ELSEVIER

Journal of Fluorine Chemistry 94 (1999) 1–5

JOURNAL OF FLUORINE CHEMISTRY

Acid fluorides and 1,1-difluoroethyl methyl ethers as new organic sources of fluoride for antimony pentachloride-catalyzed halogen-exchange reactions

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Received 17 March 1998; accepted 6 May 1998

This paper is dedicated to Professor Theodore Cohen on the occasion of his 70th birthday.

Abstract

1,1-Difluoroethyl methyl ethers such as the commercial veterinary anesthetic methoxyflurane (2,2-dichoro-1,1-difluoroethyl methyl ether, **6**) decompose in the presence of a catalytic amount of antimony pentachloride. The rate of decomposition is dependent upon the number and position of halogen atoms in the ether: a high degree of halogenation at the methyl group or at the 2-position of the ethyl group makes the ether less prone to decomposition. The decomposition products are acid fluorides and halogenated methanes. The fate of the antimony pentachloride is conversion to a fluorochloroantimony species which can be used in situ to selectively fluorinate a polychlorinated substrate. Thus, 1,2,2,2-tetrachloro-1-fluoroethyl methyl ether (**1**) is converted cleanly to the anesthetic compound 2,2,2-trichloro-1,1-difluoroethyl methyl ether (**2**) using **6** as the fluoride source, exploiting the difference in stability of **2** and **6** to the pentavalent antimony species. It is also demonstrated that the acid fluorides obtained from decomposition of the 1,1-difluoroethyl methyl ethers are fluoride sources for halex reactions.

Keywords: Antimony pentachloride; Catalyzed halogen-exchange; Acid fluorides; 1,1-difluoroethyl methyl ether

1. Introduction

Recently we disclosed the use of fluoromethyl ethers as sources of fluoride for halogen-exchange (halex) reactions [1]. For example, the commercial anesthetic sevoflurane acted as a fluoride source for the completely selective conversion of carbon tetrachloride to trichlorofluoromethane (Scheme 1). However, when the sevoflurane/antimony pentachloride system was used as the fluoride source for the conversion of 1,2,2,2-tetrachloro-1-fluoroethyl methyl ether (**1**) [2] to the anesthetic compound 2,2,2-trichloro-1,1-difluoroethyl methyl ether (**2**) [2,3], a disappointingly low yield of the desired product was seen. Use of the sevoflurane/antimony pentachloride system was prompted by our failure to achieve an acceptable yield of **2** from **1** with the usual Swarts-type antimony trifluoride/antimony pentachloride reagent. This is not surprising, considering the known tendency of 1,1-dihaloalkyl methyl ethers to decompose to acid halides and methyl halides in the presence of Lewis acids [4–8]. In this communication we wish to report observations on the stability of 1,1-dihaloalkyl ethers which culminated in a high-yielding synthesis of **2**.

2. Discussion

Treatment of **1** with 5 mol% antimony pentachloride at room temperature resulted in an immediate exotherm with evolution of methyl chloride. After 5 min, NMR analysis of the crude mixture in $CDCl_3$ showed complete conversion of the starting material to a 1.3:1 mixture of **2** and trichloroacetyl fluoride (**4**), plus an undetermined amount of trichloroacetyl chloride (**5**) (Scheme 2). Further heating at 55-60°C for 1 h resulted in complete conversion to a mixture of **4** and **5**. No products of halogen-exchange at the α-position of **4** and **5** were seen. A possible explanation is that disproportionation of the CFCl group [1,9] initially occurred, giving **2** and the unobserved **3**, which immediately decomposed to **5** and methyl chloride. However, the intermediacy of **3** is not required to explain the results, as it is also possible that the initial step is conversion of a certain percentage of **1** to **5** and methyl chloride through the loss

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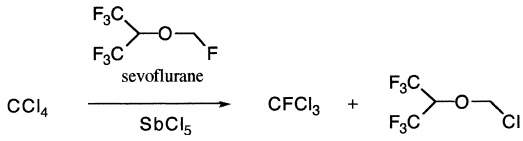
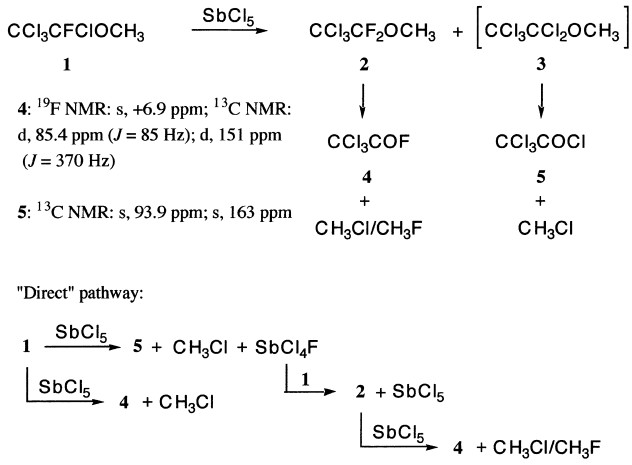
0022-1139/99/$ – see front matter
PII: S0022-1139(98)00347-9



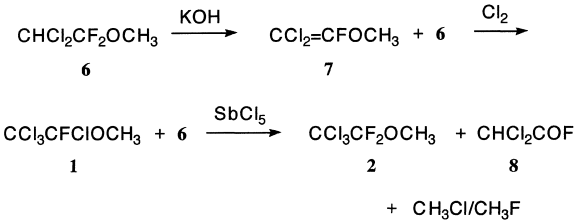
Scheme 1. Use of sevoflurane in a halex reaction.



Scheme 2. Possible decomposition pathways of 1,2,2,2-tetrachloro-1-fluoroethyl methyl ether.

of fluoride by **1** to the antimony pentachloride, thereby forming a fluorochloroantimony species. The antimony species then can fluorinate the unconverted **1** to give **2**. Compound **2** slowly decomposed to **4** and methyl halide, a pathway which is known in analogous systems [4–8]. It was apparent at this point that the above mentioned failure of **1** to undergo smooth fluorination was due to facile decomposition of the starting material.

The solution to the problem of a high-yielding synthesis of **2** was achieved by accident. Following the method of Terrell [2], the commercial veterinary anesthetic methoxyflurane (**6**) [2] was dehydrofluorinated to give a mixture of enol ether **7** and unconverted starting material (Scheme 3). Chlorination of **7** in this mixture gave **1**. At this point, the reaction mixture contained **1** and **6** in a molar ratio of approximately 1:1. Treatment of the mixture with sevoflurane and a catalytic amount of antimony pentachloride at room temperature resulted in an exotherm with rapid consumption of **6** and evolution of methyl chloride. After 50 min, aqueous work-up furnished **2** in 74% yield. Based on our earlier work (see Scheme 1, [1]), it was expected that sevoflurane was the source of fluoride, but we later found that sevoflurane could be omitted from the reaction mixture with no effect. NMR analysis of the crude mixture before work-up showed that dichloroacetyl fluoride (**8**) [10] was present. A plausible explanation of these results first requires rapid decomposition of **6** by antimony pentachloride to give **8**, methyl chloride, and a fluorochloroantimony species. Next, transfer of fluoride from the antimony to either **1** or its putative disproportionation product **3** must occur before complete decomposition to **5** and additional



Scheme 3. Synthesis of 2,2,2-trichloro-1,1-difluoroethyl methyl ether (**2**).

methyl chloride. It is apparent that transfer of fluoride from **6** is faster than complete decomposition of **1**, and that **2** is much more stable to antimony pentachloride than its closely related analogue **6**.

This prompted us to perform a qualitative stability study of closely related 1,1-difluoroethyl methyl ethers (Table 1). The decomposition products in all cases were the corresponding acid fluorides and halogenated methanes. We found that a high degree of halogenation at either the 2-position of the ethyl group or at the methyl group markedly enhances the stability of the ethers. The greater stability of **2** vs. **6**, which differ by only one halogen atom at the 2-position of the ethyl group, is a trend mirrored by the pairs **2** and **9** [11], **13** [11] and **12** [11], and **16** [11] and **15** [11]. Comparison of **11** [12] vs. **10** [12] shows an exception to the trend, although a more refined study may be required to indicate a difference between the two. The data in Table 1 also show that halogen substitution on the methyl group results in a large stability enhancement. This trend can be seen by comparing **14** (the commercial anesthetic enflurane) and **10**, **15** and **12**, and **17** [11] and **15**. Both these trends may indicate that the initial step, which would be rate-determin-

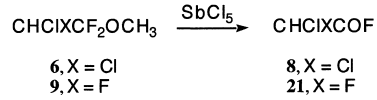
Table 1
Stability of 1,1-difluoroethyl methyl ethers to 5 mol% antimony pentachloride

Fluoroether	Time[a]	Temperature (°C)
$CHCl_2CF_2OCH_3$, **6** (methoxyflurane)	20 min	r.t.–40[b]
$CCl_3CF_2OCH_3$, **2**	1 h	55–60
$CHClFCF_2OCH_3$, **9**	30 min	r.t.
$CHClFCF_2OCH_2F$, **10**	20 min	r.t. to −20[c]
$CFCl_2CF_2OCH_2F$, **11**	20 min	r.t. to −20[c]
$CHClFCF_2OCH_2Cl$, **12**	20 min	r.t.–2[c]
$CFCl_2CF_2OCH_2Cl$, **13**	Stable at r.t. for ≥20 h	
$CHClFCF_2OCHF_2$, **14** (enflurane)	Stable at reflux for ≥1 h	
$CHClFCF_2OCHCl_2$, **15**	Conversion to enflurane[d]	
$CFCl_2CF_2OCHCl_2$, **16**	Stable at 60°C for ≥2 h	
$CHClFCF_2OCCl_3$, **17**	Stable at 60°C for ≥2 h	

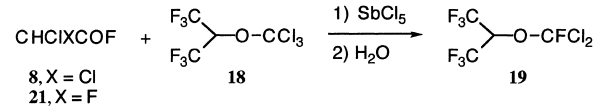
[a]Time required for complete disappearance of fluoroether.
[b]The reaction was exothermic.
[c]The temperature fell after addition of $SbCl_5$ due to evaporation of the halogenated methane decomposition product.
[d]After 20 h at r.t., the reaction consisted of a 2.3:1.8:1.8:1.5:1.0 mixture of chloroform, enflurane, $CHFClOCF_2CHFCl$ [12], **15**, and chlorofluoroacetyl fluoride, plus some unidentified components.

ing, in the decomposition of the fluoroethers is breakage of the ethyl group's C-1 to fluorine bond, as electon-withdrawing atoms at both C-2 and at the methyl group would tend to destabilize the resulting cation. The other possible first step in the decomposition reaction is complexation of the antimony pentachloride with the ether's oxygen atom. Electron-withdrawing atoms would tend to lower the electron density at oxygen, making this complexation less likely.

We have also explored the possibility of using **6** and **2** as fluoride sources for other halex reactions. The by-products of halex reactions between a chlorinated substrate and the 1,1-difluoroethers are the highly volatile methyl chloride (and/or methyl fluoride) and acid fluorides, which react readily with water during work-up to form a water-soluble acid. Thus, **6** and **2** have an advantage over sevoflurane as a fluoride source [1] (see Scheme 1), because the by-product of sevoflurane, chloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether, stays in the organic layer and must be separated from the product by distillation. As the test substrate, trichloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (**18**) [13] was chosen because the trichloromethyl group can readily be over-fluorinated in halex reactions under Swarts-type conditions [1,13–18]. Treatment of a 1:1 mixture of **18** and **6** with a catalytic amount of antimony pentachloride at room temperature did indeed result in immediate conversion to the expected product **19** [13], but a small amount of the product of difluorination, **20** [13], also was formed (Table 2). After stirring overnight at room temperature, **20** was the predominant product. Monitoring of the reaction by NMR also showed that the by-product acid fluoride **8** was converted to the corresponding acid chloride after the overnight period. This indicated that the acid fluoride **8** was acting as a secondary fluoride source, although at a much slower rate. The same trend was seen with **2** as the fluoride source. Due to some loss of fluoride as methyl fluoride in the initial decomposition reaction, further conversion to **20** was not possible if just one equivalent of **6** was used, despite prolonged heating. However, if 1.5 equivalents of **6** was present at the beginning of the reaction, then the conversion of **18** to **20** was >96% after 3.5 h at 40°C.



Scheme 4. Synthesis of acid fluorides from 1,1-difluoroethyl methyl ethers.



Scheme 5. Fluorination using acid fluorides as sources of fluoride.

We then turned our attention to the evaluation of two acid fluorides, **8** and **21** [7], as sources of fluoride in halex reactions. The acid fluorides were synthesized by antimony pentachloride-catalyzed decomposition of **6** and **9** [4–8] (Scheme 4; see also Table 1). After a short heating period, the acid fluorides were distilled from the reaction flask in $\geq$70% yield. Acid fluoride **8** was also synthesized by treatment of dichloroacetyl chloride with sevoflurane and antimony pentachloride [1] (see Scheme 1), but separation of the by-product was troublesome.

Treatment of the test substrate **18** with one equivalent of **8** and a catalytic amount of antimony pentachloride for 1.5 h at room temperature, followed by addition of water and separation of the phases, gave exclusively **19** in 91% yield (Scheme 5). Acid fluoride **21** was less prone to donate fluoride and also less selective in the halex reaction: after 1 h at 60°C, 90% of **18** was consumed, while both **19** and **20** had formed in a 13:1 ratio.

3. Conclusion

To summarize, two types of molecules were found to be sources of fluoride in antimony pentachloride-catalyzed halex reactions: halogenated acid fluorides, and 1,1-difluoroethyl methyl ethers. In the former case, fluoride transfer to a polychlorinated substrate proceeded under mild conditions and was highly selective for monofluorination, while

Table 2
Fluorination using 1,1-difluoroethyl methyl ethers as sources of fluoride

Ether	Temperature (°C)	Time	Molar ratio		Conversion of **18** (%)
			19	**20**	
6	r.t.	10 min	10	1	>90
6	r.t.	15 h	1	2.6	100
6[a]	40	1.5 h	1	7.8	100
6[a]	40	3.5 h	1	30	100
2	r.t.	1 h	100	0	67
2	50	30 min	13	1	100
2	50	15 h	1	4.7	100

[a]1.5 equivalents used.

in the latter case, lower selectivity resulted because the fluoride source decomposed after fluoride donation to give an acid fluoride, which caused an appreciable amount of fluorination itself. In both cases, the by-products from the fluoride source were either highly volatile or water-reactive, which simplified purification after aqueous work-up. The new fluorination system was applied to an improved synthesis of the anesthetic compound 2,2,2-trichloro-1,1-difluoroethyl methyl ether (**2**).

4. Experimental

4.1. General

Antimony pentachloride was obtained from Aldrich and was of 99.99+% purity. All reactions were run under an atmosphere of N_2. Boiling points are uncorrected. ^{1}H NMR spectra (TMS reference) were recorded at 300 MHz, ^{19}F NMR spectra ($CFCl_3$ reference, proton decoupled) at 282 MHz, and ^{13}C NMR spectra (TMS reference, proton decoupled) at 75 MHz.

4.2. 1,2,2,2-Tetrachloro-1-fluoroethyl methyl ether (1)

Methoxyflurane (**6**) (500 g, 3.03 mol) was heated at reflux under N_2 over KOH pellets (175 g (85%), 2.66 mol) overnight. Distillation to dryness under N_2 gave a mixture of water and crude product. The crude product was dried over KOH, giving 424 g of a mixture of methoxyflurane (**6**) and 2,2-dichloro-1-fluorovinyl methyl ether (**7**) which was carried into the chlorination without further purification. **7**: lit. bp 101°C [2], ^{1}H NMR δ 3.81 ppm (s), ^{19}F NMR δ −90.7 ppm (s).

A 413 g portion of the mixture was cooled to −40°C and chlorine was bubbled through until uptake ceased. At this point, the solution was a 50:50 mixture of **1** and methoxyflurane. Fractional distillation in vacuo gave 171 g of 1,2,2,2-tetrachloro-1-fluoroethyl methyl ether (**1**), bp 58–61°C/25 mmHg (lit. bp 57°C/18 mmHg [2]). Overall yield=42%, based on consumed methoxyflurane. **1**: ^{1}H NMR δ 3.84 ppm (s); ^{19}F NMR δ −69.5 ppm (br s).

4.3. 2,2,2-Trichloro-1,1-difluoroethyl methyl ether (2)

$SbCl_5$ (3.36 g, 11.2 mmol) was added dropwise to a stirred solution of 1,2,2,2-tetrachloro-1-fluoroethyl methyl ether (**1**) (80.9 g, 375 mmol) and methoxyflurane (**6**) (61.9 g, 375 mmol) at r.t. under N_2. Vigorous gas evolution and an exotherm to 40°C resulted. After 50 min, the mixture was cooled to 0°C and ice-cold H_2O (70 ml) was added dropwise. Vigorous gas evolution [CAUTION: probably HF] and an exotherm to 45°C resulted. After thorough mixing, the lower organic phase was dried over $CaCl_2$, giving 65.1 g clear liquid which by NMR contained 55.3 g (74%) of **2**. The contaminants methyl chloride and **8** were easily removed by distillation through a short Vigreux column to give pure **2**, bp 56°C/80 mmHg (lit. bp 46°C/46 mmHg [2]). **2**: ^{1}H NMR δ 3.77 ppm (s); ^{19}F NMR δ −89.5 ppm (s); ^{13}C NMR δ 52.7 (t, J=6.2 Hz), 94.0 (t, J=44 Hz) 120 (t, J=271 Hz) ppm.

4.4. Dichloroacetyl fluoride (8)

$SbCl_5$ (2.20 g, 7.36 mmol) was added dropwise to methoxyflurane (**6**) (56.7 g, 344 mmol) at r.t. under N_2. After heating at 40°C for 1 h, additional $SbCl_5$ (2.57 g, 8.59 mmol) was added and the mixture was heated for an additional 45 min to complete the reaction. The mixture was distilled under N_2 using a short Vigreux column, giving 31.4 g (70% yield) of dichloroacetyl fluoride (**8**) as a clear liquid, bp 68°C (lit. bp 70°C [10]). **8**: ^{1}H NMR δ 6.09 ppm (d, J=2.6 Hz); ^{19}F NMR δ +21.1 ppm (s).

4.5. Chlorofluoroacetyl fluoride (21)

$SbCl_5$ (5.00 g, 16.9 mmol) was added dropwise to 2-chloro-1,1,2-trifluoroethyl methyl ether (**9**) (50.0 g, 337 mmol) at r.t. under N_2 using a condenser kept at −5°C. After heating at 25–30°C for 30 min, distillation gave 28.1 g (73% yield) of chlorofluoroacetyl fluoride (**21**) as a clear liquid, bp 32–33°C (lit. bp 34–44°C [7]). **21**: ^{1}H NMR δ 6.45 ppm (d, J=49 Hz); ^{19}F NMR δ +20.0 (d, J=22 Hz, 1 F), −148 (d, J=22 Hz, 1 H) ppm.

4.6. Fluorination of trichloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (18) with dichloroacetyl fluoride (8)

$SbCl_5$ (1.01 g, 3.38 mmol) was added dropwise to a stirred solution of trichloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (**18**) (23.5 g, 82.5 mmol) and dichloroacetyl fluoride (**8**) (10.8 g, 82.5 mmol) at r.t. under N_2. After 1.5 h, the mixture was cooled to 3°C and ice-cold H_2O (20 ml) was added in portions with rapid stirring. After the exotherm had subsided, the organic layer was washed with dilute Na_2CO_3 solution (10 ml) and dried over $CaCl_2$. Isolated was 21.0 g liquid which by NMR contained 95% dichlorofluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)-ethyl ether (**19**) (yield=91% based on **8**); the remainder was **18**.

4.7. Fluorination of trichloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (18) with chlorfluoroacetyl fluoride (21)

$SbCl_5$ (1.57 g, 5.25 mmol) was added dropwise to a stirred solution of trichloromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (**18**) (15.0 g, 52.5 mmol) and chlorofluoroacetyl fluoride (**21**) (6.00 g, 52.5 mmol) at r.t. under N_2. The mixture was heated at 60°C for 1 h. Aqueous work-up as before gave 10.6 crude product. NMR analysis

showed **18**, **19**, and **20** in a 1.5:13:1 molar ratio. Yield of **19**=64% based on **21**.

Acknowledgements

Many thanks to Dr. Yuri Cheburkov for helpful discussions and to Dr. Ashok Krishnaswami for assistance with the NMR spectroscopy.

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