Cleavage of Aryl–Tin Bonds with Elemental Fluorine: Rapid Synthesis of [^{18}F]Fluorobenzene

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Summary [^{18}F]Fluorobenzene has been synthesized rapidly by treatment of aryltin derivatives with [^{18}F]F_2 in $CFCl_3$ or CCl_4 at −78 to 0 °C.

As part of a general program to synthesize fluorinated aromatic compounds with ^{18}F ($t_{\frac{1}{2}}$ 110 min), for use in Positron Emission Tomography (PET),[1] we have synthesized [^{18}F]-fluorobenzene by [^{18}F]F_2 cleavage of tin–phenyl bonds.†

There is ample precedent in the literature for cleavage of aryl–tin bonds by halogens and interhalogens (I_2, Br_2, Cl_2, ICl, IBr),[2] and it is known that alkyl–tin bonds are cleaved more slowly by those same reagents.[3] Given these facts, and the ease with which aromatic substrates can be metallated, and subsequently stannylated,[2,4] it occurred to us that such substances might be ideal substrates for fluorination using elemental fluorine. Although we are aware of no literature precedent for such reactions, we now demonstrate that this is a rather general method for aromatic fluorination.

$PhSnR_3$
(**1**) R = Ph
(**2**) R = Bu^n

Reaction of either tetraphenyltin (**1**) (100 μmol) or tributylphenyltin (**2**) (100 μmol) with F_2 (0·1% F_2 in Ne) (50—60 μmol) in $CFCl_3$ at −78 °C for 40 min gave fluorobenzene (identified by g.l.c. and h.p.l.c.) in 15 and 70% chemical yields, respectively [from g.l.c. analysis and based on the amount of F_2 used, calculated as described in the literature[5]]. Reaction of (**1**) or (**2**) with F_2 in CCl_4 at 0 °C for 40 min gave fluorobenzene in 56 and 48% chemical yields, respectively. The tin substrates (**1**) and (**2**) are kept in an excess to minimise fluorination of the phenyl rings on the starting material and of the produced fluorobenzene, since it is known that aromatics can be non-selectively fluorinated by F_2.[6,7] The low yield for the reaction of (**1**) in $CFCl_3$ at −78 °C is thought to be due to the poor solubility of (**1**).

Reactions of (**1**) or (**2**) with [^{18}F]F_2‡ were performed in $CFCl_3$ at −78 °C for 40 min and gave radiochemical yields of 8 and 37%, respectively, based on the total initial activity of ^{18}F; 50% yield is the maximum obtainable. Radiochemical yields were calculated after distillation of the reaction mixture and subsequent purification by h.p.l.c.; 67% of the activity in the distilled reaction product obtained from tributylphenyltin (**2**) was located in the peak due to fluorobenzene, with the remainder likely being distributed between $H^{18}F$, polyfluorinated benzenes, and, possibly, butyl fluoride.

Given the ease with which the tri-n-butyltin moiety can be attached to aromatic systems, the high selectivity of the fluorination of (**2**) augurs well for the general use of this approach for the synthesis of specifically fluorinated aromatic compounds. In the context of PET ^{18}F chemistry, the method is suitable for studies which require a medium to low specific activity (<10 Ci/mmol). The total elapsed time for the synthesis of [^{18}F]fluorobenzene is typically one hour. This includes extraction of the [^{18}F]F_2 gas from the cyclotron target system in which it is generated, distillation of the reaction mixture and reverse phase h.p.l.c. purification.

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† Preliminary results on the reaction of F_2 with aryl-mercury and other aryl-metal derivatives are encouraging and will be reported later.

‡ [^{18}F]F_2 was produced by the ^{nat}Ne(p,Spall)^{18}F reaction using 500 MeV protons from the TRIUMF cyclotron. The details of the target and gas transfer system will be described elsewhere.

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