The synthesis of [^{18}F]fluoroarenes from the reaction of cyclotron-produced [^{18}F]fluoride ion with diaryliodonium salts

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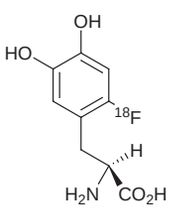
Diaryliodonium salts have been shown to react with fluoride ion at 80 °C in acetonitrile to generate aryl fluorides. The regioselectivity is controlled electronically and by the bulk of the *ortho*-substituents on the rings, with the latter the dominant factor such that electron-rich rings can be fluorinated. *ortho*-Substituted aryl fluorides can be selectively produced from unsymmetrical diaryliodonium salts. The process has been used to synthesise [^{18}F] labelled aromatics by the use of cyclotron generated [^{18}F]fluoride ion.

Positron emission tomography (PET) is an imaging technique for the absolute measurement, *in vivo*, of positron emitters,[1] enabling their pharmacokinetics and biodistribution to be elucidated by non-invasive means. It is a well established technique in clinical research as, for example, in the use of 6-[^{18}F]fluoro-L-DOPA **1**[2] in the study of brain DOPAmine storage in movement disorders such as Parkinson's disease.



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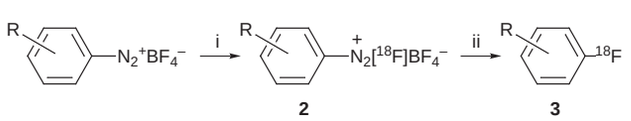
The isotope used for the latter, fluorine-18 ($t_{\frac{1}{2}}$ = 109.7 min), is an important positron emitter and is generally produced with a cyclotron as molecular [^{18}F]fluorine or as the [^{18}F]fluoride anion. The [^{18}F]F^- form has certain advantages over molecular [^{18}F]F_2, as it is produced in higher amounts and higher specific radioactivity by several orders of magnitude.[3] Furthermore, all the [^{18}F]F^- is potentially available for incorporation into a labelled compound, whereas only half the radioactivity of molecular [^{18}F]F_2 can be incorporated *via* a mono-radiofluorination reaction.

Most existing fluoride-based methods normally only work with electron deficient aromatics activated towards nucleophilic substitution.[4–7] In consequence, there is a need for a general process using [^{18}F]F^- for the preparation of [^{18}F]fluoroaromatics which is effective with electron-rich rings.

One of the earliest methods for producing [^{18}F]fluoroarenes from nucleophilic [^{18}F]F^-, and one which does not accord with the general statement above, used the Balz–Schiemann reaction. An aryldiazonium [^{18}F]tetrafluoroborate **2**, which was first prepared by exchange of the BF_4^- fluorine(s) with [^{18}F]F^-, on thermal decomposition gave an [^{18}F]fluoroarene **3** (Scheme 1).[8]

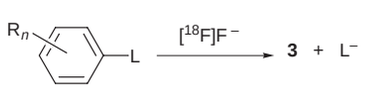


2 **3**

Scheme 1 *Reagents and conditions*: i, [^{18}F]F^-; ii, Δ

The principal drawback of the Balz–Schiemann approach is that only one fluorine atom from the fluoroborate is transferred and thus the maximum radiochemical yield is 25% and in practice as little as 2–15% is observed. This is avoided in a relatively recent modification in which the [^{18}F]F^- fluorination is carried out on diazonium salts with non-fluoride containing counterions such as aryldiazonium tetrachloroborate.[9] This leads, on thermolysis, to the preferred no-carrier-added (NCA) rather than carrier-added (CA) fluorine labelled products. An analogous method, again *via* the aryl cation, uses the decomposition of stable aryl triazenes by hydrogen [^{18}F]fluoride or anhydrous caesium [^{18}F]fluoride in acidic media to yield the NCA aryl [^{18}F]fluorides **3**.[10–12]

Most successful, however, is conventional aromatic nucleophilic substitution using the [^{18}F]F^- anion to displace a suitable leaving group L from an electron deficient benzene ring (as in **4**, Scheme 2). Leaving groups successfully used so far include



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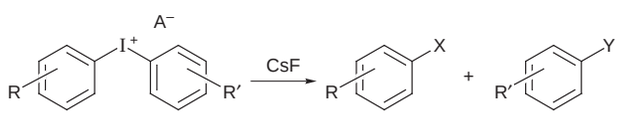
$R_n \geq$ 2- or 4-(ewg); L = F, Br, I, NR'_3^+, ArI^+
ewg = electron withdrawing group

Scheme 2

fluoride,[4] bromide,[5] nitrite (nitro),[6] tertiary amine[13] and of particular relevance to this paper, iodoarene.[7]

We now report further developments of this latter method which allow application to a wide range of NCA [^{18}F]fluoroarene syntheses. Thus a series of functionalised diaryliodonium salts have been synthesised from (diacetoxy)iodobenzene, and more generally from (diacetoxy)iodoarenes, by established methods[14,15] and by the method recently reported by us,[16] for subsequent reaction with the NCA [^{18}F]F^- anion.

Before proceeding with the radiofluorinations, 'cold' reactions of caesium fluoride with diaryliodonium salts, were investigated (Scheme 3) in order to establish the scope and



5 **6** **7**

Scheme 3

Table 1 Reaction of diaryliodonium salts with CsF

	Diaryliodonium salts **5**				Product ratios[a] **6**			**7**		
Run	Cpd.	R-aryl	R′-aryl	A^-	X = F	X = I	X = H	X = F	X = I	X = H
1	**h**	2-$CH_3C_6H_4$	4-Bu′C_6H_4	$CF_3SO_3^-$	0.01	0.31	0.06	0.07	0.55	0
2	**i**	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	$CF_3SO_3^-$	(0.06)[b]	(0.85)[b]	(0.09)[b]	—	—	—
3	**k**	2-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	0.09	0.21	0	0	0.61	0.09
4	**l**	3-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	0.08	0.31	0.08	0	0.53	0
5	**m**	2-$CH_3C_6H_4$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	0.03	0.51	0.06	0.16	0.19	0.05
6	**n**	2,4,6-$(CH_3)_3C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	0.29	0.63	0.08	—	—	—
7	**o**	2,4,6-$(CH_3)_3C_6H_2$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	0.19	0.19	0.09	0	0.44	0.09
8	**p**	3,5-$(CH_3)_2C_6H_3$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	0.15	0.48	0.03	0	0.34	0
9	**q**	4-$(CH_3)_3CCH_2C_6H_4$	3-$CH_3OC_6H_4$	$CF_3SO_3^-$	0.08	0.55	0	0	0.37	0

[a] The ratios were determined by GC–MS and the products identified against standards. [b] The 2- and 4-methyl series were inseparable. The quoted values are the combined ratios.

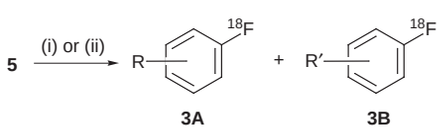
Table 2 [^{18}F]Fluoroarene synthesis

	Diaryliodonium salts **5**					Radiochem. yield[a] (%)	Radiochem. loss[b] (%)	Product ratio	
Run	Cpd.	R-aryl	R′-aryl	A^-	Salt			**3A**	**3B**
1	**a**	C_6H_5	C_6H_5	$CF_3SO_3^-$	KF-APE 2.2.2	80	NM	1.00	—
2	**b**	C_6H_5	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	KF-APE 2.2.2	96	NM	1.00	0
3	**c**	C_6H_5	4-Bu′OC_6H_4	$CF_3SO_3^-$	KF-APE 2.2.2	95	NM	1.00	0
4	**d**	C_6H_5	4-BrC_6H_4	$CF_3SO_3^-$	KF-APE 2.2.2	95	NM	0.30	0.70
5	**e**	C_6H_5	4-IC_6H_4	$CF_3SO_3^-$	KF-APE 2.2.2	94	NM	0.15	0.85
6	**f**	C_6H_5	4-FC_6H_4	$CF_3SO_3^-$	KF-APE 2.2.2	92	NM	0.10	0.90
7	**g**	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	KF-APE 2.2.2	96	NM	0	1.00
8	**h**	2-$CH_3C_6H_4$	4-Bu′C_6H_4	$CF_3SO_3^-$	CsF	60	20	0.80	0.20
9	**i**	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	$CF_3SO_3^-$	CsF	50	26	(1.00)[c]	
10	**j**	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	$CF_3CO_2^-$	CsF	45	22	(1.00)[c]	
11	**k**	2-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	CsF	64	9	1.00	0
12	**l**	3-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	CsF	66	10	1.00	0
13	**m**	2-$CH_3C_6H_4$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	CsF	65	11	0.20	0.80
14	**n**	2,4,6-$(CH_3)_3C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	CsF	50	20	(1.00)[c]	
15	**o**	2,4,6-$(CH_3)_3C_6H_2$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	CsF	67	8	1.00	0
16	**p**	3,5-$(CH_3)_2C_6H_3$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	CsF	45	19	1.00	0
17	**q**	4-$(CH_3)_3CCH_2C_6H_4$	3-$CH_3OC_6H_4$	$CF_3SO_3^-$	CsF	66	9	1.00	0

[a] The radiochemical yields are decay corrected and refer to the total radioactivity of [**3A** + **3B**] in solution as a % of initial activity. [b] This represents the handling loss of radioactivity in the total products; NM = not measured. [c] The isomeric products were inseparable by GC.

feasibility of the reaction.[17] The crude product mixtures were analyzed by GC–MS for their relative ratios (Table 1). As expected fluoroarenes (**6**, **7**; X = F) and iodoarenes (**6**, **7**; X = I) were detected, however unexpectedly protio-deiodinated arenes (**6**, **7**; X = H) were also present in the mixtures and this may have implications in understanding the mechanism of the process. It should be noted that the proportion of fluoride used for the 'cold' reactions was considerably higher than that for the radiofluorination reactions described below where NCA [^{18}F]F^- was used.

Radiochemistry was performed using either the powerfully nucleophilic radiofluorinating agent, [^{18}F]F^- K^+-APE 2.2.2 (APE 2.2.2 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane) [Scheme 4, reagents (i)] which was prepared as previously described from cyclotron-produced NCA [^{18}F]F^- (refs. 3,18) or the similarly prepared Cs^+ [^{18}F]F^- [Scheme 4, reagents (ii)].[19]



Scheme 4 *Reagents and conditions*: (i) [^{18}F]$^-$ K^+-APE 2.2.2 under N_2 (20 psi), 85 °C, 40 min; (ii) [^{18}F]F^- Cs^+, MeCN under N_2 (20 psi), 85 °C, 40 min

Experiments to optimise product yields were carried out on the reaction of diphenyliodonium trifluoromethanesulfonate (triflate) with [^{18}F]F^- K^+-APE 2.2.2. Time course observation of the radiolabelled product showed that 50% of the reaction occurred in the first 10 min and that the reaction reached 80% completion after 40 min. Of the variety of solvents examined (dichloromethane, chloroform, dimethyl sulfoxide, dimethylformamide, tetrahydrofuran and acetonitrile), the highest yields were achieved in acetonitrile, which was also the best solvent for the diaryliodonium salts. Maximal yields were obtained in reactions run at 85 °C. The results are presented in Table 2.

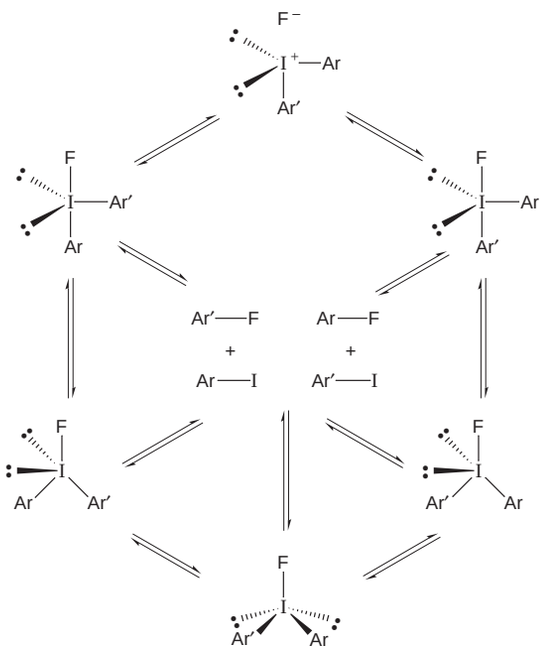
Interestingly, iodonium salts which were functionalised on both aryl rings did not apparently react with the F^- K^+-APE 2.2.2 system at all (Table 2, runs 8–17), possibly because of the steric bulk of the counterion in the presumed tight ion pair.

In general, the reactions proceeded by attack on the most activated (most electron-deficient) arene, so that when the iodonium salt contained a phenyl group and an alkyl- or alkoxy-substituted arene, fluorobenzene was the only fluorinated product. Where the substituent was a moderately electron-withdrawing halogen at the position, (Table 2, runs 4–6), both [^{18}F]fluorobenzene and [^{18}F]halofluorobenzene were formed. In the fluoride substitution reactions of iodonium salts which are functionalised on both aryl rings (Table 2, runs 8–17), the fluoride anion generally attacked the more electron deficient ring.

As has been previously noted,[20] iodonium compounds with

bulky aryl rings tend to undergo nucleophilic substitution on the bulky ring. Thus in these reactions, the mesitylene-substituted iodonium salt **5g** (Table 2, run 7) gave, as the sole fluorinated product, 2,4,6-trimethyl[^{18}F]fluorobenzene. Similarly iodonium salt **7m** (R′ = mesityl, R = *o*-tolyl: Table 2, run 13) gave 2,4,6-trimethyl[^{18}F]fluorobenzene as the major product together with minor amounts of 2-[^{18}F]fluorotoluene. However, bulk alone was not the only factor in these reactions. The 2-methyl, 4′-*tert*-butyl analogue **5h** (Table 2, run 8) gave predominantly the 2-[^{18}F]fluorotoluene with only minor amounts of 4-[^{18}F]fluoro-*tert*-butylbenzene. The critical factor appears to be bulk at the *ortho*-position and a single *o*-substituent is sufficient to induce attack in that ring.

These results are in agreement with the previously observed *ortho* effect.[21–23] Grushin *et al.* proposed a possible mechanism for nucleophilic substitution in aryliodonium salts which can be adapted to explain our observations as shown in Scheme 5.[20]



Scheme 5

Since these systems are known to be fluxional,[20] the precise forms undergoing cheletropic fragmentation are unknown but the *syn* arrangement of the F and Ar (Ar′) groups are obligatory for this process.

A combination of an *ortho*-substituent in one arene ring and/or one or more remote electron donating groups in the other therefore provides a simple means of regiocontrol of the fragmentation process. This is illustrated for the reactions of iodonium salts, **5k**, **5l**, **5o**, **5p** and **5q**, substituted with a 3- or 4-alkoxy group on one ring and alkyl groups on the other. These gave only alkyl[^{18}F]fluoroarenes with both [^{18}F]F$^-$ (Table 2, runs 10, 12, 15, 16 and 17) and cold CsF (Table 1, runs 3, 4, 7–9).

Very few methods for the synthesis of [^{18}F]fluoroarenes are so versatile and none give such high radiochemical yields. Clearly the scope for this reaction is considerable and we seek to produce a wider range of more complex [^{18}F]fluoroaromatics, including compounds useful as radiopharmaceuticals, as well as to further probe the precise mechanisms involved.

Experimental

No carrier-added (NCA) [^{18}F]fluoride (typical specific radioactivity >37 GBq) was produced at the MRC Cyclotron Unit by the ^{18}O (p, n)^{18}F reaction on ^{18}O-enriched water.[3] The [^{18}F]-fluoride was then converted within a glassy-carbon vessel into dry [^{18}F]F$^-$ K$^+$-APE 2.2.2 using APE 2.2.2 (13 mg, 0.035 mmol) and anhydrous potassium carbonate (2.3 mg, 0.017 mmol), as previously described[24,18] or into dry Cs$^+$ [^{18}F]F$^-$ using anhydrous caesium carbonate (5.539 mg, 0.017 mmol). The radiochemical products were analysed on a reversed-phase HPLC column (Lichrosphere 5 RP18) fitted with a sensitive γ-detector. The column was eluted with HPLC grade acetonitrile–water (70 : 30) at a flow rate of 1 ml min^{-1} at ambient temperature. A volume of 2.0 μl was injected for each measurement. Mass spectra were recorded on VG Micromass 7070E and Autospec-Q instruments.

Reaction of diaryliodonium salts with cold CsF: general method

The diaryliodonium salt (0.04 mmol) in anhydrous acetonitrile (0.5 ml) was treated with CsF (0.02 mmol), in a pyrex flask, under N_2. The flask was heated in an oil bath to 85 °C, with stirring for 40 min. The flask was allowed to cool to room temperature and the products in solution were identified (by comparison with standards) and their relative yields estimated by GC–MS. The results are presented in Table 1.

Reaction of diaryliodonium salts with [^{18}F]F$^-$ K$^+$-APE 2.2.2: general method

The diaryliodonium salt (20 mg) along with acetonitrile (0.5 ml) was added to a glassy-carbon vessel containing dry [^{18}F]F$^-$ K$^+$-APE 2.2.2 (*ca.* 110 MBq). The vessel was sealed, pressurised to 20 psi with nitrogen and heated to 85 °C for a reaction time of 40 min. The vessel was allowed to cool to room temperature and the solution was analysed for radiochemical products by radio-HPLC. The radiochemical yields of [^{18}F]-fluoroarenes (decay-corrected) were calculated from the radiochromatograph relative to the amount of unreacted starting [^{18}F]fluoride present after the reaction. It should be noted that some loss of radioactivity (in the range 2–20%) possibly as volatile [^{18}F]fluoroarenes was observed in some cases. The results are presented in Table 2, runs 1–7.

Reaction of diaryliodonium salts with Cs$^+$ [^{18}F]F$^-$: general method

The diaryliodonium salt (20 mg) along with acetonitrile (0.5 ml) was added to a glassy-carbon vessel containing dry Cs$^+$ [^{18}F]F$^-$ (*ca.* 110 MBq). The vessel was sealed, pressurised to 20 psi with nitrogen and heated to 85 °C for 40 min. The vessel was allowed to cool to room temperature and the solution was analysed for radiochemical products by radio-HPLC. The radiochemical yields of [^{18}F]fluoroarenes (decay-corrected) which were calculated from the radiochromatograph, are presented in Table 2, runs 8–17.

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