An improved method for the fluorination of arylsulfur chlorotetrafluorides to arylsulfur pentafluorides

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A B S T R A C T

A new method for the fluorination of arylsulfur chlorotetrafluorides to arylsulfur pentafluorides is described. The reaction is promoted by hydrogen fluoride generated from potassium hydrogen fluoride and trifluoroacetic acid which also serves as a solvent. The reaction is performed under mild conditions and uses substochiometric amounts of potassium hydrogen fluorides in certain cases. Recovery and reuse of trifluoroacetic acid was successfully demonstrated which makes this method safe, simple to use, and atom- and cost-effective.

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1. Introduction

The pentafluorosulfanyl group (SF$_5$) is a functionality that has received much attention in recent years, mainly in material, medicinal, and agrochemical research [1]. The incorporation of strongly electron-withdrawing pentafluorosulfanyl group into organic molecules can dramatically modify a variety of properties including lipophilicity, solubility, metabolic, thermal and chemical stability, bioavailability, bioactivity, or pK_a [1,2]. This functional group is starting to appear in compounds in development for various applications including pharmaceuticals, agrochemicals, energetic materials, liquid crystals, ionic liquids, and others [3]. Recently, the electron-acceptor and steric properties of the SF$_5$ group were also exploited in catalysis [4].

There is a limited number of commercially available compounds with the SF$_5$ group (compared to, for example, the CF$_3$-containing compounds), although, in recent years, many new products (mostly SF$_5$-aromatics) became available. In case of aromatic SF$_5$ compounds, there are two main methods for their practical synthesis available. The first one was developed in the 1990s and is based on direct fluorination of electron-deficient bis(aryl) disulfides (such as bis(*m*- or *p*-nitrophenyl) disulfides) with F$_2$/N$_2$ [5]. Building upon earlier studies of Sharp [6], Shreeve [7] and Janzen [8], the second method by Umemoto is based on a

two-step process of conversion of diaryl disulfides (**1**) or aryl thiols to aromatic sulfur chlorotetrafluorides (**2**) using chlorine in the presence of alkali metal fluorides in acetonitrile [9]. Arylsulfur trifluorides [10] were identified as intermediates in these reactions. In the second step, arylsulfur chlorotetrafluorides were fluorinated to arylsulfur pentafluorides (**3**) using either ZnF$_2$ under elevated temperature, SbF$_3$/SbF$_5$(SbCl$_5$) in a halocarbon solvent, excess of 70% HF-pyridine complex, or excess of anhydrous hydrogen fluoride (Scheme 1) [9]. A fluoropolymer reactor or reaction flask is required for all of the methods. These methods have some drawbacks: the zinc fluoride method uses high temperature, HF-pyridine and anhydrous hydrogen fluoride methods use large excess of very toxic and corrosive chemicals. Despite this, the last method seems to be the most suitable for bigger scale production.

Umemoto's synthesis represents a significant development for economical production of arylsulfur pentafluorides. Importantly, various substitutions on the phenyl ring are tolerated including fluoro, chloro, bromo, nitro, alkyl, and methylsulfonyl. A weak point of this process is the second step which calls for improvements. Safe, inexpensive and atom-economic fluorination method would be highly desirable.

2. Results and discussion

First, a range of substituted phenylsulfur chlorotetrafluorides (**2**) were synthesized in good to high yields using Umemoto's

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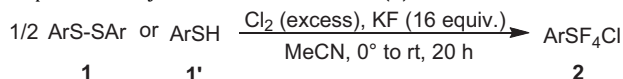
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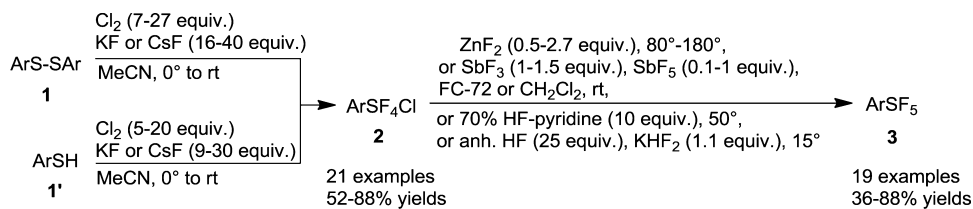
Scheme 1. Umemoto's two-step synthesis of arylsulfur pentafluorides [9].

Table 1

Preparation of arylsulfur chlorotetrafluorides (**2**).

| Entry	1 or 1′	Ar	Product and yield (%)[a]
1	**1a**	Ph	**2a**, 84
2	**1b**	4-FC$_6$H$_4$	**2b**, 85
3	**1c**	4-ClC$_6$H$_4$	**2c**, 81
4	**1d′**	4-t-BuC$_6$H$_4$	**2d**, 55
5	**1e**	2,4-F$_2$C$_6$H$_3$	**2e**, 63
6	**1f**		**2f**, 84

^a Isolated yield.

conditions. The reliability of the method was validated on a multi-gram scale. Commercial spray-dried potassium fluoride further dried by heating *in vacuo* for several hours was used, and the reaction was performed in dry acetonitrile at ambient temperature using excess of chlorine (Table 1). Compounds **2a–d** were synthesized previously [9] while compounds **2e** and **2f** are new. Compound **2d** could be prepared from *p-t*-butylthiophenol; however, we found that this method is not suitable for thiophenols substituted with electron-withdrawing group (4-F, 4-Cl or 2,4-F$_2$), and for these compounds, it was necessary to start from the corresponding diaryl disulfides. The products were purified either by distillation under reduced pressure (**2a–c** and **2e**) or by crystallization (**2d**) and were found to be stable in a perfluoropolymer container but they decomposed over the course of hours or days on contact with glass.

The fluorine for chlorine exchange in arylsulfur chlorotetrafluorides (**2**) to arylsulfur pentafluorides (**3**) was previously achieved with Lewis acidic fluorides (BF$_3$, SnF$_4$, TiF$_4$ in low yields, or SbF$_3$/SbF$_5$, CuF$_2$ or ZnF$_2$) in good yields [9]. We confirmed that with alkali metal fluorides (excess spray-dried KF or CsF) in THF under ambient temperature with ultrasound activation for 1 h, no fluorination of **2a** took place. An alternative fluorination reagent to Lewis acidic fluorides is hydrogen fluoride. Safety hazards associated with anhydrous HF, the necessity to use special equipment for handling it and cost of disposal of large excess of the reagent prompted us to think about modification of reaction

Table 2

Optimization of fluorination of phenylsulfur chlorotetrafluoride (**2a**) to phenylsulfur pentafluoride (**3a**).
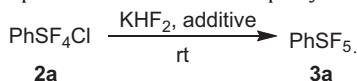
Entry	2a (mmol)	KHF$_2$ (equiv.) + additive (equiv.)	Solvent (mL)	Time (h)	Products	Yields (%)[a]
1	0.7	13 + 48% HF (11)	CH$_2$Cl$_2$ (3.5)	16	**3a**	0
2	0.6	5 + TFA (0.5)	CH$_2$Cl$_2$ (2)	16	**3a**	0
3	2.8	2 + TFA (2)	AcOH (4.7)	3.5	**3a**	0
					PhSO$_2$Cl	91
					PhSO$_2$F	9
4	2.2	1	MeSO$_3$H (2.2)	1	**3a**	0
5	1.8	1	CF$_3$SO$_3$H (2.25)	1.5	**3a**	5
					PhSO$_2$Cl	15
					PhSO$_2$F	14
					PhSO$_2$Ph	9
6	2	2	H$_2$SO$_4$ (3)	0.5	**3a**	14
					PhSO$_2$Cl	44
					PhSO$_2$F	36
					PhSO$_2$Ph	6
7	6	2[b]	TFA (6)	4	**3a**	100 (59)
8	2	1	TFA (2)	1.5	**3a**	100
9	2	0.6	TFA (2)	1	**3a**	65
10	2	0.6	TFA (2)	68	**3a**	100
11	30	1 + TFA (1)	–	16	**3a**	(8)
12	19	0.6[b]	TFA (19)	20	**3a**	(82)

^a Determined by GCMS, in brackets isolated yields.
^b KHF$_2$ was added in two portions every 15 min.