Solid-Supported Iodonium Salts for Fluorinations


Abstract: Solid-supported iodonium salt precursors have been prepared and used for the production of fluoroarenes. 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]Ffluoride 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’. 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 radiolabelled compounds. This is a highly desirable feature when producing compounds with a short half-life time (18F: $t_{1/2} = 110$ 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.[2] Diarylodonium salt precursors can be used for the nucleophilic incorporation of fluoride into electron-rich aromatic compounds. The use of diarylodonium salts for the formation of [18]F labelled aromatic compounds was first reported by Pike et al. using both symmetrical and unsymmetrical diarylodonium precursors.[8] If an unsymmetrical diarylodonium 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.[9] Adaption of this methodology to solid-supported iodonium salts for the introduction of fluorine combines the rapid and selective fluorination of diarylidonium 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]Ffluorobenzene and [18]Ffluoroacetic acid reported by Brady et al.[10] Furthermore, a patent published by Carroll et al. shows the synthesis of diarylidonium salt precursors for radiofluorination linked to an aminomethyl resin via amide linkage.[11] Herein we report the synthesis and evaluation of polystyrene-supported diarylidonium 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 began with the attempted production of solid-supported diarylidonium salts previously reported in a patent by Carroll et al.[12] 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.

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

Scheme 2. Synthesis of iodoaryl linker 1.

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 (%) a</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>

a 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 1 and aniline to give 9 in excellent yield (Scheme 3).

\[
\begin{align*}
\text{HO-C\text{-}C\text{-}C\text{-}O\text{-}H} & \quad \text{1} \\
\text{PNNH_2} & \quad \text{TPP} \text{ DIPCA} \\
\text{EIOAc} & \quad \text{9} \quad (91\%) \\
\end{align*}
\]

Scheme 3. Amide coupling of carboxylic acid 1 to aniline.

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-butylphosphine and TFA afforded the solid-supported diaryliodonium salt 12(TFA) in quantitative yield.

\[
\begin{align*}
\text{DPPC, DIPEA} & \quad \text{CH}_2\text{Cl}_2, 43 \text{h} \\
11 & \quad \text{12(TFA)} \quad (1.16 \text{ mmol g}^{-1}, 55\%) \\
10 & \quad \text{AcOH} \\
\end{align*}
\]

Scheme 4. Amide coupling of 1 to tris(2-aminomethyl)amine resin and synthesis of solid-supported iodonium salt 12(TFA).

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 [18F]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 [18F]4-fluorobenzaldehyde and [18F]4-fluorophenol.

[18F]4-fluorobenzaldehyde ([18F]FBA) is a prosthetic group used for the 18F labelling of peptides. Conjugation to unprotected peptides can be achieved under mild conditions via oxime formation with aminooxy-functionalised peptides.[10] The second target, [18F]4-fluorophenol, is an important 18F labelled synthon for the production of labelled molecules bearing the [18F]4-fluorophenyl 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).

Fluorination of the solid-supported salt 12(TFA) using no carrier added (n.c.a.) [18F]fluoride produced [18F]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.

\[
\begin{align*}
\text{F_2CCOD}_2^+ & \quad \text{12(TFA)} \\
\text{Ph} & \quad \text{18F} \\
\end{align*}
\]

Scheme 5. ‘Hot’ fluorination of polymer-supported iodonium salt 12.

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-catalysed reaction with the boronic acid provided the iodonium
The reaction gave a very low increase in the mass of the resin suggesting a low conversion of the diacetate to the iodonium salt (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).

**Figure 2.** Precursors for [18F]4-fluorobenzaldehyde production.

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)diboron 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.

**Scheme 8.** Synthesis of iodonium salt 21(Br) via Aryl BPin moiety 23.

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 iodophenol ether 3, oxidation of the O-benzyl 4-iodophenol 23 was conducted. Optimisation for the oxidation of aryl iodide to diacetate 24 is shown in Table 2.

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.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>NaI, NaOAc, AcOH, AcO</td>
<td>2</td>
<td>120</td>
<td>Impure</td>
</tr>
<tr>
<td>2</td>
<td>NaI, 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>

Conversion of the diacetate to the Koser reagent derivative 25 followed by reaction with electron 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.
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.

After the synthesis of the iodonium precursors 20(Br), 20(TsO), and 21(TsO) 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).

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).

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.

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 diacetoxiodo 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(aminocarbonyl)amine resin. Under argon tris(2-amino-phenyl)amine-polymer resin (0.25 g, 0.88 mmol, 0.75 equiv) in freshly distilled CH₂Cl₂ (7 mL) was treated with 6-(4-iodophenoxy)hexanoyl chloride (0.39 g, 1.17 mmol, 1 equiv), disopropylaminylamine (0.34 g, 2.63 mmol, 2.25 equiv) and diphenylphosphorylchloride (0.31 g, 1.17 mmol, 1 equiv). The reaction was sealed under agitation for 5 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 1. 6-(4-Iodophenoxy)hexanoyl acid - tris(2-aminoethyl)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 6.26%, N 3.67%, I 9.53%.

Procedure for the formation of resin bound iodonium salt 12(TFA). 6-(4-Iodophenoxy)hexanoyl acid - aminomethyl polystyrene resin amide (0.15 g, 0.174 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 continued at -41 °C for 2 h. The reaction was then warmed 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. [131]Ffluoride incorporation using resin bound iodonium salt 12(TFA). [131]Ffluoride derived from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the 18O enriched water. The [131]Ffluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) in MeCN (3 mL) and 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 continued at -41 °C for 2 h. The reaction was then warmed 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 the formation of diacetate 24. A solution of O-benzyl 4-iodo phenol 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 acetonitrile was evaporated in vacuo and water was added to the residue before extraction with CH₂Cl₂. The combined organic layers were washed with water and dried over MgSO₄. Removal of the solvent gave the crude product as a yellow solid. Trituration with hexane gave the pure product as a yellow solid (0.15 g, 0.174 mmol, 1.16 mmol g⁻¹). The reaction mixture was azeotropically dried twice with the addition of acetonitrile (2 mL) and cooled to 0 °C before addition of the electron-rich arene (0.405 mmol, 1.01 equiv) and TEMPO (6.56 mg, 0.042 mmol, 0.35 equiv). The reaction mixture was heated in a silicon oil bath at 90 °C for 15 min. The product solution was then heated at 90 °C for 15 min on a hot plate. The product solution was then collected from the filtration apparatus and removed from the glove box. 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 19F NMR and GC.

General procedure for the formation of 4-benzyloxy Koser reagent 25. In a glove box tetramethylammonium fluoride (TMAF) was added to a NMR tube 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 the solution through the septum equipped with an argon balloon. The reaction mixture was then 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 19F NMR and GC.

General procedure for the formation of diiodoaryl chlorides from 4-benzyloxy Koser reagent 25. Koser reagent 25 (0.401 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C before addition of the electron-rich arene (0.405 mmol, 1.01 equiv) (anisole or 26). TFE (0.3 mL) was added to the solution and the reaction was allowed to warm to room temperature over 2 h. The solvents were removed in vacuo and the product was triturated with Et₂O. Filtration gives the iodonium salt which may be recrystallized from CH₂Cl₂ and Et₂O if necessary.

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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.