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Synthesis of 1-iodo-3-perfluoroalkylpropanes and 1-iodo-4-perfluoroalkylbutanes

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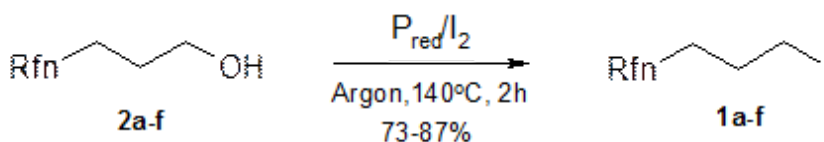
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Abstract: Simple method for the preparation of perfluoroalkyl-alkyl iodides is suggested.

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3-(Perfluoroalkyl)-propyl iodides ($C_nF_{2n+1}CH_2CH_2CH_2I$, **1a-e**, $n = 4, 6, 8, 9, 10$) are important reagents and building blocks for *fluorous* chemistry [1], material science [2], polymer chemistry [3], and drug discovery [4]. Their syntheses mostly based on the transformation of the precursor *F*-alcohols into iodides. For laboratory syntheses of such *fluorous* iodides using KI/phosphoric acid [5], NaI/chlorotrimethylsilane [4] or $I_2/P(C_6H_5)_3$ /imidazole [6] reagent systems are well acceptable.

However, we demonstrate here that phosphorus (III) iodide - generated *in situ* from red phosphorus and iodine - reacts with 3-perfluoroalkylpropanols (**2a-e**) or fluorous-butanol (**2f**) to afford the title compounds in high yields and purities.



$R_{fn} =$ (a) $n-C_4F_9$, (b) $n-C_6F_{13}$, (c) $n-C_8F_{17}$, (d) $(CF_3)_2CF(CF_2CF_2)_3$, (e) $n-C_{10}F_{21}$, (f) $n-C_8F_{17}CH_2$

This process can easily be upscaled to the synthesis of several hundred gram quantities if the controlled introduction of iodine under an inert atmosphere is carried out by using a 'hot-melt dropping funnel' (Figure 1) [7].

The precursor 3-perfluoroalkylpropanols [8] can be made by the reduction of the corresponding *F*-iodohydrin adducts formed by the addition of perfluoroalkyl iodides to allylic alcohol in the presence of radical initiators, such as azobis(isobutyronitrile) [9] or the $Cu(OAc)_2$ /hydrazine hydrate redox system [10]. The latter *F*-iodohydrins are versatile intermediates allowing the preparation of valuable *fluorous* building blocks including *fluorous* allylic alcohols as well [11].

The products obtained were characterized by 1H -, ^{13}C and ^{19}F -NMR spectra and GC. The last traces of alcohol impurities can be removed by treatment of their ether solution with P_2O_5/SiO_2 (SicaPent) [12], or by distillation over CaH_2 [3].

Experimental

Perfluoroalkyl-propanols (**2a-e**) were prepared as reported in [8a], with GC purities >98%. Fluorous butanol **2f** was prepared similarly but using homoallylic alcohol [13]. 1H -, ^{13}C - and ^{19}F -NMR spectra were recorded on a Bruker Avance 250 instrument using a 5 mm inverse $^1H/^{13}C/^{31}P/^{19}F$ probe head at room temperature. Chemical shifts (δ) are given in parts per million (ppm) units relatively to the internal standard TMS ($\delta = 0.00$ for 1H , $\delta = 0.00$ for ^{13}C) and to $CFCl_3$ as external standard ($\delta = 0.00$ for

¹⁹F). Melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. The reactions were monitored by gas chromatography (Hewlett-Packard 5890 Series II, PONA [crosslinked methylsilicone gum] 50 m x 0.2mm x 0.5 mm column, H₂ carrier gas, FID detection; Program: 120 °C, 5 min, 10 °C/min, 250 °C, 5 min, Inj.: 250°C, Det: 280°C).

Typical Procedure (TP):

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-11-iodo-undecane (1c)

A flame dried 1 liter volume four-necked glass reactor was equipped with a stirrer, thermometer, 'hot-melt dropping funnel' and a condenser attached to an argon by-pass. Then the reactor was charged with perfluorooctylpropanol (**2c**, 574 g, 1.20 mol) and red phosphorus (13.0 g, 0.42 mol P), while the 'hot-melt dropping funnel' with iodine (160 g; 0.63 mol I₂). The mixture was heated with an oil-bath of about 100°C temperature until the fluorous alcohol melted, then stirring was started and the iodine addition was controlled by applying hot air flow with the aid of a heat gun; about 60 minutes required for completing iodine addition. The reaction mixture was heated and stirred for 2 h at 135-140°C internal temperature. Then the oil bath was removed and the reaction mixture was allowed to cool to ~40°C and the product was separated from the H₃PO₃ precipitate as a liquid and transferred into an Erlenmeyer flask. Partitioning between ether (1 L) and water (0.5 L) and decolorizing with aqueous NaHSO₃ solution gave a colorless extract. It was dried (Na₂SO₄), filtered and the solvent evaporated by distillation. The pale yellow residue was purified by vacuum distillation to afford 607 g (86%) product, colorless liquid, bp = 111°C/16mmHg, which solidifies at room temperature and has an mp = 33-34°C (GC assay: 99.5%).

¹H NMR (250 MHz, CDCl₃) δ 3.24 (t, 2 H, CH₂I), 2.08–2.33 (2 m, 4 H, C₈F₁₇CH₂CH₂); ¹⁹F NMR δ -81.9 (t, 3 F), -114.5 (2 F), -122.7 (6 F), -123.5 (2 F), -124.2 (2 F), -127.0 (2 F); ¹³C NMR δ 32.30 (t, C₈F₁₇CH₂); 24.66 (t, CH₂CH₂I); 3.65 (s, CH₂CH₂I). This product displays equal ¹H-, ¹⁹F-, and ¹³C NMR spectra, bp, mp and GC purity values that reported by our laboratory [12].

1,1,1,2,2,3,3,4,4-Nonafluoro-7-iodo-heptane (1a)

R_{f4}-propanol (**2a**, 33.4g, 120 mmol) was reacted with a slight excess of PI₃ [prepared from red phosphorus (1.30 g, 42 mmol) and iodine (16 g, 63 mmol I₂)] in a 250 mL volume heavy walled closed Pyrex tube for 3 h at 135-140°C and worked up to yield 34.0 g (73%) colorless oil, bp 70 °C/15 mmHg, (GC assay: 98%).

¹H NMR (250 MHz, CDCl₃) δ 3.23 (t, 2 H, CH₂I), 2.06–2.32 (2 m, 4 H, C₈F₁₇CH₂CH₂); ¹⁹F NMR δ -82.3 (t, 3 F), -115.1 (2 F), -125.5 (2 F), -127.2 (2 F); ¹³C NMR δ 32.1 (t, C₈F₁₇CH₂); 24.5 (t, CH₂CH₂I); 3.1 (s, CH₂CH₂I)

This product obtained showed agreeable physical properties and ¹H-, ¹⁹F-, and ¹³C NMR spectra to that reported in [3, 4].

1,1,2,2,3,3,4,5,5,6,6-Tridecafluoro-9-iodo-nonane (1b)

The R_{f6}-propanol (**2b**, 227g, 0.60 mol) was reacted with red phosphorus (6.50 g, 0.21 mol) and iodine (80 g, 0.315 mol I₂) according to Typical Procedure for 2 h at 135-140°C and worked up to yield 237 g (81%) colorless oil, bp = 108°C/20 mmHg (GC assay: 99.5%).

¹H NMR (250 MHz, CDCl₃) δ 3.23 (t, 2 H, CH₂I), 2.07–2.34 (2 m, 4 H, C₈F₁₇CH₂CH₂); ¹⁹F NMR δ -82.1 (t, 3 F), -114.8 (2 F), -122.8 (2 F), -123.8 (2 F); -124.4 (2F); -127.2(2F). ¹³C NMR δ 32.2 (t, C₈F₁₇CH₂); 24.6 (t, CH₂CH₂I); 3.0 (s, CH₂CH₂I)

This product showed agreeable physical properties and NMR spectra to that reported [2, 5].

1,1,1,2,3,3,4,4,5,5,6,6,7,7,8,8-Hexadecafluoro-11-iodo-2-trifluoromethyl-undecane (1d)

iso-R_{f9}-propanol (15.84 g, 30 mmol), red phosphorus (0.325 g, 10.5 mmol) and iodine (4.00g, 15.75 mmol I₂) was reacted in a closed heavy walled Pyrex tube for 5 h at 135-140°C and worked up. Yield: 14.33 g (75%) colorless oil, bp = 110°C/1.0 mmHg (GC assay: 98% GC), mp = 28-29°C.

^1H NMR (250 MHz, CDCl_3) δ 3.25 (t, 2 H, CH_2I), 2.07–2.35 (2 m, 4 H, $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2$); ^{19}F NMR δ -72.2 - (-72.4) (m, 7 F), -114.2 (2 F), -115.4 (2 F), -121.2 (2 F); -122.0 (4 F); -123.9 (2F). ^{13}C NMR δ 32.3 (t, $\text{C}_8\text{F}_{17}\text{CH}_2$); 24.7 (t, $\text{CH}_2\text{CH}_2\text{I}$); 4.1 (s, $\text{CH}_2\text{CH}_2\text{I}$)

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-Heneicosafluoro-13-iodo-tridecane (1e)

R_{10} -propanol (**2e**, 11.56g, 20 mmol), red phosphorus (0.22g, 7 mmol) and iodine (2.67g, 10.5 mmol I_2) was reacted in a closed heavy walled Pyrex tube for 4 h at 135-140°C and worked up. The crude product (~14 g) was recrystallized from cyclohexane (90 mL) to afford 11.96 g (87%) white crystals, mp: 75-76 °C (GC assay 97%); Lit [14] mp = 80-82°C.

^1H NMR (250 MHz, CDCl_3) δ 3.25 (t, 2 H, CH_2I), 2.08–2.34 (2 m, 4 H, $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2$); ^{19}F NMR δ -81.2 (t, 3 F), -114.2 (2 F), -122.2 (10 F), -123.2 (2 F); -123.9 (2F); -126.6 (2F). ^{13}C NMR δ 32.3 (t, $\text{C}_8\text{F}_{17}\text{CH}_2$); 24.6 (t, $\text{CH}_2\text{CH}_2\text{I}$); 3.8 (s, $\text{CH}_2\text{CH}_2\text{I}$)

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-12-iodo-dodecane (1f)

R_8 -butanol (10.1 g, 20 mmol), red phosphorus (0.22g, 7 mmol) and iodine (2.67 g, 10.5 mmol I_2) was reacted in a closed heavy walled Pyrex tube for 9 h at 135-140°C and worked up. Yield 10.07 g (82%) colorless liquid, by short-path distillation (bath temperature: 135-140°C/1.0 mmHg), mp = 40-42°C (GC assay: 97%). Lit. [13] mp = 50-51°C.

^1H NMR (250 MHz, CDCl_3) δ 3.21 (t, 2 H, CH_2I), 2.20–1.71 (m, 6 H); ^{19}F NMR δ -81.4 (t, 3 F), -114.9 (2 F), -122.5 (6 F), -123.3 (2 F); -124.4 (2 F); -126.7 (2 F). ^{13}C NMR δ 32.9 (s, $\text{C}_8\text{F}_{17}\text{CH}_2$); 30.2 (t, one of $\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_2$); 21.7 (t, one of $\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_2$); 5.2 (s, CH_2I).

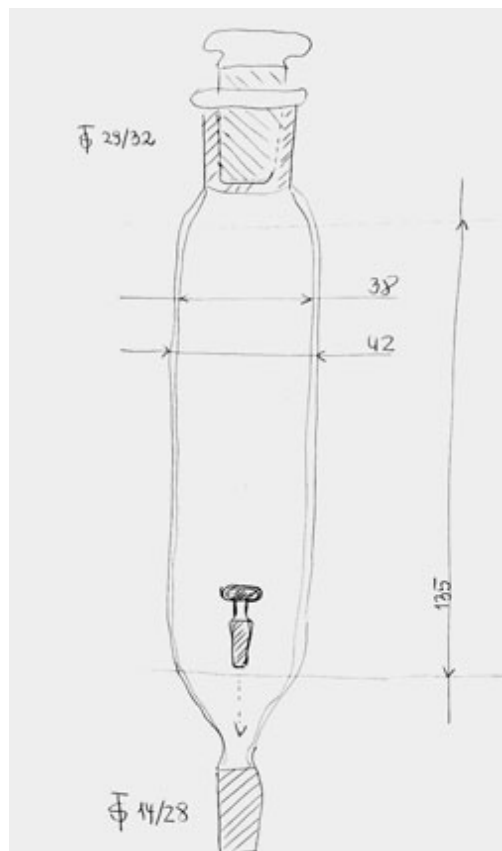


Figure 1. Hot-melt dropping funnel (cf. Ref. [7]).

The 'hot-melt' dropping funnel is an apparatus for the incremental addition of solids under an inert atmosphere. It was fabricated from an ST 29/32 female and an ST 14/28 male joint, both 60 mm long and a 120 mm length of 38 mm glass tubing. The above joints were flared to the glass tubing. Before using the apparatus it was fixed in an upright position and a small T shaped glass stopper (15 mm *6 mm *25 mm) was placed in to prevent the falling down of the solids when they are charged into the funnel. The 'hot-melt' dropping funnel can be charged with low melting solids such as iodohydrin or

iodine. Finally the funnel was closed with an ST 29/32 stop-cock and fitted to the four-necked reactor. The addition rate of iodine was easily controlled by heating the lower end of the funnel by a 'hot-air' heat gun since the T-shaped glass stopper means no barrier for dropping down the melted iodine. The fabrication and use of an improved dropping funnel for liquid or melt additions has already been disclosed [15].

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