Methyl Perfluorooctanethionate as a Tool for Indirect Perfluoroalkylmethylation and Perfluoroalkylation of Amines

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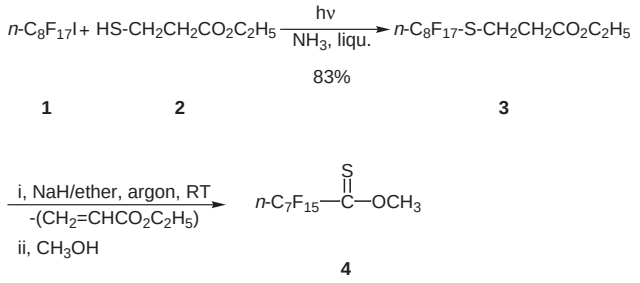
Abstract: Methyl perfluorooctanethionate **4** is a novel reagent for fluorophilization of amines and can be prepared effectively from ethyl 3-(perfluorooctylthio)propionate **3** in a one-pot procedure.

The applications of two-phase catalysis for commercial bulk processes[1a] as fluorous biphase systems for catalytic reactions, for engineered product separations, or for carrying out fluorous syntheses call for effective design and preparations of fluorophilic catalysts and reagents.[1b] Since the phase preference is determined by the interactions at the molecular level, fluorophilic compounds must have an appropriate balance between the perfluorocarbon-like and other constituents in their molecules. At one extreme these molecules are fluorophilic (i.e. prefer to stay in the fluorocarbon phase) or at the other extreme are amphiphilic (fluorocarbon/water or fluorocarbon/hydrocarbon).[2] To quantify the extent of the fluorous phase preference of a compound, we define the term fluorophilicity (*f*) as $f = \ln P$, where P is the partition coefficient between perfluoro(methylcyclohexane) and toluene phases at 25 °C (Table 1).[3]

We wish to report, that thionoester **4** is a novel reagent for increasing the fluorophilicity of appropriate amines. Experimentally determined fluorophilicity data indicate, that the phase preference of the compounds shown here is highly sensitive to small differences in their molecular structures (cf. boiling point, fluorine content and *f* values, Table 1). Reagent **4,** a longer chain alkyl perfluoroalkanethionate, was prepared as follows (Scheme 1). A mixture of perfluorooctyl iodide **1** and ethyl 3-mercaptopropionate **2** dissolved in liquid ammonia was UV-irradiated[4] to furnish ethyl (3-perfluorooctylthio)propionate **3**.[5] Ester **3** was reacted with sodium hydride (reverse Michael, with loss of ethyl acrylate[6]) in ether, then quenched with methanol to afford **4** in 59% yield.[7] Only short chain perfluoroalkanethionoesters and thionoacyl fluorides prepared under forcing reaction conditions are known hitherto[8], while the synthesis of alkyl perfluoroalkanedithiocarboxylates of longer perfluoroalkyl chains has been reported recently.[9]



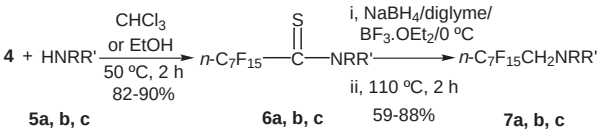
Scheme 1

The reaction of methyl perfluorooctanethionate **4** with a slight excess of an alkyl amine, such as morpholine (**5a**), dimethylamine (**5b**) and (+)-1-phenylethylamine (**(+)-5c**) results in the formation of the appropriate thioamides, **6a**, **6b** and **(+)-6c,** respectively, in high yields (Scheme 2). The present procedure could be a preferred alternative to the known thionation reactions of amides using phosphorus pentasulfide[10] or Lawesson's reagent.[11] Perfluoroalkyl-alkylamines are receiving much attention recently in the field of both homogeneous catalysis and synthesis.[12-15] Because perfluoroalkanethioamides can be easily obtained via thioacylation of amines, we devised a new route for the synthesis of perfluoroalkylmethyl-amines from these precursors. Thus, diborane generated *in situ*,[16] was reacted with **6a, 6b** and **(+)-6c** to afford amines **7a,**[17] **7b**[18] and **(+)-7c,** respectively (Scheme 2).[19]

Table 1. Selected compound properties including fluorophilicity (*f*)

Compound[a]	b.p. (°C/mmHg)	F content (%)	*f*
1	160-161/760	59.16	2.04
2	75-76/20	0	-5.22
3	75/0.10	58.48	0.04
4	<80/0.10[b]	64.16	1.08
6a	108/0.10	57.08	-1.56
6b	67/0.10	62.33	-0.66
6c	95-105/0.10	53.44	-1.84
7a	65/20	60.74	0.14
7b	161/760	66.71	1.53
7c	not determined	56.63	-0.87
8a	<50/20[b]	63.93	0.86
8b	<50/20[b]	69.74	—[c]
9	72/20	64.16	1.16

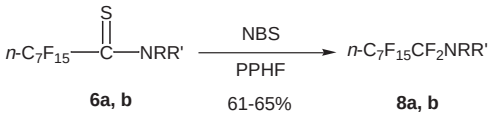
[a]For spectral and analytical data, cf.[25]; [b]Bath temperature and pressure during short path distillation; [c]Not determined due to its facile hydrolysis to *n*-$C_7F_{15}CON(CH_3)_2$.



(**a**) R-R'=[-CH_2CH_2]$_2$O (**b**) R=R'=CH_3 (**c**) R=H,R'= -$CH(CH_3)C_6H_5$

Scheme 2

Furthermore, when **6a** and **6b** are treated with *N*-bromosuccinimide in pyridinium poly(hydrogen fluoride),[20] *gem*-difluorination occurs to give the corresponding N-perfluoroalkylamine derivatives, **8a** and **8b,** respectively (Scheme 3).[21] However, amines of the latter type are known to readily hydrolyze to the corresponding amides.[22]

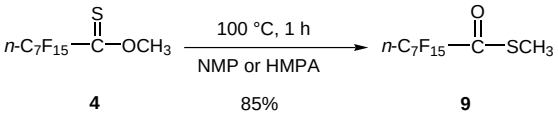


(**a**) R-R'=[-CH_2CH_2]$_2$O (**b**) R=R'=CH_3

Scheme 3

In summary, thionoester **4** is a suitable reagent for N-(perfluoroheptyl) methylation or N-perfluorooctylation of appropriate alkyl amines in a

two-step procedure. However, a thionocarboxylate rearrangement[23] occurs yielding methyl thioperfluorooctanoate **9**, when **4** is heated as a solution in dipolar aprotic solvents (Scheme 4).[24] Compounds **1**, **3, 4, 7a, 7b, 8a** and **9** were found to be fluorophilic ($f > 0$, Table 1).



Scheme 4

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References and Notes

1. a) *Aqueous Organometallic Chemistry and Catalysis*, NATO ASI Series, Vol. 5.; Horváth, I. T.; Joó, F., Ed.; Kluwer, Dordrecht, 1995. *Aqueous-Phase Organometallic Catalysis;* Cornils, B.; Herrmann, W. A., Ed.; Wiley-VCH, Weinheim, 1998.
b) Horváth, I. T.; Rábai, J. *Science* **1994,** *266*, 72. *idem* U.S. Patent 5,463,082 (1995); *Chem. Abstr.* **1995**, *123*, 87349a. Curran, D. P. *Chemtracts-Org. Chem.* **1996,** *9*, 75. Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997,** *275*, 823. Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997,** *36*, 2057. Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998,** *37*, 1174. Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, in press.
2. Kissa, E. *Fluorinated Surfactants (Surfactant Science Series, Vol. 50.)*; Marcel Dekker: New York, 1994.
3. Fluorophilicity (*f*) values were determined by GC (HP 5890 Series II, PONA) analysis of the respective phases at equilibrium.
4. Boiko, V. N.; Schupak, G. M.; Yagupol'skii, L.M. *Zh. Org. Khim*. **1977,** *13*, 1057.
5. A solution of **1** (42 mmol) and **2** (40 mmol) in liquid ammonia (200 mL) was UV-irradiated and refluxed for 40 min using a 'Tungsram' HGL 125 lamp. Then the evaporation of ammonia left a solid residue, which was dissolved in ether (150 mL), washed with brine (2 x 50 mL), and dried ($MgSO_4$). Compound **3** was isolated by distillation (Table 1).[25]
6. Rábai, J. *Synthesis* **1989,** 523.
7. Under an argon atmosphere a suspension of sodium hydride (120 mmol) in ether (300 mL) was treated with **3** (40 mmol) and the mixture stirred for 30 min at room temperature. After cautious addition of the mixture to methanol (100 mL) the solvent was removed *in vacuo* and followed by extractive work-up with ether. The combined organic phases were washed successively with 1N HCl, aqueous $NaHCO_3$, and water, and dried ($MgSO_4$). Thionoester **4** was isolated by distillation (Table 1).[25]
8. Middleton, W. J.; Howard, E. G.; Sharkey, W. H. *J. Org. Chem.* **1965,** *30*, 1375. Middleton, W. J. *J. Org. Chem*. **1975,** *40*, 129.
9. Portella, C.; Shermolovich, Y. G.; Tschenn, O. *Bull. Soc. Chim. Fr.* **1997,** *134*, 697.
10. Voss, J.; Walter, W. *Liebigs Ann. Chem*. **1968,** *716*, 209.
11. Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett*. **1994,** *35*, 3983.
12. Hayashi, T.; Matsumoto, Y.; Morikawa, I.; Ito, Y. *Tetrahedron: Asymmetry* **1990,** *1*, 151.
13. Vincent, J-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem., Int. Ed. Engl*. **1997,** *36*, 2346.
14. Pozzi, G.; Cavazzini, M.; Quici, S.; Fontana, S. *Tetrahedron Lett.* **1997,** *38*, 7605.
15. Katritzky, A. R.; Zhang, Z.; Qi, M. *Tetrahedron Lett.* **1997,** *38*, 7015.
16. Bissell, E. R.; Finger, M. *J. Org. Chem*. **1959,** *24*, 1256.
17. Allouch, M.; Selve, C. *J. Fluorine Chem.* **1994,** *66*, 31.
18. Berry, J. S. U.S. Patent 3,194,840 (1965). *Chem. Abstr.* **1965,** *63*, 14711g.
19. To an ice-cold solution of the thioamide (8.0 mmol) and sodium borohydride (16 mmol) in diglyme (20 mL) borontrifluoride etherate (25.6 mmol) was added dropwise. Then the mixture was heated at 110°C for 2 h. The colorless solution was poured into a mixture of 6N HCl (10 mL) and ice (10 g). The precipitate ($R_FCH_2NR_2$.HCl) formed was filtered and partitioned between ether (2 x 30 mL) and $NaHCO_3$ solution. The ether phase was dried ($MgSO_4$) and the product isolated by distillation (Table 1).[25]
20. Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes I.; Olah, J. A. *J. Org. Chem.* **1979,** *44*, 3872.
21. In a polyethylene flask the thioamide (8.7 mmol) was dissolved in anhydrous dichloromethane (15 mL) at 0 °C. After cautious addition of PPHF (2 mL) and NBS (34.8 mmol) the mixture was allowed to warm to room temperature and stirred for 1 h. Then it was added to saturated aqueous $NaHCO_3$ (20 mL) and followed by extractive work-up with ether and distillation (Table 1).[25]
22. Yarovenko, N. N.; Raksha, M. A.; Shemanina, V. N.; Vasil'eva, A.S. *Zhur. Obshchei Khim*. **1957,** *27*, 2246.
23. Voss J. In: *Supplement B: The Chemistry of Acid Derivatives*. Patai, S., Ed.; Wiley: New York, 1979: pp. 1021-1062.
24. A solution of **4** (5 mmol) in HMPA or NMP (10 mL) was heated at 100 °C for 1 h. Addition into 6N HCl (10 mL) was followed by extractive work-up with ether (2 x 20 mL). The combined organic phases were washed with brine, dried and distilled to isolate compound **9** (Table 1).[25]
25. ***Selected spectroscopic and analytical data.*** The NMR spectra were measured in $CDCl_3$ [25 °C, δ(ppm), *J*(Hz)] using TMS and $CFCl_3$ as the reference for ^1H, ^{13}C and ^{19}F nuclei, respectively. Purity and *f* values were determined by GC. **3**: pale yellow oil, GC: 99%. ^1H: $SCH_2CH_2CO_2Et$ 3.20, t; $SCH_2CH_2CO_2Et$ 2.74, t, $^3J_{HH}$ = 7.2; ^{13}C: $SCH_2CH_2CO_2Et$ 24.0; $SCH_2CH_2CO_2Et$ 35.4; C(O) 170.9; ^{19}F: CF_2S -88.1, tt, $^3J_{FF}$ = 14.6, $^5J_{FF}$ = 2.8; MS m/z 552 $[M]^+$, 133 $[SCH_2CH_2CO_2Et]^+$. **4**: yellow-green oil, GC: 98%. Anal. Calcd. for $C_9H_3F_{15}OS$: S 7.22; Found: S 7.06. ^1H: OCH_3 4.27, t, $^5J_{HF}$ = 0.4; ^{13}C: OCH_3 60.2; C(S) 197.0, t, $^2J_{CF}$ = 29.0; ^{19}F: $CF_2C(S)$ -108.7, t, $^3J_{FF}$ = 13.3, $^5J_{FF}$ = 2.9; MS m/z 444 $[M]^+$, 425 $[M\text{-}F]^+$, 75 $[C(S)OCH_3]^+$. UV-Vis (hexane): λ_{max} 242 nm (ε 7,040). **6a**: yellow crystals, m.p. 28 °C, GC: 99.9%. ^1H: OCH_2 3.77, s, OCH_2 3.85, s; NCH_2 3.86, s, NCH_2 4.37, s; ^{13}C: C(S) 182.1, t, $^2J_{CF}$ = 24.8; $O(CH_2\text{-})_2$ 52.7, 53.9; $N(CH_2\text{-})_2$ 66.6, 66.8; ^{19}F: $CF_2C(S)$ -97.2, tt, $^3J_{FF}$ = 16.1, $^4J_{FF}$ = 3.8. MS m/z 499 $[M]^+$, 480 $[M\text{-}F]^+$, 467 $[M\text{-}S]^+$. UV-Vis (hexane): λ_{max} 297 nm (ε 11,990). **6b**: yellow crystals, m.p. 48 °C, GC: 99.9%. ^1H: CH_3 3.47, tt, $^5J_{HF}$ = 2.2, $^6J_{HF}$ = 0.9; CH_3 3.52, t, $^5J_{HF}$ = 1.2; ^{13}C: C(S) 182.5, t, $^2J_{CF}$ = 26.2; CH_3 43.7, t, J_{CF} = 4.3; ^{19}F: $CF_2C(S)$ -98.15, $^3J_{FF}$ = 16.0. MS m/z 457 $[M]^+$, 438 $[M\text{-}F]^+$, 413 $[R_F{}^7C(S)]^+$, 88 $[C(S)N(CH_3)_2]^+$. UV-Vis (hexane): λ_{max} 287 nm (ε 11,080). **(+)-6c**: yellow-green oil, GC: 97%. ^1H: $C(S)NHCH(CH_3)$ 8.0; $C(S)NHCH(CH_3)$ 5.67, quint, J_{NH} = 7; $C(S)NHCH(CH_3)$ 1.66, d, $^3J_{HH}$ = 6.9; ^{13}C: $C(S)NHCH(CH_3)$ 55.0; $C(S)NHCH(CH_3)$ 19.5; C(S)NHCH(CH_3) 181.3; ^{19}F: $CF_2C(S)$ -110.7. UV-Vis (hexane): λ_{max} 278 nm (ε 11,840). **7a:** colorless oil, GC: 98%. ^1H: R_FCH_2

3.02, tt, $^{3}J_{HF}$ = 15.8, $^{4}J_{HF}$ = 1.5; C$\underline{H}_2$O 2.66, t, NC$\underline{H}_2$ 3.71, t, $^{3}J_{HH}$ = 4.6; ^{13}C: $R_FC\underline{C}H_2$ 58.1, t, $^{2}J_{CF}$ = 22.5; $\underline{C}H_2O$ 67.4, s; N$\underline{C}H_2$ 55.0, s; ^{19}F: C$\underline{F}_2CH_2N$ -115.6, m. MS m/z 469 $[M]^+$, 450 $[M\text{-}F]^+$, 100 $[CH_2N(CH_2CH_2)_2O]^+$. **7b:** colorless oil, GC: 99.2%. ^{1}H: $R_FC\underline{H}_2$ 2.98, tt, $^{3}J_{HF}$ = 16, $^{4}J_{HF}$ = 2.2; C$\underline{H}_3$ 2.42, s; ^{13}C: $CF_2\underline{C}H_2$ 58.4, t, $^{2}J_{CF}$ = 22.5; $\underline{C}H_3$ 46.4, s; ^{19}F: $\underline{C}F_2CH_2$ -116.7, m. MS m/z 427 $[M]^+$, 426 $[M\text{-}H]^+$, 408 $[M\text{-}F]^+$, 58 $[CH_2N(CH_3)_2]^+$. **(+)-7c**.**HCl:** white needles, m.p. 167 ^{o}C/ethanol. $[\alpha]_{578}$ +14.9, $[\alpha]_{546}$ +17.3, $[\alpha]_{436}$ +27.9, $[\alpha]_{406}$ +34.7, $[\alpha]_{306}$ +47.2 (c = 0.52, CH_3OH, 25 ^{o}C). **(+)-7c:** colorless oil, GC: 99.5%. ^{1}H: $R_FC\underline{H}_2NHCH(CH_3)$ 3.11, t, $^{3}J_{HF}$ = 15.6; $CH_2NHC\underline{H}(CH_3)$ 3.12 q; $CH_2NHCH(C\underline{H}_3)$ 1.38, d, $^{3}J_{HH}$ = 6.6; ^{19}F: C$\underline{F}_2CH_2$ -117.8, -118.4, $^{2}J_{FF}$ = 282. **8a:** colorless oil, GC: 99%. ^{1}H: OC$\underline{H}_2$ 3.72; NC$\underline{H}_2$ 3.02. ^{13}C: O$\underline{C}H_2$ 66.3; N$\underline{C}H_2$ 44.6, sept, $^{3}J_{CF}$ = 2; ^{19}F: NC$\underline{F}_2$ -98.0, $^{3}J_{FF}$ = 13. **8b:** colorless oil, easily decomposes in a glass vial to afford amide and SiF_4, GC: 91% and 9% $C_7F_{15}CON(CH_3)_2$. ^{1}H: NC$\underline{H}_3$ 3.19, $^{4}J_{HF}$ = 0.9. **9:** colorless oil, GC: 98%. ^{1}H: SC$\underline{H}_3$ 2.50, s; ^{13}C: C(O) 187, t, $^{2}J_{CF}$ 30.1, S$\underline{C}H_3$ 11.8, s; ^{19}F: C$\underline{F}_2$C(O) -117, tt, $^{3}J_{FF}$ 14. MS m/z 443 $[M\text{-}H]^+$, 425 $[M\text{-}F]^+$.