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Short Research Article

A convenient synthesis of (^{14}C)-labeled aromatic iodides as versatile synthetic intermediates†

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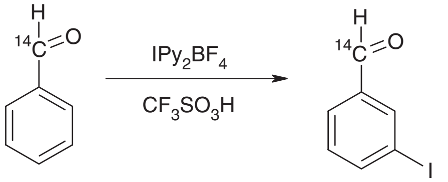
Introduction

One of the commonest methods for the introduction of iodine into an aromatic ring involves the reaction of a diazonium salt with an iodide ion. Recently, we needed to synthesize a number of [^{14}C]-labeled aromatic iodides with a 1,3-disubstitution pattern and found that an alternative strategy to conventional diazotization was required. The reaction of bis(pyridine)iodonium(I)tetrafluoroborate (IPy_2BF_4) in the presence of tetrafluoroboric acid or trifluoromethanesulphonic acid with unsaturated compounds[1] and aromatic substrates[2] has been reported.

Results and discussion

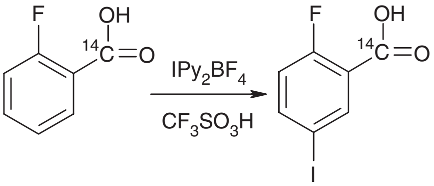
Our first example of using IPy_2BF_4 was to iodinate [carboxyl-^{14}C]benzaldehyde, in the presence of trifluoromethane sulphonic acid in dichloromethane, meta to the aldehyde in a yield of 47% (Scheme 1). The reaction was slow, three days in total, however, the starting material was recoverable from the reaction.



Scheme 1

Another example using IPy_2BF_4 is the preparation of 2-fluoro-5-iodo[carboxyl-^{14}C]benzoic acid. Initial studies concentrated on the carbonation of 4-iodofluorobenzene[3] and yielded only 6% of the desired compound. This reaction is possible if the lithium species can be applied rapidly to a large excess of solid carbon dioxide in diethyl ether. The anion prefers to react with the carbon dioxide rather than eliminating lithium fluoride to give benzyne. Due to the fact that [^{14}C]carbon dioxide is normally manipulated as a gas, this proved very difficult to replicate and an alternative route was investigated. The 2-fluoro[carboxyl-^{14}C]benzoic acid was prepared and reacted with IPy_2BF_4 in the presence of trifluoromethane sulphonic acid in dichloromethane. An isolated yield of 58% was obtained (Scheme 2).

A third example is the iodination of 2-fluoro [U-^{14}C]aniline using IPy_2BF_4 (Scheme 3). Initial studies concentrated on the iodination of 2-fluoro[U-^{14}C]aniline·hydrochloride with sodium hydrogen carbonate and iodine in methanol/water at 10°C. This yielded very little product. 2-Fluoro-4-iodo[U-^{14}C]aniline was prepared by reacting 2-fluoro[U-^{14}C]aniline with IPy_2BF_4 in the presence of tetrafluoroboric acid in



Scheme 2

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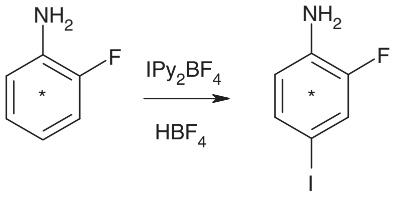
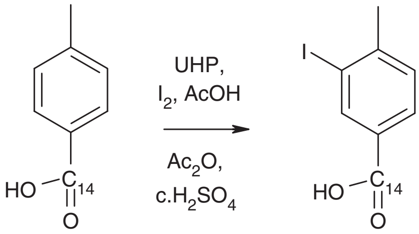


Scheme 3



Scheme 4

dichloromethane. An isolated yield of 86% was obtained.

This is a very clean way of iodinating molecules without the need for a functional group to be present in the molecule, whereas diazotization requires the presence of an amino group. Some further examples include the iodination of benzene using iodine(lll)species,[4] which can either monoiodinate or diiodinate depending upon the quantities of sodium periodate and iodine used. For the synthesis of 1,4-diiodo[ring-U-^{14}C]benzene an isolated yield of 55% was obtained after recrystallization. Other examples of this type of oxidative iodination involve using the stable commercially available solid urea/hydrogen peroxide addition compound (UHP) in place of sodium periodate.[5] The synthesis of 3-iodo-4-methyl[carbonyl-^{14}C]benzoic acid was achieved in a yield of 96% (Scheme 4).

The examples have shown several iodination methods producing good yields, reproducibility with high selectivity. This demonstrates a convenient method to produce versatile synthetic intermediates.

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