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Elemental fluorine
Part 20. Direct fluorination of deactivated aromatic systems using microreactor techniques☆

Richard D. Chambers [a,*], Mark A. Fox [a], Graham Sandford [a,**], Jelena Trmcic [a], Andres Goeta [b]

[a] Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, United Kingdom
[b] Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, United Kingdom

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Abstract

Continuous flow microreactor technology has been used for the direct fluorination of a range of deactivated di- and tri-substituted aromatic systems.

Keywords: Gas liquid continuous flow microreactor; Direct fluorination; Fluoroarene

1. Introduction

Fluoroarene derivatives have been used for many applications in the life-science and materials industries [2] and are usually synthesised on the commercial scale by either Balz–Schiemann-type fluorodediazotisation or halogen exchange ('Halex') methodologies [3]. Since both of these strategies require multi-step synthetic sequences, a more direct method for the synthesis of fluoroaromatic systems is the transformation of carbon–hydrogen to carbon–fluorine bonds by reaction of an aromatic substrate with an electrophilic fluorinating agent, such as elemental fluorine.

Grakauskas [4] showed that mono-substituted benzene derivatives gave isomeric mixtures of fluorinated products upon reaction with fluorine, consistent with an electrophilic process. Recently, the use of acids as reaction media for direct fluorination, allowed the Durham group [5,6] to fluorinate selectively a variety of 1,4-disubstituted aromatic derivatives, in which the aromatic ring bears both an electron withdrawing and electron releasing group.

Recently, we have reported the successful use of various continuous flow microreactor systems for direct fluorination processes [6–10] and, in the context of fluorination of aromatic derivatives, studies concerning the fluorination of toluene [11] using falling film and microbubble microreactor technology [12] giving largely a mixture of mono-fluorotoluene isomers have been described [11,13]. There are, of course, many benefits to using continuous flow methodology (no downtime, controllability, etc.) and the further advantages of using microchannels as reaction vessels (better mixing, heat transfer, control, safety, etc.) have been discussed at length [14–16].

In recent years, we have developed a very effective multichannel continuous flow modular reactor for direct fluorination reactions (Fig. 1) and this is described in detail in our earlier paper [10]. Fluorination of 1,3-dicarbonyl systems occurs very effectively and multi-gram quantities of selectively fluorinated derivatives have been produced.

In this paper, we extend the use of our microreactor techniques [7,9,10,17,18] to the synthesis of various fluoroaromatic systems derived from the fluorination of 1,4- and 1,3-disubstituted aromatic substrates. Whilst the fluorination of 1,4-disubstituted systems using batch-wise procedures has

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* Corresponding author. Tel.: +44 191 334 2020; fax: +44 191 384 4737.
** Corresponding author. Tel.: +44 191 334 2039; fax: +44 191 384 4737.
E-mail addresses: R.D.Chambers@durham.ac.uk (R.D. Chambers), Graham.Sandford@durham.ac.uk (G. Sandford).

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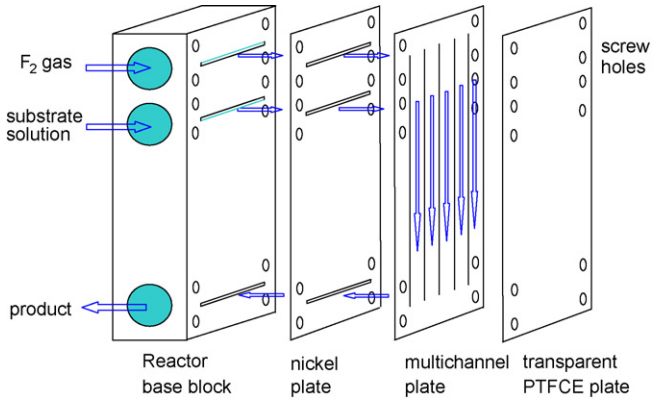


Fig. 1. Schematic representation of modular microreactor device.

been reported earlier [6], effective direct fluorination of highly deactivated 1,3-disubstituted systems bearing two electron withdrawing groups, has not been described previously.

2. Results and discussion

Representative direct fluorination reactions of 1,4-disubstituted aromatic systems bearing an electron withdrawing and releasing group, using microreactor technology, are collated in Table 1. In each case, high selectivity and yields of monofluorinated products are obtained using either acetonitrile or formic acid reaction media. High relative permittivity solvents or protonic acids have been used very effectively for the fluorination of aromatic systems previously [5,6] because, in these media, the fluorine molecule is rendered more susceptible towards nucleophilic attack by interaction with the solvent while competing free radical processes are minimised. Indeed, the products obtained here are consistent with an electrophilic substitution process. Typically, reactions would be carried out over a 16 h period enabling 5–10 g of crude product to be collected. All fluoroaromatic products were identified by comparison with literature data [6] or comparison with an authentic sample.

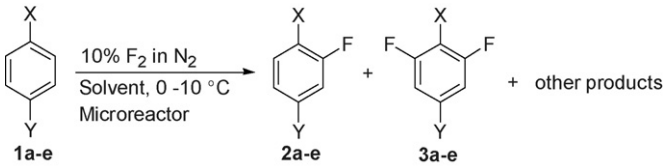
Aromatic rings bearing two strong electron withdrawing groups are, of course, relatively unreactive towards electrophilic attack. However, reactions between such substrates and fluorine using a microreactor is possible giving low conversions to fluorinated products in very selective, clean reactions (Table 2). Fluorinated products were separated by column chromatography and identified by comparison with literature data or full characterisation.

The conversion of **4** to products can be increased by recycling the entire crude reaction mixture through the microreactor device several times. For instance the chloro-derivative **4d** gave 53% conversion to product **5d** after passing through the microreactor once but this increased to 75% conversion after two passages of the same reaction mixture without any decrease in selectivity.

In addition, **2c** and **3c** were characterised by X-ray crystallography. Crystals of the fluorinated nitrophenols **2c** and **3c** were grown from chloroform and their structures were determined by X-ray crystallography (Fig. 2). In **2c**, the orientation of the hydroxy group with an H···F distance of 2.32(3) Å suggests a favourable intramolecular H···F interaction. Geometry optimisations at the *ab initio* (MP2/6-31G*) level of theory using the Gaussian94 package [19] located two minima of **2c** one with the hydroxy group orientated towards the F2 atom (as in the crystal of **2c**) and the other orientated towards the H6 atom. The minimum containing an intramolecular H···F interaction is computed to be more stable than the minimum without the H···F interaction by *ca.* 4.4 kcal mol^{-1}. The crystal packing in **2c** is probably driven by a strong intermolecular H1···O2 interaction between the hydroxy and nitro groups with a H···O distance of 2.05(3) Å. In the unit cell of **3c**, there are two unique molecules of similar geometries forming chains along the [2 1 1] direction through hydroxyl–nitro interactions [H1A···O2B, 1.96(4) Å; H1B···O3A, 2.08(4) Å]. These chains are interconnected through weaker C–H···O contacts (H5B···O2B, 2.54(3) Å; H3A···O3A, 2.60(3) Å) forming layers held together by aromatic π–π interactions (Fig. 3).

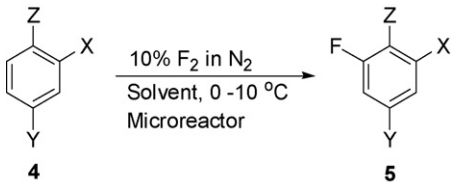
In summary, these representative examples show that direct fluorination of aromatic derivatives is effective using

Table 1
Fluorination of 1,4-disubstituted aromatic derivatives



Substrate	X	Y	Solvent	Conversion (%)	Yield **2** (%)	Yield **3** (%)
1a	OCH_3	NO_2	CH_3CN	87	**2a**, 77	**3a**, 11
1a	OCH_3	NO_2	CH_3CN/HCOOH (3:2, v/v)	43	**2a**, 78	**3a**, 4
1b	OCH_3	CN	CH_3CN	82	**2b**, 74	**3b**, 12
1c	OH	NO_2	HCOOH	67	**2c**, 71	**3c**, 18
1d	CH_3	CN	CH_3CN	78	**2d**, 75	**3d**, 7
1e	OCH_3	CHO	CH_3CN	91	**2e**, 82	**3e**, 9

Table 2
Fluorination of 1,3-disubstituted aromatic derivatives



4 **5**

Substrate **4**	X	Y	Z	Solvent	Conversion (%)	Yield **5** (%)
4a	NO_2	NO_2	CH_3	CH_3CN	38	**5a**, 98
4b	NO_2	NO_2	OCH_3	CH_3CN/HCOOH (3:2, v/v)	86	**5b**, 79
4c	NO_2	NO_2	F	CH_3CN	16	**5c**, 96
4c	NO_2	NO_2	F	HCOOH	34	**5c**, 94
4d	NO_2	NO_2	Cl	HCOOH	53	**5d**, 97
4e	NO_2	CN	H	CH_3CN	18	**5e**, 95
4f	NO_2	NO_2	H	HCOOH	19	**5f**, 96
4f	NO_2	NO_2	H	CH_3CN	27	**5f**, 94
4g	CN	CN	H	CH_3CN	28	**5g**, 85

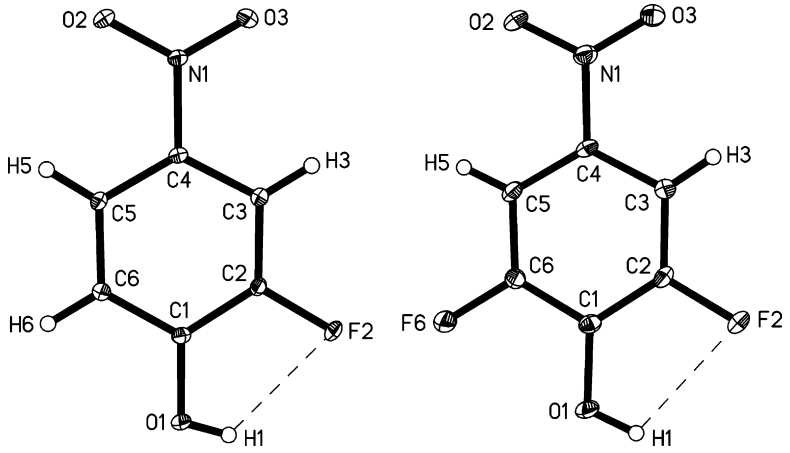


Fig. 2. Molecular structures of **2c** and **3c**. Only one of two unique molecules in the crystal of **3c** is shown. Thermal ellipsoids are drawn at 30% probability level. Selected bond lengths for **2c**: C2–F2 1.3542(14), C1–O1 1.3436(16), O1–H1 0.79(3), N1–O2 1.2441(15), N1–O3 1.2201(15), C4–N1 1.4544(16).

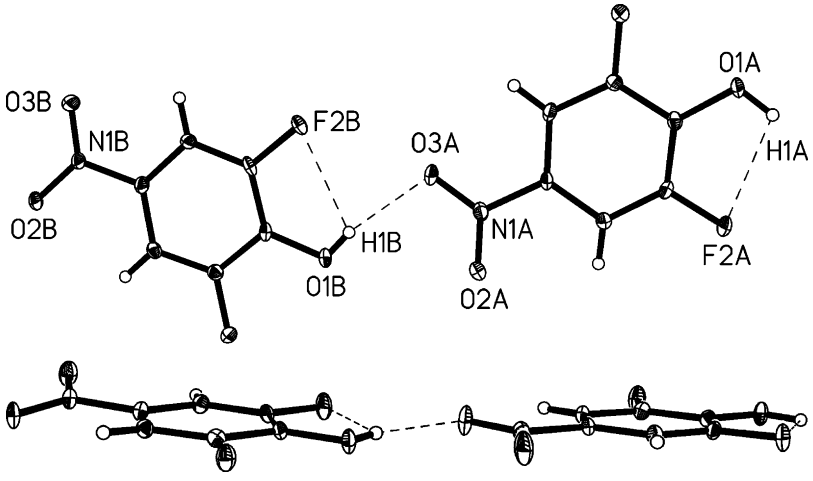


Fig. 3. Views of the two unique molecules in the crystal of **3c** with some inter- and intra-molecular hydrogen interactions.

Table 3
Fluorination of aromatic substrates using microreactor techniques

Substrate	Solvent	Substrate flow[a]	F_2 flow[a]	F_2 substrate	Conversion (%)	Product(s)	(%)
1a	CH_3CN	0.43	1.72	4	87	**2a**, 77	**3a**, 11
1a	CH_3CN/HCOOH (3:2, v/v)	0.43	1.72	4	43	**2a**, 78	**3a**, 4
1b	CH_3CN	0.43	1.72	4	82	**2b**, 74	**3b**, 12
1c	HCOOH	0.43	1.72	4	67	**2c**, 71	**3c**, 18
1d	CH_3CN	0.43	1.72	4	78	**2d**, 75	**3d**, 7
1e	CH_3CN	0.35	1.78	5	91	**2e**, 82	**3e**, 9
4a	CH_3CN	0.87	2.60	3	38	**5a**, 98	
4b	CH_3CN/HCOOH (3:2, v/v)	0.44	1.78	4	86	**5b**, 79	
4c	CH_3CN	0.43	1.72	4	16	**5c**, 96	
4c	HCOOH	0.30	1.78	6	34	**5c**, 94	
4d	HCOOH	0.43	1.72	4	53	**5d**, 97	
4e	CH_3CN	0.42	1.76	4.2	18	**5e**, 95	
4f	HCOOH	0.45	1.78	4	19	**5f**, 96	
4f	CH_3CN	0.14	1.78	12	27	**5f**, 94	
4g	CH_3CN	0.14	1.78	12	28	**5g**, 85	

[a] mmol per channel per hour.

microreactor technology and offers an alternative for the large scale synthesis of appropriate fluoroarene systems as opposed to established batch-wise procedures.

3. Experimental

3.1. General

All starting materials were obtained commercially (Aldrich). NMR spectra were recorded in deuteriochloroform on a Varian VXR 400S NMR spectrometer operating at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR). Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl-silicone) column. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Accurate mass measurements were performed at the EPSRC National Mass Spectrometry Service Centre. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040–0.063 mm) and TLC analysis was performed on silica gel TLC plates (Merck). Fractional distillation was performed on a Fisher Spahltrohr MS 225 apparatus.

3.2. Direct fluorination of aromatic compounds: general procedure

After purging the apparatus with nitrogen, fluorine, as a 10% mixture in nitrogen (v/v), was passed through the microreactor, described in more detail elsewhere [10] via an inlet port at a prescribed flow rate, typically around 10 ml min^{-1} per channel, that was controlled by a mass flow controller (Brooks® Instruments). The microreactor was cooled by an external cryostat to 0–10 °C as required. Substrate mixture was injected by a mechanised syringe pump into the microreactor channel at a prescribed flow rate through the substrate inlet port. Typically, reactions would be carried out over a 16 h period enabling 5–10 g of crude product to be collected. Substrate and fluorine gas flow used for the reactions are given in Table 3.

After passing through the microreactor and outlet port, excess fluorine gas and volatile waste products were passed through a scrubber filled with soda lime. Liquid products were collected in an FEP tube and the crude product mixture was examined by ^{19}F NMR spectroscopy. The product mixture was added to water and extraction of the products from the aqueous layer into dichloromethane was continued until ^{19}F NMR spectroscopy showed no carbon-fluorine resonances in the aqueous layer. Washing the dichloromethane layer with saturated $NaHCO_3$ solution, drying ($MgSO_4$) and evaporation of the solvent gave an oil which was analysed by ^{19}F and ^{1}H NMR spectroscopy and GC–MS. The composition of a weighed crude reaction mixture was determined by GC–MS analysis and the conversion of starting material was calculated from GC peak areas. The amount of fluorinated derivative 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 amount of starting material consumed, i.e., the conversion obtained above.

Purification of products was carried out by column chromatography on silica gel with ethylacetate/hexane as eluent. For all fluorination experiments, the major mono-fluorinated products were characterised by NMR, MS and elemental analysis and/or by comparison with literature data [6,10,20,21] and/or an authentic sample (Aldrich, Fluorochem). Spectral data for novel fluorinated products are listed below.

1,2-Fluoro-3,5-dinitrobenzene (**5c**). (Found: $[M]^+$, 203.9984. $C_6H_2N_2O_4F_2$ requires: $[M]^+$, 203.9982); δ_F −126.0 (dd, $^3J_{FF}$ 20.8, $^4J_{HF}$ 7.73, F-2), −129.0 (dd, $^3J_{FF}$ 20.4, $^3J_{HF}$ 20.4, F-1); δ_H 8.1 (1H, m, H-6), 8.3 (1H, m, H-4); δ_c 115.2 (d, $^3J_{CF}$ 3.1, C-4), 117.1 (dd, $^2J_{CF}$ 22.3, $^3J_{CF}$ 2.3, C-6), 137.2 (m, C-3), 141.5 (m, C-5), 149.5 (dd, $^1J_{CF}$ 278.1, $^2J_{CF}$ 15.7, C-2), 151.3 (dd, $^1J_{CF}$ 259.1, $^2J_{CF}$ 13.2, C-1); *m/z* (EI$^+$) 204 ($[M]^+$, 58%), 112 (100).

2-Chloro-1-fluoro-3,5-dinitrobenzene (**5d**). (Found: $[M]^+$, 219.9683. $C_6H_2ClFN_2O_4$ requires $[M]^+$, 219.9687); δ_F −103.3 (d, $^3J_{HF}$ 7.8); δ_H 8.1 (1H, dd, $^3J_{HF}$ 7.5, $^4J_{HH}$ 2.4, H-6), 8.5 (1H,

Table 4
Crystal data for **2c** and **3c**

Compound	**2c**	**3c**
Formula	$C_6H_4FNO_3$	$C_6H_3F_2NO_3$
M (g/mol)	157.10	175.09
Crystal system	Orthorhombic	Triclinic
a (Å)	7.1637(3)	6.8014(9)
b (Å)	11.1219(4)	9.7327(12)
c (Å)	7.6021(3)	10.0234(13)
α (°)	90	93.181(2)
β (°)	90	102.156(2)
γ (°)	90	97.314(2)
V (Å^3)	605.69(4)	641.03(14)
T (K)	120(2)	120(2)
Space group	*Pna*2(1)	$P\bar{1}$
Z	4	4
μ (mm^{-1})	0.159	0.182
Reflns measured	7825	7055
Reflns unique [R_{int}]	982 [0.0231]	3106 [0.0423]
Goodness-of-fit (on F^2)	1.272	1.071
$R(F)$, $I > 2\sigma(I)$	0.0344	0.0627
$wR(F^2)$, all data	0.0922	0.1400

dd, $^4J_{HH}$ 2.4, $^5J_{HF}$ 1.4, H-4); δ_c 115.5 (d, $^2J_{CF}$ 26.9, C-6), 116.5 (d, $^4J_{CF}$ 2.9, C-4), 123.2 (d, $^2J_{CF}$ 21.8, C-2), 146.0 (s, C-5), 149.0 (s, C-3), 160.0 (d, $^1J_{CF}$ 258.2, C-1); *m/z* (EI$^+$) 220 ([*M*]$^+$, 8%), 128 (100), 92 (98).

3.3. X-ray crystallography[1]

Single crystal structure determinations were carried out from data collected using graphite monochromated Mo Kα radiation (λ = 0.71073) on Bruker three-circle diffractometers equipped with an APEX (for **2c**) and a SMART-1K (for **3c**) CCD detector. Both data collections were carried out at 120 K using Oxford Cryosystems Cryostream N2 flow cooling devices [22]. Series of narrow ω-scans (0.3°) were performed at several ϕ-settings in such a way as to cover in each case a sphere of data to a maximum resolution of 0.71 Å. Data collection was controlled using the SMART software [23], while raw frame data were integrated using the SAINT program [24]. No absorption correction was applied to any of the datasets. The structures were solved using Direct Methods and refined by full-matrix least squares on F^2 using SHELXTL [25]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters (adps). Hydrogen atoms were located from difference Fourier maps and their fractional coordinates refined. Isotropic displacement parameters for hydrogen atoms were restrained to that of their parent C atom, with $U_{iso}(H) = 1.2U_{eq}(C)$. Crystal data and experimental details are given in Table 4.

[1] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 612547 and 612548. Copies of the data can be obtained, free of charge, on application via http://www.ccdc.cam.ac.uk/cont/retrieving.html or to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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