Regiospecific Radiofluorination of Arylpentafluorosilicates as a General Route to ^{18}F-Labelled Aryl Fluorides

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Radiofluorinations of potassium arylpentafluorosilicates, $K_2[RSiF_5]$, with ^{18}F-labelled acetyl hypofluorite in acetic acid give ^{18}F-labelled aryl fluorides in 6—20% yield.

The growing interest in metabolic studies *via* positron emission tomography (PET)[1] calls for new synthetic methodologies which allow rapid and efficient incorporation of short-lived radionuclides (*e.g.*, halogen radioisotopes) into organic molecules. Recently, organopentafluorosilicates, $K_2[RSiF_5]$ have been shown as one of the most suitable and versatile classes of intermediates in the regio- and stereospecific electrophilic halogenation of organic compounds with chlorine, bromine, and iodine, equation (1).[2]

$$K_2[RSiF_5] \xrightarrow{+X_2} R\text{–}X + K_2SiF_5X \qquad (1)$$

R = alkyl, aryl
X = Cl, Br, I

The viability of this approach in radiosynthesis has also been demonstrated in the preparation of a variety of no-carrier-added (NCA) radiobrominated and radioiodinated model compounds from the corresponding organopentafluorosilicate precursors.[3] Since the fluorinations of this class of compounds have not been studied, and the ^{18}F-labelled aryl fluorides are important structural components of a number of ^{18}F-labelled radiopharmaceuticals,[4] we have extended this reaction to the radiofluorination of these substrates with ^{18}F-labelled acetyl hypofluorite as a new route to ^{18}F-labelled aryl fluorides.

Potassium arylpentafluorosilicates (**1a—c**) were synthesized and purified as previously described.[3,5] Since these compounds are practically insoluble in most organic solvents, (*e.g.*, Freon-11) we have carried out the fluorination of these compounds with acetyl hypofluorite ($MeCO_2F$) in acetic acid.[6]

Reactions of compounds (**1a—c**) with $MeCO_2{}^{18}F$ in $MeCO_2H$ at room temperature for 10 min followed by purification gave the corresponding ^{18}F-labelled aryl fluorides in 6—20% yield [Table 1, equation (2)]. Extension of the reaction time up to 60 min does not lead to any appreciable difference in the yields and distribution of the products.

$$\underset{(1)}{K_2[RSiF_5]} \xrightarrow[MeCO_2H]{MeCO_2{}^{18}F} R\text{–}{}^{18}F \qquad (2)$$

Table 1. Radiochemical yields of ^{18}F-labelled aryl fluorides from the fluorinations of potassium arylpentafluorosilicates with $MeCO_2{}^{18}F$ in $MeCO_2H$ at 25 °C.[a]

(1)	Radiochemical yield (%)[b,c] $R^{18}F$
a; R = Ph	13—20
b; R = $PhCH_2$	6
c; R = *p*-MeC_6H_4	18

[a] Reaction time: 10 min. Substrate concentration: *ca.* 30—50 μmol. F_2 carrier concentration: *ca.* 40 μmol. [b] Products were identified using radio h.p.l.c. [Perkin–Elmer Series 3B Liquid Chromatograph equipped with a u.v. detector and connected to a Berthold Model LB 503 radioactivity detector. C18 column with H_2O : MeOH (2 : 3) as elution solvent] and radio g.l.c. [Varian Aerograph Model 920 Gas Chromatograph equipped with a hot-wire detector and connected to a heated flow proportional counter. A 20% Carbowax 20M on AW Chromosorb W (3.6m × 6mm) column was used] and comparison of retention times with those of authentic samples. [c] It should be noted that the acetic acid solution of ^{18}F-labelled acetyl hypofluorite contains an equivalent amount of $NH_4{}^{18}F$. Therefore, the maximum radiochemical yield of ^{18}F-labelled organic products would be 50%;

$$[^{18}F]F_2 + MeCO_2NH_4 \rightarrow MeCO_2{}^{18}F + NH_4{}^{18}F$$

These results indicate that rapid regiospecific incorporation of ^{18}F into simple aromatic molecules can be accomplished by fluorination of arylpentafluorosilicates with $MeCO_2{}^{18}F$ under very mild conditions, and the pronounced reactivity of these arylpentafluorosilicates toward electrophilic reagents is further confirmed by this study. Since organopentafluorosilicates are practically insoluble in common organic solvents, the ^{18}F-labelled organic products resulting from this reaction are more easily purified than those from the fluorination of arylsilanes.[7—9] However, since the electrophilic radiofluorination procedures such as the one we describe here require $MeCO_2{}^{18}F$ which is generated from $[^{18}F]F_2$,[10] the maximum radiochemical yield of the organic product is 50%. In addition the specific activity of $[^{18}F]F_2$ is only moderately high with the resulting radiotracers being produced in a specific activity of *ca.* 10 Ci/mmol. This method thus provides an alternative

route to ^{18}F-labelled radiopharmaceuticals which are not required to be NCA and contain an aromatic ring without activating groups.[11,12] An obvious application of this method would be the syntheses of 6-[^{18}F]fluoro-3,4-dihydroxyphenylalanine (6-fluoro-DOPA)[13] and *p*-fluoroamphetamine from the corresponding silicates. The mechanism of this reaction is under investigation.

This research was carried out under contracts with the U.S. Department of Energy at Brookhaven National Laboratory and at Los Alamos National Laboratory. We acknowledge grants from the Office of Health and Environmental Research (C. Y. S., A. P. W., and D. S. W.) and the National Institutes of Health (M. S. and G. A.). We thank Dr. J. S. Fowler for her constructive comments.

Received, 12th June 1984; Com. 815

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