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Short Research Article

Diaryliodonium salts: a solution to 3-(^{18}F)fluoropyridine†

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Abstract: Fluorine-18 labelled fluoropyridines have found increasing application in the medical imaging technique of Positron Emission Tomography. The fluorine-18 has largely been restricted to the 2- and 6-position where its introduction may be readily achieved, from a range of appropriate precursors, by nucleophilic aromatic substitution using [^{18}F]fluoride. However, fluorine at this position may be labile *in vivo* limiting the potential of the radiotracer. To date the more stable 3-fluoro and 5-fluoropyridines have not been exploited due to unsuitable methods of preparation. Pyridyliodonium salts provide a convenient way to overcome this restriction and allow the introduction of fluorine-18, as fluoride, into the 3- or 5-position.

Keywords: fluorinated aromatics; fluorine-18; hypervalent iodine

Introduction

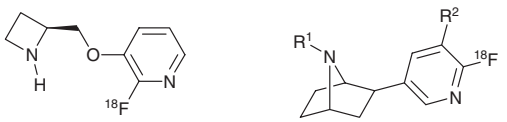
Diaryliodonium salts have been shown to be suitable precursors for the preparation of fluorine-18 labelled aromatics[1] which are employed extensively in clinical research using the medical imaging technique—Positron Emission Tomography. This new approach has several distinct advantages over conventional procedures to this important class of materials.

- 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]

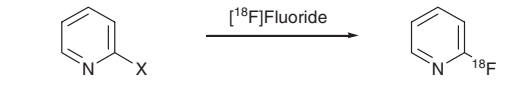
Fluoropyridines have found increasing applications in PET[3] with the 2-fluoro derivatives (For examples see Figure 1) providing radiolabelled material in both high purity and high radiochemical yield.[4]

These materials are accessed by nucleophilic aromatic substitution of an appropriate precursor by [^{18}F]fluoride (Scheme 1), a similar approach provides



2-[^{18}F]F-A85380 [^{18}F]FEP derivatives

Figure 1 2-[^{18}F]Fluoropyridines.



X = F, Cl, Br, NO_2, $[NMe_3]^+$ >80%

Scheme 1

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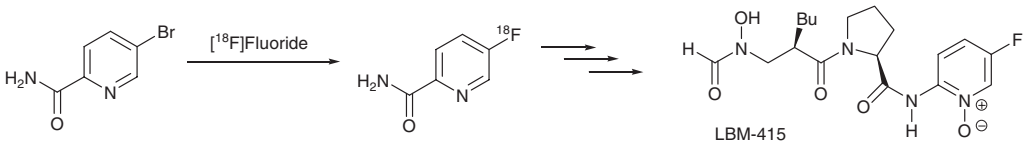
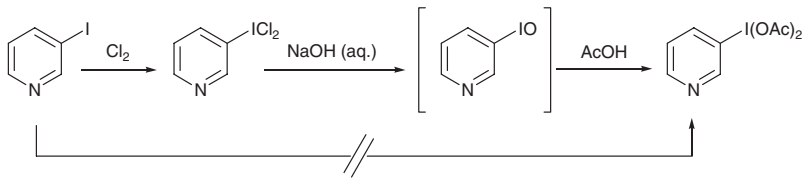
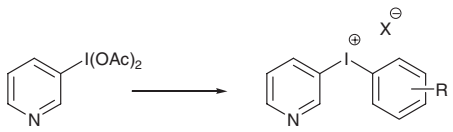


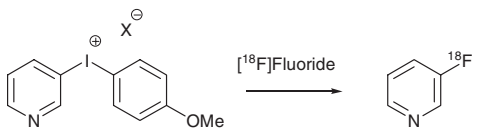
Scheme 2



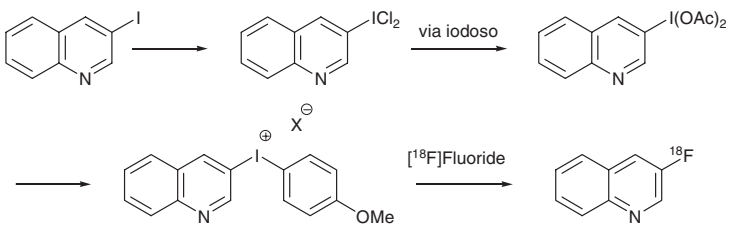
Scheme 3



Scheme 4



Scheme 5



Scheme 6

the 4-[^{18}F]fluoroderivatives. As expected the 3-fluoro derivative is not available using this approach unless very strongly electron-withdrawing groups are present on the pyridine ring, and then only in low yield.

Substitution may also be effected at the desired position providing a suitable electron-withdrawing group is *ortho* or *para* to the leaving group. An example of this approach (Scheme 2) is in the formation of LBM-415.[5] In this case a carbonyl group is employed *para* to the bromine leaving group allowing conventional S_NAr chemistry to occur and the introduction of the fluorine-18. Subsequent post-radiolabel transformations convert the [^{18}F]fluoropyridine into the final target.

We proposed diaryliodonium salts as a more generic route to 3-fluoropyridines as this approach has been shown to place little or no restriction on the aromatic substituents allowing it be used much later in the synthetic sequence. In the case of benzene based systems we generated the required iodobis (acetate) by oxidation of the aryliodide with sodium perborate or other oxidising agent however this proved an unsuitable route for the corresponding 3-pyridyliodobis (acetate).

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An alternative route to this key iodine (III) precursor was developed with the iododichloride installing the necessary oxidation state for the iodine. Treatment of this material with aqueous sodium hydroxide generated the iodosopyridine which was rapidly converted to the 3-pyridyliodobis (acetate) by the action of acetic acid (Scheme 3).

A range of 3-pyridyl(aryl)iodonium salts were then prepared (Scheme 4) according to our standard procedures[6] and the selectivity of the fluoridation process determined. It was found that when 4-methoxyphenyl was the alternative aromatic ring that the fluorinated product was exclusively 3-fluoropyridine.

The radiochemical study (K[^{18}F], 30 min) using this substrate was found to give the target 3-[^{18}F]fluoropyridine in radiochemical yields of 55–63% (Scheme 5).

Fluoroquinolines have also demonstrated biological activity and we were interested whether the same approach may be employed to access 3-fluoroquinoline. During this study it was also found that quinoline-3-iodobis(acetate) also had to be prepared via the iododichloride derivative. Formation of the corresponding iodonium salts proceeded as expected as did the selectivity of the fluoridation process. Radiofluoridation was also successful although the yields were slightly lower (22–25% RCY) than for the pyridine example (Scheme 6).

Summary

Iodonium salts provide a practical route to 3-[^{18}F] fluoropyridines and 3-[^{18}F]fluoroquinolines using [^{18}F]fluoride ion. The use of 4-methoxyphenyl as the alternate aromatic ring provides the necessary degree of selectivity in the fluoridation process.

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