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The Preparation of Methyl 9-iodo-perfluorononanoate: an Access to Reverse Fluorinated Amphiphiles

Zoltán Szlávik, Antal Csámpai, Marie Pierre Krafft[†], Jean G. Riess[*§], and József Rábai[*]

Department of Organic Chemistry, Eötvös University, P.O. Box 32, H-1518 Budapest 112, Hungary

[†]Unité de Chimie Moléculaire, URA 426 au CNRS, Faculté des Sciences, Université de Nice-Sophia Antipolis, 06108 Nice Cédex 02, France

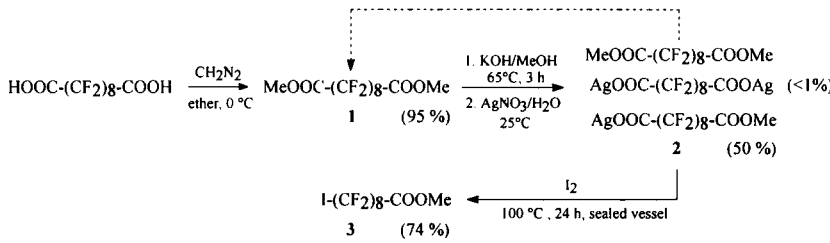
[§]Medical Centre, University of California at San Diego, 225 Dickinson St., San Diego CA-92102-1990

Abstract: ω-Functionalized *F*-alkyl iodides are useful building blocks of compounds containing perfluoroalkyl segments in an inner position. A convenient and effective synthesis of methyl 9-iodo-perfluorononanoate, a precursor molecule of this kind, is described, as well as the synthesis of a member of a new class of amphiphiles, called reverse *F*-amphiphiles. © 1997 Elsevier Science Ltd.

Fluorinated amphiphiles, i.e. amphiphiles with hydrophobic chains terminated by perfluoroalkyl segments, exhibit exceptional surface properties[1] and readily form a range of supramolecular structures when dispersed in water and other media[2], due to the strong ordering capacity of the perfluoralkyl group. Such amphiphiles, and in particular the neutral, dimorpholinophosphate derivatives have potential in biomedical applications[3]. The preparation of amphiphiles in wich the *F*-alkyl segment inserted inbetween the hydrocarbon chain and the hydrophilic unit, called reverse *F*-amphiphiles, is needed in order to further investigate the self-aggregation and ordering capacity of *F*-amphiphiles, and requires novel synthetic precursor molecules.

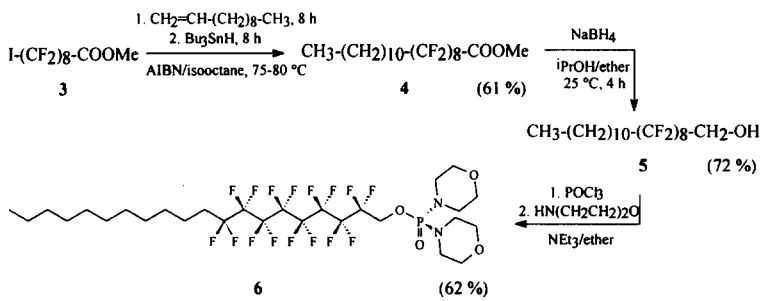
Free radical addition of perfluoroalkyl iodides to C-C double bonds followed by reductive dehalogenation is a well-known procedure for connecting long chain *F*-alkyl groups to various alkyl chains[4]. This method allows the formation of molecules terminated by the perfluoroalkyl chains, but not molecules containing the perfluoroalkyl segments in central position. Obviously, ω-functionalized *F*-alkyl iodides could be effective building blocks of such systems, but there existed no efficient method yet for their preparation. Since the commercially available bifunctional long chain fluorinated compounds are symmetrical, the key synthetic task was to modify only one of the reactive terminal functions.

The synthesis of methyl 9-iodo-perfluorononanoate **3** (Scheme 1), the precursor spacer unit we selected, was developed from dimethyl *F*-sebacate **1**, obtained from *F*-sebacic acid in a nearly quantitative reaction with diazomethane in ether[5]. The diester was refluxed for 3 hours with half equivalent amount of KOH in methanol. The mixture was cooled to room temperature and treated with a slight excess of aqueous $AgNO_3$ to yield a colourless precipitate, which was dried and washed with hot isooctane to remove and recover unreacted **1** and separate the silver salt of the monoester **2**[6]. Compound **2** was treated in a Hunsdiecker-type reaction with iodine to obtain the expected ω-functionalized F-alkyl iodide **3**[7].



Scheme 1

This is also the first report of the synthesis of a neutral "reverse" fluorosurfactant[8], (2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluoro-eicosyl)dimorpholinophosphoramidate **6**. It consists in connecting **3** to the long hydrocarbon segment and subsequently creating the neutral hydrophilic head (Scheme 2). The radical addition of the iodo compound **3** to 1-undecene and the dehalogenation of the adduct with tributyltin hydride[9] was carried out in the presence of azoisobutyronitrile (AIBN) in a one-pot reaction to obtain **4**[10]. The long chain ester **4** was reduced to alcohol **5** in a 1:1 (v/v) mixture of 2-propanol and ether with $NaBH_4$ according to the literature[11]. Finally the dimorpholinophosphate unit was made using the one-pot method described by Krafft et al.[12].



Scheme 2

In summary, the dissymmetrical α,ω-functionalized *F*-alkylating reagent **3** is a useful tool for synthesizing surfactants with a long fluorinated spacer inside their hydrophobic chain. The study of the self-organization properties of such reverse *F*-amphiphiles and the systematic preparation of a series of different analogues are in progress[13].

REFERENCES AND NOTES

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4. Brace, N. O. *J. Org. Chem.* **1962,** *27*, 3033-38.; *ibid.* **1966,** *31*, 2879-85.
5. CAUTION! For large scale preparation use alternative esterification methods; *cf.* McLoughlin, V. C. R. *Tetrahedron Lett.* **1968,** *46*, 4761-62. The crude product was purified by distillation (b.p.: 126-127 °C / 25 mmHg, same as reported: Ward, R. B. *J. Org. Chem.* **1965,** *30*, 3009-11). Analytical data for **1**: FT-IR (Bruker IFS 55) (film, cm^{-1}): $\upsilon_{asC\text{-}H}$ (CH_3) 2969.1, $\upsilon_{sC\text{-}H}$ (CH_3) 2860.5, $\upsilon_{C=O}$ 1786.8, $\upsilon_{C\text{-}F}$ 1214.0, 1149.3; NMR (500 MHz) ($CDCl_3$, ppm): ^1H δ (CH_3) 3.99 s; ^{13}C δ (CH_3) 54.69 s, δ ($(CF_2)_8$) 106.11-113.12, δ (C=O) 158.99 t; purity was tested with GC (HP 5890 Series II, PONA): 97.6%.
6. The hydrolysis of **1** (19.3 mmol) with KOH (19.3 mmol) was carried out in 70 ml methanol, and for the precipitation $AgNO_3$ (23.5 mmol) was used in 160 ml distilled water. Analytical data for **2**: FT-IR (KBr, cm^{-1}) $\upsilon_{asC\text{-}H}$ (CH_3) 2969.4, $\upsilon_{sC\text{-}H}$ (CH_3) 2857.5, $\upsilon_{C=O}$ (ester) 1773.3, $\upsilon_{asC=O}$ (carboxylate) 1663.5, $\upsilon_{sC=O}$ (carboxylate) 1407.8, $\upsilon_{C\text{-}F}$ 1205.8, 1148.2; purity was tested with GC after esterification with EtI in ether: 94.8 % I-$(CF_2)_8$-COOMe, 1.12 % MeOOC-$(CF_2)_8$-COOMe, 0.94 % EtOOC-$(CF_2)_8$-COOEt.
7. Experimental details and analytical data for **3**: In a 150 ml sealed Pyrex tube the mixture of **2** (6.71 mmol) and iodine (8.50 mmol) was heated for 24 hr at 100 °C in an oven. The tube was cooled down to - 80 °C and opened carefully. The product was extracted with ether and washed with concentrated $NaHSO_3$ solution and several times with water. The etherous phase was dried, the solvent was removed and the residue was purified by distillation (b.p.: 170-180 °C / approx. 16 mmHg). FT-IR (film, cm^{-1}): $\upsilon_{asC\text{-}H}$ (CH_3) 2967.1,

$\upsilon_{sC\text{-}H}$ (CH_3) 2859.8, $\upsilon_{C=O}$ 1787.1, $\upsilon_{C\text{-}F}$ 1213.0, 1152.2; NMR ($CDCl_3$, ppm): ^1H δ (CH_3) 3.99 s; ^{13}C δ (CH_3) 54.67 s, δ (I-CF_2) 93.45 tt, δ ((CF_2)$_7$) 105.86-113.29, δ (C=O) 159.01 t; MS (EI): $[M]^+$: 586.

8. Some $R_HR_FCO_2CH_3$, $R_HR_FSO_3Na$ and $R_HR_FOCF_2CF_2SO_3Na$ have been prepared; see: Hu, C.-M.; Qing, F.-L. *J. Org. Chem.* **1991,** *56,* 6348-51.

9. Brace, N. O. *J. Fluorine Chem.* **1982,** *20,* 313-327.

10. Experimental details and analytical data for **4**: 1-undecene (5.00 mmol), **3** (3.93 mmol) and AIBN (0.2 mmol) were reacted in isooctane (5 ml) at 75-80 °C for 8 hours under by-pass nitrogen flow. The mixture was cooled to room temperature and tributyltin hydride (5.00 mmol) and AIBN (0.2 mmol) were added and reacted at 75-80 °C for further 8 hours. After the removal of the solvent, the crude oily product was crystallized from methanol at - 20 °C; m.p.: 34-35 °C. FT-IR (KBr, cm^{-1}): $\upsilon_{asC\text{-}H}$ (CH_3) 2923.9, $\upsilon_{sC\text{-}H}$ (CH_3) 2854.0, $\upsilon_{C=O}$ 1785.4, $\upsilon_{C\text{-}F}$ 1211.7, 1149.5; NMR ($CDCl_3$, ppm): ^1H δ ($^{20}CH_3$) 0.88 t, δ ($^{19\text{-}13}CH_2$) 1.27, δ ($^{12}CH_2$) 1.36 m, δ ($^{11}CH_2$) 1.59 qi, δ ($^{10}CH_2$) 2.04 tt; ^{13}C δ ($^{20}CH_3$) 14.11 s, δ ($^{11}CH_2$) 20.17 s, δ ($^{12}CH_2$) 29.17 s, δ ($^{10}CH_2$) 31.00 t, δ ($^{19\text{-}13}CH_2$) 29.27-31.96, δ ((CF_2)$_8$) 108.21-118.57, δ (C=O) 159.00 t; MS: $[M]^+$: 614.

11. Takahashi, M.; Nagasaki, Y.; Fujii, S., **Jpn. 02,169,528** (1990); *Chem. Abstr.* **1993,** *113,* 190741q. Analytical data for **5**: m.p.: 75-76 °C (perfluoro-2-butyltetrahydrofuran); FT-IR: (KBr, cm^{-1}) $\upsilon_{O\text{-}H}$ 3611.2, $\upsilon_{asC\text{-}H}$ (CH_3) 2924.5, $\upsilon_{sC\text{-}H}$ (CH_3) 2854.3, $\upsilon_{C\text{-}F}$ 1212.1, 1149.7; NMR ($CDCl_3$, ppm): ^1H δ ($^{20}CH_3$) 0.88 t, δ ($^{19\text{-}13}CH_2$) 1.27, δ ($^{12}CH_2$) 1.36 m, δ ($^{11}CH_2$) 1.59 m, δ ($^{10}CH_2$) 2.04 m; δ (CH_2O) 4.10 m; ^{13}C δ ($^{20}CH_3$) 14.08 s, δ ($^{11}CH_2$) 20.09 s, δ ($^{10}CH_2$) 30.93 t, δ ($^{19\text{-}12}CH_2$) 29.10-31.88, δ (CH_2O) 60.70 t; MS: $[M]^+$: 586.

12. Krafft, M. P.; Vierling, P.; Riess, J. G. *Eur. J. Med. Chem.* **1991,** *26,* 545-550.; Analytical data for **6**: m.p.: 64-66 °C (perfluoro-2-butyltetrahydrofuran : 1H,1H,2H,2H-perfluorooctan-1-ol = 9:1 $^v/_v$); NMR ($CDCl_3$, ppm): ^1H δ ($^{20}CH_3$) 0.88 t, δ ($^{19\text{-}13}CH_2$) 1.27, δ ($^{12}CH_2$) 1.38 qi, δ ($^{11}CH_2$) 1.60 qi, δ ($^{10}CH_2$) 2.05 m, δ (CH_2O) 4.43 m, δ ($N(CH_2)_2$) 3.15 m, δ ($O(CH_2)_2$) 3.66 t; ^{13}C δ ($^{20}CH_3$) 14.09 s, δ ($^{11}CH_2$) 20.17 s, δ ($^{10}CH_2$) 31.03 t, δ ($^{19\text{-}12}CH_2$) 29.16-31.94, δ (CH_2O) 61.73 t, δ ($N(CH_2)_2$) 44.73 s, δ ($O(CH_2)_2$) 67.09 d; ^{31}P δ 15.53 s.

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