the preparation of allylic alcohols **2a** and **2b** followed by their reduction to provide alcohol **3**. Ultrasound-promoted addition[3] of perfluoroethyl

iodide to propargyl alcohol in the presence of zinc powder was unsuccessful. However, free radical addition[4] in the presence of azobis(isobutylnitrile) gave a (1:1) mixture of alcohols **2a** and **2b** in 50% yield. However, purification of alcohols from the mixture was usually difficult. On the other hand, the method of Tang *et. al.*,[5] which used sodium hydrosulfite/sodium bicarbonate (1:1) gave very high yield (99%) of products **2a** and **2b** (E/Z, 1:1).



Scheme 1

Selective deiodination of the E/Z isomers *via* catalytic hydrogenation over Raney Ni or Pd/C in the presence of a base (NaOH, KOH or KOAc) gave a mixture of partial deiodination products, allyl alcohols and 4,4,5,5,5-pentafluoropentan-1-ol (**3**).[6] When hydrogenation over platinum oxide (PtO_2)[7] was carried out in the presence of triethylamine (Et_3N)[8] in ethyl acetate where the salt ($Et_3NH^+I^-$) could selectively be precipitated out, alcohol **3** was obtained in one step in excellent yield. Deiodination along with reduction of the double bond also occured. Two equivalents of triethylamine gave the best result (95%). The thiol **1** from the alcohol **3** was prepared by first converting to thiol ester **4** followed by basic hydrolysis. Thus, the reaction of thiolacetic acid with alcohol **3** under modified Mitsunobu conditions[9] gave thiol ester **4** which, without much purification, was treated with sodium hydroxide to give thiol **1** at a 65% yield.[10]

In conclusion, the present approach, while being very practical and efficient, provides an opportunity to prepare the thiol **1** in gram quantities. All steps can be carried out on a bench top without much extra precautions. All reaction conditions are mild.[11]

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10. (a) Preparation of (E/Z)-2-iodo-4,4,5,5,5-pentafluoro-2-penten-1-ols (**2a/2b**): In a high pressure reaction vessel, perfluoroethyl iodide (43.0 g, 174.9 mmol) was bubbled into a stirring mixture of acetonitrile (350 mL) and water (300 mL) at -20°C. Propargyl alcohol (9.81 g, 174.9 mmol) was added followed by a mixture of sodium hydrosulfite (30.44 g, 174.9 mmol) and sodium hydrogen carbonate (14.7 g, 174.9 mmol). After the addition, the mixture was stirred at 0°C for 5 h. The reaction mixture was diluted with water (300 mL) and extracted with ether (3 X 400 mL). The combined organic layer was washed with a sat. NaCl solution and then dried ($MgSO_4$). Removal of solvent under reduced pressure gave the products **2a** and **2b** (52.4 g, 99%). The NMR analysis indicated the presence of a mixture of two isomers (E/Z, 1:1): IR (neat, cm^{-1}) 3347 (br), 1640, 1336, 1198, 1130, 1048; ^{1}H-NMR (CD_3Cl) δ 3.42 (s, 2 H, E/Z-OH), 4.30 (dd, J = 1.5, 2.0 Hz, 2 H, E-CH_2), 4.32 (dd, J = 1.3, 2.0 Hz, 2 H, Z-CH_2), 6.39 (t, J = 14.8 Hz, 1 H, Z-CH), 6.71 (t, J = 14.2 Hz, 1 H, E-CH). ^{13}C-NMR (CD_3Cl) δ 64.2 (E-C-1), 72.1 (Z-C-1), 115.4 (t, J_{FCCC} = 4.2 Hz, E-C-2), 118.9 (t, J_{FCC} = 23.3 Hz, E-C-3), 123.8 (t, J_{FCCC} = 5.6 Hz, Z-C-2), 126.4 (t, J_{FCC} = 23.5 Hz, Z-C-3), 113.3 (qt, J_{FC} = 252.9, 38.7 Hz, C-5), 113.3 (tq, J_{FC} = 287.1, 34.1 Hz, C-4).
(b) 4,4,5,5,5-Pentafluoropentan-1-ol (**3**): To a stirring solution of compounds **2a/2b** (52.2 g, 172.9 mmol) in ethyl acetate (400 mL) were added platinum oxide (2.5 g) and triethylamine (35.0 g, 345.8 mmol). After the addition, the system was evacuated three times with hydrogen and the reaction was carried out under hydrogen atmosphere filled in a balloon at 25°C for 3 h (a triethylamine-hydrogen iodide salt was formed which precipitated out as a white solid form the solution). The catalyst and the salt were removed by filtration and the solid was washed with ethyl acetate (2 X 80 mL). The combined organic phase was washed with 1% HCl followed by a sat. NaCl solution, and then dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude compound, which after distillation provided the product **3** (29.3 g, 95%) as a colorless liquid, b.p. 133-135°C (Lit[7] b.p. 133-135°C). IR (neat, cm^{-1}) 3347 (br), 2995, 2889, 1362, 1346, 1316, 1196, 1060, 1012; ^{1}H-NMR (CD_3Cl) δ 1.78-1.88 (m, 2 H, 2-CH_2), 1.96 (br s, 1 H, OH), 2.04-2.22 (m, 2 H, 3-CH_2), 3.72 (t, J = 6.0 Hz, 2 H, 1-CH_2). ^{13}C-NMR (CD_3Cl) δ 119.0 (qt, J_{F3C} = 285.5, J_{F2CC} = 36.5 Hz, C-5), 115.9 (tq, J_{F2C} = 251.6, J_{F3CC} = 36.4 Hz, C-4), 61.3 (C-1), 27.3 (t, J_{FCC} = 22.0 Hz, C-3), 23.5 (C-2).
(c) 4,4,5,5,5-pentafluoropentan-1-thiolacetate (**4**): To an efficiently stirring solution of triphenylphosphine (62.8 g, 239.3 mmol) in THF (650 mL) at 0°C, diisopropyl azodicarboxylate (DIAD) (48.4 g, 239.3 mmol) was added and the mixture was stirred at 0°C for 30 min. A white precipitate formed. 4,4,5,5,5-Pentafluoropentan-1-ol (**3**) (21.3 g, 119.7 mmol) followed by

thioacetic acid (18.2 g, 239.3 mmol) in THF (150 mL) were added dropwise over 20 min and the mixture was stirred for 30 min at 0°C followed by 1 h at 25 °C. The color of the mixture changed form gray-green to a clear yellow solution. THF was removed by a regular fractional distillation, and the resulting mixture was then cooled at 0°C for 16 h (triphenylphosphine oxide and triphenylphosphine were precipitated out). The precipitates was removed by filtration and was then washed with petroleum ether (3 X 50 mL). After distilling out petroleum ether at 85°C (oil bath), thiolacetate **4** (24.6 g, 88%) was distilled out at 135-140°C (oil bath) under reduced pressure as a colorless liquid, b.p. 88-90°C/30 mmHg. IR (neat, cm^{-1}) 2947, 1697, 1358, 1197, 1134, 1102, 1066; ^{1}H-NMR (CD_3Cl) δ 1.84-1.98 (m, 2 H, 2'-CH_2), 2.01-2.20 (m, 2 H, 3'-CH_2), 2.36 (s, 3 H, 2-CH_3), 2.95 (t, J = 7.1 Hz, 2 H, 1'-CH_2). ^{13}C-NMR (CD_3Cl) δ 195.2 (C-1), 119.0 (qt, J_{F3C} = 284.9, J_{F2CC} = 36.5 Hz, C-5'), 115.7 (tq, J_{F2C} = 289.1, J_{F3CC} = 36.3 Hz, C-4'), 30.6 (C-2), 29.5 (t, J_{F2CC} = 22.2 Hz, C-3'), 28.0 (C-1'), 20.9 (C-2').

(d) 4,4,5,5,5-pentafluoropentan-1-thiol (**1**): Thiolacetate **4** (24.4 g, 103.4 mmol) in 2N sodium hydroxide solution (200 mL) was heated at 100°C for 3 h. The reaction mixture was cooled down to 0°C and acidified to pH 4 with 6N HCl solution. The acidic solution was saturated with a NaCl and stirred at 0°C for 10 min and then extracted with ether (3 X 150 mL). The combined organic phase was washed with a sat. NaCl solution and dried ($MgSO_4$). After filtration, ether was distilled out at 85°C (oil bath) under argon, followed the compound **1** (13.1 g, 65%) at 145-155°C (oil bath)as a colorless liquid, b.p. 112-114 °C. IR (neat, cm^{-1}) 3389 (br), 1312, 1194, 1115, 1068, 1012; ^{1}H-NMR (CD_3Cl) δ 1.38 (t, J = 8.2 Hz, 1 H, SH), 1.85-1.96 (m, 2 H, 2-CH_2), 2.11-2.24 (m, 2 H, 3-CH_2), 2.61 (dt, J = 7.0, 8.0 Hz, 2 H, 1-CH_2). ^{13}C-NMR (CD_3Cl) δ 118.9 (qt, J_{F3C} = 284.5, J_{F2CC} = 36.2 Hz, C-5), 115.8 (tq, J_{F2C} = 289.5, J_{F3CC} = 36.6 Hz, C-4), 29.2 (t, J_{F2CC} = 22.3 Hz, C-3), 24.7 (C-2), 23.8 (C-1).

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