Preparation of Fluorine-18 Aryl Fluorides: Piperidyl Triazenes as a Source of Diazonium Salts

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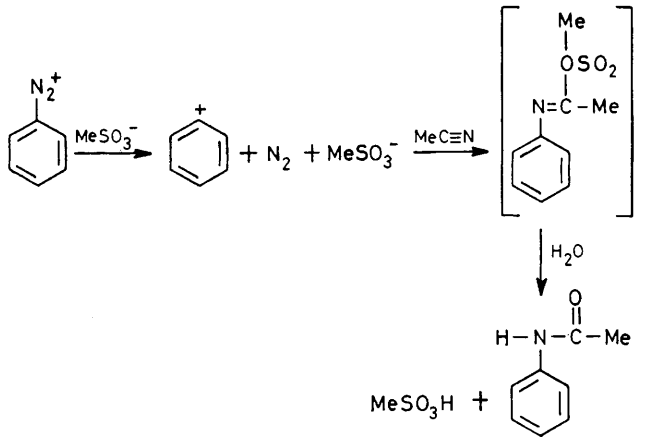
Summary Thermal decomposition of aryl diazonium salts of nonfluorinated acids in anhydrous media, generated by protonation of piperidyl triazenes, gives products resulting from reaction with added nucleophiles including high specific activity ^{18}F-fluoride ions.

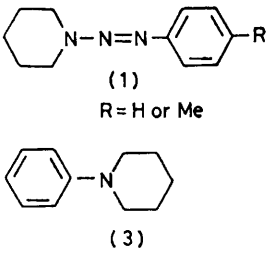
THE recent report of the preparation of aryl radioiodine and astatine compounds at true tracer levels *via* decomposition of diazonium salts[1] prompts us to report our preliminary results on the preparation of aryl fluorides containing fluorine-18, the longest-lived radioisotope of fluorine ($t_{1/2}$ = 110 min, β^+ decay, E_{max} = 0·63 MeV). Our continuing interest in high specific activity ^{18}F-labelled compounds for nuclear medicine studies[2] prompted us to investigate new routes for the preparation of aryl fluorides. Conventional reagents, *i.e.*, BF_4^-, XeF_2,[3] require a stoicheiometric excess of fluorine, which makes their use with high specific activity fluorine-18 statistically unlikely. (The theoretical specific activity for fluorine-18 HF is $1{\cdot}71 \times 10^6$ Ci mmol^{-1}.)

The involvement of phenyl cations in diazonium salt decomposition reactions has been the subject of considerable controversy.[4] Recent studies of the thermal decomposition of hindered diazonium tetrafluoroborates in 2,2,2-trifluoroethanol under conditions where both electron transfer and hydride abstraction are unlikely showed that a phenyl cation is a probable reaction intermediate.[5] We felt that if this reaction could be extended to non-fluorinated solvents and anions and unhindered aromatic compounds, then the phenyl cation would be likely to intercept any incipient nucleophiles, including ^{18}F-fluoride ion.

As diazonium salts without fluorinated anions are unstable and difficult to handle except in aqueous solutions, 1-aryl-2-[1-piperidyl]-1,2-diazaethylene (**1**), 'piperidyl triazenes,' were prepared by a conventional route.[6] These triazenes on treatment with methanesulphonic acid in organic solvents dissociate to the diazonium salt and piperidine. The products of thermal decomposition of the diazonium salts are solvent dependent. In hexamethylphosphoric triamide the hydrocarbon is the major product, as has been shown previously,[7] although the source or nature of the hydrogen atom is not clear. In acetonitrile a labile intermediate is formed, which on aqueous workup gives acetanilide, presumably *via* a Ritter-style reaction,[8] as shown in the Scheme.

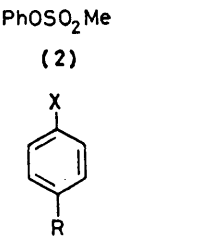


SCHEME



(1)
R = H or Me

(3)



(4)
R = H or Me
X = $MeCO_2$, Br, F, ^{18}F

In ethereal solution [tetrahydrofuran (THF), dimethoxyethane] the major products (85% of the reaction mixture) are phenyl methanesulphonate (**2**) and piperidylbenzene (**3**).

The ratio of the products is dependent on the amount of methanesulphonic acid used to protonate the triazene: with one equivalent (**3**) : (**2**) is 9 : 1; with three equivalents 1 : 9. The remaining 15% of the reaction mixture is apparently products of reaction with solvent, and no hydrocarbon can be detected by g.l.c. Addition of sodium acetate, potassium bromide or caesium fluoride to the reaction mixture gives the appropriate acetoxy-, bromo-, or fluoro-compounds, showing that incorporation of added nucleophiles is feasible.

^{18}F-caesium fluoride is prepared at the Washington University Medical School cyclotron by the $^{20}Ne(d,\alpha)$ reaction, as has been previously described.[9] 15% hydrogen is added to the target gas and the nucleogenic fluorine atoms react with the hydrogen to produce fluorine-18 HF. This is then passed over a silver wool plug containing caesium hydroxide to give very high specific activity ^{18}F-caesium fluoride. The silver wool plug is added to a THF solution (2 ml, freshly distilled from lithium aluminum hydride) of the triazene (**1**) (0·01 mmol) and methane sulphonic acid (0·03 mmol). Refluxing for 4 min then gives the aryl fluorides at a specific activity of *ca.* 10^5 Ci $mmol^{-1}$,† containing *ca.* 50% of the fluorine-18 activity present in solution (**4**). The efficiency of extraction of the fluorine-18 from the silver wool is somewhat variable. In a typical experiment, 11 mCi of absorbed activity gave 8 mCi in solution from which 4 mCi of fluorobenzene were isolated by liquid chromatography.

These results imply, but do not require, that a phenyl cation is involved as a reaction intermediate, and provide a route for the preparation of ^{18}F-labelled compounds with a specific activity suitable for *in vivo* receptor binding studies.

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† Although the $H^{18}F$ is extracted from the target containing no detectable quantities of $H^{19}F$, preparation of the silver wool/caesium hydroxide plug introduces nanogram quantities of fluoride ion, thus diluting the $^{18}F^-$ 10—100 fold.

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