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Polyfluorination of Aryl Alkyl Sulfides by IF_5 with Concomitant Migration of the Arylthio Group

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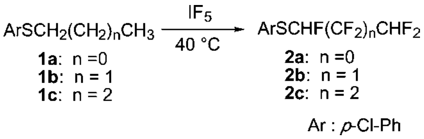
ABSTRACT

$$ArSCH_2(CH_2)_nCH_3 \xrightarrow{IF_5} CHF_2(CF_2)_nCHFSAr$$

In the reaction of *p*-chlorophenyl alkyl sulfides with IF_5, polyfluorination reaction took place on the alkyl chain with the migration of the arylthio group. Consequently, *p*-chlorophenyl polyfluoroalkyl sulfides, having 3–7 fluorine atoms depending on alkyl chain length, could be obtained selectively.

Oxidative fluorination of alkyl sulfides has been conveniently used to introduce fluorine atoms into the α-position of a sulfur group under mild conditions.[1] Recently, we reported that IF_5/Et_3N-3HF is also a versatile fluorination reagent for the introduction of one or two fluorine atoms into the α-position of alkyl sulfides.[2] We wish to report here that an unusual polyfluorination reaction took place in the reaction of *p*-chlorophenyl alkyl sulfide with IF_5. For instance, *p*-chlorophenyl ethyl sulfide (**1a**) reacted with IF_5 in hexane at 40 °C for 24 h to give 1,2,2-trifluoroethyl sulfide (**2a**) in 65% yield. Surprisingly, fluorine atoms were introduced not only to the α-position but also to the *β*-position of the sulfur group. Furthermore, from *p*-chlorophenyl propyl sulfide (**1b**) and *p*-chlorophenyl butyl sulfide (**1c**), *p*-chlorophenyl 1,2,2,3,3-pentafluoropropyl sulfide (**2b**) and *p*-chlorophenyl 1,2,2,3,3,4,4-heptafluorobutyl sulfide (**2c**) were obtained in 72 and 45% yields, respectively. The fluorine atoms were introduced at all carbons of the alkyl group (Scheme 1).

Scheme 1



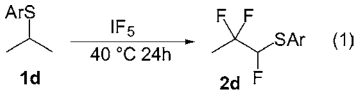
$$ArSCH_2(CH_2)_nCH_3 \xrightarrow[40\ °C]{IF_5} ArSCHF(CF_2)_nCHF_2$$

1a: n =0
1b: n = 1
1c: n = 2

2a: n =0
2b: n = 1
2c: n = 2

Ar : *p*-Cl-Ph

It is unusual that fluorination takes place at other than the α-position of a sulfur group in the oxidative fluorination reactions.[3] Therefore, we carried out the reaction of IF_5 with *p*-chlorophenyl isopropyl sulfide (**1d**) in order to examine the reaction mechanism, and 1,2,2-trifluoropropyl sulfide (**2d**) was obtained in 45% yield (eq 1).



The fluorine atoms were introduced at only the α- and *β*-carbons of the sulfur group, and a *γ*-carbon remained unfluorinated. Furthermore, the arylthio group migrated from the inner to a terminal carbon during the reaction and the fluorination took place at the carbons where the arylthio group had attached. This migration of the arylthio group and the fluorination sequence could be confirmed from the reaction with functionalized sulfides shown in Table 1.

When α-arylthio esters (**1e**,**f**) were used for the reaction with IF_5, the sulfur group moved from the α- to the *ω*-carbon, and the fluorine atoms were introduced at all carbons where the arylthio group had attached. In the reaction with *β*-arylthio ester and amide (**1g**,**h**), the sulfur group moved

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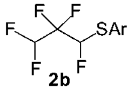
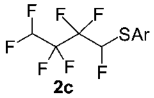
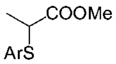
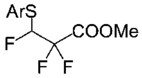
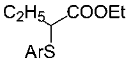
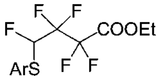
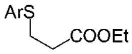
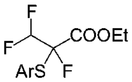
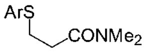
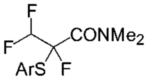
[1] Hiyama, T. In *Organofluorine Compounds*; Springer: Berlin, 2000; p 59 and refernces are cited therein.

[2] Ayuba, S.; Yoneda, N.; Fukuhara, T.; Hara, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1597.

[3] Recently, Motherwell et al. reported an introduction of fluorine atoms at the α- and *β*-positions of the sulfur group of arylthiolactames using iodotoluene difluoride without migration of the arylthio group; see: Greaney, M. F.; Motherwell, W. B.; Tocher, D. A. *Tetrahedron Lett.* **2001**, *42*, 8523.

10.1021/ol034912s CCC: $25.00

Table 1. Polyfluorination of *p*-Chlorophenyl Alkyl Sulfides Using IF_5[a]

sulfide[b]	product	time (h)	yield (%)[c]
$ArSC_2H_5$ **1a**	$CHF_2CHFSAr$ **2a**	24	65[d]
$ArSC_3H_7$ **1b**	 **2b**	48	72
$ArSC_4H_9$ **1c**	 **2c**	72	45[e]
$ArSCH(CH_3)_2$ **1d**	$CH_3CF_2CHFSAr$ **2d**	24	45[d]
 **1e**	 **2e**	6	81
 **1f**	 **2f**	96	66[e]
 **1g**	 **2g**	48	55
 **1h**	 **2h**	96	60

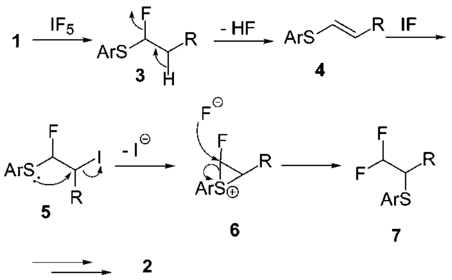
[a] Hexane solution of **1** and IF_5 was stirred in a Teflon PFA vessel with a tight screw cap at 40 °C. If otherwise not mentioned, 2.4 equiv of IF_5 to **1** was used. [b] Ar: *p*-chlorophenyl. [c] Isolated yield based on **1** used. [d] Performed with 1.2 equiv of IF_5. [e] Performed with 3.6 equiv of IF_5.

from the β- to the α-carbon, and the fluorination took place at α- and β-carbons.

The proposed reaction mechanism of the present unusual polyfluorination reaction is as follows. Monofluorination of **1** by IF_5 took place at the α-position of the sulfur group to give monofluorinated sulfide (**3**).[2] Elimination of HF from **3** gave alkenyl sulfide (**4**), which reacted with IF generated in situ to give the adduct (**5**).[4,6]

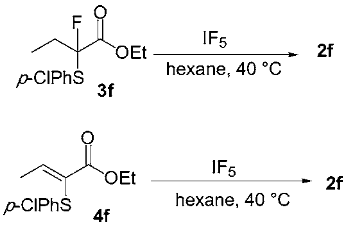
The formation of episulfonium ion (**6**), followed by the addition of a fluoride under migration of the sulfur group, provided difluorinated sulfide (**7**).[7] The fluorination, HF-elimination, IF-addition, and ArS-migration sequence was repeated until the sulfur group arrived at the terminal carbon and the polyfluorination product **2** was formed (Scheme 2).

Scheme 2



Ethyl 2-fluoro-2-(*p*-chlorophenylthio)butanoate (**3f**) and ethyl 2-(*p*-chlorophenylthio)-2-butenoate (**4f**), which could be intermediates in the reaction of **1f** with IF_5, were prepared and subjected to the same reaction conditions. In both cases, the pentafluorinated product **2f** was obtained in 60 and 40% yields, respectively (Scheme 3). These results support the proposed mechanism shown in Scheme 2.

Scheme 3



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Supporting Information Available: Representative experimental procedures and spectroscopic characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) IF might be generated during the reaction. After the conversion of compound **1** to **3**, IF_5 changes to HF and unstable IF_3, which disproportionates to IF_5 and IF.[5]

(5) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342.

(6) As for the addition of IF to double bonds, see: Yagupolskii, L. M. In *Organo-Fluorine Compounds*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Georg Thime; Stuttgart, 2000, p 234 and references cited therein.

(7) A similar mechanism involving episulfonium ion was postulated in an electrochemical fluorination of vinyl sulfids; see: Andres, D. F.; Laurent, E. G.; Marquet, B. S. *Tetrahedron* **1995**, *51*, 2605.