Elemental fluorine. Part 4.[1-3] Use of elemental fluorine for the halogenation of aromatics

Richard D. Chambers,[*,a] **Christopher J. Skinner,**[a] **Malcolm J. Atherton**[b] **and John S. Moilliet**[b]

[a] *Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham DH1 3LE, UK*
[b] *BNFL Fluorochemicals Ltd., Bldg. 619, Springfields Works, Salwick, Preston, Lancashire PR4 0XJ, UK*

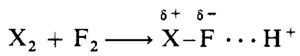
New methodolgy for direct iodination of benzenoid compounds has been developed; the aromatic substrate is simply mixed with iodine and sulfuric acid, suspended in an inert medium, such as 1,1,2-trichlorotrifluoroethane ($CF_2ClCFCl_2$) or perfluorocarbon, and elemental fluorine is passed through the system at room temperature. High conversions to iodoaromatic products occur, even with some deactivated systems, *e.g.* nitrobenzene. A very powerful brominating system is produced using the analagous methodology.

Introduction

Iodoarenes are valuable, versatile synthetic intermediates that have been widely used in organic chemistry for more than 100 years.[4] Also, iodoaromatic compounds have recently gained considerable importance in metabolic studies with thyroid hormones, amphetamines and corticosteriods, where investigations are conducted by the synthesis of appropriate radio-iodine labelled derivatives.[5] However, in contrast to other halogens, iodine is an extremely poor electrophile for aromatic systems and, generally, direct iodination is only effective with activated aromatic systems.[6] This inability to perform iodination using methodology similar to that of chlorination or bromination has prompted the development of a range of alternative methods for introducing iodine, which is the subject of an excellent review by Merkuskev.[7]

Since this review, a number of other synthetic methodologies for direct iodination have been reported. For instance, Olah *et al.* described the preparation of iodoaromatic compounds in high yields using *N*-iodosuccinimide (NIS) in the presence of a two molar equivalent of trifluoromethanesulfonic acid, and they suggested that the process involves *in situ* generation of a protosolvated iodine(I) trifluoromethanesulfonate.[8] Rozen *et al.* have described the introduction of iodine into organic molecules using iodine monofluoride (IF), preformed *via* the reaction of iodine with 10% fluorine in nitrogen, using trichlorofluoromethane ($CFCl_3$) as a solvent at −78 °C.[9] In a later publication, the iodination of a range of aromatic compounds was described and it was demonstrated that, depending on reaction temperature and time, iodination of aromatic molecules is possible without the presence of Friedel–Crafts catalysts.[10]

In preceding work in our laboratory we systematically explored the effect of acids in promoting electrophilic reactions of elemental fluorine with a range of aromatic systems and found that the reactivity of fluorine varies significantly with the medium and in some cases dramatically so.[11] Indeed, we concluded that use of concentrated sulfuric acid as a reaction medium for direct fluorination provided fluorine as a very powerful electrophile. In this paper, we describe related methodology in which attempted '*in-situ*' generation of iodine- or bromine-monofluoride in sulfuric acid (**1**) provides remarkably powerful sources of electrophilic iodine and bromine.



$$X_2 + F_2 \longrightarrow \overset{\delta+}{X}-\overset{\delta-}{F}\cdots H^+$$

1

Results

Iodination of polyfluorobenzenes

The procedure developed for iodination is an extension of that described earlier for fluorination[1,11] and involves preparation of a mixture containing the required quantity of iodine, concentrated sulfuric acid and the aromatic substrate, then passing fluorine, diluted with nitrogen, into this mixture while it is efficiently stirred. Following reaction, work-up is simply achieved by pouring the reaction mixture into ice–metabisulfite solution, followed by extraction with a suitable solvent. Recrystallisation or distillation produces the pure iodoaromatic compound. All iodination reactions proceeded with complete conversion of the starting material but, in the absence of fluorine, little iodination of the systems was observed in these control experiments (see Table 1).

The results shown in Table 1 include those in which 1,1,2-trichlorotrifluoroethane ($CF_2ClCFCl_2$) was present in the reaction mixture. This had the beneficial effect of dissolving some of the iodine at the beginning of the reaction, which allowed us to reduce substantially the volume of acid required for the process, thus making work-up easier. Clearly, yields were improved by the addition of this 'co-solvent'.

The remarkable reactivity of this system is illustrated by the range of examples shown in Table 2, where high yields of iodo compounds are recorded from relatively deactivated systems, and it is important to emphasise that these reactions are conducted at *room temperature.* Indeed, we are unaware of any other direct iodination procedure with this level of activity under such mild conditions.

We were interested to establish whether sulfuric acid could be used at catalytic levels in inert solvents and results with 98% H_2SO_4 in $CF_2ClCFCl_2$ are shown in Table 3. However, these results suggest that a proportion of 10–20% (v/v) sulfuric acid in the organic medium is *optimal* for high conversion and yield.

Use of other co-solvents in the iodination process was studied by conducting an identical series of iodinations of nitrobenzene using a 1:1 (v/v) mixture of co-solvent and sulfuric acid (see Table 4) and it is evident that a range of options is available. In

Table 1 Iodination of fluoroaromatic compounds

Starting material	Product	Conditions	Yield (%)
1,2,3,4-Tetrafluorobenzene	1,2,3,4-Tetrafluorodiiodobenzene	*a*	66
1,3,5-Trifluorobenzene	1,3,5-Trifluorotriiodobenzene	*b*	39
4,4'-Difluorobenzophenone	4,4'-Difluoro-3,3'-diiodobenzophenone	*a*	38
1,2,3,4-Tetrafluorobenzene	1,2,3,4-Tetrafluorodiiodobenzene	*a, c*	76
1,2,4,5-Tetrafluorobenzene	1,2,4,5-Tetrafluorodiiodobenzene	*a, c*	86
1,3,5-Trifluorobenzene	1,3,5-Trifluorotriiodobenzene	*b, c*	63

[a] Room temp., F_2 (2.2 equiv.), I_2 (2.2 equiv.), H_2SO_4 (98%). [b] Room temp., F_2 (3.2 equiv.), I_2 (3.2 equiv.), H_2SO_4 (98%). [c] $CF_2ClCFCl_2$.

Table 2 Iodination of aromatic compounds[a]

Starting material	Product	Yield (%)
Trifluoromethylbenzene	3-Iodo-1-trifluoromethylbenzene	83
1,3-Bis(trifluoromethyl)benzene	1,3-Bis(trifluoromethyl)-5-iodobenzene	83
4-Fluorobenzoic acid	4-Fluoro-3-iodobenzoic acid	59
2,4-Difluorobenzoic acid	2,4-Difluoro-5-iodobenzoic acid	77
4-Fluoro-1-nitrobenzene	4-Fluoro-3-iodo-1-nitrobenzene	70
2,4-Difluoro-1-nitrobenzene	2,4-Difluoro-5-iodo-1-nitrobenzene	84
4-Fluorobenzonitrile	4-Fluoro-3-iodobenzonitrile	84
Nitrobenzene	3-Iodonitrobenzene	51

[a] Room temp., H_2SO_4 (98%)–$CF_2ClCFCl_2$, F_2 (1.2 equiv.), I_2 (0.6 equiv.).

Table 3 The iodination of nitrobenzene using $CF_2ClCFCl_2$ as a co-solvent

CF_2ClCCl_2F (v/v, %)	H_2SO_4 (v/v, %)	Conversion (%)	Crude yield (%)
100	0	0	0
99	1	0	0
90	10	98.4	82
80	20	100	79
50	50	100	74
30	70	100	64
0	100	100	55

Table 4 The use of co-solvents in the iodination of nitrobenzene

Co-solvent	Conversion (%)	Yield (%)
CF_2ClCCl_2F	100	72
CH_2Cl_2	100	75
$CHCl_3$	100	73
$C_{10}F_{18}$	100	69

Table 5 The iodination of trifluoromethylbenzene in a range of acids

Acid	Conversion (%)
H_2SO_4	100
CF_3CO_2H	38
HCO_2H	30
CH_3CO_2H	4

the case of perfluorodecalin the reaction mixture is simply in suspension in the inert medium, rather than in solution, and the perfluorocarbon acts as a very convenient bulking agent substantially reducing the volume of acid that would otherwise be required and which is very simply recovered at the end of the reaction. We envisage that these commercially available perfluorocarbon fluids could be used in a similar way, as bulking agents, in a number of processes to substantially reduce the amount of solvent used, and this would be especially useful in situations where disposal or recovery of solvent presents a problem.

A study was also made of the role of acid in the iodination process, in this case by performing a series of iodinations of trifluoromethylbenzene in a number of mineral and organic acids (see Table 5) but otherwise using the procedure described above. The results clearly show that the acidity of the system is extremely important and Table 5 suggests that tailoring of the activity of the system can be achieved for a range of reactivities of the substrate and level of iodination required, simply by adjusting the acid strength of the medium.

Not all systems were successfully iodinated by these procedures because, at room temperature, only 14% conversion of 3-nitro-1-trifluoromethylbenzene to 3-nitro-5-trifluoromethyl-1-iodobenzene occurred, while 1,3- and 1,4-dinitrobenzenes were unaffected at room temperature.

Bromination

There are, of course, many procedures available for direct bromination but, nevertheless, we have developed methodology that is analogous to that described above involving iodine, and consequently a very powerful bromination system has evolved. A number of bromination reactions were performed under equivalent conditions to those described above and complete conversion of starting materials to the corresponding bromoaromatic derivatives was observed in each reaction (see Table 6). The species produced by the passage of fluorine through bromine in sulfuric acid proved to be extremely powerful and reacted even at room temperature with 1,3-dinitrobenzene, in contrast to the iodination system. The 1,4-isomer was, however, unreactive under these conditions.

Reactions using interhalogens

For comparison, the effect of elemental fluorine on halogenation using iodine chloride was also investigated, giving the results shown in Scheme 1. Iodine chloride alone gave only 9% conversion to a chlorinated product, presumably arising from some chlorine produced in the mixture, whereas the passage of fluorine rapidly led to quantitative conversion to a mixture of the 3-iodo- and 3-chloro-1-nitrobenzenes, suggesting the formation of both IF and ClF as intermediates.

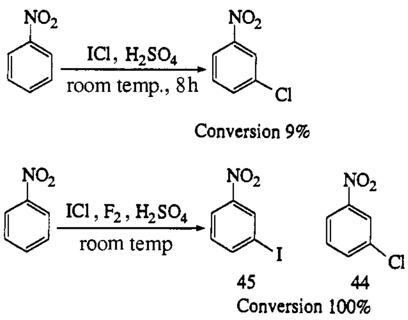
Mechanism

Previously Rozen and his co-workers have demonstrated that preformed IF did not react with deactivated aromatics such as nitrobenzene.[10] Repeating this attempted iodination of nitrobenzene confirmed that preformed IF does not react with

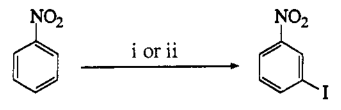
Table 6 The bromination of aromatics in sulfuric acid[a]

Starting material	Product	Yield (%)
4-Fluoro-1-nitrobenzene	3-Bromo-4-fluoro-1-nitrobenzene	59
2,4-Difluoro-1-nitrobenzene	5-Bromo-2,4-difluoro-1-nitrobenzene	65
4-Fluorobenzoic acid	3-Bromo-4-fluorobenzoic acid	65
2,4-Dinitro-1-fluorobenzene	6-Bromo-2,4-dinitro-1-fluorobenzene	60

[a] Room temp., H_2SO_4 (98%), F_2 (1.2 equiv.), Br_2 (0.6 equiv.)



Scheme 1

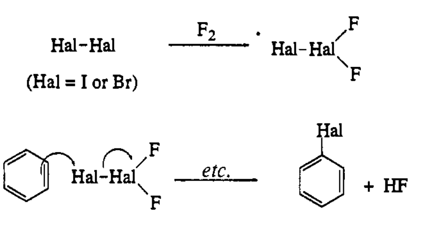


Scheme 2 *Reagents and conditions:* i, IF, $CF_2ClCFCl_2$, −78 °C to room temp., no reaction; ii, preformed IF, H_2SO_4, −78 °C to room temp., 12% conversion

nitrobenzene even when warmed to room temperature (Scheme 2). However, when preformed IF was reacted with nitrobenzene dissolved in sulfuric acid, a low conversion to 3-iodo-1-nitrobenzene was observed. In marked contrast to these reactions, the iodination of nitrobenzene using our described methodology produces 3-iodo-1-nitrobenzene in high conversion and yield, and this raises the question of mechanism.

As we see it there are, overall, three potential processes that could explain our observations and these are outlined in eqns. (2)–(4). The process that we originally envisaged, eqn. (2),

$$\text{I-I} + \text{F-F} \xrightarrow{\text{HX}} \text{I-F}\cdots\text{H-X} \longrightarrow \text{I-Ar} \quad (2)$$



(3)

$$\text{I-I} + \text{XO-F} \longrightarrow \text{XO-I} + \text{I-F} \longrightarrow \text{I-Ar} \quad (4)$$

(HX = Acid)

involves *in situ* formation of halogen–fluoride and then hydrogen bonding of the acid, preferentially to the fluorine rather than iodine (or bromine in the analogous case). However, as we have demonstrated, the level of observed reactivity of our *in situ* procedure is significantly higher than for the preformed system. In principle, a possible alternative could be process eqn. (4), where fluorine reacts faster with the acid, to produce an intermediate O–F compound. However, we have demonstrated that fluorine has minimal reactivity with sulfuric acid under these conditions.[12] Therefore, we are led to the mechanism illustrated in eqn. (3), where fluorine adds to one atom of iodine, expanding its covalency, and creating *in situ* what amounts to a super leaving group, which is reminiscent of the so-called FITS reagents.[13] However, if the mechanism in eqn. (3) operates, then it is unclear what the subsequent stages are because the stoichiometry, conversions and yields of many of the iodination and bromination reactions make it clear that most of the available iodine or bromine enters the substrate. Furthermore, starting with ICl, both iodine and chlorine enter the substrate. Therefore, there remain uncertainties about the details of mechanism, but the procedure developed provides a powerful new range of environmentally friendly (*i.e.* no metal catalysts are required and the hydrogen fluoride produced could be recycled) iodination and bromination processes, that could be scaled up if required.

Experimental

The ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian VXR200, Bruker AC250, Varian VXR400S or a Bruker AC500 spectrometer; J values are given in Hz. ^{19}F NMR spectra were recorded at 235 MHz, using $CFCl_3$ as internal reference, and ^{13}C spectra at 100 MHz, from Me_3Si, and unless stated, as solutions in $CDCl_3$. Mass spectra were determined on a VG 7070E or a Fisons TRIO Spectrometer linked to a Hewlett-Packard 5790A gas chromatograph fitted with a DB-624 capillary column. Fractional distillation was carried out using a Fischer Spahltrohr NMS255 small concentric tube apparatus. Boiling points were recorded during distillation. Carbon, hydrogen and nitrogen elemental analyses were obtained using a Carlo Erba Strumentazione 1106 Elemental Analyser. Melting points were carried out at atmospheric pressure and are uncorrected. Unless otherwise stated, chemicals were used as received from suppliers. Prior to the following halogenations, a passivated 3700 cm^3 steel cylinder was charged with 2 atm of 50% fluorine in nitrogen (Air Products). This was then diluted with dry nitrogen to produce a 10% (v/v) mixture of fluorine in nitrogen.

Iodination

General procedure without co-solvent. A solution containing the polyfluorobenzene and iodine in 98% sulfuric acid (150 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40 cm^3 min^{-1}. After fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). The dichloromethane was then removed under vacuum to leave an oil or solid which was then purified by distillation or recrystallisation (ethanol) to afford a single product.

1,2,3,4-*Tetrafluorodiiodobenzene*.—1,2,3,4-Tetrafluorobenzzene (11.3 g, 75 mmol) and iodine (41.9 g, 165 mmol) gave 1,2,3,4-tetrafluorodiiodobenzene (20 g, 66%); mp 48–50 °C (lit.,[14] 50.5–51.8 °C) (Found: C, 18.1. $C_6F_4I_2$ requires C, 17.93%); δ_F −102.4 (2 F, AA′XX′, J_{AX} 22.5, $J_{AX'}$ −4.4, $J_{AA'}$ 19.2, J_{XX} 9.3, 2-F, 3-F) and −151.2 (2 F, AA′XX′, J_{AX} 22.5, $J_{AX'}$ −4.4, $J_{AA'}$ 19.2, J_{XX} 9.3, 1F, 4-F); δ_C 90.6 (m, $^2J_{C-F}$ 24.4, 5-C, 6-C), 134.0 (m, $^1J_{C-F}$ 260.0, 1-C, 4-C) and 147.8 (m, $^1J_{C-F}$ 247.0, 2-C, 3-C); m/z (EI^+) 402 (M^+, 100%).

1,3,5-*Trifluorotriiodobenzene*.—1,3,5-Trifluorobenzene (6.8 g, 51.5 mmol) and iodine (41.9 g, 165 mmol) gave 1,3,5-trifluorotriiodobenzene (10.2 g, 39%); mp 143–145 °C[15] (Found: C, 14.0. $C_6F_3I_3$ requires C, 14.14%); δ_F −69.0 (3F, s, 1-F, 3-F, 5-F); δ_C 63.8 (td, $^2J_{C-F}$ 34.5, $^4J_{C-F}$ 3.8, 2-C) and 162.2 (dt, $^1J_{C-F}$ 243.8, $^3J_{C-F}$ 7.6, 1-C, 3-C, 5-C); *m*/*z* (EI$^+$) 510 (M$^+$, 30.8%).

4,4′-*Difluoro*-3,3′-*diiodobenzophenone*.—4,4′-Difluorobenzophenone (16.4 g, 75.2 mmol) and iodine (41.9 g, 165 mmol) gave 4,4′-difluoro-3,3′-diiodobenzophenone (13.5 g, 38.3%); mp 129–131 °C (Found: C, 33.0; H, 1.2. $C_{13}H_6F_2I_2O$ requires C, 33.2; H, 1.3%); δ_H 7.18 (2 H, dd, $^3J_{H-F}$ 8.4, $^3J_{H-H}$ 7.6, 5-H, 5-H′), 7.74 (2 H, ddd, $^3J_{H-H}$ 8.5, $^4J_{H-F}$ 4.8, $^4J_{H-H}$ 2.0, 6-H, 6-H′) and 8.20 (2 H, dd, $^4J_{H-F}$ 6.0, $^4J_{H-H}$ 2.0, 2-H, 2-H′); δ_F −86.0 (2 F, ddd, $^3J_{F-H}$ 7.2, $^4J_{F-H}$ 4.9, 4-F, 4-F′); δ_C 81.8 (2 C, d, $^2J_{C-F}$ 26.7, 3-C, 3-C′), 115.7 (2 C, d, $^2J_{C-F}$ 24.4, 5-C, 5-C′), 132.1 (2 C, d, $^3J_{C-F}$ 8.8, 6-C, 6-C′), 141.2 (2 C, d, $^4J_{C-F}$ 2.6, 2-C, 2-C′), 141.4 (2 C, d, $^3J_{C-F}$ 3.1, 1-C, 1-C′), 164.4 (2 C, d, $^1J_{C-F}$ 253.7, 4-C, 4-C′) and 191.0 (1 C, s, C=O); *m*/*z* (EI$^+$) 470 (M$^+$, 83.3%).

General procedure with co-solvent. A solution containing the aromatic compound and iodine in 98% sulfuric acid (120 cm^3) and 1,1,2-trichloro-1,2,2-trifluoroethane (30 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca.* 40 cm^3 min^{-1}. After fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). The dichloromethane was then removed under vacuum to leave an oil or solid which was then purified by distillation or recrystallisation (ethanol) to afford a single product.

1,2,3,4-*Tetrafluorodiiodobenzene*.—1,2,3,4-Tetrafluorobenzene (11.3 g, 75 mmol) and iodine (21.9 g, 86 mmol) gave 1,2,3,4-tetrafluorodiiodobenzene (23 g, 76%).

1,2,4,5-*Tetrafluorodiiodobenzene*.—1,2,4,5-Tetrafluorobenzene (11.3 g, 75 mmol) and iodine (21.9 g, 86 mmol) gave 1,2,4,5-tetrafluorodiiodobenzene (20.5 g, 68%); mp 109–111 °C (lit.,[16] 109–111 °C) (Found: C, 17.6. $C_6F_4I_2$ requires C, 17.93%); δ_F −118.0 (4 F, s, 1-F, 2-F, 3-F, 4-F); δ_C 72.9 (t, $^2J_{C-F}$ 27.9, 3 C, 6-C) and 146.6 (m, $^1J_{C-F}$ 250.4, 1-C, 2 C, 4-C, 5-C); *m*/*z* (EI$^+$) 402 (M$^+$, 46.7%).

1,3,5-*Trifluorotriiodobenzene*.—1,3,5-Trifluorobenzene (6.9 g, 52.3 mmol) and iodine (21.9 g, 86 mmol) gave 1,3,5-trifluorotriiodobenzene (16.6 g, 63%).

m-*Iodonitrobenzene*.—Nitrobenzene (16.9 g, 137.5 mmol) and iodine (21.0 g, 82.7 mmol) gave *m*-iodonitrobenzene (17.4 g, 51%); bp 116 °C at 1.5 mmHg (lit.,[14] 280 °C) (Found: C, 28.8; H, 1.5; N, 5.5. $C_6H_4INO_2$ requires C, 28.94; H, 1.62; N, 5.63%); δ_H 7.34 (1 H, dd, $^3J_{H-H}$ 4.0, 5-H), 8.0 (1 H, ddd, $^3J_{H-H}$ 7.8, $^4J_{H-H}$ 1.6, $^4J_{H-H}$ 1.0, 4-H), 8.17 (1 H, ddd, $^3J_{H-H}$ 8.1, $^4J_{H-H}$ 2.2, $^4J_{H-H}$ 1.1, 6-H) and 8.45 (1 H, t, $^4J_{H-H}$ 2.0, 2-H); δ_C 94.3 (1 C, s, 3-C), 115.7 (1 C, s, 6-C), 132.1 (1 C, s, 5-C), 141.2 (1 C, s, 2-C), 141.4 (1 C, s, 4-C) and 164.4 (1 C, s, 1-C); *m*/*z* (EI$^+$) 249 (M$^+$, 100%).

m-*Iodo*-1-*trifluoromethylbenzene*.—1-Trifluoromethylbenzene (21.4 g, 144.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 3-iodo-1-trifluoromethylbenzene (32.6 g, 82.9%); bp 116 °C at 1.5 mmHg (lit.,[14] 82–82.5 °C at 25 mmHg) (Found: C, 30.8; H, 1.4. $C_7H_4F_3I$ requires C, 30.88; H, 1.47%); δ_H 7.10 (1 H, t, $^3J_{H-F}$ 8.4, $^3J_{H-H}$ 7.9, 5-H), 7.50 (1 H, d, $^3J_{H-H}$ 7.8, 4-H), 7.7 (1 H, d, $^3J_{H-H}$ 7.9, 6-H) and 7.9 (1 H, s, 2-H); δ_F −86.0 (2 F, ddd, $^3J_{F-H}$ 7.2, $^4J_{F-H}$ 4.9, 4-F); δ_F −69.2 (3 F, s, CF_3); δ_C 94.5 (1 C, s, 3-C), 123.5 (1 C, q, $^1J_{C-F}$ 272.9, CF_3), 124.9 (1 C, q, $^3J_{C-F}$ 3.6, 6-C), 130.8 (1 C, s, 5-C), 132.8 (1 C, q, $^2J_{C-F}$ 32.7, 1-C), 134.7 (1 C, q, $^3J_{C-F}$ 3.8, 2-C) and 141.0 (1 C, s, 4-C); *m*/*z* (EI$^+$) 272 (M$^+$).

1,3-*Bis*(*trifluoromethyl*)-5-*iodobenzene*.—1,3-Bis-(trifluoromethyl)benzene (29.4 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 1,3-bis(trifluoromethyl)-5-iodobenzene (27.5 g, 83%); bp 58 °C at 26 mmHg (Found: C, 28.0; H, 0.9. $C_8H_3F_6I$ requires C, 28.24; H, 0.88%); δ_H 7.9 (1 H, s, 2-H) and 8.1 (2 H, s, 4-H, 6-H); δ_F −63.7 (6 F, s, CF_3); δ_C 94.2 (1 C, s, 5-C), 122.2 (1 C, m, $^3J_{C-F}$ 3.7, 2-C), 122.6 (2 C, q, $^1J_{C-F}$ 273.1, CF_3), 133.5 (1 C, q, $^2J_{C-F}$ 33.8, 1-C, 3-C) and 138.1 (1 C, m, $^3J_{C-F}$ 3.4, 4-C, 6-C); *m*/*z* (EI$^+$) 340 (M$^+$, 76.3%).

4-*Fluoro*-3-*iodobenzoic acid*.—4-Fluorobenzoic acid (19.3 g, 137.5 mmol) and iodine (21.2 g, 83.5 mmol) gave 4-fluoro-3-iodobenzoic acid (21.4 g, 58.5%); mp 174–176 °C (lit.,[17] 175–176 °C) (Found: C, 31.5; H, 1.4. $C_7H_4FIO_2$ requires C, 31.58; H, 1.50%); δ_H 7.1 (1 H, dd, $^3J_{H-H}$ 7.5, $^3J_{H-F}$ 8.6, 5-H), 7.0 (1 H, ddd, $^3J_{H-H}$ 8.6, $^4J_{H-F}$ 4.9, $^4J_{H-H}$ 2.1, 6-H) and 8.5 (1 H, dd, $^4J_{H-H}$ 2.2, $^4J_{H-F}$ 6.1, 2-H); δ_F −88.8 (1 F, s, 4-F); δ_C 81.3 (1 C, d, $^2J_{C-F}$ 26.6, 3-C), 115.8 (1 C, d, $^2J_{C-F}$ 24.8, 5-C), 127.0 (1 C, d, $^4J_{C-F}$ 3.3, 1-C), 132.6 (1 C, d, $^3J_{C-F}$ 8.9, 6-C), 142.0 (1 C, d, $^3J_{C-F}$ 3.3, 2-C), 165.2 (1 C, d, $^1J_{C-F}$ 254.3, 4-C) and 169.8 (1 C, s, C=O); *m*/*z* (EI$^+$) 266 (M$^+$, 100%).

2,4-*Difluoro*-5-*iodobenzoic acid*.—2,4-Difluorobenzoic acid (21.8 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 2,4-difluoro-5-iodobenzoic acid (29.9 g, 76.6%); mp 151–152 °C (Found: C, 29.6; H, 1.1. $C_7H_3F_2IO_2$ requires C, 29.58; H, 1.06%); δ_H 6.9 (1 H, dd, $^3J_{H-F}$ 10.3, $^3J_{H-F}$ 7.6, 3-H) and 8.5 (1 H, t, $^4J_{H-F}$ 7.4, 6-H); δ_F −81.3 (1 F, m, 2-F) and −83.7 (1 F, s, 4-F); δ_C 75.0 (1 C, dd, $^2J_{C-F}$ 26.5, $^4J_{C-F}$ 4.0, 5-C), 105.8 (1 C, t, $^2J_{C-F}$ 27.3, 3-C), 142.8 (1 C, m, 6-C), 143.1 (1 C, d, $^3J_{C-F}$ 3.8, 1-C), 163.6 (1 C, dd, $^1J_{C-F}$ 266.4, $^3J_{C-F}$ 11.9, 2-C), 165.3 (1 C, dd, $^1J_{C-F}$ 256.4, $^3J_{C-F}$ 12.3, 4-C) and 167.1 (1 C, d, $^3J_{C-F}$ 3.4, C=O); *m*/*z* (EI$^+$) 284 (M$^+$, 100%).

2,4-*Difluoro*-5-*iodonitrobenzene*.—2,4-Difluoronitrobenzene (21.1 g, 144.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 2,4-difluoro-5-iodonitrobenzene (32.8 g, 83.6%) (Found: C, 25.1; H, 0.7; N, 4.9. $C_6H_2F_2INO_2$ requires C, 25.30; H, 0.70; N, 4.91%); δ_H 7.2 (1 H, dd, $^3J_{H-F}$ 10.3, $^3J_{H-F}$ 7.8, 3-H) and 8.5 (1 H, t, $^4J_{H-F}$ 7.2, 6-H); δ_F −78.8 (1 F, s, 2-F) and 112.0 (1 F, s, 4-F); δ_C 73.4 (1 C, dd, $^2J_{C-F}$ 26.6, $^4J_{C-F}$ 4.6, 5-C), 105.0 (1 C, dd, $^2J_{C-F}$ 29.5, $^2J_{C-F}$ 25.2, 3-C), 132.7 (1 C, s, 1-C), 134.8 (1 C, s, 6-C), 154.9 (1 C, dd, $^1J_{C-F}$ 268.4, $^3J_{C-F}$ 12.3, 2-C) and 163.2 (1 C, dd, $^1J_{C-F}$ 257.3, $^3J_{C-F}$ 11.4, 4-C); *m*/*z* (EI$^+$) 285 (M$^+$, 77.1%).

4-*Fluoro*-3-*iodobenzonitrile*.—4-Fluorobenzonitrile (16.6 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 4-fluoro-3-iodobenzonitrile (28.5 g, 84%); mp 57–59 °C (Found: C, 34.4; H, 1.2; N 5.6. C_7H_3FIN requires C, 34.01; H, 1.21; N, 5.67%); δ_H 7.2 (1 H, m, 5-H), 7.0 (1 H, m, 6-H) and 8.1 (1 H, m, 2-H); δ_F −83.8 (1 F, s, 4-F); δ_C 82.1 (1 C, d, $^2J_{C-F}$ 27.5, 3-C), 110.3 (1 C, d, $^4J_{C-F}$ 4.0, 1-C), 116.5 (1 C, s, CN), 116.6 (1 C, d, $^2J_{C-F}$ 25.4, 5-C), 134.3 (1 C, d, $^3J_{C-F}$ 8.8, 6-C), 143.3 (1 C, d, $^4J_{C-F}$ 3.2, 2-C) and 164.3 (1 C, d, $^1J_{C-F}$ 255.0, 4-C); *m*/*z* (EI$^+$) 247 (M$^+$, 100%).

4-*Fluoro*-3-*iodonitrobenzene*.—4-Fluoronitrobenzene (21.1 g, 144.5 mmol) and iodine (21.9 g, 86.2 mmol) gave 4-fluoro-3-iodonitrobenzene (25.7 g, 70%) (Found: C, 26.9; H, 1.1; N, 5.2. $C_6H_3FINO_2$ requires C, 26.97; H, 1.12; N, 5.24%); δ_H 7.2 (1 H, dd, $^3J_{H-H}$ 6.9, $^3J_{H-F}$ 9.0, 5-H), 8.3 (1 H, ddd, $^3J_{H-H}$ 9.1, $^4J_{H-F}$ 4.3, $^4J_{H-H}$ 2.8, 6-H) and 8.7 (1 H, dd, $^4J_{H-H}$ 2.8, $^4J_{H-F}$ 5.3, 2-H); δ_F −83.6 (1 F, s, 4-F); δ_C 81.3 (1 C, d, $^2J_{C-F}$ 28.6, 3-C), 116.0 (1 C, d, $^2J_{C-F}$ 26.6, 5-C), 125.9 (1 C, d, $^3J_{C-F}$ 9.3, 6-C), 135.2 (1 C, d, $^3J_{C-F}$ 3.7, 2-C), 144.6 (1 C, d, $^4J_{C-F}$ 1.8, 1-C) and 165.5 (1 C, d, $^1J_{C-F}$ 265.2, 4-C); *m*/*z* (EI$^+$) (M$^+$, 100%).

Iodination in different volumes of co-solvent. A solution containing nitrobenzene (16.9 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) in the required volumes of sulfuric acid and 1,1,2-trichloro-1,2,2-trifluoroethane was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After the fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS was used to determine the conversion. Removal of the dichloromethane under reduced pressure allowed determination of the crude yield.

Iodination in a variety of co-solvents. A solution containing nitrobenzene (16.9 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) in 98% sulfuric acid (75 cm^3) and the co-solvent (75 cm^3) was placed in the fluorination apparatus. Elemental fluorine

(165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After the fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS was used to determine the conversion. Removal of the dichloromethane under reduced pressure allowed determination of the crude yield.

Iodination in a variety of acids. A solution containing trifluoromethylbenzene (20.1 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) in the required acid (150 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS was used to determine the relative conversion.

Iodination of 3-*nitrotrifluorobenzene*.—A solution containing 3-nitro-1-trifluoromethylbenzene (26.3 g, 137.5 mmol) and iodine (21.9 g, 86.2 mmol) in 98% sulfuric acid (120 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS showed a conversion of 14% from 3-nitro-1-trifluoromethylbenzene to 5-iodo-3-nitro-1-trifluoromethylbenzene, δ_C(100.6 MHz; $CDCl_3$; TMS) 93.9 (s, 5-C), 120.4 (m, 6-C), 128.2 (m, CF_3), 135.8 (s, 4-C), 140.3 (M, 2-C), 142.7 (m, 4-C); δ_H(200.6 MHz; $CDCl_3$; TMS) 7.9 (m, 4-H), 8.3 (m, 6-H), 8.8 (m, 2-H); *m*/*z* (EI$^+$) 317 (M$^+$, 65.7%), 271 (M$^+$ − NO_2, 23.6).

Bromination

General procedure. A solution containing the aromatic compound and bromine in sulfuric acid (150 cm^3) was placed in the fluorination apparatus and elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After the passage of fluorine the solution was poured into an approximate 5% mixture of sodium metabisulfite in ice and extracted with dichloromethane (3 × 100 cm^3) which was then dried ($MgSO_4$). The dichloromethane was removed under vacuum leaving a solid or oil which was then purified by recrystallisation from ethanol or distilled to afford a pure product.

4-*Bromo*-4-*fluoro*-1-*nitrobenzene*.—4-Fluoro-1-nitrobenzene (19.4 g, 137.5 mmol) and bromine (21.2 g, 83.5 mmol) gave 3-bromo-4-fluoro-1-nitrobenzene (21.4 g, 58.5%); mp 57–59 °C (lit.,[18] 58–59 °C) (Found: C, 32.6; H, 1.3; N, 6.1. $C_6H_3BrFNO_2$ requires C, 32.9; H, 1.37; N, 6.39%); δ_H 7.3 (1 H, dd, $^3J_{H-H}$ 7.4, $^3J_{H-F}$ 9.1, 5-H), 8.2 (1 H, ddd, $^3J_{H-H}$ 9.0, $^4J_{H-H}$ 2.8, $^4J_{H-F}$ 4.1, 6-H) and 8.5 (1 H, dd, $^4J_{H-H}$ 2.7, $^4J_{H-F}$ 5.8, 2-H); δ_F −96.0 (1 F, ddd, $^3J_{F-H}$ 7.3, $^4J_{F-H}$ 7.3, $^4J_{F-H}$ 5.9, $^4J_{F-H}$ 4.1, 4-F); δ_C 110.1 (1 C, d, $^2J_{C-F}$ 23.5, 3-C), 117.1 (1 C, d, $^2J_{C-F}$ 24.6, 5-C) 124.9 (1 C, d, $^3J_{C-F}$ 9.1, 6-C), 128.3 (1 C, s, 1-C), 129.6 (1 C, d, $^3J_{C-F}$ 2.2, 1-C) and 162.9 (1 C, d, $^1J_{C-F}$ 258.3, 4-C); *m*/*z* (EI$^+$) 221 (M$^+$, 46.8%) and 219 (M$^+$, 55.1).

5-*Bromo*-2,4-*difluoro*-1-*nitrobenzene*.—2,4-Difluoro-1-nitrobenzene (21.9 g, 137.5 mmol) and bromine (21.2 g, 83.5 mmol) gave 5-bromo-2,4-difluoro-1-nitrobenzene (21.2 g, 65.4%); bp 98 °C at 8 mmHg (Found: C, 30.4; H, 0.8; N, 5.9. $C_6H_2BrF_2NO_2$ requires C, 30.38; H, 0.84; N, 5.91%); δ_H 7.2 (1 H, dd, $^3J_{H-F}$ 7.8, $^3J_{H-F}$ 10.3, 3-H) and 8.4 (1 H, t, $^4J_{H-F}$ 7.4, 6-H); δ_F −91.2 (1 F, ddd, $^3J_{F-H}$ 14.3, $^4J_{F-H}$ 7.9, $^4J_{F-H}$ 7.1, 2-F) and −112.0 (1 F, ddd, $^3J_{F-H}$ 14.3, $^4J_{F-H}$ 10.2, $^4J_{F-H}$ 7.9, 4-F); δ_C 104.7 (1 C, dd, $^2J_{C-F}$ 23.5, $^4J_{C-F}$ 4.5, 5-C), 107.6 (1 C, t, $^2J_{C-F}$ 27.4, 3-C), 129.1 (1 C, s, 1-C), 131.0 (1 C, t, $^3J_{C-F}$ 2.5, 6-C), 155.7 (1 C, dd, $^1J_{C-F}$ 268.7, $^3J_{C-F}$ 11.8, 2-C) and 162.4 (1 C, dd, $^1J_{C-F}$ 260.3, $^3J_{C-F}$ 11.4, 4-C); *m*/*z* (EI$^+$) 239 (M$^+$, 23.8%) and 237 (M$^+$, 24.1).

3-*Bromo*-4-*fluorobenzoic acid*.—4-Fluorobenzoic acid (19.3 g, 137.5 mmol) and bromine (21.2 g, 83.5 mmol) gave 3-bromo-4-fluorobenzoic acid (16.8 g, 65%); mp 137–139 °C (lit.,[14] 138–140 °C) (Found: C, 38.5; H, 1.6. $C_7H_4BrFO_2$ requires C, 38.53; H, 1.8%); δ_H 7.2 (1 H, dd, $^3J_{H-F}$ 8.4, $^3J_{H-H}$ 8.4, 5-H), 8.1 (1 H, ddd, $^3J_{H-H}$ 4.7, $^4J_{H-F}$ 4.3, $^4J_{H-H}$ 2.1, 6-H) and 8.4 (1 H, dd, $^4J_{H-F}$ 6.6, $^4J_{H-H}$ 2.1, 2-H); δ_F −98.0 (1 F, ddd, $^3J_{F-H}$ 8.3, $^3J_{F-H}$ 6.8, $^4J_{F-H}$ 4.9, 4-F); δ_C 110.1 (1 C, d, $^2J_{C-F}$ 21.6, 3-C), 117.2 (1 C, d, $^2J_{C-F}$ 23.1, 2-C), 127.2 (1 C, s, 1-C), 132.0 (1 C, d, $^3J_{C-F}$ 8.8, 6-C), 136.6 (1 C, dd, $^3J_{C-F}$ 1.9, 2-C), 163 (1 C, dd, $^1J_{C-F}$ 256.3, 4-C) and 170.8 (1 C, s, C=O); *m*/*z* (EI$^+$) 220 (M$^+$, 99.5%) and 218 (M$^+$, 100).

2-*Bromo*-4,6-*dinitro*-1-*fluorobenzene*.—2,4-Difluoro-1-nitrobenzene (25.4 g, 137.5 mmol) and bromine (21.2 g, 83.5 mmol) gave 2-bromo-4,6-dinitro-1-fluorobenzene (21.8 g, 60.0%) (Found: C, 27.3; H, 0.7; N, 10.4. $C_6H_2BrFN_2O_4$ requires C, 27.3; H, 0.76; N, 10.6%); δ_H 9.0 (2 H, m, 3-H, 5-H); δ_F −99.8 (1 F, s, 1-F); δ_C 113.7 (1 C, d, $^2J_{C-F}$ 22.9, 2-C), 121.7 (1 C, s, 5-C), 134.2 (1 C, s, 3-C), 137.9 (1 C, d, $^3J_{C-F}$ 10.3, 6-C), 143.7 (1 C, d, $^4J_{C-F}$ 4.6, 4-C) and 156.6 (1 C, d, $^1J_{C-F}$ 273.0, 4-C); *m*/*z* (EI$^+$) 266 (M$^+$, 36.8%) and 264 (M$^+$, 38.5).

Bromination of *m*-dinitrobenzene. A solution containing *m*-dinitrobenzene (23.1 g, 137.5 mmol) and bromine (26.1 g, 165 mmol) in 98% sulfuric acid (120 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After the fluorination the mixture was poured into a 5% solution of sodium metabisulfite in ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS showed a conversion of 48% from 1,3-dinitrobenzene to 3,5-dinitro-1-bromobenzene, *m*/*z* (EI$^+$) 248 (M$^+$, 26.0%), 202 (−NO_2, 5.6).

Bromination of *p*-dinitrobenzene. A solution containing *p*-dinitrobenzene (23.1 g, 137.5 mmol) and bromine (26.1 g, 165 mmol) in 98% sulfuric acid (120 cm^3) was placed in the fluorination apparatus. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 40 cm^3 min^{-1}. After the fluorination the mixture was poured into a 5% solution of sodium metabisulfite ice (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). GC–MS showed no conversion to brominated product.

Reactions using interhalogens

A solution of nitrobenzene (16.9 g, 137.5 mmol), iodine monochloride (26.8 g, 82.5 mmol) and sulfuric acid (150 cm^3) was placed in the fluorination apparatus with attached soda lime filled drying tube. Elemental fluorine (165 mmol) as a 10% mixture in nitrogen was then passed through the stirred solution at *ca.* 10 cm^3 min^{-1}. After the fluorine had been added the solution was poured into a 5% solution of sodium metabisulfite (1500 cm^3), extracted with dichloromethane (3 × 100 cm^3) and then dried ($MgSO_4$). The dichloromethane was removed under vacuum to leave a red liquid (22 g). Analysis by GC–MS showed a 100% conversion from nitrobenzene to two major products which were confirmed as 3-chloro-1-nitrobenzene (44%) [*m*/*z* (EI$^+$) 159 (M$^+$, 20.0%), 157 (M$^+$, 61.2%)] and 3-iodo-1-nitrobenzene (45%) [*m*/*z* (EI$^+$) 249 (M$^+$, 100%), 203 (M$^+$ − NO_2)].

Acknowledgements

We would like to thank BNFL Fluorochemicals Ltd. and ZENECA plc for financial support (to C. J. S.).

References

1 For part 3, see R. D. Chambers, J. Hutchinson and J. Thomson, *J. Fluorine Chem.*, submitted for publication.

2 Preliminary communication: R. D. Chambers, C. J. Skinner, M. A. Atherton and J. S. Moilliet, *J. Chem. Soc., Chem. Commun.*, 1995, 19.

3 Presented in part at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, August 1994.

4 P. E. Fanta, *Synthesis*, 1974, 9; N. Nilsson, *Tetrahedron Lett.*, 1966, 679; H. Suzuki, H. Abe and A. Ouska, *Chem. Lett.*, 1980, 1363; L. M. Yagupolskii, N. V. Krondratenko and K. P. Samibur, *Synthesis*, 1975, 721.

5 L. G. Colombetti, in *Principles of Radiopharmacology*, CRC Press, Boca Raton, 1979, vol. 1, p. 189.

6 A. R. Butler, *J. Chem. Educ.*, 1971, **48**, 508.

7 E. B. Merkuskev, *Synthesis*, 1988, 923 and references cited therein.

8 G. A. Olah, Q. Wang, G. Sandford and G. K. S. Prakash, *J. Org. Chem.*, 1993, **58**, 3194.

9 S. Rozen and M. Brand, *J. Org. Chem.*, 1985, **50**, 3342.

10 S. Rozen and D. Zamir, *J. Org. Chem.*, 1990, **55**, 3552.

11 R. D. Chambers, C. J. Skinner, J. Hutchinson and J. Thomson, *J. Chem. Soc., Perkin Trans. 1*, submitted for publication.

12 Dr M. P. Greenhall, unpublished results.

13 T. Umemoto, *Tetrahedron Lett.*, 1984, **25**, 81.

14 Aldrich Chemical Company Ltd., *Catalogue of Fine Chemicals.*

15 G. B. Deacon and R. N. M. Richard, *Aust. J. Chem.*, 1982, **35**, 1587.

16 M. Hellman, *J. Am. Chem. Soc.*, 1955, **77**, 3650.

17 S. G. Mittelbtaedt and G. L. Jenkins, *J. Am. Pharm. Assoc.*, 1950, **39**, **4**.

18 W. B. Austin, *J. Org. Chem.*, 1981, **48**, 2280.

Paper 6/01099G
Received 14*th February* 1996
Accepted 9*th April* 1996