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Fluoro-Pummerer Rearrangement under Oxidative Desulfurization Fluorination Conditions. Facile Synthesis of Oligofluoroalkyl Sulfides

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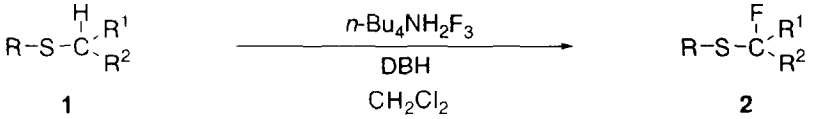
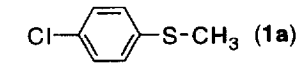
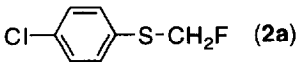
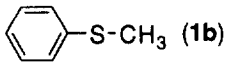
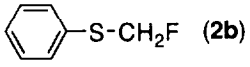
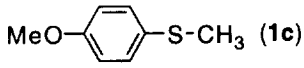
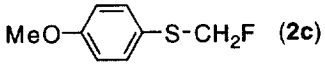
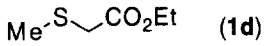
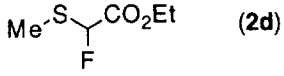
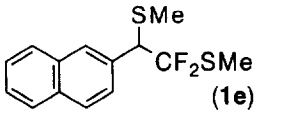
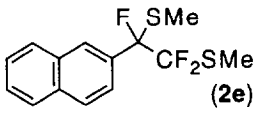
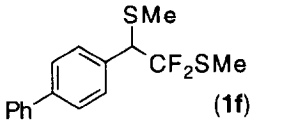
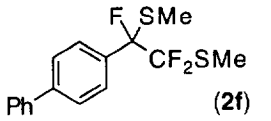
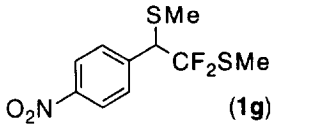
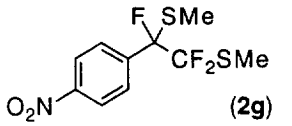
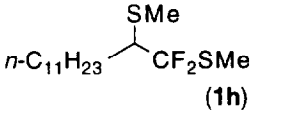
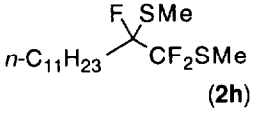
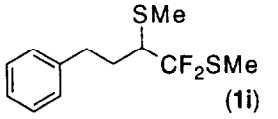
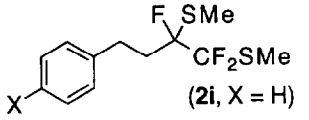
Abstract: Upon treatment with *n*-$Bu_4NH_2F_3$ and 1,3-dibromo-5,5-dimethylhydantoin, various organic sulfides were readily fluorinated to give α-fluoro sulfides. When (HF)9-Py was used as the fluorinating agent, normal oxidative desulfurization fluorination occurred depending on the structure of the substrates.

Organofluorine compounds contribute often to remarkable enhancement and/or modification of biological activities of agrochemicals and pharmaceuticals.[1] Physical properties of materials[2] are also improved by introduction of fluorine functionality. In particular, the amino acid[3] and nucleic acid[4] containing α-fluoroalkylthio moiety are biologically active. In addition, α-fluoro sulfides by themselves are useful synthetic intermediates[5] and are readily available *via* the fluoro-Pummerer rearrangement. This reaction is achieved by: (1) direct fluorination of sulfides with XeF_2,[6] (2) treatment of sulfoxides[7] or sulfides[8] with Et_2NSF_3, (3) fluorination of sulfides with *N*-fluoropyridinium salts,[9] or (4) electrolytic partial fluorination in the presence of $Et_3N{\cdot}3HF$.[10] From the viewpoint of organic synthesis, however, some of these methods are not always convenient. To enhance the synthetic utility of the fluoro-Pummerer rearrangement, we applied the oxidative desulfurization fluorination conditions to this transformation and found that the treatment of sulfides with tetrabutylammonium dihydrogentrifluoride (TBADTF)[11] and 1,3-dibromo-5,5-dimethylhydantoin (DBH) provided us with satisfactory results. Thus, we report herein a new version of the Pummerer-type fluorination as applied to the synthesis of oligofluorinated compounds.



1 **2**

Table 1. Fluorination of Organic Sulfides

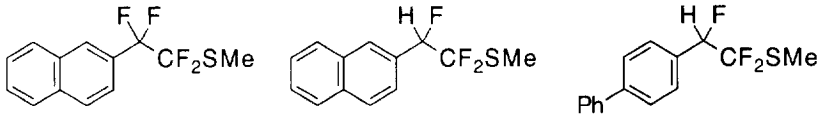
Entry	Substrate (1)	Reagent (mol eq)/Temp	Product (2)	Yield/%[a]
1	 (**1a**)	*n*-$Bu_4NH_2F_3$ (1.4) DBH (1.4), r.t.	 (**2a**)	90
2	 (**1b**)		 (**2b**)	52
3	 (**1c**)		 (**2c**)	59
4	 (**1d**)		 (**2d**)	46
5	 (**1e**)	*n*-$Bu_4NH_2F_3$ (3.5) DBH (2.5), r.t.	 (**2e**)	55
6	 (**1f**)		 (**2f**)	33
7	 (**1g**)		 (**2g**)	70
8	 (**1h**)		 (**2h**)	35
9	**1h**	$(HF)_9$-Py (5.0) NIS (3.0), 0 °C	**2h**	55
10	 (**1i**)	*n*-$Bu_4NH_2F_3$ (3.5) DBH (2.5), r.t.	 (**2i**, X = H)	72
11	**1i**	$(HF)_9$-Py (5.0) NIS (3.0), 0 °C	**2i** (X = H) **2j** (X = I)	36 7
12	**1i**	$(HF)_9$-Py (5.0) NBS (3.0), 0 °C	**2i** (X = H) **2k** (X = Br)	27 13

a) Isolated yields.

A typical experimental procedure follows. To a dichloromethane solution of sulfide **1** and TBADTF[12] was added DBH at room temperature, and the resulting mixture was stirred at room temperature for 10 to 20 min before workup and purification.[13] Monofluorination took place thus in moderate to good yields (Entries 1-4, Table 1). Advantages of the present method are that the fluorinating agent TBADTF is a safe, stable, and easy-to-handle reagent which can be stored at room temperature. In addition, conventional glassware can be used without any special care. The fluoro-Pummerer rearrangement is applicable to 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes (**1e-1i**) available from $RCH(OH)C(SMe)_3$ and Et_2NSF_3.[14] Hereby, the substrates are converted selectively into trifluoro sulfides (**2e-2i**).

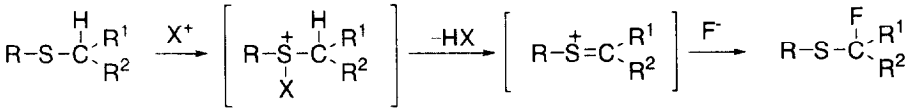
In place of TBADTF, $(HF)_9$-Py can be employed for the fluorination, but an alternative reaction pathway resulted depending on the kind of substituent R^1. The sulfide **1h** underwent the fluoro-Pummerer rearrangement to give **2h** (Entry 9, Table 1), whereas **1i** afforded the Pummerer rearrangement product **2i**, in addition to an aryl halogenation product **2j** or **2k** (Entries 11 or 12, respectively).[15]

With $(HF)_9$-Py (5.0 mol eq) and DBH (3.0 mol eq), **1e** underwent oxidative desulfurization fluorination to give a difluorination product **3** (41 %) in place of **2e**. Replacing DBH by NIS resulted in the formation of **3** (20 %) and a monofluorination product **4** (33 %). The sulfide **1f** was fluorinated with $(HF)_9$-Py (5.0 mol eq) and DBH (4.0 mol eq) to give **5** (38 %). In these reactions, the aryl group remained unhalogenated.



3 **4** **5**

The formation of product **2** can be rationalized by the following scheme. Electrophilic attack of the halonium ion X^+(X = Br or I) to **1** produces a sulfonium ion **6**. Elimination of HX from **6** gives another sulfonium species **7**, which is attacked by the fluoride ion to give the final product **2**.



1 **6** **7** **2**

In summary, we have demonstrated that the fluoro-Pummerer rearrangement of R-S-CHR^1R^2 using TBADTF and a positive halogen oxidant is readily carried out to afford R-S-CFR^1R^2 in moderate to good yields. This reaction, coupled with an oxidative desulfurization fluorination reaction, allows us to selectively introduce two, three or four fluorine atoms into an organosulfur compound, depending on the fluorinating agent used.

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13. a) The reaction mixture was diluted with a mixture of hexane and diethyl ether (10 : 1), and the resulting insoluble material was filtered through a short silica gel column. Concentration under reduced pressure, followed by silica gel column chromatography, afforded the product. This procedure was applied to the reactions of **1a-1d**. b) Alternatively, the reaction mixture was poured into an aqueous solution of $NaHCO_3$ and $NaHSO_3$ and extracted several times with diethyl ether. The combined ethereal layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography or thin layer chromatography. This recipe was applied to the reactions of **1e-1i**.
14. Kuroboshi, M.; Furuta, S.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 6121.
15. When $(HF)_9$-Py (20 mol eq) and NIS (3.0 mol eq) were used at room temperature, **2i** and **2j** were isolated both in 24% yield.

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