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Short Research Article

Fluoridation of 2-thienyliodonium salts†

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Introduction

The importance of fluoridation has come to the fore due to the recent renewed interest in the medical imaging technique—Positron Emission Tomography. This requires new methodologies for the fluoridation of compounds as radiotracers and radiopharmaceuticals, allowing us to use PET for diagnosis and to increase our knowledge of *in vivo* pharmacokinetics.

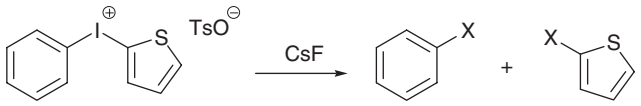
Results and discussion

Diaryliodonium salts have been shown to be suitable precursors for the preparation of fluorine-18 labelled aromatics[1] and there are several distinct advantages over many conventional procedures.

- The use of [^{18}F]fluoride, which may be produced in much higher amounts and higher specific radioactivity than [^{18}F]F_2 and derived reagents (cf. fluorodestannylation).
- Iodonium salts place little or no restriction on the nature and pattern of aromatic substituents of the target (cf. S_NAr processes).

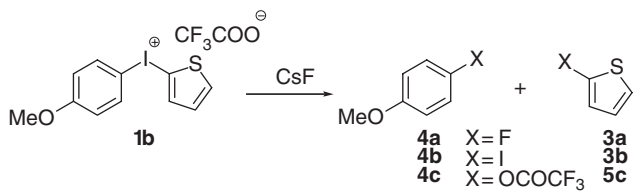
The outcome of the fluoridation has been shown to be dependent on both steric and electronic factors. The *ortho* effect states that if an aromatic ring on the iodonium salt is substituted at the *ortho* position then it is this ring that undergoes fluoridation. The electronic effect results in the fluoridation of the most electron-deficient ring. We have found that the electronic factors take precedence over the *ortho* effect.[2]

Following our initial report[3] on the fluoridation of heteroaromatic iodonium salts and the potential of the 2-thienyl substituent as a non-participating aromatic ring,[4] in the formation of fluorine-18 labelled radiopharmaceuticals, the synthesis and fluoridation of a range of 2-thienyliodonium salts was investigated.



Scheme 1

The fluoridation of salt **1a** gave fluorobenzene **2a**, as the sole fluoroarene (Scheme 1). However analysis of the crude reaction mixture, by GC-MS, indicated that both aryl iodides (**2b**, **3b**) were present suggesting that both possible fluoroarene products should also be present. Also both possible products (**2c**, **3c**) from the nucleophilic substitution by the counter-ion were present. These results suggest that the fluoridation result—lack of **3a**—was misleading in terms of selectivity of the process. The other products were in similar amounts suggesting that the phenyl and 2-thienyl substituents were similar in electronic profile as would be expected.



Scheme 2

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The fluoridation of the 4-methoxyphenyl(2-thienyl) iodonium salt **1b** (Scheme 2) was also investigated. Again both possible aryliodides (**4b**, **3b**) were present in the crude reaction mixture as were both possible products (**4c**, **5c**) from counter-ion addition—this suggested that both possible fluoroarenes were produced however the only fluoroarene detected was 4-fluoroanisole **4a** (in trace amounts)—this is again consistent with the electronic nature of the 2-thienyl substituent.

In these reactions both fluoroarenes should be present, however in both cases 2-fluorothiophene was not detected. These results suggest that 2-thienyl may not be the ideal non-participating ring for the production of fluoroarenes by the fluoridation of diaryliodonium salts and that it is the analysis/detection of 2-fluorothiophene that may be a problem. This lack of detection may be due to the highly volatile nature of 2-fluorothiophene (boiling point 82°C[5]) which may be lost under the reaction conditions (T > b.p.) or on work-up/analysis. It may also be unstable—e.g. subject to hydrolysis leading to only fluoride being detected. In addition it may also co-elute by HPLC and GC due to very similar properties to other components (e.g. PhF, b.p. 80°C) or co-elute or pre-run the solvent. 2-Fluorothiophene also has limited UV activity making detection by TLC and HPLC difficult/inconsistent.

Analysis of the radiofluoridation of 2-thienyl(phenyl) iodonium tosylate initially gave a single peak by radio HPLC however after extensive method development (following our concerns, in this case about co-elution) this was found to actually consist of two components—the first fluorobenzene was as expected, the second appeared to be 2-fluorothiophene (an authentic sample was prepared by lithiation of thiophene and a quench with NFSI[6]).

In summary the detection, characterization and isolation of 2-fluorothiophene is extremely problematic. In addition the analysis of the non-fluorinated products from the fluoridation of 2-thienyliodonium salts strongly suggests that the process is not as selective as would appear from the fluoroarene products only.

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