Solid-Supported Iodonium Salts for Fluorinations


Abstract: Solid-supported iodonium salt precursors have been prepared and used for the production of fluorooaromatics. The importance of the resin functionality for the attachment of the iodonium salt moieties is demonstrated. Furthermore the production of novel iodonium salt precursors for fluorination is achieved using an alternative and improved method to those previously described. The successful radiofluorination of a simple solid-supported precursor with no carrier added (n.c.a) [18]fluoride shows the suitability of the method for the production of useful PET synthons.

Introduction

Solid-phase organic synthesis is ‘synthesis in which the starting material and synthetic intermediates are linked to an insoluble support’.[1] The use of a solid-support for synthesis was first reported by Merrifield in 1963:[2] Merrifield utilised chloromethyl functionalised resin for the production of peptides.

Since this pioneering work, the use of polymer-bound precursors and reagents has become widespread in organic synthesis.[3] The general advantage provided by the methodology is the ability to mechanically separate intermediates from reagents and solvents.[4] Most commonly used are polystyrene supports.[5] The cleavage of the polymer-bound molecule is a key step in solid-supported organic synthesis and is not only used to cleave the product from the resin but can also be used to introduce functionality into the molecule being cleaved. This includes the introduction of halogens such as fluorine.[6] The use of solid-supported precursors for the introduction of the [18]F isotope during this cleavage step has been described.[7] Here, the solid-supported methodology offers an opportunity for rapid purification of radio-labelled compounds. This is a highly desirable feature when producing compounds with a short half-life time (1/2. t1/2 = 110 min). Such compounds find utility in positron emission tomography (PET) imaging. This highly sensitive and versatile imaging technique allows for the pharmacokinetic and biodistribution of positron emitters to be studied in vivo.[8]

Diaryliodonium salt precursors can be used for the nuclophilic incorporation of fluoride into electron-rich aromatic compounds. The use of diaryliodonium salts for the formation of [18]F labelled aromatic compounds was first reported by Pike et al. using both symmetrical and unsymmetrical diaryliodonium precursors.[9] If an unsymmetrical diaryliodonium salt is used, selective fluorination can be achieved by tuning the steric and electronic properties of the second aryl substituent. Small, electron-rich aryl groups (commonly 2-thienyl and 4-methoxyphenyl) are used as ‘non-participating’ aryl rings to direct fluorination to the desired aromatic moiety. Other non-participating groups include a [2,2]paracyclophane moiety.[10] Adaption of this methodology to solid-supported iodonium salts for the introduction of fluorine combines the rapid and selective fluorination of diaryliodonium salts with the facile purification available to solid-supported precursors. Work in this area includes radiofluorination of solid-supported iodonium salt precursors for the production of [18]fluorobenzene, and [18]fluorouracil reported by Brady et al.[11] Furthermore, a patent published by Carroll et al. shows the synthesis of diaryliodonium salt precursors for radiofluorination linked to an aminomethyl resin via amide linkage.[12]

Herein we report the synthesis and evaluation of polystyrene-supported diaryliodonium salts for fluorination and radiofluorination. Different methods for the production of the resin-bound precursors are investigated. Key factors in optimising the functionalisation of the resin and iodonium salt formation are discussed.

Results and Discussion

Investigation begun with the attempted production of solid-supported diaryliodonium salts previously reported in a patent by Carroll et al.[13] The strategy uses amide bond formation as the key step, linking the precursor to the resin. Amino methyl functionalised polystyrene resin is used for coupling to carboxylic acids 1 and 2(TFA) (Figure 1).

Figure 1. Iodoaryl functionalised carboxylic acid 1 for amide coupling followed by oxidation to the iodonium salt and iodonium salt functionalised linker 2(TFA) ready for amide coupling to the amine resin.

The two carboxylic acids 1 and 2(TFA) provide the starting materials to two possible routes to the same resin bound precursor. As shown in Scheme 1 on the right side, compound 1 is attached to a polymer and then takes part in subsequent transformations to produce the polymer-supported iodonium salt 6(TFA). In the second route (Scheme 1, left side), the iodonium salt 8(TFA) is formed first which is then, after hydrolysis to 2, bound via an amide linkage to the amino methyl resin.

Supporting information for this article is given via a link at the end of the document.

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The synthesis of the iodoaryl linker 1 was very successful in our hands with both the formation and hydrolysis of ethyl 6-(4-iodophenoxy) hexanoate 3 proceeding with excellent yields (Scheme 2).

However, the functionalisation of the amino methyl resin with the linker 1 proved to be difficult. Only a low loading could be attained using the reported conditions and reproducibility was a problem (Table 1, entries 1-3). A number of different conditions were used to obtain a higher loading (Table 1). The procedure was carried out under inert conditions which gave an increased loading as determined by weight increase of the polymer (entry 4). All future experiments were carried out under inert conditions (entries 5-11). Despite some improvement, yields were still unacceptable and repeats of the experiment gave again inconsistencies in the observed loading.

Increasing the equivalents of diisopropylethylamine did not change the loading (entry 5). The use of anhydrous DMF as the solvent was also investigated as such polar aprotic solvents can give beneficial ‘swelling’ of the support. However, this was detrimental to the reaction (entry 8). The use of T₃P (propylphosphonic anhydride) as a coupling agent also failed to improve the functionalisation of the polystyrene support in a number of solvents (entries 7-9).

### Table 1. Optimisation for amide coupling of linker 1 to amino functionalised resin

<table>
<thead>
<tr>
<th>Entry</th>
<th>Resin</th>
<th>Coupling Agent</th>
<th>Time (h)</th>
<th>DIPEA (equiv.)</th>
<th>Solvent</th>
<th>Loading (mmol g⁻¹)</th>
<th>Yield (%) *</th>
<th>elemental analysis (I %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>18</td>
<td>2.25</td>
<td>CH₂Cl₂</td>
<td>0.36</td>
<td>37</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>18</td>
<td>2.25</td>
<td>CH₂Cl₂</td>
<td>0.27</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>18</td>
<td>2.25</td>
<td>CH₂Cl₂</td>
<td>0.17</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>18</td>
<td>2.25</td>
<td>CH₂Cl₂</td>
<td>0.66</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>25</td>
<td>3</td>
<td>CH₂Cl₂</td>
<td>0.49</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>aminomethyl</td>
<td>DPPC</td>
<td>25</td>
<td>3</td>
<td>DMF</td>
<td>0.07</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>aminomethyl</td>
<td>T₃P</td>
<td>48</td>
<td>2</td>
<td>EtOAc</td>
<td>0.33</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>aminomethyl</td>
<td>T₃P</td>
<td>25</td>
<td>2</td>
<td>DMF</td>
<td>0.19</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>aminomethyl</td>
<td>T₃P</td>
<td>25</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>0.29</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>tris(aminomethyl)</td>
<td>T₃P</td>
<td>65</td>
<td>2</td>
<td>EtOAc</td>
<td>1.73</td>
<td>69</td>
<td>12.3</td>
</tr>
<tr>
<td>11</td>
<td>tris(aminomethyl)</td>
<td>DPPC</td>
<td>43</td>
<td>2.25</td>
<td>CH₂Cl₂</td>
<td>2.11</td>
<td>85</td>
<td>13.6</td>
</tr>
</tbody>
</table>

* Yields based on gain in mass of resin or by elemental analysis when available (see supporting information for details).
The poor results prompted a test reaction in which the amide
linkage was performed between the 6-(4-iodophenoxy)hexanoic
acid proceeded to give diacetate diaryliodonium salt
of tri-
Oxidation of the supported iodoaryl moiety in
functionalisation of the resin is shown below (Scheme 4).

These results implied complications had originated from the
solid-supported amine and a solution was realised by the use of
a different resin. Coupling reactions with tris(aminomethyl) resin
gave substantially higher loadings with both coupling agents
(Table 1, entries 10 and 11). This suggested that a steric effect
from the resin may have inhibited penetration of the reagents to
the functionalised sites.

The reaction using the optimized conditions for iodoaryl
functionalisation of the resin is shown below (Scheme 4). Oxidation of the supported iodoaryl moiety in 10 with peracetic
acid proceeded to give diacetate 11 in 55% yield before addition
of tri-\(n\)-butylphenyltin and TFA afforded the solid-supported
diaryliodonium salt 12(TFA) in quantitative yield.

Fluorination of the solid-supported salt 12(TFA) using no carrier
added (n.c.a.) \(^{18}\)F fluoride produced \(^{18}\)F fluorobenzene 13
(Scheme 5). TLC showed a radiochemical conversion (RCC) of
3%. Identity of the radiolabelled compound was confirmed using
radio HPLC by co-elution with a ‘cold’ standard.

In order to achieve the maximum potential of the solid-supported
methodology, it was proposed that solid-supported TEMPO
could be used in conjunction with the solid-supported precursor
12(TFA). This meant that in the event of a clean and selective
reaction it should be possible to isolate pure product using a
simple cartridge purification. The reaction, however, was not as
successful as reported for the unsupported TEMPO. The extra
resin in the reaction mixture caused an increase in the amount of
activity retained by the resin (12% unsupported TEMPO, 19%
supported TEMPO) and radio TLC showed a reduction in the
radiochemical conversion to <1%. Furthermore, radio HPLC
analysis showed a significant increase in impurities (see
supporting information).

The successful production of \(^{18}\)F fluorobenzene prompted an
expansion of the methodology to the production of fluorinated
aromatic compounds with application in PET. Two compounds
considered for their valuable application were \(^{18}\)F4-fluorobenzaldehyde and \(^{18}\)F4-fluorophenol.

\(^{18}\)F4-fluorobenzaldehyde/\(^{18}\)FBA is a prosthetic group used
for the \(^{18}\)F labelling of peptides. Conjugation to unprotected
peptides can be achieved under mild conditions via oxime
formation with aminooxy-functionalised peptides. \[10\]

The second target, \(^{18}\)F4-fluorophenol, is an important \(^{18}\)F
labelled synthon for the production of labelled molecules bearing
the \(^{18}\)F4-fluorophenol functionality. The labelled species is
employed in the synthesis of a number of valuable tracers of
biological interest.\[11\]

With these targets in mind, the solid-supported precursors 14(Br) and 16(Br) based on the
tris(aminomethyl) resin were investigated (Scheme 6).

Precursors for 4-fluorobenzaldehyde synthesis
As well as solid-supported iodonium salt 14(Br), the solution
phase precursor 18(Br) was also targeted for comparison with
the solution phase approach.

Initial investigation began with the solution phase reaction in
order to probe the iodonium salt forming reaction (Scheme 7).

However, the reaction to 18(Br) proceeded poorly. The initial
conditions using the diacetate 19 and a boron trifluoride-
decatalysed reaction with the boronic acid provided the iodonium
salt 18(Br) in poor yield. It should also be noted that the iodonium salt obtained could not be isolated with a high purity. Attempts to improve the yield by tuning reaction conditions were unsuccessful (see supporting information for full table of conditions attempted to improve the yield). This is presumably due to the electron-rich nature of the hypervalent iodine compound as reaction with (diacetoxyiodo)benzene proceeds well as described by Richarz et al.[12]

Aryl stannanes can also be used in the synthesis of diaryliodonium salts[13] and offer an alternative to the boronic acid protocol. Therefore, the appropriate stannane [4-(trimethylstannyl)benzaldehyde] was produced for utility in the synthesis of diaryliodonium salt 18(Br). However, reactions with in situ produced 4-methoxy Koser reagent, using conditions adapted from those reported by Wirth et al.[14] failed to produce the iodonium salt 18(Br) (see supporting information for all attempted conditions).

Attempts to produce the resin-bound precursor were also unsuccessful. The reaction gave a very low increase in the mass of the resin suggesting a low conversion of the diacetate to the diaryliodonium salt. Fluorination of the supported precursor did not produce the desired fluorinated product, providing further evidence for the lack of success forming the iodonium salt (see supporting information for details).

**Precursors for 4-fluorophenol synthesis**

As well as the solid-supported precursor 16(Br), the solution phase precursor 20(Br) was targeted for comparison. Protected linker iodonium salt 21(Br) was also synthesised to investigate if the linker moiety had any effect on the fluorination reaction (Figure 2).

Iodonium salt 21(Br) was synthesised first to probe the reactivity of the linker moiety. Furthermore, subsequent transformation would provide a carboxylic acid for linkage to the amino methyl resin.

Firstly, aryl BPin moiety 22 was synthesised by benzyl protection of 4-iodophenol and subsequent coupling reaction with bis(pinacolato)dbor in as shown in Scheme 8. Subsequent reaction with diacetate 7 produced the desired product 21(Br) but with poor yields so an alternative approach was investigated.

Conversion of the diacetate to the Koser reagent derivative 25 followed by reaction with electon rich aromatic 26 gave the desired iodonium tosylate 21(TsO) in good yields. The iodonium salt 21(TsO) could then be hydrolysed using trifluoroacetic acid (TFA) in water to yield 27(TsO). Interestingly, the tosylate counterion in acid 27(TsO) was not exchanged to a trifluoroacetate counterion after the hydrolysis as confirmed by 1H NMR. Coupling to solid support was achieved using the standard conditions to produce 16(TsO/Cl) which was converted to 16(Br) as shown in Scheme 10.

### Table 2. Optimisation for the oxidation of O-benzyl 4-iodophenol to diacetate 24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Solvent</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOAc, NaOAc, AcOH, AcO</td>
<td>2</td>
<td>120</td>
<td>Impure</td>
</tr>
<tr>
<td>2</td>
<td>NaOAc, NaOAc, AcOH, AcO</td>
<td>24</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>AcOONa, CHCl₃</td>
<td>2</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor®, AcOH, MeCN</td>
<td>5</td>
<td>rt</td>
<td>95</td>
</tr>
</tbody>
</table>

The use of Selectfluor® as an oxidant in acetonitrile and acetic acid proved optimal giving an excellent yield of the corresponding diacetate 24. This method showed improvements on those previously reported.[15]

It was found that significant improvements to the yield could be made by using a slightly altered synthesis strategy (Scheme 9). Rather than oxidation of iodo phenol ether 3, oxidation of the O-benzyl 4-iodophenol 23 was conducted. Optimisation for the oxidation of aryl iodide to diacetate is shown in Table 2.

![Figure 2. Precursors for [18]F4-fluorobenzaldehyde production.](image)

![Scheme 8. Synthesis of iodonium salt 21(Br) via Aryl BPin moiety 23.](image)

![Scheme 9. Synthesis of iodonium salt precursor 21(TsO) via diacetate 24.](image)
Synthesis of the solution phase iodonium bromides was also successful (Scheme 11). Iodonium tosylate 20(TsO) was produced using an analogous procedure for reaction with anisole. The isolated iodonium tosylates 20(TsO) and 21(TsO) were then converted to their respective iodonium bromides by washing with aqueous saturated KBr.

Scheme 11. Synthesis of iodonium bromides 20(Br) and 21(Br).

After the synthesis of the iodonium precursors 16(Br), 20(Br) and 21(Br) it was important to test their efficacy in the fluorination reaction. Optimisation was conducted using iodonium salt 20(Br) with tetramethyl ammonium fluoride (TMAF) as fluoride source (Table 3).

Table 3. Fluorination of solution phase iodonium salt 20(Br).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conc. of 20(Br) (mol cm⁻³)</th>
<th>TMAF (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>5</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>5</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>2.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>1.25</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>5</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>5</td>
<td>4</td>
<td>22</td>
</tr>
</tbody>
</table>

* Yields determined using GC analysis.

Optimal conditions were found using GC analysis of the reaction mixture subsequent to the thermal breakdown of the iodonium salt. Of the solvents tested acetonitrile provided the best result giving a 13% yield (Table 3, entry 1). When the reaction was performed in DMF or DMSO, the yields obtained dropped to 7% and 8%, respectively. Decreasing the concentration of the iodonium bromide was detrimental to the reaction. Yields could be improved by increasing the equivalents of TMAF; 2 equivalents increasing the yield to 20% and 4 equivalents giving 22%.

Interestingly, when performing the fluorination reaction with precursor 21(Br) under optimised reaction conditions, the yields improved to 30% of the desired fluorinated product 17 as analysed by GC (Scheme 12).

Scheme 12. Fluorination of linker derived iodonium salt 21(Br).

This showed that the linker moiety was beneficial for the fluorination reaction. Fluorination of the solid-supported precursor was successful as well giving yields between 22% and 24% depending on the scale of the reaction (Scheme 13). The results show that the reaction is reproducible and scalable.

Scheme 13. Fluorination of solid-supported iodonium salt 16(Br).

The high number of equivalence used for the cold fluorination reactions mean that conditions are far from emulating those used for the 'hot' fluorination with [¹⁸F]fluoride. Investigations of the solid-supported precursor under radiofluorination conditions will be conducted in the future as this is the application where such a precursor would be of greatest value.

Conclusions

A number of synthetically relevant iodonium salt precursors have been synthesised on a solid support. The utility of these compounds has been shown for the production of [¹⁸F]fluorobenzene. The successful radiofluorination shows a proof of concept for the production of valuable [¹⁸F]labelled synthons / prosthetic groups using this method. Furthermore, the importance of the resin functionality has been demonstrated. Limitations of amino methyl functionalised resin for amide linkage were discovered. The problem was addressed by the use of a resin with improved amine availability for a much improved loading via amide bond formation.

The production of a resin bound precursor for FBA production could not be realised using the linker strategy investigated here. However, the production of such a precursor with an alternative linker bearing an aromatic of lower electron density is an area of future investigation. Production of a solid-supported precursor for O-benzyl 4-fluorophenol was successful. An efficient route via the diacetoxyiodo derivative 24 was established for the synthesis of the resin-bound iodonium salt and proceeded with excellent yields. This method provides a promising alternative strategy to those previously reported for the synthesis of polymer-supported iodonium salts. Fluorination of the precursor was successful providing acceptable yields of the fluorinated product. Adaptation of this procedure for the incorporation of [¹⁸F]fluoride could provide a suitable method for the production of valuable PET synthons.
Experimental Section

Procedure for the functionalization of tris(aminomethyl)amine resin. Under argon tris(2-aminomethyl)amine-polymer resin (0.25 g, 0.88 mmol, 0.75 equiv) in freshly distilled CH2Cl2 (7 mL) was treated with 6-(4-iodophenoxy)hexanoic acid (0.39 g, 1.17 mmol, 1 equiv), disopropylphosphynitrene (0.34 g, 2.63 mmol, 2.25 equiv) and diphenylphosphorylchloride (0.31 g, 1.17 mmol, 1 equiv). The reaction kept under agitation for 43 h. The reaction was then filtered and washed thoroughly with CH2Cl2 (100 mL) and 20 % water in methanol (100 mL). The resin was then dried under vacuum to give a beige sand like product (0.47 g, 1.73 mmol g⁻¹, 85-100%). Found C 68.12%, H 6.34%, N 3.57%, I 13.6%.

Procedure for the oxidation of 11. 6-(4-iodophenoxy)hexanoic acid - tris(2-aminomethyl)amine-polymer resin amide (0.25 g, 0.52 mmol) in CH2Cl2 (7 mL) was treated with peracetic acid (48 wt%, 2 mL). The reaction was agitated at room temperature for 18 h before the reaction was filtered and washed with CH2Cl2. The resin was then dried under vacuum to give a sand like solid (0.284 g, 1.16 mmol g⁻¹, 55%). Found C 66.34%, H 6.62%, N 3.67%, I 9.53%.

Procedure for the formation of resin bound iodonium salt 12(TFA). 6-(4-iodophenoxy)hexanoic acid - aminomethyl polystyrene resin amide (0.15 g, 0.34 mmol, 1 equiv) in CH2Cl2 (5 mL) was coupled in acetonitrile and dry ice bath to −41 °C and treated with tri-n-butylphosphine (128 mg, 0.348 mmol, 2 equiv). The reaction was agitated and trifluoroacetic acid (79 mg, 0.696 mmol, 4 equiv) was added and allowed to warm to room temperature over 2 h. The resin was then washed with CH2Cl2 to give a beige sand like solid (0.244 g, 1.16 mmol g⁻¹, 100%). Found C 62.55%, H 6.16%, N 3.29%, I 19.97%, F 5.99%.

General procedure for n.c.a. [18F]fluoride incorporation using resin bound iodonium salt 12(TFA). [18F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the [18F]fluoride was eluted with a Kryptofix 2.2.2 carbonate enriched K13.6%.

General procedure for the formation of diacetate 24. A solution of O-benzyl 4-iodophenol 23 (5.0 mmol, 1.0 equiv) and Selectfluor® (25.0 mmol, 5.0 equiv) in MeCN/AcOH (3:1) (200 mL) was stirred for 5 h at room temperature. The reaction was agitated and the volume was reduced to 90 °C and cooled to room temperature. The reaction was monitored by NMR and GC.

General procedure for the fluorination of solution phase iodonium salt precursors. In a glove box tetramethylammonium fluoride (TMAF) was added to a reaction vessel containing supported iodonium salt 16(Br) before it was sealed with a rubber septum and removed from the glove box. Iodonium salt precursor was dissolved in the appropriate dry deuterated solvent and added to the TMAF by injecting through the septum equipped with an argon balloon. The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and cooled to room temperature. The reaction was monitored by [18F]NMR and GC.

General procedure for the fluorination of solid-supported iodonium salt precursors. In a glove box tetramethylammonium fluoride (TMAF) was added to a reaction vessel containing supported iodonium salt 18(Pr) before it was sealed with a rubber septum and removed from the glove box. The appropriate dry deuterated solvent was added to the TMAF and precursor by injection through the septum equipped with an argon balloon. The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and cooled to room temperature. The reaction was monitored by [18F]NMR and GC.

Acknowledgements

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Keywords: diaryl iodonium salts • fluorination • hypervalent iodine • solid-supported reagents • radiochemistry

The preparation of solid-supported iodonium salt precursors has been investigated and their utility in the synthesis of fluoroarenes has been established. The successful radiofluorination of a simple solid-supported precursor shows the suitability of the method for the production of useful PET synthons.