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Selective aliphatic fluorination by halogen exchange in mild conditions

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Abstract

HF-Base media, in particular $(HF)_{10}$-pyridine or $(HF)_3$-triethylamine, allow aliphatic chlorine–fluorine exchanges on acid-sensitive molecules. Depending on the nature (pyridine or triethylamine), stoichiometry of the base and temperature, selective mono-, di-, or tri-chlorine–fluorine exchanges on trichloromethyl groups alpha to sulfur, oxygen and carbon atoms can be obtained.

Keywords: Selective aliphatic chlorine–fluorine exchange; HF-Base; $(HF)_{10}$-pyridine; $(HF)_3$-triethylamine

1. Introduction

Fluorine–chlorine exchange is the most widely used technology to synthesize fluorinated molecules. When this exchange reaction occurs in an aliphatic molecule or at the benzylic position, anhydrous hydrogen fluoride is the most versatile industrial reagent. Using this type of reaction, trifluoromethylbenzene is manufactured from phenylchloroform on an industrial scale using liquid HF, and trifluoromethoxybenzene from trichloroanisole [1]. The limitation of this technology comes from the acidity of anhydrous HF. Its use on fragile or functionalized molecules is limited due to formation of cationic intermediates and undesired side reactions. Thus, it is of interest to find mild conditions that allow fluorine–chlorine exchanges on acid-sensitive molecules.

2. Results

2.1. Synthesis of trifluoromethylbenzylsulfide

The starting point of our study was the synthesis of trifluoromethylbenzyl sulfide **2** which is a useful intermediate, for example to obtain trifluoromethylsulfonyl chloride or other derivatives by chlorination [2]. Our approach to synthesize **2** is shown in Scheme 1 and includes a fluorine–chlorine exchange on trichloromethylbenzyl sulfide **1**.

In accordance with conditions published by Makosza and Fedorynski [3], trichloromethylbenzyl sulfide **1** is obtained from benzylthiocyanate and chloroform in basic conditions and with phase transfer catalysis with 70% yield.

First trials of fluorination of trichloromethylbenzyl sulfide **1** with anhydrous HF even at low temperature (<0 °C) gave total decomposition of the starting material and formation of tars. Analysis of these tars revealed polymers that contain biphenylmethylene groups. This shows that the carbon–sulfur bond is broken and that benzyl carbocation is formed under these acidic conditions. These first results show that anhydrous HF is a too acidic medium towards a benzylic position to allow the chlorine–fluorine exchange reaction on trichloromethylbenzyl sulfide **1**.

We thus decided to find fluorination media where chlorine–fluorine exchange reactions would be favoured with limited side reactions due to cationic pathways. HF-Base mediums appeared to be interesting for our goal. HF-Base media are well known specially $(HF)_{10}$-pyridine known as Olah's reagent [4] and $(HF)_3$-triethylamine [5].

Use of $(HF)_{10}$-pyridine and $(HF)_3$-triethylamine on trichloromethylbenzyl sulfide **1** give the results shown in Table 1.

Trichloromethylbenzyl sulfide **1** is totally fluorinated at 20 °C in 18 h in $(HF)_{10}$-pyridine (40 molar equivalents of HF)

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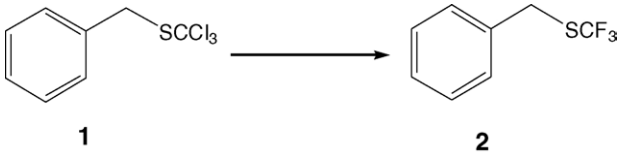
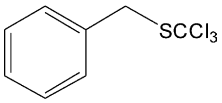
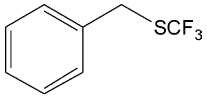
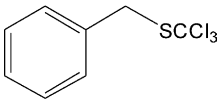
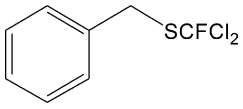
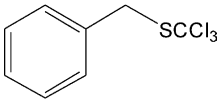
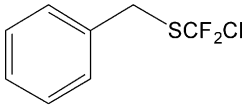


Scheme 1.

and leads to trifluoromethylbenzyl sulfide **2** with 94% selectivity (^{19}F NMR assay) and 85% isolated yield (entry 1, Table 1).

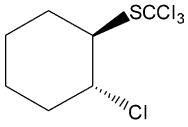
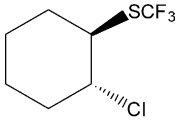
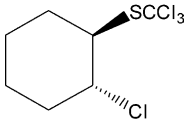
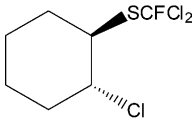
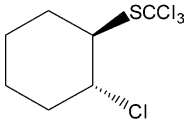
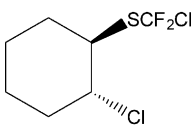
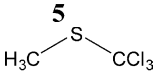
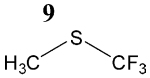
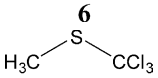
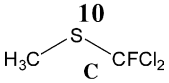
Surprisingly $(HF)_3$-triethylamine (50 molar equivalents of HF) leads to selective fluorination on trichloromethylbenzyl sulfide **1** through exchange of one or two chlorine atoms

Table 1

Entry	Substrate	Conditions	Product	Yield[a]
1	 **1**	$(HF)_{10}$-pyridine HF/substrate = 40, 20 °C, 18 h	 **2**	94% (85%)[b]
2	 **1**	$(HF)_3$-triethylamine HF/substrate = 50, 20 °C, 4 h	 **3**	90%
3	 **1**	$(HF)_3$-triethylamine HF/substrate = 55, 50 °C, 10 h	 **4**	88% (72%)[b]

[a] ^{19}F NMR assay.
[b] Isolated yield.

Table 2

Entry	Substrate	Conditions	Product	Yield (%)[a]
1	 **5**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 12 h	 **7**	83
2	 **5**	$(HF)_3$-triethylamine HF/substrate = 50, 20 °C, 5 h	 **8**	78
3	 **5**	$(HF)_3$-triethylamine HF/substrate = 50, 50 °C, 12 h	 **9**	85
4	 **6**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 16 h	 **10**	79
5	 **6**	$(HF)_3$-triethylamine HF/substrate = 50, 20 °C, 7 h	 **11**	75

[a] ^{19}F NMR assay.

depending on the temperature; at 20 °C in 4 h monofluorodichlorobenzyl sulfide **3** is obtained with 90% selectivity (entry 2, Table 2), at 50 °C in 10 h difluorochlorobenzyl sulfide **4** is obtained with 88% selectivity (entry 3, Table 2). These results are in accordance with the lower acidity of $(HF)_3$-triethylamine compared to $(HF)_{10}$-pyridine; the less acidic is the medium of fluorination the lower is the rate of chlorine–fluorine exchange.

2.2. Selective Cl–F exchange on trichloromethylsulfides

To study the scope and limitation of this selective chlorine–fluorine exchange reaction several trichloromethylsulfides have been synthesized. Sulfide **5** is obtained by reaction between cyclohexene and perchloromethylmercaptan CCl_3SCl with 78% yield [6]. Trichloromethyl-methyl sulfide **6** is obtained by chlorination of dimethylsulfide with sulfuryl chloride with 70% yield [7].

In the following trials, the stoichiometric ratio between HF in the HF-Base medium and the substrate is around 50.

On sulfides **5** and **6**, $(HF)_{10}$-pyridine gives complete chlorine–fluorine exchange at 20 °C with 83% and 79% selectivity respectively (entries 1 and 4, Table 2). With $(HF)_3$-triethylamine at 20 °C, sulfides **5** and **6** are fluorinated to corresponding monochloro-difluoromethylsulfides **8** (78% selectivity) and **11** (75% selectivity) (entries 2 and 5, Table 2). Difluorination of sulfide **5** is obtained in $(HF)_3$-triethylamine at 50 °C in 12 h and difluoro-chloromethylsulfide **9** is formed with 85% selectivity (entry 3, Table 2).

Interestingly, in the case of fluorination of trichloromethylsulfides, we have shown that $(HF)_{10}$-pyridine medium can be recycled. In effect, more than 90% of the HCl formed as the co-product of the fluorination distils during the reaction; hydrochloride salts of pyridine are not formed in our conditions. Also, it is not necessary to hydrolyse the reaction mixture to extract the trifluoromethylsulfides formed. Addition of a solvent, such as dichloromethane which is not miscible with $(HF)_{10}$-pyridine, leads to two easily separable liquid phases. The dichloromethane phase contains the trifluoromethylsulfide. The $(HF)_{10}$-pyridine phase can be recycled and used for another batch of fluorination reaction, see Table 3. After several runs, anhydrous HF can be added to the $(HF)_{10}$-pyridine phase to increase the fluorination power of this medium.

Recycling of $(HF)_3$-triethylamine is more difficult because most organic solvents are miscible with this medium.

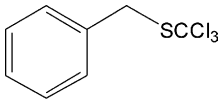
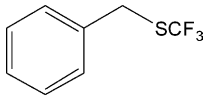
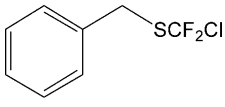
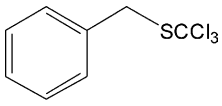
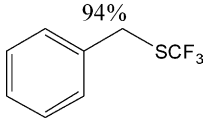
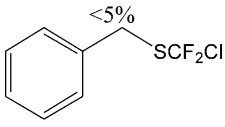
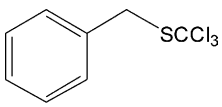
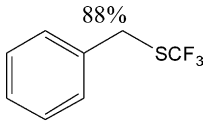
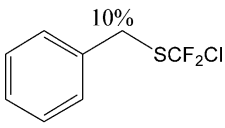
These results confirm that the HF-Base media not only give good results for complete chlorine–fluorine exchange reaction on trichloromethylsulfides but lead to selective mono- or di- or tri-chlorine–fluorine exchange using different HF-Base systems with varying acidities.

2.3. Selective Cl–F exchange on trichloromethylethers and phenylchloroform

The results on trichloromethylsulfides prompted us to study the use of HF-Base media on other substrates, specifically on trichloromethylethers and phenylchloroform. Table 4 summarises these results.

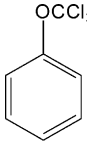
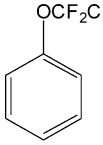
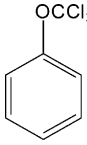
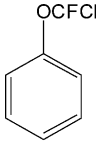
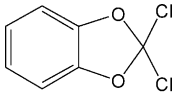
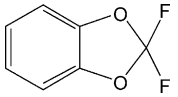
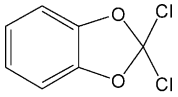
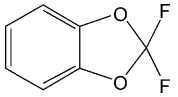
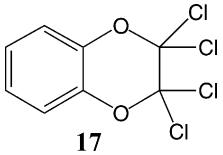
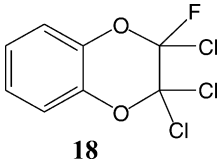
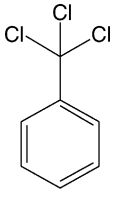
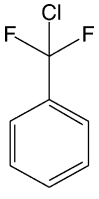
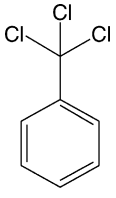
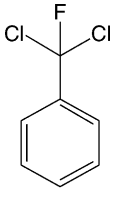
Trichloromethoxybenzene **12** in $(HF)_{10}$-pyridine (40 molar equivalents) at room temperature (entry 1, Table 4) leads to the chloro-difluoromethoxybenzene **13** with 97% selectivity (GC and NMR assays). Monofluorination of **12** is observed using $(HF)_3$-triethylamine at 50 °C with 93% selectivity (entry 2, Table 4). To obtain complete fluorination of trichloromethoxybenzene **12**, it is necessary to warm the medium to 80–100 °C and to use anhydrous HF [8]. At this temperature the $(HF)_{10}$-pyridine medium looses HF and its acidity and fluorination powers decrease, so trifluoroanisole

Table 3

Run no.	Substrate	Conditions	Products	Yield[a]
1	 **1**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 18 h	 **2**	 **4**
2	 **1**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 18 h	 94% **2**	 <5% **4**
3	 **1**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 18 h	 88% **2** 79%	 10% **4** 20%

[a] ^{19}F NMR assay.

Table 4

Entry	Substrate	Conditions	Product	Yield (%)[a]
1	 **12**	$(HF)_{10}$-pyridine HF/substrate = 40, 20 °C, 6 h	 **13**	97
2	 **12**	$(HF)_3$-triethylamine HF/substrate = 40, 50 °C, 25 h	 **14**	93
3	 **15**	$(HF)_{10}$-pyridine HF/substrate = 40, 20 °C, 2 h	 **16**	91
4	 **15**	$(HF)_3$-triethylamine HF/substrate = 40, 20 °C, 5 h	 **16**	85
5	 **17**	$(HF)_{10}$-pyridine HF/substrate = 50, 20 °C, 15 h	 **18**	15
6	 **19**	$(HF)_{10}$-pyridine HF/substrate = 40, 25 °C, 2 h	 **20**	92
7	 **19**	$(HF)_3$-triethylamine HF/substrate = 40, 75 °C, 5 h	 **21**	86

[a] ^{19}F NMR assay.

cannot be obtained using $(HF)_{10}$-pyridine or other HF-Base media.

On dichloromethylenedioxobenzene **15**, chlorine–fluorine exchange is easier and $(HF)_{10}$-pyridine (entry 3, Table 4) or $(HF)_3$-triethylamine (entry 4, Table 4) give complete fluorination to difluoromethylenedioxobenzene **16**. On tetrachlorobenzodioxane **17**, obtained from 1,2-dihydroxybenzene and tetrachloroethylene carbonate in presence of PCl_5 [9], $(HF)_{10}$-pyridine leads only to monofluorination of one CCl_2 group with low yield (entry 5, Table 4).

Here again we confirm a relationship between the acidity and fluorination power of HF-Base media and the stabilisation by heteroatoms, oxygen in our case, of the carbocationic species which can explain the level (mono, di or tri exchanges) of fluorination.

On dichloromethylenedioxobenzene **15**, the two oxygen atoms stabilise the positive intermediate charge on the carbon that bears the two chlorine atoms and so complete chlorine–fluorine exchange is obtained even with $(HF)_3$-triethylamine. On the other hand, in the cases of trichloromethoxybenzene **12** and

tetrachlorobenzodioxane **17**, the stabilisation of cationic species is not enough efficient (only one oxygen atom) and fluorination is limited to one or two chlorine–fluorine exchange reactions.

Similar results are obtained on phenylchloroform **19**; in $(HF)_{10}$-pyridine at room temperature difluorochloromethylbenzene **20** is obtained with 92% yield (entry 6, Table 4). With $(HF)_3$-triethylamine at 75 °C the major product is monofluorochloro-methylbenzene **21** (entry 7, Table 4). Trifluoromethylbenzene can be synthesized from phenylchloroform with anhydrous HF at 80 °C, showing that the introduction of the third fluorine atom needs an acidic medium and high temperature [1].

These results have been patented by Rhodia [10].

3. Experimental

NMR spectra were recorded as $CDCl_3$ solutions on a Bruker AMX-300 spectrometer. Reported coupling constants and chemicals shifts were based on a first order analysis. Internal reference was the residual peak of $CHCl_3$ (7.27 ppm) for ^1H (200 MHz), central peak of $CDCl_3$ (77 ppm) for ^{13}C (75 MHz) spectra and internal CCl_3F (0 ppm) for ^{19}F (282 MHz) NMR spectra. GCMS analyses were performed with JW Scientific Agilent DB-5 chromatography column, length 30 m, diameter 0.53 mm, film thickness 5 μm, initial temperature 50 °C, gradient 10 °C/min, final temperature 230 °C on a quadrupolar mass spectrometer. Chemical yields and selectivity of fluorination were determined by ^{19}F NMR assays with internal standard ($PhOCF_3$ or PhF or $PhCF_3$). Purity of isolated products was determined by GC and ^{19}F, ^1H NMR analysis.

$(HF)_{10}$-pyridine was synthesized by slow addition of anhydrous HF (72 g, 3.6 mol) to pyridine (29 g, 0.36 mol) cooled to −10 °C. $(HF)_{10}$-pyridine was used without any treatment.

$(HF)_3$-triethylamine was purchased from Aldrich.

3.1. General procedure

The substrate was slowly added to $(HF)_{10}$-pyridine or $(HF)_3$-triethylamine in polypropylene vessel cooled at 0 °C, with generally a stoichiometric amount of HF/substrate between 40 and 50. The reaction mixture was stirred and warmed to the temperature desired, allowing gaseous HCl to distil. The level of fluorination of the starting material was monitored by GC analysis. After cooling to 0 °C, hydrolysis with ice (100 g) and extraction with dichloromethane (2 × 150 ml), the organic layers were combined, washed with water, dried over sodium sulfate, concentrated in vacuo and possibly purified by distillation.

3.1.1. Benzyl trifluoromethylsulfide 2 [2]

Benzyltrichloromethylsulfide **1** [2] (30 g, 0.124 mol) was slowly added to $(HF)_{10}$-pyridine (140 g, HF: 5 mol; pyridine: 0.5 mol) at 0 °C. The mixture was stirred at 20 °C for 18 h. After work-up, crude benzyl trifluoromethylsulfide **2** (22.4 g, yield 94%; ^{19}F NMR assay) was obtained. The product was purified by distillation (yellow oil; 85%).

Boiling point: 77 °C/30 mmHg (54–56 °C/11 mmHg [2]).

NMR: ^{19}F NMR (300 MHz): −42.1 (CF_3, s). ^1H NMR (200 MHz): 4.12 (2H, s, benzylic CH_2), 7.35 (5H, m, H aromatic). GCMS: $m/z = 192$ (45%, $M^{\bullet+}$), 123 (65%, $M^+ - CF_3$), 91 (100%, $PhCH_2$).

3.1.2. Benzyl chloro-difluoromethyl sulfide 4 [11]

Benzyltrichloromethylsulfide **1** [2] (20 g, 0.08 mol) was slowly added at 0 °C to $(HF)_3$-triethylamine (200 g, HF: 4.58 mol; triethylamine: 1.53 mol). The mixture was stirred at 50 °C for 10 h. After work-up, crude benzyl chloro-difluoromethyl sulfide **4** was obtained (15.8 g, yield 88%; ^{19}F NMR assay; benzyl dichloro-fluoromethyl sulfide **3**: 5%).

The product was purified by distillation (yellow oil; 72%).

Boiling point: 112 °C/30 mmHg (87.5 °C/13 mmHg [11]).

NMR: ^{19}F NMR (300 MHz): −27.2 ($CClF_2$, s). ^1H NMR (200 MHz): 4.1 (2H, s, benzylic CH_2), 7.4 (5H, m, H aromatic). GCMS: $m/z = 208$–210 (28%, $M^{\bullet+}$), 173 (75%, $M^+ - Cl$), 91 (100%, $PhCH_2$).

3.1.3. 1-Chloro-2-trifluoromethylsulfenyl-cyclohexane 7 [12]

1-Chloro-2-trichloromethylsulfenyl-cyclohexane **5** [4] (10 g, 0.037 mol) was slowly added at 0 °C to $(HF)_{10}$-pyridine (52 g, HF: 1.86 mol; pyridine: 0.19 mol). The mixture was stirred at 20 °C for 12 h. After work-up, crude 1-chloro-2-trifluoromethylsulfenyl-cyclohexane **7** was obtained (8.1 g, yield 83%; ^{19}F NRM assay).

NMR: ^{19}F NMR (300 MHz): −43.5 (CF_3, s). ^1H NMR (200 MHz): 1.47, 1.73, 2.16, 2.31 (8H, m, CH_2), 3.39 (1H, m, C*H*–S), 4.06 (1H, m, C*H*–Cl), J ^1H–^1H (C*H*–S, C*H*–Cl) = 4Hz.

GCMS: $m/z = 218$–220 (65%, $M^{\bullet+}$), 149–151 (100%, $M^+ - CF_3$), 114 (36%, M^+–CF_3–Cl).

4. Conclusion

HF-amine reagents are efficient media to accomplish chlorine–fluorine exchange on fragile molecules without side reactions involving carbocation intermediates. Depending on the nature of the amine (pyridine or triethylamine), the stoichiometry of the HF-Base system and the temperature, selective mono-, di- or tri-halogen exchanges are obtained with good yields on trichloromethyl groups alpha to sulfur, oxygen and carbon atoms. On trichloromethylsulfides (**1**, **5**, **6**), $(HF)_{10}$-pyridine leads to complete fluorination and $(HF)_3$-triethylamine leads to mono- or di-chlorine–fluorine exchange depending on the temperature. On trichloromethoxybenzene **12** and phenylchloroform **19**, $(HF)_{10}$-pyridine leads to difluorination and $(HF)_3$-triethylamine affords monofluorinated derivatives with good selectivity.

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References

[1] B. Langlois, Using these process Rhodia is producer of trifluoromethylbenzene and trifluoroanisole, in: R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry, Principles and Commercial Applications, Plenum Press, 1994, pp. 221–235.
[2] C. Francese, M. Tordeux, C. Wakselman, J. Fluorine Chem. 43 (1979) 27–34.
[3] M. Makosza, M. Fedorynski, Synthesis (1974) 274–276.
[4] G.A. Olah, J.T. Welch, Y.D. Vankar, M. Nojima, I. Kerekes, J.A. Olah, J. Org. Chem. 44 (22) (1979) 3872–3881;
N. Yoneda, Tetrahedron 47 (1991) 5329–5365.
[5] M.A. McClinton, Acta Chim. Acta 28 (1995) 31–35;
G. Haufe, J. Prakt. Chem. 338 (2) (1996) 99–113.
[6] E. Kühle, Synthesis (1971) 563–586.
[7] W.E. Truce, G.H. Birum, T. Mc Bee, J. Am. Chem. Soc. 74 (1952) 3594–3599.
[8] Rhodia industrial process data.
[9] A. Marhold, Ger. Offen. (1985). DE 3412079 (to Bayer) (Chem. Abs. 104 (1986) 109657).
[10] L. Saint-Jalmes, PCT Int. Appl. WO 9743231 (1997) (to Rhodia, Rhône-Poulenc Chimie SA, Fr) (Chem. Abs. 128 (1997) 34573);
L. Saint-Jalmes, R. Janin, Eur. Pat. Appl. EP 729930 (1996) (to Rhodia, Rhône-Poulenc Chimie SA, Fr) (Chem. Abs. 125 (1996) 246885).
[11] J.F. Harris Jr., J. Org. Chem. 44 (4) (1979) 563–569.
[12] A. Haas, M. Lieb, Y. Zhang, J. Fluorine Chem. 30 (1985) 203–210.