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The preparation of trifluoromethyl aryl sulfides using KF and thiophosgene

James H. Clark, Stewart J. Tavener

Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

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Abstract

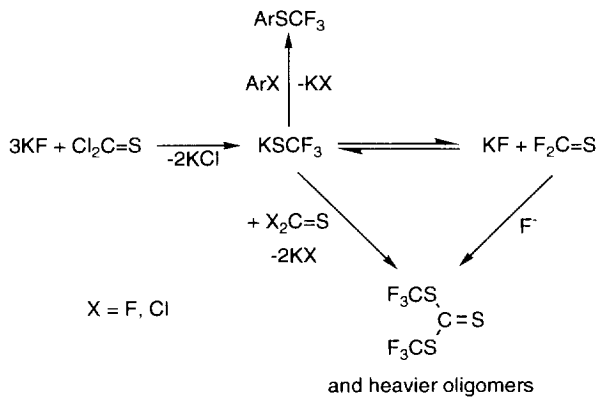
The trifluoromethanethiolate anion may be generated in situ by the reaction of thiophosgene with potassium fluoride in acetonitrile. This system is used to prepare trifluoromethyl aryl sulfides from activated fluoro- and chloroaromatic substrates via nucleophilic substitution.

Keywords: Trifluoromethyl aryl sulphides; Fluoride; Trifluoromethanethiolate anion

1. Introduction

The trifluoromethylthio group has good chemical stability and can impart high lipophilicity and strong electron withdrawing effects on an aromatic ring [1]. This group is one of the most lipophilic known (more so than either the trifluoromethyl or trifluoromethoxy groups as measured by 1-octanol–water partition coefficients [2]), and is also chemically very stable. These properties make it an important group for the preparation of dyes and biologically active compounds [1]. However, conventional routes to aromatic trifluoromethylsulfides generally require harsh conditions and/or expensive reagents [3]. They may be prepared by the treatment of intermediate trichlorothiomethoxy compounds with antimony trifluoride [4], by reaction of iodoaromatics with $Hg(SCF_3)_2$ (prepared by reaction of mercury metal with CF_3SSCF_3 or CF_3SCl) [5], or $CuSCF_3$ (from the reaction of AgF with CS_2 followed by transmetallation with CuI) [6]. They may also be prepared by reductive methods, using CF_3Br and NaS_2O_4 and an aromatic disulfide [7]. A convenient new method has recently been described, based on thermally inducing the decarboxylation of potassium trifluoroacetate in the presence of an aryl disulfide [8].

Dmowski and Haas used thiocarbonyl fluoride ($F_2C{=}S$) and an alkali metal fluoride (KF or CsF) to produce trifluoromethanethiolate anion in acetonitrile at −15 °C, which reacted with pentafluoropyridine to produce 4-(trifluoromethylthio)tetrafluoropyridine [9]. Vigorous stirring helped to prevent self condensation of the thiocarbonylfluoride. The trimer of thiocarbonyl fluoride, bis(trifluoromethyl)trithiocarbonate ($(CF_3S)_2C{=}S$) could also be used if the reaction was conducted at higher temperatures. Polysubstitution of the pentafluoropyridine substrate only occurred if higher temperatures (+20 °C) and the trimer were used. Further heating to 100 °C caused scrambling to the thermodynamically preferred 3,5-disubstituted product.



Scheme 1. Generation of trifluoromethanethiolate from thiophosgene and potassium fluoride, and subsequent reactions.

Neither thiocarbonyl fluoride or its trimer are commercially available, but thiocarbonyl fluoride may be prepared by the reaction of thiophosgene ($Cl_2C{=}S$) with potassium fluoride in acetonitrile; essentially the same conditions as for the nucleophilic substitution described above. This has led to the development of a convenient "one pot" synthesis of trifluoromethyl aryl sulfides, which uses cheap and readily available thiophosgene and potassium fluoride.

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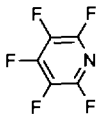
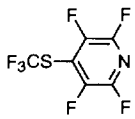
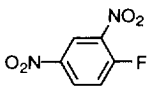
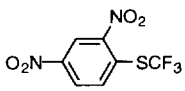
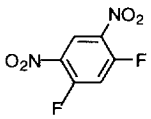
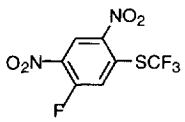
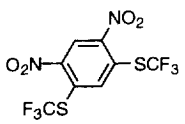
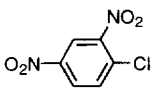
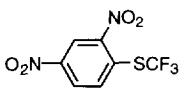
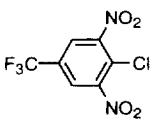
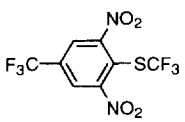
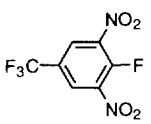
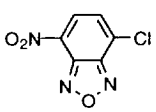
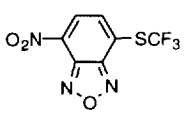
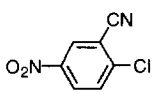
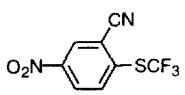
Table 1
Reactions of haloaromatic substrates with KF-thiophosgene

Substrate	Product(s)	Yield (%) (GC areas)	^{19}F-NMR δ (ppm)	Observed MS molecular ion
		70	−41.5 (3F, s) −90.2 (2F, m) −133.6 (2F, m)	251
		85	−42.0 (s)	268
		33	−42.4 (3F, s) −106.7 (1F, s)	286
		23	−41.4 (s)	368
		50	−42.0 (s)	268
		83	−42.2 (s)	336
		14	−63.0	254
		80	−42.0 (s)	265
		5	−40.8 (s)	248

Conditions: KF (78 mmol), substrate (13 mmol) and thiophosgene (13 mmol). The reaction was kept at −15 °C for 4 h, and then stirred at room temperature overnight.

2. Results and discussion

Thiophosgene reacts reversibly with potassium fluoride in acetonitrile at −15 °C to form a useful source of trifluoromethanethiolate anions (Scheme 1). Potassium fluoride has no significant solubility in acetonitrile, so this is presumably a heterogeneous reaction. $KSCF_3$ is not a stable compound at room temperature and exists in equilibrium with thiocarbonyl fluoride and KF [9].

The trifluoromethane thiolate anion will react with a range of fluoro- and chloroaromatic substrates under conditions mild enough to leave nitro, cyano, trifluoromethyl and furazan substituents intact. The reaction presumably proceeds via an aromatic nucleophilic substitution mechanism, as only haloaromatics containing two or more strongly electron withdrawing groups react under these conditions. Table 1 shows the results of reaction of thiophosgene and potassium fluoride with activated haloaromatic substrates. The reaction is selective to the trifluoromethylthio product, with no mixed fluorochloromethylthio products. No significant halogen exchange or fluorodenitration occurs, and little (< 1%) polysubstitution was seen for pentafluoropyridine.

Yields are generally high, with fluoroaromatics giving better results than the corresponding chloro compounds, probably because the fluoride leaving group may react with further thiophosgene molecules. When 1,5-difluoro-2,4-dinitroben-

Table 2
Effect of reaction conditions on the reaction of 2-chloro-5-nitrobenzonitrile in the KF-thiophosgene system

Reactant ratio			Conditions	Products (%) [a]			
ArCl	KF	$Cl_2C=S$		$ArSCF_3$	ArF	ArOH	FDN [b]
1	6	1	a	5	–	–	–
1	6	1	a,c	28	7	–	–
1	12	2	a,c	49	13	3	–
1	12	2	b,c	29	21	4	–
1	12	2	a,c,d	14	74	1	–
1	12	2	b,c,d	1	80	2	8

[a] Measured by GC (% areas, uncorrected); remainder is starting material.
[b] Fluorodenitration product, 2-chloro-5-fluorobenzonitrile.
Conditions: a, reaction cooled to −15 °C for 4 h, then allowed to warm to RT; b, reaction started at RT; c, reflux overnight; d, addition of 1 mol equivalent of tetraphenylphosphonium bromide as a phase transfer agent.

zene was used as the substrate, the mono and disubstituted $ArSCF_3$ products account for 80% of the thiophosgene used. When large excesses of KF and thiophosgene were employed with this substrate the disubstituted product was produced exclusively. Byproducts formed also included self-condensation products of thiocarbonyl fluoride, including the trimer and heavier oligomers (identified by gas chromatography-mass spectrometry (GC-MS)). These were seen in greatest quantities when the aromatic substitution was least successful. Their presence was associated with a characteristic dark red colour, which was absent from the crude reaction mixture when high yields of the $ArSCF_3$ product were obtained. This colour provided a convenient visual indication of the probable success of the reaction.

For the reaction to be successful the aromatic ring must have strong electron withdrawing substituents. The following compounds did not react under the conditions employed: 4-fluoronitrobenzene, 2-fluoronitrobenzene, hexachlorobenzene, hexafluorobenzene, 4-fluoro-benzonitrile, 2-fluoro-5-nitro-benzotrifluoride, and 4-chloro-3-nitrobenzonitrile. 2-Chloro-5-nitro-benzonitrile was found to be at the reactivity borderline, and was therefore chosen to probe the effect of changing reaction conditions (Table 2).

Increasing the quantity of potassium fluoride improved the yield, as did refluxing (to break up any thiocarbonyl fluoride oligomers which have formed [9]) after initial reaction at low temperature. These two improvements raised the yield tenfold, from 5% to a respectable 49%. Addition of a phase transfer agent (tetraphenylphosphonium bromide) did not improve the yield of the $ArSCF_3$ product formed, but did dramatically increase the quantity of halex and fluorodenitration products. Starting the reaction at room temperature rather than at −15 °C substantially decreased the yield of $ArSCF_3$, both with and without a PTC.

This method eliminates the need to store hazardous thiocarbonyl fluoride gas, reagents are cheap and available, and trifluoromethyl aryl sulfides may be prepared in useful yields from chloro and- fluoroaromatic substrates containing electron withdrawing groups.

3. Experimental

3.1. Instrumentation

^{19}F-NMR spectra were recorded in CD_3CN at 20 °C on a Jeol EX270 spectrometer operating at 254 MHz. GCMS spectra were obtained on a VG Analytical Autospec instrument.

3.2. Typical reaction conditions

KF (spray dried, 78 mmol) was oven dried at 300 °C for at least 4 h, placed in a flask with a magnetic stirrer bar, the substrate (13 mmol) and acetonitrile (30 ml, freshly distilled from calcium hydride), and fitted with a rubber septum. The reaction was flushed with argon and cooled to −15 °C in an ethylene glycol–dry ice bath, at which point thiophosgene (13 mmol) was injected through the septum. The reaction was kept at −15 °C for 4 h, and then allowed to warm to room temperature. If required, the reaction was then fitted with a reflux condenser and heated to reflux overnight.

The reaction mixture was separated using diethylether and washed with aqueous sodium hydrogen carbonate solution, to neutralise any residual thiophosgene. the ether layer was dried over magnesium sulfate, filtered, and reduced on a rotary evaporator. Products were identified by GC-MS and ^{19}F-NMR.

Acknowledgements

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References

[1] J.H. Clark, D. Wails, T.W. Bastock, Aromatic Fluorination, CRC Press, Boca Raton, Fl, 1996, p. 119.
[2] J.A.C. Allison, G.H. Cady, J. Am. Chem. Soc. 81 (1959) 1089.

[3] M.A. McClinton, D.A. McClinton, Tetrahedron 48 (1992) 6555.
[4] J. Dickey, US Patent, 2 436 100 (1938).
[5] E.H. Man, D.D. Coffman, E.L. Muetterties, J. Am. Chem. Soc. 81 (1959) 3575; J.F. Harris, J. Org. Chem. 32 (1967) 2063.
[6] N.V. Kondratenko, A.A. Kolomeytsev, V.I. Popov, L.M. Yagupolskii, Synthesis (1985) 667.
[7] J.L. Clave, B. Langlois, C. Wakselman, M. Tordeux, Phosphorus, Sulfur and Silicon 59 (1991) 129.
[8] B. Quiclet-Sire, R.N. Saicic, S.Z. Zard, Tetrahedron Lett. 37 (1996) 9057.
[9] W. Dmowski, A. Haas, J. Chem. Soc. Perkin Trans. 1 (1987) 2119; (1988) 1179.