

Difluorodiphenoxymethanes and fluorotriphenoxymethanes: two unusual types of fluorine-containing molecule from the same reaction

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O,O-Diarylthiocarbonates react with silver(I) fluoride, under conditions mild enough to leave a wide range of ring substituents intact, to produce difluorodiphenoxymethanes and fluorotriphenoxymethanes.

Small fluorine-containing groups are of interest to the pharmaceutical and agricultural industries because of their ability to impart increased lipophilicity and hydrophobicity to biologically active molecules.¹ The difluoromethylene unit ($-\text{CF}_2-$) is particularly attractive in terms of novelty and its potential as an oxygen atom replacement or mimic.² There has been recent interest in the unusual $-\text{OCF}_2\text{O}-$ group, which appears in the 2,2-difluorobenzodioxole moiety found in fungicides such as Fludioxonil, which has greatly increased lipophilicity compared with the unfluorinated analogue.³ However, many routes to such fluorinated groups are of limited utility as they require harsh fluorinating conditions involving HF or F_2 , which severely restricts the variety of functional groups which may be present on the molecule.¹ As a consequence, there is a continuing need for fluorination reactions which proceed under mild conditions.

Silver(I) fluoride (AgF) is known to react with CS_2 to form AgSCF_3 and Ag_2S , the driving force being the extremely high lattice energy of silver sulfide and the strength of the $\text{C}-\text{F}$ bonds.^{4,5} Whilst relatively expensive, AgF requires no special handling techniques. Fluorodesulfurisation using AgF has not been exploited as a synthetic method for the preparation of $-\text{CF}_2-$ containing molecules, although other fluorodesulfurisation systems have been described. Desulfurisation of 1,3-dithiolanes using iodine and fluorine gas has recently been reported as a viable method for the production of $-\text{CF}_2-$ containing compounds.⁶ Hiyama and co-workers have described a number of fluorodesulfurisation reactions using an excess of HF-pyridine or $\text{Bu}_4\text{N}^+[\text{H}_2\text{F}_3]^-$, but these require the presence of an oxidant such as *N*-bromosuccinamide or *N,N*-dibromo-5,5-dimethylhydantoin in approximately five-fold excess.⁷ Similarly, alkanol xanthates may be converted into either fluoroalkanes or trifluoromethoxyalkanes in the presence of HF-pyridine and bis(trifluoroacetoxy)iodobenzene.⁸

Difluorodiphenoxymethanes are unusual, with only two reports of synthetic methods for their preparation in the chemical literature, both of which employ harsh conditions. A few difluorodiphenoxymethanes have been prepared by reaction of diphenylcarbonates with anhydrous HF in dichloromethane, but these required the presence of a trichloromethyl function in the 2-position on one of the rings which was converted to a benzoyl fluoride group during fluorination.⁹ The preparation of perfluoro(diphenoxymethane) from pentafluorophenol and a source of difluorocarbene has also been described.¹⁰ Compounds containing three oxygens and a fluorine attached to a single carbon atom are even rarer, with just four reported compounds.¹¹ Fluorotriphenoxymethanes have not previously been reported.

We report the preparation of both fluorotriphenoxymethanes and difluorodiphenoxymethanes by fluorodesulfurisation of *O,O*-diarylthiocarbonates using silver(I)

fluoride. The reaction conditions are mild enough to leave a wide variety of ring substituents, including NO_2 , CN, Br, CH_3O , CF_3O , CH_3 and CF_3 , intact.

Results and Discussion

O,O-Diarylthiocarbonates were prepared by an adaptation of Barton *et al.*'s method for preparing *O*-arylchlorothionoformates,¹² from thiophosgene and an excess of sodium phenoxide to ensure complete conversion to the thiocarbonate. The isolated yields after recrystallisation ranged between 24 and 88%. Desulfurisation of *O,O*-diarylthiocarbonates in the presence of AgF was found to proceed steadily with complete conversion of the starting material over 3 hours. The reactions were performed in refluxing anhydrous acetonitrile in a teflon flask under an argon atmosphere, with care being taken to exclude moisture. The reaction products include difluorodiphenoxymethanes, fluorotriphenoxymethanes and diarylcarbonates, with the product distribution being dependent on the nature of any ring substituents (Table 1).

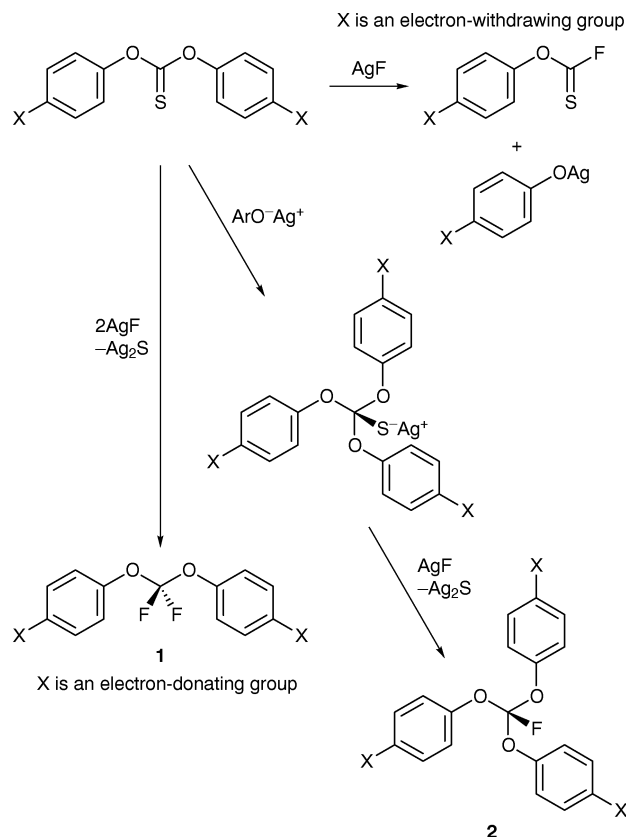
Formation of difluorodiphenoxymethanes (**1**) is favoured by the presence of electron-donating groups on the ring. Electron-withdrawing groups stabilise the phenoxide as a leaving group, with attack by fluoride leading to the formation of the fluorothionoformate instead (Scheme 1). The formation of fluorotriphenoxymethanes (**2**) in these systems appears to be due to reaction of the diarylthiocarbonate with AgF to form the *O*-arylfluorothionoformate [$\text{ArOC}(\text{S})\text{F}$, observed by GCMS] and silver phenoxide, which in turn reacts with another thiocarbonate molecule to form a silver(I)

Table 1 Reactions of *O,O*-diarylthiocarbonates with silver(I) fluoride^a

Substituent X	Product distribution ^b / % GC area (isolated yield ^c)		
	$(\text{ArO})_2\text{CF}_2$	$(\text{ArO})_3\text{CF}^d$	$(\text{ArO})_2\text{CO}$
CH_3O	93 (75)	0	7
CH_3	65 (31)	0	35
H	67 (36)	23	10
Br	18	82 (40)	0
CF_3O	0	100 (12)	0
CF_3	0	100 (55)	0
CN	0	100 (64)	0
NO_2	0	100 (54)	0

^a Figures given are % areas by GC, uncorrected; isolated yield in brackets. Product identities were confirmed by GC-MS, ^1H and ^{19}F NMR. ^b Not including *O*-arylfluorothionoformate byproduct.

^c Products isolated by column chromatography over silica gel [$(\text{ArO})_2\text{CF}_2$], or by recrystallisation from cyclohexane-dichloromethane [$(\text{ArO})_3\text{CF}$]. ^d Yields based on $2 (\text{ArO})_2\text{C}=\text{S} + 2 \text{AgF} \rightarrow \text{ArOC}(\text{S})\text{F} + (\text{ArO})_3\text{CF} + \text{Ag}_2\text{S}$.



Scheme 1 Reactions of *O,O*-diarylthiocarbonates with silver(I) fluoride

triphenoxymethanethiolate $[(\text{ArO})_3\text{CS}^-\text{Ag}^+]$. This intermediate is then attacked by a second molecule of silver(I) fluoride to produce the fluorotriphenoxymethane. The reaction is very selective in the case of strongly electron-withdrawing groups, with no detectable diarylcarbonate formation. No fluoro-desulfurisation of the *O*-phenylfluorothionoformate to the corresponding trifluoromethyl aryl ether was observed for any of these reactions, even when an excess of AgF was used.

The formation of the diarylcarbonate byproduct is presumably due to reaction with silver(I) oxide impurities, and was much greater when the reaction was performed in glass, due to the reaction of the AgF with the glass to produce Ag_2O . In a separate reaction performed in teflon under the same conditions, *O,O*-diphenylthiocarbonate reacted with 2 equivalents of freshly precipitated silver(I) oxide¹³ to form diphenylcarbonate (54% after 3 hours). The deliberate addition of a five-fold excess of water to a reaction of *O,O*-diphenylthiocarbonate with AgF was found to cause complete conversion to the diphenylcarbonate in three hours. No reaction occurs in the absence of the silver salts.

The reaction products are easily isolated by column chromatography over silica gel (difluorodiphenoxymethanes) or recrystallisation from dichloromethane–cyclohexane (fluorotriphenoxymethanes). The difluorodiphenoxymethanes are colourless liquids or low melting point solids, and the fluorotriphenoxymethanes are colourless crystalline solids, with the exception of the tris(4-nitrophenoxy)fluoromethane, which is a yellow solid.

The ^{19}F NMR chemical shifts for the difluorodiphenoxymethanes were found in the range -55 to -57 ppm [relative to CFCl_3], which is in the region reported by Alles *et al.*,⁹§ for their $(\text{ArO})_2\text{CF}_2$ compounds. Those for the fluorotriphenoxymethanes appeared in the region -53 to -57

ppm. The chemical shift values within each group of compounds were found to become more negative (move to higher field) as the electron donating character of the ring substituent increased, passing more electron density to the fluorine atom(s).

In addition to the expected bands due to aromatic C—H stretches, ring breathing and substituent vibrations, the infrared spectra of these compounds showed several characteristic strong, broad absorption bands in the 1250 to 1050 cm^{-1} region, due to the coupled stretching vibration modes of the C—F and C—O bonds. At slightly lower frequency (*ca.* 1000 cm^{-1}) there are either one $[(\text{ArO})_3\text{CF}]$ or two $[(\text{ArO})_2\text{CF}_2]$, asymmetric and symmetric stretches] C—F stretching bands, although these sometimes overlap with the coupled vibrations.

These compounds showed good chemical stability in the presence of nucleophiles. In separate experiments, difluorodiphenoxymethane and tris(4-cyanophenoxy)fluoromethane were heated to 50°C in acetonitrile solution in the presence of KCN, KF or KOH. Neither compound reacted with any of these salts.

Difluorodiphenoxymethanes are very soluble in a wide range of solvents of different polarities, from cyclohexane to methanol, but insoluble/immiscible with water even when heated to just below reflux. None of the difluorodiphenoxymethanes are soluble/miscible with the fluorinated solvent perfluoro(dimethyl)cyclohexane even at reflux. The fluorotriphenoxymethanes are soluble in dichloromethane, acetonitrile and chloroform, slightly soluble in methanol and insoluble in cyclohexane and water.

Experimental

NMR spectra were recorded in CD_3CN or CDCl_3 at 20°C on a Jeol EX270 spectrometer operating at 270 MHz for ^1H and 254 MHz for ^{19}F . ^{19}F NMR spectra were referenced to CFCl_3 . GCMS spectra were obtained on a VG Analytical Autospec instrument. Anhydrous acetonitrile was obtained from Aldrich Chemical Co.

Preparation of *O,O*-diarylthiocarbonates (typical reaction conditions)

The phenol (40 mmol) was dissolved in a solution of NaOH (1.6 g, 40 mmol) in water (25 ml). This was added dropwise over 20 min to a rapidly stirred solution of thiophosgene (1 ml, 1.5 g, 13 mmol) in dichloromethane (25 ml), and then stirred overnight in an oil bath at 65°C . The reaction was then allowed to cool before adding 100 ml each of dichloromethane and saturated aqueous NaHCO_3 solution. The layers were separated and the dichloromethane layer washed with $2 \times 100\text{ ml}$ water, 100 ml saturated aqueous NaCl solution and then dried over magnesium sulfate. This was followed by filtration and removal of solvent *in vacuo*. Recrystallisation from a mixture of dichloromethane and cyclohexane gave pure ($>99\%$ by GC) product in yields ranging between 24 and 88%. Satisfactory GCMS and ^1H NMR spectra were obtained, and melting points were in agreement with literature values (where available).¹⁴

Reaction of *O,O*-diarylthiocarbonates with silver(I) fluoride (typical conditions)

Silver(I) fluoride (0.28 g, 2.2 mmol), the *O,O*-diarylthiocarbonate (1.0 mmol), and acetonitrile (20 ml) were stirred together at 80°C under an argon atmosphere in a teflon flask for 3 h. The reaction was then allowed to cool to room temperature and another 20 ml of acetonitrile was added. The mixture was then filtered to remove insoluble silver salts, and the solvent removed *in vacuo*. The crude product was then purified either by column chromatography over silica gel $[(\text{ArO})_2\text{CF}_2]$ or recrystallised from dichloromethane–cyclohexane $[(\text{ArO})_3\text{CF}]$. Compound identities were confirmed by ^1H and ^{19}F NMR

§ Note that ^{19}F NMR chemical shifts given in ref. 9 are referenced to CF_3COOH acid, not CFCl_3 , and that higher field is assigned to positive ppm.

spectroscopy, and GCMS. Molecular ions were not observed for the triphenoxyfluoromethanes under EI conditions, but were seen using CI (NH₃).

Selected analytical data: Bis(4-methoxyphenoxy)difluoromethane. MS (EI): M⁺ = 296 (99); m/z = 296 (99), 173 (39), 123 (38), 107 (100), 95 (24), 77 (48), 64 (20), 52 (8); ¹⁹F NMR (CDCl₃): δ -56.9.

Bis(4-methylphenoxy)difluoromethane. MS (EI): M⁺ = 264 (49); m/z = 264 (49), 245 (5), 157 (19), 107 (6), 91 (100), 79 (8), 77 (19), 65 (26); ¹⁹F NMR (CDCl₃): δ -56.1.

Difluorodiphenoxymethane. MS (EI): M⁺ = 236 (100); m/z = 236 (100), 217 (75), 169 (8), 153 (8), 143 (26), 141 (43), 115 (13), 77 (28); ¹⁹F NMR (CDCl₃): δ -55.8.

Tris(4-bromophenoxy)fluoromethane. MS (EI): m/z = 377 (49), 375 (100), 373 (52), 296 (14), 294 (14), 157 (14), 155 (16), 76 (15); ¹⁹F NMR (CDCl₃): δ -56.2.

Tris(4-trifluoromethoxyphenoxy)fluoromethane. MS (EI): m/z = 385 (100), 252 (7), 177 (8), 161 (23), 95 (35), 83 (9), 75 (7), 69 (22); ¹⁹F NMR (CDCl₃): δ -54.8 (s, 1F), -62.0 (s, 9F).

Tris(4-trifluoromethylphenoxy)fluoromethane. MS (EI): m/z = 353 (100), 269 (13), 189 (8), 145 (75), 133 (8), 125 (9), 113 (9), 95 (11); ¹⁹F NMR (CDCl₃): δ -53.8 (s, 1F), -62.4 (s, 9F).

Tris(4-cyanophenoxy)fluoromethane. MS (EI): m/z = 267 (100), 203 (4), 102 (38), 90 (6), 75 (7), 73 (4), 63 (8), 51 (5); ¹⁹F NMR (CDCl₃): δ -52.2. Elemental microanalysis: C₂₂H₁₂O₃N₃F requires C, 68.57; H, 3.14; N, 10.90; found C, 68.53; H, 2.89; N, 10.93%.

Tris(4-nitrophenoxy)fluoromethane. MS (EI): m/z = 307 (100), 169 (39), 139 (14), 122 (7), 92 (14), 76 (13), 63 (13), 50 (7); ¹⁹F NMR (CDCl₃): δ -53.1. Elemental microanalysis: C₁₉H₁₂O₉N₃F requires C, 51.25; H, 2.72; N, 9.44; found C, 51.71; H, 2.53; N, 9.38%.

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