The ^{18}F Radiofluorination of Arylsilanes[1]

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The synthesis of ^{18}F labelled compounds by cleaving silanes with $[^{18}F]F_2$ is reported.

Fluorine-18 is a particularly useful tracer isotope because its substitution for hydrogen in organic molecules generally does not alter their biological properties from those of the parent compounds,[2] since the size and energy of the C–F bond is comparable to that of the C–H bond.

Arylsilanes react with electrophilic halogens such as Cl_2, Br_2, and I_2 to give the corresponding aryl halides.[3] Perhaps because of the high reactivity of F_2 however, its reaction with arylsilanes has not been investigated in detail. We studied the fluorination of 'silicon-activated' aryl positions for the purpose of introducing ^{18}F into radiopharmaceuticals. Because it is a positron emitting radioisotope ($t_{1/2}$ 110 min), fluorine-18 has been widely used in nuclear medicine research especially in studies of blood flow and brain metabolism by positron emission tomography (PET).[4]

Adam *et al.*[5] fluorinated tetraphenylsilane, but their chemical yield was rather low: 2.4% in Freon and 7% in CCl_4. We prepared several arylsilanes (**1**)—(**4**), in good yields (*ca.* 70%), by metallating the aryl bromides by lithium–halogen exchange (BuLi in tetrahydrofuran, −78 °C) followed by silylation (R_3SiCl, room temp.). The silanes were characterized by ^1H n.m.r. and electron impact mass spectroscopy. We then examined their reaction with [^{18}F]fluorine.

The radiofluorination of (**1**)—(**5**)† was conducted as follows: the silyl compound (1 mmol) in trichlorofluoromethane (Freon-11, 12 ml) was added to a reaction vessel and purged with N_2. After cooling to −78 °C, $[^{18}F]F_2$ (*ca.* 80 μmol, 0.5% F_2 in neon)[6] was bubbled into the reaction vessel for 8 min

p-$R^1C_6H_4R^2$

(**1**); R^1 = H, R^2 = $SiMe_3$
(**2**); R^1 = H, R^2 = $SiMe_2Bu^t$
(**3**); R^1 = H, R^2 = $SiMePh_2$
(**4**); R^1 = CN, R^2 = $SiMe_3$
(**5**); R^1 = Cl, R^2 = $SiMe_3$
(**6**); R^1 = H, R^2 = F (^{18}F)
(**7**); R^1 = CN, R^2 = F (^{18}F)
(**8**); R^1 = Cl, R^2 = F (^{18}F)

followed by helium for 1 min to flush the system. After passing the compound through a silica gel column using 1% ethyl acetate in hexane as solvent to remove inorganic impurities, we obtained the labelled compounds, in 14—21% radiochemical yields (Table 1).‡

These results indicate that arylsilanes can be fluorinated over a short reaction time to give products in good radiochemical yields and purity. The yield is highest with trialkylsubstituted arylsilanes; it is reduced somewhat when electron withdrawing substituents are on the aryl ring.

† The silane (**5**) was obtained from the Petrarch Chem. Co., Levittown, Pennsylvania, U.S.A.

‡ Products were identified using h.p.l.c. [Partisil 10-PAC or Partisil 10-OS columns with hexane and water–propan-2-ol (2:3) as elution solvent, respectively], a u.v. detector at λ = 260 nm, a radiochemical detector, and by thin layer radiochromatography (silica gel) and comparison of R_f values with those of authentic samples. The maximum possible yield is 50%. The chemical and radiochemical yields were estimated from the area under the peak that corresponds to the product in the h.p.l.c. chromatogram and from the activity of $[^{18}F]F_2$ extracted from the target as measured by titration with hydrogen sulphite ion (ref. 6), respectively. After purification by h.p.l.c. the products were isolated in a radiochemical purity of at least 90% (specific activity of *ca.* 310 Ci/mol).

Table 1. Yields of [^{18}F]aryl fluorides from the reaction of [^{18}F]F_2 with arylsilanes.

Starting material	Product	Radiochemical[a] (chemical) yield/%
(1)	**(6)**[b]	20 (23)
(2)		21 (24)
(3)		14 (16)
(4)	**(7)**[c]	14 (16)
(5)	**(8)**[c]	14 (16)

[a] Reaction time *ca.* 20 min. [b] Has been proposed as a myelin tracer (ref. 5). [c] Intermediate in the synthesis of haloperidol and spiroperidol.

The use of organosilanes as intermediates for radiofluorination offers several advantages. Organosilanes are readily obtained from inexpensive starting materials. They are non-toxic, in contrast with organotin compounds which are toxic, particularly the more volatile ones. Moreover, organosilanes are quite stable, and do not require storing under anhydrous or inert atmospheres.[7] The time required for fluorinating the aryl–tin bond is *ca.* 1 h;[8] our synthesis requires only *ca.* 20 min, which means that less time is required for handling the radioactive reaction mixtures. The procedure, therefore, is a valuable method for ^{18}F-radiofluorination of aryl components because of its ease and also the relatively high yields that are obtained.

We have used this approach in the preparation of 4-[^{18}F]-phenazone[9] from the corresponding 4-silane.[10] This radiosynthesis will be described elsewhere.

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