

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

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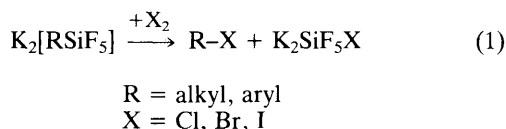
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Radiofluorinations of potassium arylpentafluorosilicates,  $\text{K}_2[\text{RSiF}_5]$ , with  $^{18}\text{F}$ -labelled acetyl hypofluorite in acetic acid give  $^{18}\text{F}$ -labelled aryl fluorides in 6–20% yield.

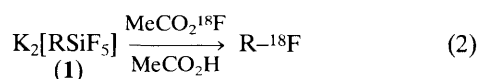
The growing interest in metabolic studies *via* positron emission tomography (PET)<sup>1</sup> calls for new synthetic methodologies which allow rapid and efficient incorporation of short-lived radionuclides (*e.g.*, halogen radioisotopes) into organic molecules. Recently, organopentafluorosilicates,  $\text{K}_2[\text{RSiF}_5]$  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).<sup>2</sup>



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.<sup>3</sup> Since the fluorinations of this class of compounds have not been studied, and the  $^{18}\text{F}$ -labelled aryl fluorides are important structural components of a number of  $^{18}\text{F}$ -labelled radiopharmaceuticals,<sup>4</sup> we have extended this reaction to the radiofluorination of these substrates with  $^{18}\text{F}$ -labelled acetyl hypofluorite as a new route to  $^{18}\text{F}$ -labelled aryl fluorides.

Potassium arylpentafluorosilicates (**1a–c**) were synthesized and purified as previously described.<sup>3,5</sup> 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 ( $\text{MeCO}_2\text{F}$ ) in acetic acid.<sup>6</sup>

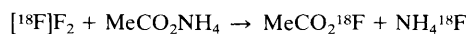
Reactions of compounds (**1a–c**) with  $\text{MeCO}_2^{18}\text{F}$  in  $\text{MeCO}_2\text{H}$  at room temperature for 10 min followed by purification gave the corresponding  $^{18}\text{F}$ -labelled aryl fluorides in 6–20% yield [Table 1, equation (2)]. Extension of the reaction time up to 60 min does not lead to any appreciable difference in the yields and distribution of the products.



**Table 1.** Radiochemical yields of  $^{18}\text{F}$ -labelled aryl fluorides from the fluorinations of potassium arylpentafluorosilicates with  $\text{MeCO}_2^{18}\text{F}$  in  $\text{MeCO}_2\text{H}$  at 25 °C.<sup>a</sup>

(1)	Radiochemical yield (%) <sup>b,c</sup> R $^{18}\text{F}$
a; R = Ph	13–20
b; R = PhCH <sub>2</sub>	6
c; R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	18

<sup>a</sup> Reaction time: 10 min. Substrate concentration: *ca.* 30–50 μmol. F<sub>2</sub> carrier concentration: *ca.* 40 μmol. <sup>b</sup> 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<sub>2</sub>O: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. <sup>c</sup> It should be noted that the acetic acid solution of  $^{18}\text{F}$ -labelled acetyl hypofluorite contains an equivalent amount of  $\text{NH}_4^{18}\text{F}$ . Therefore, the maximum radiochemical yield of  $^{18}\text{F}$ -labelled organic products would be 50%;



These results indicate that rapid regiospecific incorporation of  $^{18}\text{F}$  into simple aromatic molecules can be accomplished by fluorination of arylpentafluorosilicates with  $\text{MeCO}_2^{18}\text{F}$  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  $^{18}\text{F}$ -labelled organic products resulting from this reaction are more easily purified than those from the fluorination of arylsilanes.<sup>7–9</sup> However, since the electrophilic radiofluorination procedures such as the one we describe here require  $\text{MeCO}_2^{18}\text{F}$  which is generated from  $[^{18}\text{F}]\text{F}_2$ ,<sup>10</sup> the maximum radiochemical yield of the organic product is 50%. In addition the specific activity of  $[^{18}\text{F}]\text{F}_2$  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  $^{18}\text{F}$ -labelled radiopharmaceuticals which are not required to be NCA and contain an aromatic ring without activating groups.<sup>11,12</sup> An obvious application of this method would be the syntheses of 6- $^{18}\text{F}$ fluoro-3,4-dihydroxyphenylalanine (6-fluoro-DOPA)<sup>13</sup> and *p*-fluoroamphetamine from the corresponding silicates. The mechanism of this reaction is under investigation.

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