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Elemental fluorine. Part 24.[1]: Fluorination of ethers by fluorine and Selectfluor

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ABSTRACT

Reactions of dialkyl ethers with either fluorine or Selectfluor™ led to the formation of unusual difluorinated polyether products in modest yields. A mechanism involving initial fluorination of the site adjacent to ether oxygen followed by elimination of hydrogen fluoride, reaction of the generated enol system with a further equivalent of fluorinating agent giving an oxonium system which reacts with water during aqueous work-up to lead eventually to the products observed, is suggested.

1. Introduction

It is estimated that approximately 25% of currently available pharmaceutical and 40% of agrochemical products currently under development possess fluorine atoms in their structure [2,3] and, since fluorine containing systems are largely absent in nature [4], effective methodology for the regio- and stereo-selective synthesis of carbon–fluorine bonds continues to be in demand to meet the needs of both academia and industry. Whilst selective fluorination of organic systems can be accomplished by reactions of nucleophilic fluorinating agents, such as HF, KF and $Et_3N{\cdot}3HF$, with appropriately functionalised systems [5,6], perhaps the most direct method of fluorination of an organic substrate is the transformation of carbon–hydrogen to carbon–fluorine bonds and, in these cases, the use of electrophilic fluorination agents such as elemental fluorine and Selectfluor™ is required [7–10].

In a series of papers [1], we have been developing the use of elemental fluorine as a viable reagent for organic synthesis and have described direct selective fluorination of, for example, various dicarbonyl [11,12], aromatic [13,14], heterocyclic [15–17] and steroid [1] systems. In many of the processes we have reported, the use of acidic or high dielectric constant reaction media were found to be important for controlling the selectivity of the direct fluorination reactions in which fluorine can be considered to be electrophilic in nature [18]. Fluorinations of hydrocarbons, for example, are regioselective at the most nucelophilic, tertiary carbon–hydrogen bonds and are considered to proceed by electrophilic aliphatic substitution reactions involving 3-centre-2-electron bond intermediates [9] consistent with earlier observations by Rozen and Gal [19,20]. In initial research aiming to explore the effects of functional groups on fluorination reactions [10], fluorination of, for example, ester **1** gave mixtures of products **2a–d** where the major products arise from fluorination of the most nucleophilic carbon–hydrogen bonds located at the methylene sites furthest removed from the electron withdrawing functional group, consistent with the proposed electrophilic process (Scheme 1). Furthermore, we have shown [10] that Selectfluor™, an electrophilic fluorinating agent of the N–F class, also gives fluorinated systems **2a–d** arising from electrophilic aliphatic substitution when heated in acetonitrile with ester derivative **1** following a similar electrophilic aliphatic substitution process to that of fluorine discussed above (Scheme 1).

In this paper, we report fluorination reactions of dialkyl ethers **3** using both fluorine and Selectfluor™ to assess the effect of fluorination processes involving systems containing ether linkages and extend our studies that are investigating the outcome of reactions of electrophilic fluorinating agents with functional aliphatic systems as models for more structurally sophisticated systems.

2. Results and discussion

Fluorination of a short range of model dialkyl ether derivatives **3** was carried out using both elemental fluorine and Selectfluor™ and these results are collated in Table 1.

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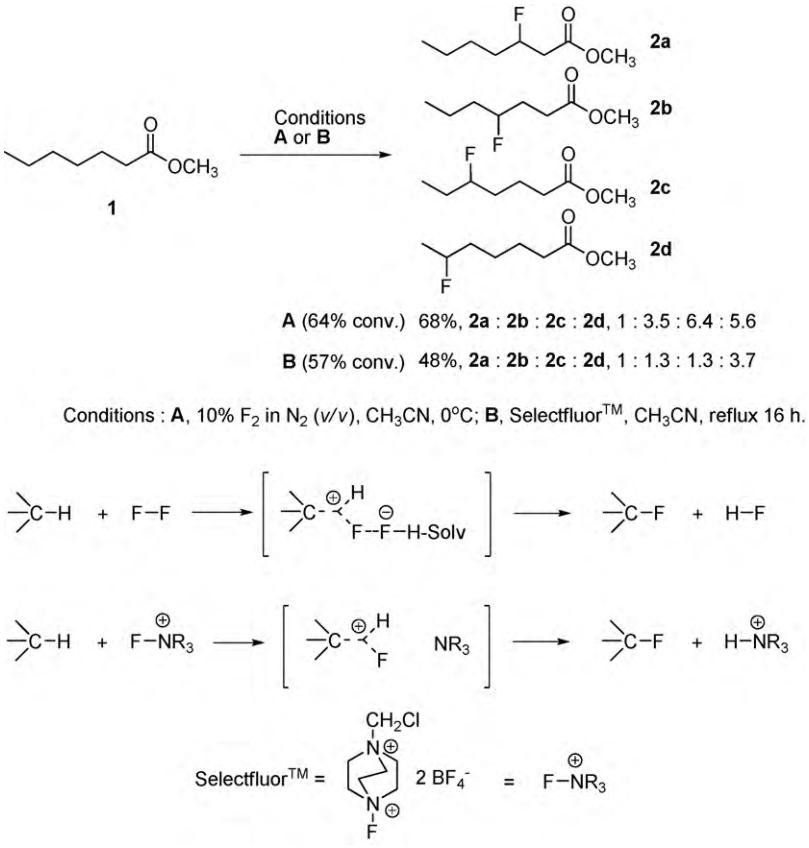


Scheme 1. Direct fluorination of aliphatic systems.

Direct fluorination was achieved by passing a stream of fluorine gas, diluted in nitrogen (10%, v/v), through a rapidly stirred solution of the appropriate dialkyl ether **3** in dry acetonitrile, cooled to 0 °C. In all cases, the reaction mixtures become very dark upon addition of fluorine but, after aqueous work-up, extraction and column chromatography, we were able to isolate modest quantities of the major difluorinated products **4** as mixtures of diastereoisomers from the tarry product residues.

The identities of the unexpected difluorinated products **4** were determined by a combination of elemental analysis, mass spectrometry and, in particular, NMR data. In the ^{19}F NMR spectra [21], the fluorine resonances for the major diastereoisomers of **4** occur at approximately −196 ppm, consistent with the C–CFH–C structural unit proposed. ^{13}C NMR was particularly useful in identifying the products [22], for example, the major diastereoisomer of the dibutyl ether system **4a** shows eight resonances between 5 and 110 ppm and appropriate multi-bond carbon–fluorine coupling as shown in Fig. 1.

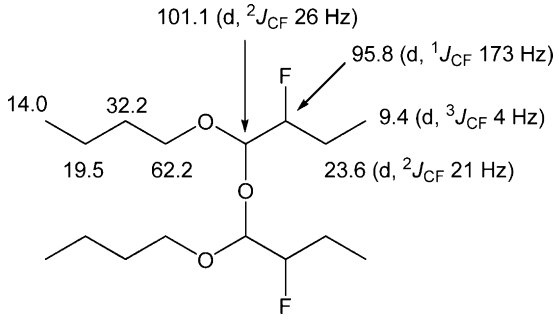
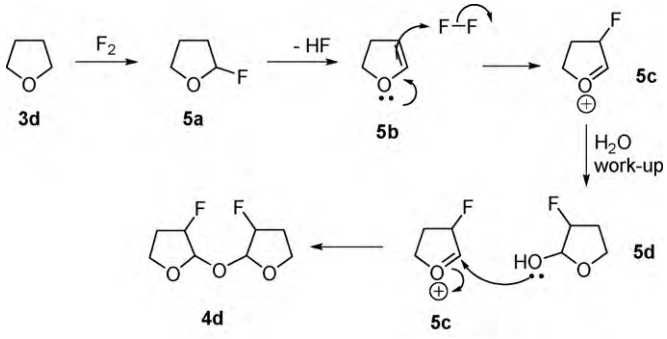


Fig. 1. ^{13}C NMR data for polyfluoroether **4a**.

In the ^{13}C NMR spectrum of **4a**, the four resonances of the fluorobutyl group are all doublets each with the appropriate J_{CF} coupling constants. The resonance at 95.8 ppm attributed to the CHF moiety has a coupling constant of 173 Hz which is consistent with one bond J_{CF} coupling. The O–C–O carbon atom appears at a distinctive chemical shift of 101.1 ppm and possesses appropriate two-bond J_{CF} coupling of 26 Hz. The four resonances of the non-fluorinated butyl groups are all singlets and consistent with an aliphatic butyl chain.

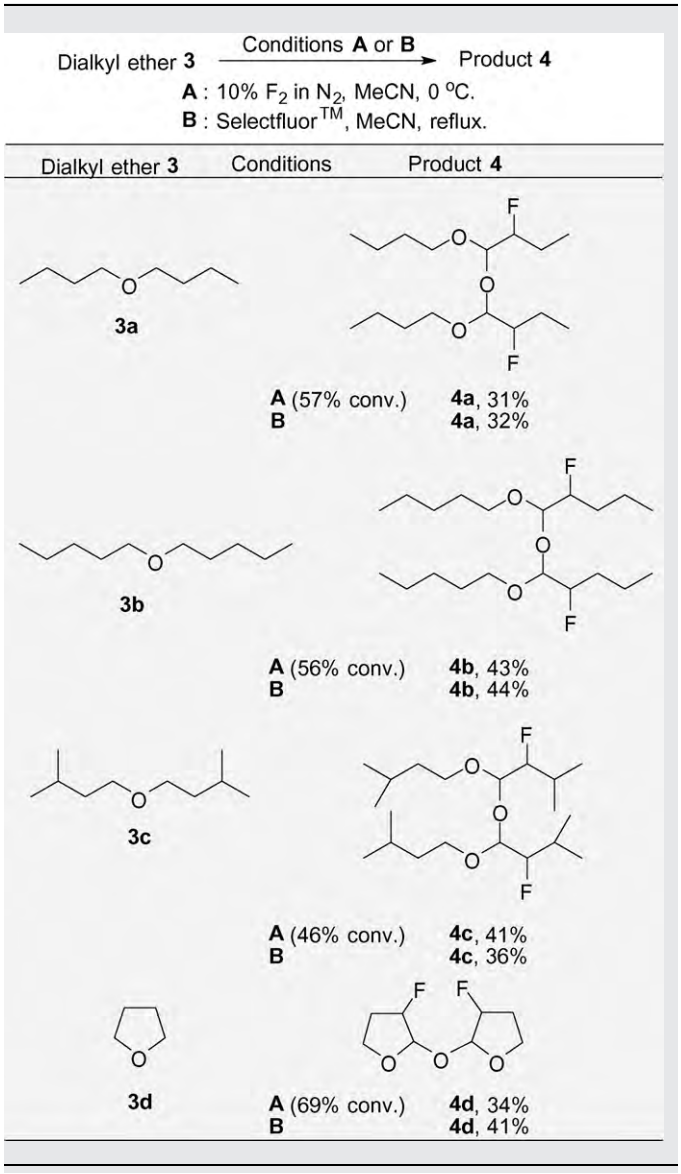
Reactions of the dialkyl ether systems **3** with Selectfluor™ proceed upon heating at reflux temperature in acetonitrile and, after aqueous work-up, the major products **4** were obtained as mixtures of diastereoisomers by column chromatography from the tarry product residue (Table 1).

Our proposed mechanism for the formation of these unusual fluorinated polyethers is indicated in Scheme 2 using fluorination of tetrahydrofuran **3d** as an example. We envisage that the first



Scheme 2. Mechanism of fluorination of ethers in acetonitrile.

Table 1
Reactions of dialkyl ethers **3** with fluorine and Selectfluor™.



step of the process is fluorination of the site adjacent to ether oxygen giving **5a** because the developing positive charge in the transition state would be stabilised by the attached oxygen atom, consistent with the electrophilic aliphatic substitution mechanism discussed above (Scheme 1). In the acidic reaction medium, elimination of hydrogen fluoride from **5a** provides the enol system **5b** which would react with a further equivalent of fluorinating agent to give the oxonium derivative **5c**. Subsequent hydrolysis of **5c** by reaction with expeditious moisture on the glass surface of the reaction vessel or in the work-up stage leads to **5d** which reacts with a further equivalent of **5a** to give the polyfluoropolyether **4d** observed. In support of this mechanism, ^{19}F NMR analysis of the reaction mixture shows the presence of a multiplet at −124.2 (dt, $^{2}J_{HF}$ 67.3, $^{3}J_{HF}$ 15.4) corresponding to the formation of the α-fluoroether derivative **5a** which is not present in the ^{19}F NMR spectrum of the product mixture after aqueous work-up.

3. Conclusions

Reactions of dialkyl ethers **3** with either fluorine or Selectfluor™ in acetonitrile led to the formation of unusual difluorinated polyether products **4** in modest yields. Although the reactions produce very significant amounts of tar and are not suggested to be synthetically useful, these results suggest that reactions of fluorine or Selectfluor™ with structurally elaborate polyfunctional systems bearing aliphatic ether linkages are unlikely to be selective.

4. Experimental

4.1. General

All starting materials were obtained commercially and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on a VG 7070E spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. The progress of reactions was monitored by ^{19}F NMR and column chromatography was carried out on silica gel.

4.2. Direct fluorination reactions

4.2.1. General procedure

Elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed at a rate of ca. 50 mL min^{-1} through a stirred, cooled (0 °C) mixture which consisted of the substrate and acetonitrile. After addition of the fluorine, the reaction mixture was poured into water (100 mL), neutralised ($NaHCO_3$) and extracted with dichloromethane (3 × 40 mL). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product. The amount of fluorinated product in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture. Comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield of fluorinated derivative, based upon the conversion obtained by GCMS analysis. Analytical samples of fluorinated products were obtained by column chromatography on silica gel. Yields of fluorinated products are based on the conversion of starting material and only spectroscopic data for the major diastereoisomer obtained are given below for clarity.

4.2.2. Fluorination of n-dibutyl ether 3a

Elemental fluorine (46.8 mmol), *n*-dibutyl ether **3a** (3.0 g, 23.4 mmol) and acetonitrile (30 mL) gave a dark brown crude product (57% conv.). Purification by column chromatography using hexane/dichloromethane (20:1) as eluent gave 2-fluoro-1-(2-fluoro-l-butoxybutoxy)-dibutyl ether **4a** (0.67 g, 31%) as a colourless liquid; bp 86 °C (l0 mm Hg) (Found: C, 62.1; H, 10.0. $C_{16}H_{32}F_2O_3$ requires: C, 61.9; H, 10.3%); υ_{max} (film)/cm^{-1} 2961, 1079; δ_H 0.8 (3H, t, $^{3}J_{HH}$ 7.9, CH_3), 0.9 (3H, t, $^{3}J_{HH}$ 7.6, CH_3), 1.40–1.55 (2H, m, CH_2CH_3), 1.55–1.65 (2H, m, OCH_2CH_2), 3.30–3.45 (2H, m, $CHCHFCH_2$), 3.55–3.60 (1H, m, CHF), 4.14–4.28 (1H, m, CH–CHF), 4.36–4.44 (2H, m, OCH_2); δ_C 9.4 (d, $^{3}J_{CF}$ 4.4, CH_3), 14.0 (s, CH_3), 19.5 (s, CH_2CH_3), 23.6 (d, $^{2}J_{CF}$ 21, $CHFCH_2$), 32.2 (s, OCH_2CH_2), 66.2 (s, OCH_2), 95.8 (d, $^{1}J_{CF}$ 173, CHF), 101.1 (d, $^{2}J_{CF}$ 26, CHCHF); δ_F −196.4 to −196.7 (m); *m/z* (CI^+) 310 ($[M]^+$, 90%), 238 (92), 90 (100).

4.2.3. Fluorination of n-dipentyl ether 3b

Elemental fluorine (38 mmol), *n*-dipentyl ether **3b** (2.0 g, l2.6 mmol) and acetonitrile (30 mL) gave a dark brown crude product (56% conv.). Purification by column chromatography using hexane/dichloromethane as eluent gave 2-fluoro-l-(2-fluoro-l-pentyloxypentyloxy)-dipentyl ether **4b** (0.55 g, 43%) as a colourless liquid; bp 82–84 °C (5 mm Hg) (Found: C, 65.8; H, 10.8.

$C_{20}H_{40}F_2O_3$ requires: C, 65.6; H, 10.9%); υ_{max} (film)/cm^{-1} 2912, 1061; δ_H 0.71–0.92 (6H, m, CH_3), 1.10–1.50 (10H, m, CH_2), 3.37–3.42 (1H, m, CHF), 3.63 (2H, t, $^3J_{HH}$ 7.9, OCH_2), 4.54 (1H, dd, $^3J_{HF}$ 21.7, $^3J_{HH}$ 17.7, O*C*HCHF); δ_C 6.7 (s, CH_3), 14.0 (s, CH_3), 18.4 (d, $^3J_{CF}$ 3.7, CH_2), 22.7 (s, CH_2), 28.6 (s, CH_2), 29.2 (s, CH_2), 32.1 (d, $^2J_{CF}$ 18, CHF*C*H_2), 68.9 (s, OCH_2), 95.1 (d, $^1J_{CF}$ 173, CHF), 102.9 (d, $^2J_{CF}$ 26, *C*HCHF); δ_F −186.2 to −186.6 (m); *m*/*z* (Cl^+) 366 ($[M]^+$, 31%), 280 (100), 104 (96).

4.2.4. Fluorination of n-isoamyl ether 3c

Elemental fluorine (47.4 mmol), *n*-isoamyl ether **3c** (2.5 g, l5.7 mmol) and acetonitrile (30 mL) gave a dark brown crude product (46% conv.). Purification by column chromatography with hexane/dichloromethane as eluent gave 2-fluoro-l-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether **4c** (0.54 g, 41%) as a colourless liquid; bp 83 °C (9 mm Hg) (Found: $[M]^+$, 366.2948. $C_{20}H_{40}F_2O_3$ requires: $[M]^+$, 366.2946); υ_{max} (film)/cm^{-1} 2954, 1087; δ_H 0.85 (6H, d, $^3J_{HH}$ 7.9, CH_3), 0.93 (6H, d, $^3J_{HH}$ 7.6, CH_3), 1.37–1.44 (2H, m, CH_2), 1.60–1.63 (1H, m, CH_2), 1.93–1.97 (1H, m, CHFCH), 3.63 (2H, td, $^3J_{HH}$ 9.4, $^4J_{HH}$ 6.8, OCH_2), 4.21 (1H, ddd, $^2J_{HF}$ 47.2, $^3J_{HF}$ 6.2, $^3J_{HF}$ 3.6, CHF), 4.43 (1H, dd, $^3J_{HF}$ 7.9, $^3J_{HH}$ 6.3, OCH); δ_C 9.4 (d, $^3J_{CF}$ 4.4, CH_3), 14.0 (s, CH_3), 19.5 (s, CH_2), 23.6 (d, $^2J_{CF}$ 20.5, CHF*C*H), 32.2 (s, CH), 66.2 (s, OCH_2), 96.8 (d, $^1J_{CF}$ 170, CHF), 101.7 (d, $^2J_{CF}$ 26.5, OCH); δ_F −206.5(m); *m*/*z* (Cl^+) 366 ($[M]^+$, 90%), 280 (92), 104 (100).

4.2.5. Fluorination of tetrahydrofuran 3d

Elemental fluorine (177 mmol), tetrahydrofuran **3d** (4.25 g, 5 mmol) and acetonitrile (30 mL) gave a dark brown crude product (69% conv.). Purification by column chromatography with hexane/dichloromethane as eluent gave 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran **4d** (0.11 g, 34%) as a colourless liquid; (Found: C, 48.7; H, 6.1. $C_8H_{12}F_2O_3$ requires: C, 48.7; H, 6.2%); υ_{max} (film)/cm^{-1} 2961, 1099; δ_H 2.00–2.15 (2H, m, CH_2), 4.02–4.18 (1H, m, CHF), 5.13 (2H, t, $^3J_{HH}$ 5.7 OCH_2), 5.25–5.35 (1H, m, OCH); δ_C 30.4 (d, $^2J_{CF}$ 20.8, CH_2), 66.9 (s, OCH_2), 97.3 (d, $^1J_{CF}$ 178, CHF), 101.5 (d, $^2J_{CF}$ 33.3, OCH); δ_F −185.2 to −185.7 (m); *m*/*z* (Cl^+) 194 ($[M]^+$, 6%), 106 (79), 89 (33).

4.3. Fluorination reactions with Selectfluor™

4.3.1. General procedure

A solution consisting of dialkyl ether **3**, Selectfluor™ and acetonitrile was stirred and heated to reflux. After 24 h, the reaction mixture was poured into water, neutralised ($NaHCO_3$) and extracted with DCM (3 × 50 mL). The combined, dried ($MgSO_4$) organic extracts were evaporated to give a crude product which was purified by column chromatography.

4.3.2. Fluorination of n-dibutyl ether 3a

n-Dibutyl ether **3a** (3.31 g, 25.8 mmol), Selectfluor™ (20.0 g, 56 mmol) and acetonitrile (150 mL) and purification by column chromatography gave 2-fluoro-l-(2-fluoro-1-butoxy-butoxy)-dibutyl ether **4a** (1.23 g, 32%) as a colourless liquid; spectral data as above.

4.3.3. Fluorination of n-dipentyl ether 3b

n-Dipentyl ether **3b** (2.40 g, 15 mmol), Selectfluor™ (14.8 g, 34 mmol) and acetonitrile (50 mL) and purification by column chromatography gave 2-fluoro-1-(2-fluoro-l-pentyloxy-pentyloxy)-dipentyl ether **4b** (1.21 g, 44%) as a colourless liquid; spectral data as above.

4.3.4. Fluorination of isoamyl ether 3c

Isoamyl ether **3c** (1.20 g, 7 mmol), Selectfluor™ (7.6 g, 16 mmol) and acetonitrile (50 mL) and purification by column chromatography gave 2-fluoro-l-[2-fluoro-3-methyl-1-(3-methyl-butoxy)-butoxy]-isoamyl ether **4c** (0.46 g, 36%) as a colourless liquid; spectral data as above

4.3.5. Fluorination of tetrahydrofuran 3d

Tetrahydrofuran **3d** (1.29 g, 18 mmol), Selectfluor™ (14.0 g, 40 mmol) and acetonitrile (50 mL) and purification by column chromatography gave 3-fluoro-2-(3-fluoro-tetrahydrofuran-2-uloxy)-tetrahydrofuran **4d** (0.71 g, 41%) as a colourless liquid; spectral data as above.

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