Elemental fluorine. Part 1.† Synthesis of fluoroaromatic compounds

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Direct fluorination of 4-fluorobenzoic acid, as a model substrate in a variety of reaction media, shows that 98% formic acid and concentrated sulfuric acid are excellent for promoting electrophilic fluorination. A high degree of fluorination may be achieved using concentrated sulfuric acid, showing that in this medium fluorine will act as a powerful electrophile.

Introduction

This series will be concerned with the application of elemental fluorine to the formation of carbon–fluorine bonds, selectively and exhaustively and the equally important application of fluorine as a general reagent for the organic chemist. Various of these aspects will be described in due course and, in doing so, we hope that the current perception that fluorine is essentially 'untameable' will be modified to the extent that elemental fluorine becomes regarded as a viable reagent for the organic chemist. Other workers have made major contributions to this area, notably Rozen[1] and Lagow[2] and their respective co-workers. An excellent review by Purrington, Kagan and Patrick covers much of the early literature.[3]

This paper is concerned with the use of elemental fluorine for the synthesis of some fluoroaromatic compounds, but first we must address the general question of mechanism of fluorination. The bond dissociation energy of fluorine is very low, 159 kJ mol^{-1},[4] but fluorine is not appreciably dissociated at room temperature ($F_2 \longrightarrow 2F^{\bullet}$, $K \approx 10^{-20}$).[5] The low activation energy for the hydrogen abstraction reaction could mean that even this low degree of dissociation would be sufficient to start a radical chain process. However, the suggestion by Miller and co-workers that molecular fluorine may react with hydrocarbons directly (Scheme 1) is much more likely.[6] Such a

$$R\text{–}H + F_2 \longrightarrow R^{\bullet} + F^{\bullet} + HF$$

Scheme 1

molecule-induced homolysis has ample precedent[7] *e.g.* molecular iodine and styrene interact at 25 °C, to produce radicals at a rate 10^6 greater than can be explained either by homolysis of iodine or thermal initiation by the styrene. Thus, there exists the potential problem of a competing free-radical process in any system attempting the use of elemental fluorine as an *electrophile*.

It may be argued that the problem of electrophilic fluorination has been solved through the synthesis of a number of stable electrophilic fluorinating agents containing N–F bonds.[8] These are extremely interesting reagents and important for laboratory scale use but they are all made using elemental fluorine; the direct use of fluorine as an electrophile would clearly be beneficial, especially on a large scale.

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Table 1 The fluorination of 4-fluorobenzoic acid in a range of solvents

Solvent	Conversion to 3,4-difluorobenzoic acid (%)
98% Sulfuric acid	84
98% Formic acid	65
Trifluoroacetic acid	56
Acetonitrile	53
Acetic acid	25
2,2,2-Trifluoroethanol	10
1,1,2-Trichloro-1,2,2-trifluoroethane	0

Therefore we have considered approaches to promoting an electrophilic process at the expense of fluorine atom reactions. In principle, this could be achieved by interaction of fluorine with strong acids (protonic or Lewis) (Scheme 2) and/or by the

$$F\text{–}F \longrightarrow {}^{\delta+}F \cdots F \cdots X \; (X = \text{solvent})$$

$$F\text{–}F \longrightarrow {}^{\delta+}F \cdots F \cdots H \cdots Y \; (HY = \text{acid})$$

Scheme 2

use of high relative permittivity media. Other workers have used anhydrous and aqueous hydrogen fluoride and trifluoroacetic acid,[9] while water (high relative permittivity) has also been explored as a potential medium for fluorination.[10] Nevertheless, we are not aware of any systematic investigation of acid and medium effects on fluorination processes of the type we describe here. We elected to explore the fluorination of 4-fluorobenzoic acid as a useful model substrate, partly because there is much interest in routes to 2,4,5-trifluorobenzoic acid, an intermediate in the synthesis of fluoroquinolone antibacterials.[11]

Results

Role of solvent

Earlier work in this laboratory indicated that direct fluorination of deactivated aromatic systems in acetonitrile is possible, but fluorination was accompanied by the formation of significant quantities of tar even at low temperatures.[12] However, our subsequent use of trifluoroacetic acid as a solvent allowed similar reactions to be conducted at room temperature, and this result encouraged us to survey a variety of solvent systems for the fluorination of 4-fluorobenzoic acid to 3,4-

Table 2 The pK_a values and relative permittivities for a range of solvents

Solvent	pK_a	ε_r(20 °C)
Sulfuric Acid	−3.6	100
Formic Acid	3.8	58.5
Trifluoroacetic Acid	3.1[a]	
Acetonitrile	25[b]	35.9
Acetic acid	4.8	6.2
2,2,2-Trifluoroethanol	12.4[b]	
1,1,2-Trichloro-1,2,2-trifluoroethane	—	2.4

[a] See ref. 13. [b] See ref. 14.

Table 3 The fluorination of 4-fluorobenzoic acid in a range of formic acid–water mixtures

Formic acid in water (%)	Conversion to 3,4-difluorobenzoic acid (%)
100	90
98	86
80	78
60	72
40	38

difluorobenzoic acid. The results of this study, shown in Table 1, do indeed demonstrate the dramatic effect that solvent can have on the fluorination process.

The range of reactivity suggests that acidity (pK_a) and/or relative permittivity (ε_r) play an important role in the fluorination process, because formic acid and sulfuric acid both have high acidity and relative permittivities (Table 2). However, we were extremely surprised to discover that neither of these acids had been investigated as a medium for fluorination. Perhaps investigation of sulfuric acid as a solvent had been inhibited by thoughts of fluorination of the solvent, and possibly leading to explosive products.[15] However, in our investigations we have not experienced any evidence of fluorination of sulfuric acid, nor any explosive incidents, even in prolonged contact with fluorine.

Relative permittivity *vs.* acidity

Because formic acid and sulfuric acid each have both high relative permittivities and high acidities, we attempted to determine which of these factors is the more important to the fluorination process. We compared the proportion of 4-fluorobenzoic acid converted to 3,4-difluorobenzoic acid in a range of formic acid–water mixtures (Table 3).

When the respective relative permittivities of water [ε_r 79.5 (20 °C)] and formic acid [ε_r 58.5 (20 °C)] are considered, dilution of the formic acid *decreases the acidity* of the mixture whilst the *relative permittivity increases*, and the results suggest that acidity is the more important factor. However, in separate experiments we established that fluorine reacts faster with formic acid itself when in various states of dilution with water, than with the acid in the near anhydrous state and this clearly complicates conclusions concerning the effect of relative permittivity *vs.* acidity. Nevertheless, it is clear that solvents of both high acidity and high relative permittivity are excellent media for the selective fluorination of deactivated aromatics, a situation which applies to both formic and sulfuric acids.

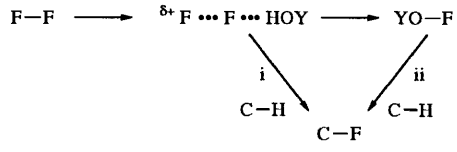
Effect of acidity

A more detailed investigation into the effect of acidity showed a very significant effect of strong acid, with sulfuric acid converting fluorine into a very powerful *in situ* electrophile. This was clearly demonstrated by fluorination of 4-fluorobenzoic acid over a range of ratios of fluorine to substrate in both formic acid and sulfuric acid. Detailed analysis of the resulting product mixtures shows that fluorination in sulfuric acid can result in the formation of 2,3,4,5-tetrafluorobenzoic acid at room temperature (Tables 4 and 5).

Yields are consistently higher with sulfuric acid and the remarkable observation is that only very small amounts of uncharacterised material (unknowns) are obtained in reactions using either sulfuric or formic acid as the reaction medium. Even more surprising is the level of fluorination that may be achieved with these systems, pointing to the generation of a very powerful electrophile in these media. Thus, passing more fluorine through a sulfuric acid solution of 4-fluorobenzoic acid gave increasing amounts of the more highly fluorinated derivatives, including pentafluorobenzoic acid, the latter also being formed during the fluorination of 2,4-difluorobenzoic acid.

Mechanism

Elements of the mechanism of the process are not entirely clear because, in principle, the interaction of fluorine with acid could lead to formation of O–F bonds before reaction with the substrate (Scheme 3), each in an electrophilic process.



Scheme 3

We are unable to distinguish between routes i and ii, although when we passed fluorine into sulfuric acid, and then added substrate, we did not detect fluorinated products. This could mean, however, that any derived O–F compound has a relatively short life-time and does not survive to react with the substrate in a two-step procedure.

Experimental

Instrumentation

The ^{19}F NMR spectra were recorded on a Bruker AC250; J values are given in Hz. Mass spectra were determined on a Fisons TRIO 100 linked to a Hewlett Packard 5790A gas chromatograph fitted with a DB-624 capillary column.

General procedures

Prior to the fluorinations, either a passivated 800 cm^3 or 3700 cm^3 steel cylinder was charged with 2 atm‡ of 50% fluorine in dry nitrogen. This was then diluted to 9 atm with dry nitrogen to produce a 10% mixture of fluorine in dry nitrogen which was then used for the fluorination reactions. Unless otherwise stated, chemicals were used as received from suppliers.

Fluorination using a variety of reaction media. A solution containing 4-fluorobenzoic acid (2.1 g, 15 mmol) in the required solvent (30 cm^3) was placed in a fluorination apparatus, consisting of a glass vessel fitted with a high-speed stirrer, a dip-pipe (PTFE) and an exit port leading to a scrubbing tube filled with soda lime. Elemental fluorine (35 mmol) as a 10% mixture in nitrogen was passed through the stirred solution using PTFE tubing. Following fluorination, the mixture was purged with dry nitrogen to remove any traces of fluorine or hydrogen fluoride. The mixtures of fluoro- and polyfluoro-benzoic acids were then analysed by comparison of the ^{19}F NMR spectra with those of the authentic samples,[16] quantitative analysis of the 4-fluorobenzoic acid to 3,4-difluorobenzoic acid conversion being achieved by adding a standard of α,α,α-trifluorotoluene or fluorobenzene to the crude reaction mixture.

‡ 1 atmosphere = 101 323 Pa.

Table 4 Fluorination of 4-fluorobenzoic acid in formic acid over a range of substrate to fluorine ratios (product mixtures analysed by NMR)

Substrate : F_2	Starting material/g	Product mixture/g	Conversion (%)	Benzoic acid products/g				
				4-Fluoro-	3,4-Difluoro-	3,4,5-Trifluoro-	2,4,5-Trifluoro-	Unknown
1 : 1.6	11.5	10.5	32	7.8	2.7	—	—	0.1
1 : 2	11.6	8.8	52	5.6	2.8	—	—	0.4
1 : 3	4.0	3.1	65	1.4	1.6	—	—	0.1
1 : 4	6.0	5.3	79	1.8	3.5	0.2	0.2	0.3

Table 5 Fluorination of 4-fluorobenzoic acid in sulfuric acid over a range of substrate to fluorine ratios (product mixtures analysed by NMR)

Substrate : F_2	Starting material/g	Product mixture/g	Conversion (%)	Benzoic acid products/g							
				4-Fluoro-	2,4-Difluoro-	3,4-Difluoro-	2,4,5-Trifluoro-	2,3,4-Trifluoro-	3,4,5-Trifluoro-	2,3,4,5-Tetrafluoro-	Unknown
1 : 1.6	14.4	11.6	83	2.5	—	6.8	1.2	0.6	0.2	—	0.2
1 : 2	11.5	10.6	85	1.8	—	6.2	0.8	0.4	0.4	0.7	0.4
1 : 2.4	7.1	5.2	88	0.8	0.1	2.7	0.4	0.1	0.2	0.5	0.4
1 : 3	7.7	5.9	92	0.6	0.1	3.4	0.6	0.2	0.5	0.3	0.3

Fluorination using formic acid of different concentration. A solution containing 4-fluorobenzoic acid (1.63 g, 11.6 mmol) in 100–40% formic acid (80 cm^3) was placed in a fluorination apparatus fitted with a soda lime scrubbing tube. Elemental fluorine (35 mmol) as a 10% mixture in nitrogen was passed through the stirred solution using PTFE tubing. Following fluorination, the mixture was purged with dry nitrogen to remove any traces of fluorine or hydrogen fluoride. The mixtures of fluoro- and polyfluoro-benzoic acids were then analysed by comparison of the ^{19}F NMR spectra with those of the authentic samples, measurement of the percentage conversion of 4-fluorobenzoic acid to 3,4-difluorobenzoic acid being achieved by ^{19}F NMR spectroscopy after addition of α,α,α-trifluorotoluene or fluorobenzene, as a standard, to the crude reaction mixture.

Larger scale fluorinations. In each of the following examples the mixtures of fluoro- and polyfluoro-benzoic acids were first analysed by comparison of the ^{19}F NMR spectra of the mixtures with those of the authentic samples; quantitative analysis was carried out by ^{19}F NMR spectroscopy, against a standard of α,α,α-trifluorotoluene. Further proof of the identity of the components was obtained by conversion of the polyfluorocarboxylic acids to their more volatile silyl esters by treatment with *N,O*-bis(trimethylsilyl)acetamide followed by analysis by GC–MS and compared with the spectra of authentic samples.[17] The quoted mass spectrometry data refers to the corresponding trimethylsilyl esters.

Fluorinations in 98% formic acid

General procedure

A solution containing 4-fluorobenzoic acid in 98% formic acid (200 cm^3) was placed in a large scale fluorination apparatus. Fluorine gas (165 mmol, except where stated) as a 10% mixture in dry nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. Following fluorination the mixture was purged with nitrogen to remove any traces of fluorine and hydrogen fluoride and then poured into an excess of ice–water (1000 cm^3) and the resulting solid product filtered off under vacuum. The filtrate was also extracted with dichloromethane (3 × 50 cm^3). After drying ($MgSO_4$), the dichloromethane was removed under vacuum to leave a solid which was then combined with the residue, dissolved in dichloromethane and analysed by ^{19}F NMR against α,α,α-trifluorotoluene or fluorobenzene. An aliquot from this solution was then treated with *N,O*-bis(trimethylsilyl)acetamide and analysed by GC–MS for further identification of the products.

1:1.63 Substrate to fluorine ratio. 4-Fluorobenzoic acid (11.5 g, 82.1 mmol), when treated with fluorine (134 mmol), gave a white solid (10.5 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (7.3 g, 50.1 mmol), showed a conversion of 32% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid [7.8 g; δ_F(235 MHz, $CFCl_3$) −104.2 (1 F, tt, $^3J_{F-H}$ 8.3, $^4J_{F-H}$ 5.6, 4-F); *m/z* (EI^+) 212 (M^+, 4.3%), 197 (M − CH_3, 100%)], 3,4-difluorobenzoic acid [2.7 g; δ_F −128.2 (1 F, m, 4-F), −135.9 (1 F, m 3-F); *m/z* (EI^+) 230 (M^+, 2.9%), 215 (M − CH_3, 100%)] and unidentified material (0.1 g).

1:2 Substrate to fluorine ratio. 4-Fluorobenzoic acid (11.6 g, 82.9 mmol) gave a white solid (8.8 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (5.0 g, 34.2 mmol), showed a conversion of 52% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (5.6 g), 3,4-difluorobenzoic acid (2.8 g) and unidentified material (0.4 g).

1:3 Substrate to fluorine ratio. 4-Fluorobenzoic acid (4.0 g, 28.6 mmol) when treated with fluorine (85.8 mmol), gave a white solid (3.1 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (1.7 g, 11.6 mmol), showed a conversion of 65% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (1.4 g), 3,4-difluorobenzoic acid (1.6 g) and unidentified material (0.1 g).

1:4 Substrate to fluorine ratio. 4-Fluorobenzoic acid (6.0 g, 42.9 mmol) produced a white solid (5.3 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (5.7 g, 39.0 mmol), showed a conversion of 79% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (1.8 g), 3,4-difluorobenzoic acid (3.5 g), 3,4,5-trifluorobenzoic acid [0.2 g; δ_F(235 MHz, $CFCl_3$) −132.0 (2 F, m, 3-F, 5-F) and −150.5 (1 F, m, 4-F); *m/z* (EI^+) 248 (M^+, 0.43%), 233 (M − CH_3, 46.3%)], 2,4,5-trifluorobenzoic acid [0.2 g; δ_F(235 MHz, $CFCl_3$) −107.6 (1 F, dtd, $^3J_{F-H}$ 15.8, $^4J_{F-H}$ 9.8, $^4J_{F-F}$ 6.8, 2-F), −122.8 (1 F, ddd, $^3J_{F-H}$ 21.4, $^3J_{F-F}$ 19.2 and $^4J_{F-H}$ 9.8, 4-F) and −140.7 (1 F, dtd, $^3J_{F-H}$ 27.5, $^3J_{F-E}$ 10.6, $^4J_{F-H}$ 6.0, 5-F); *m/z* (EI^+) 248 (M^+, 1.3%), 233 (M − CH_3, 100%)] and unidentified material (0.3 g).

Fluorinations in 98% sulfuric acid

General procedure

A solution containing 4-fluorobenzoic acid in sulfuric acid (150 cm^3) was placed in a fluorination apparatus. Fluorine gas (165 mmol, except where stated) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. Following fluorination the mixture was purged with nitrogen to remove any traces of fluorine and hydrogen fluoride, then poured into an excess of ice–water (1000 cm^3) and the resulting solid product filtered off under vacuum. The filtrate was then extracted with dichloromethane (3 × 50 cm^3). After drying ($MgSO_4$), the dichloromethane was removed under vacuum to leave a solid which was combined with the residue, dissolved in dichloromethane and analysed by ^{19}F NMR against α,α,α-trifluorotoluene. An aliquot from this solution was then treated with *N,O*-bis(trimethylsilyl)acetamide and analysed by GC–MS for further identification of the products.

1:1.63 Substrate to fluorine ratio. 4-Fluorobenzoic acid (14.4 g, 102.9 mmol) produced a white solid (11.6 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (2.7 g, 18.8 mmol), showed a conversion of 82.6% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (2.5 g), 3,4-difluorobenzoic acid (6.8 g), 2,4,5-trifluorobenzoic acid (1.2 g), 2,3,4-trifluorobenzoic acid [0.6 g; δ_F(235 MHz, $CFCl_3$) −123.8 (1 F, m, 4-F), −128.1 (1 F, m, 2-F) and −158.1 (1 F, m, 3-F); *m/z* (EI^+) 248 (M^+, 3%), 233 (M − CH_3, 100%)], 3,4,5-trifluorobenzoic acid (0.2 g)and unidentified material (0.2 g).

1:2 Substrate to fluorine ratio. 4-Fluorobenzoic acid (11.5 g, 82.1 mmol) produced a white solid (10.6 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (3.2 g, 21.9 mmol), showed a conversion of 84.8% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (1.8 g), 3,4-difluorobenzoic acid (6.2 g), 2,4,5-trifluorobenzoic acid (0.8 g), 2,3,4-trifluorobenzoic acid (0.4 g), 3,4,5-trifluorobenzoic acid (0.4 g), 2,3,4,5-tetrafluorobenzoic acid [0.7 g; δ_F(235 MHz, $CFCl_3$) −133.6 (1 F, m, 5-F), −137.2 (1 F, m, 2-F), −144.8 (1 F, m, 4-F) and −152.8 (1 F, m, 3-F); *m/z* (EI^+) 266 (M^+, 0.8%), 251 (M − CH_3, 100%)] and unidentified material (0.4 g).

1:2.4 Substrate to fluorine ratio. 4-Fluorobenzoic acid (7.1 g, 51.0 mmol), when treated with fluorine (122.4 mmol) produced a white solid (5.2 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using an external standard of α,α,α-trifluorotoluene (3.6 g, 24.7 mmol), showed a conversion of

87.9% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (0.8 g), 3,4-difluorobenzoic acid (2.7 g), 2,4,5-trifluorobenzoic acid (0.4 g), 2,3,4-trifluorobenzoic acid (0.1 g), 3,4,5-trifluorobenzoic acid (0.2 g), 2,3,4,5-tetrafluorobenzoic acid (0.5 g) and unidentified material (0.4 g).

1:3 Substrate to fluorine ratio. 4-Fluorobenzoic acid (7.7 g, 55.0 mmol) produced a white solid (5.9 g). Analysis of the solid by a combination of GC–MS and ^{19}F NMR, using external standard of α,α,α-trifluorotoluene (3.6 g, 24.7 mmol), and GC–MS showed a conversion of 92.3% from 4-fluorobenzoic acid. The ^{19}F NMR spectrum indicated that the product contained 4-fluorobenzoic acid (0.6 g), 3,4-difluorobenzoic acid (3.4 g), 2,4,5-trifluorobenzoic acid (0.6 g), 2,3,4-trifluorobenzoic acid (0.2 g), 3,4,5-trifluorobenzoic acid (0.5 g), 2,3,4,5-tetrafluorobenzoic acid (0.3 g) and unidentified material (0.3 g).

Fluorination of 2,4-difluorobenzoic acid; 1:2 substrate to fluorine ratio. 2,4-Difluorobenzoic acid (13.0 g, 82.3 mmol) produced a white solid (9.0 g). Analysis of the solid by ^{19}F NMR against an external standard of α,α,α-trifluorotoluene (4.1 g, 28.1 mmol) showed that 89% of the starting material had been converted to products which contained 2,4-difluorobenzoic acid (1.4 g), 2,4,5-trifluorobenzoic acid (3.7 g), 2,3,4-trifluorobenzoic acid (1.4 g), 2,3,4,5-tetrafluorobenzoic acid (1.1 g), pentafluorobenzoic acid [0.3 g; δ_F(235 MHz, $CFCl_3$) −136.9 (2 F, ddd, 2-F, 6-F), −147.1 (1 F, tt, 4-F) and −160.4 (2 F, m, 3-F, 5-F); *m/z*, (EI^+) 284 (M^+, 1.90%), 269 (M − CH_3, 100%)] and unidentified material (1.1 g).

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