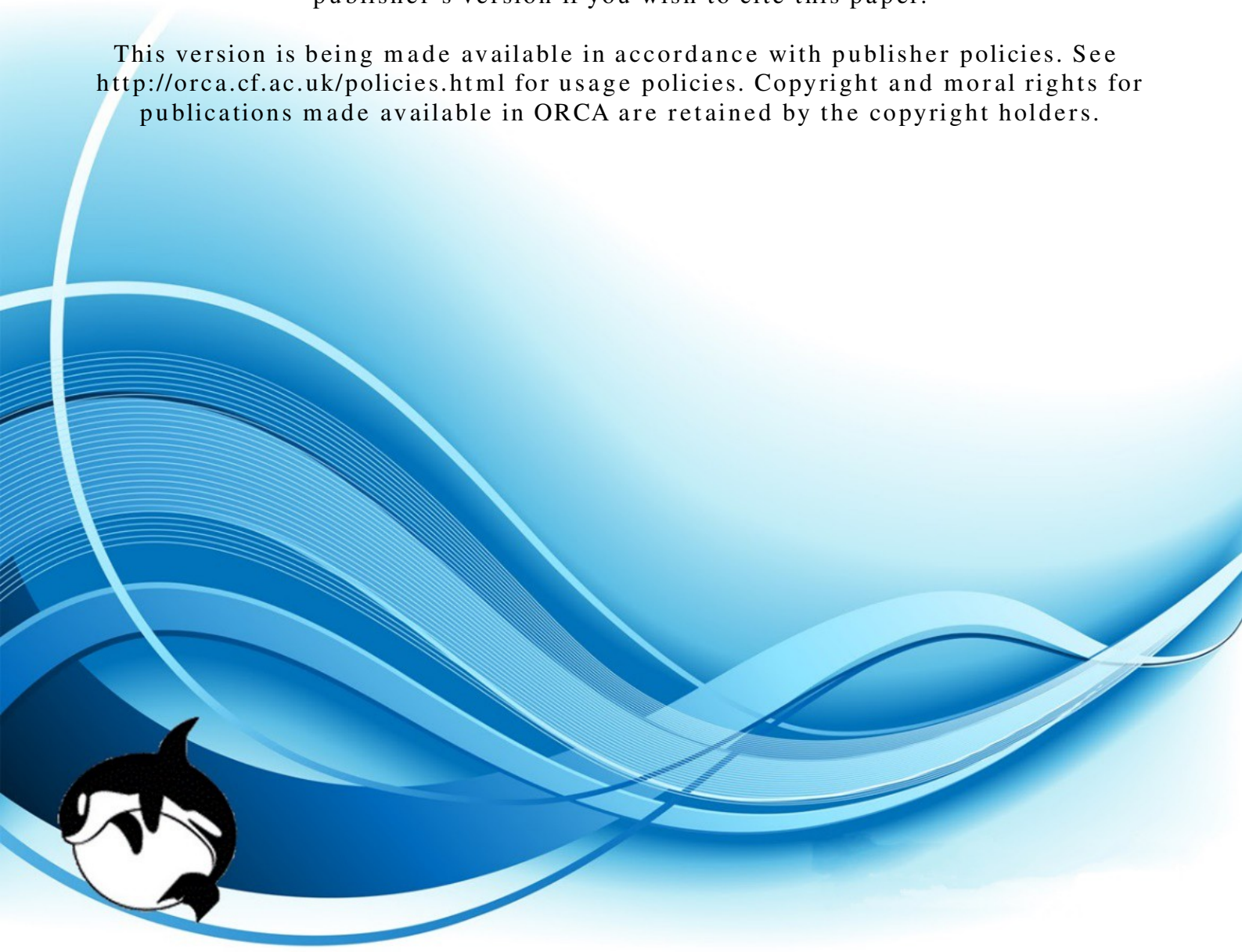

Solid-Supported Iodonium Salts for Fluorinations

Richard Edwards,[a] Wilke de Vries,[a] Andrew D. Westwell,[b] Stephen Daniels[c] and Thomas Wirth*[a]

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}F]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.[1] Most commonly used are polystyrene supports.[3c]

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.[3b] The use of solid-supported precursors for the introduction of the ^{18}F isotope during this cleavage step has been described.[4] 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 (^{18}F: $t_{1/2}$ = 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*.[5]

Diaryliodonium salt precursors can be used for the nucleophilic 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.[6] 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.[7]

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}F]fluorobenzene and [^{18}F]fluorouracil reported by Brady *et al.*[8] 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.[9]

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*.[9] 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).

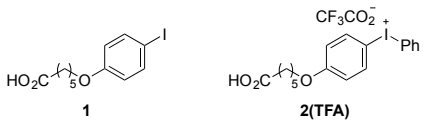

Figure 1. Iodoaryl functionalised carboxylic acid **1** for amide coupling followed by oxidation to the iodonium salt and iodonium salt functionalised linker **2(TFA)** ready for amide coupling to the amine resin.

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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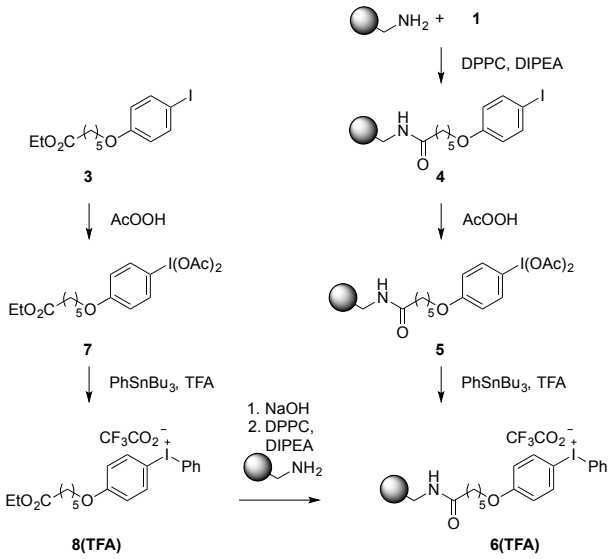
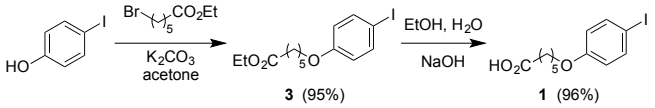


Scheme 1. Two routes for the synthesis of resin bound iodonium salt **6** from **1** or **3**. (DIEPA = diisopropylethylamine, DPPC = diphenylphosphoryl chloride, TFA = trifluoroacetic acid).

The right route starting with **1** in Scheme 1 was chosen for initial investigations as a higher loading with regards to iodine was reported for this method using elemental analysis (11.59% I for left route vs 7.49% I for right route).

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.[1] However, this was detrimental to the reaction (entry 8). The use of T_3P (propylphosphonic anhydride) as a coupling agent also failed to improve the functionalisation of the polystyrene support in a number of solvents (entries 7-9).

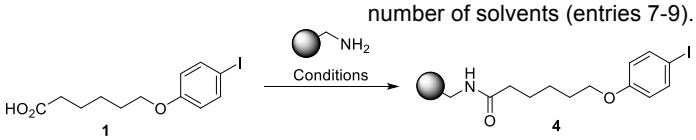
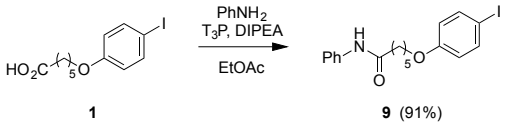


Table 1. Optimisation for amide coupling of linker **1** to amino functionalised resin

Entry	Resin	Coupling Agent	Time (h)	DIPEA (equiv.)	Solvent	loading (mmol g^{-1})	Yield (%)[a]	elemental analysis (% I)
1	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.36	37	3.5
2	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.27	18	-
3	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.17	12	-
4	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.66	44	-
5	aminomethyl	DPPC	25	3	CH_2Cl_2	0.49	33	-
6	aminomethyl	DPPC	25	3	DMF	0.07	4	-
7	aminomethyl	T_3P	48	2	EtOAc	0.33	37	-
8	aminomethyl	T_3P	25	2	DMF	0.19	13	-
9	aminomethyl	T_3P	25	2	CH_2Cl_2	0.29	19	-
10	tris(aminoethyl)	T_3P	65	2	EtOAc	1.73	69	12.3
11	tris(aminoethyl)	DPPC	43	2.25	CH_2Cl_2	2.11	85	13.6

[a] Yields based on gain in mass of resin or by elemental analysis when available (see supporting information for details).

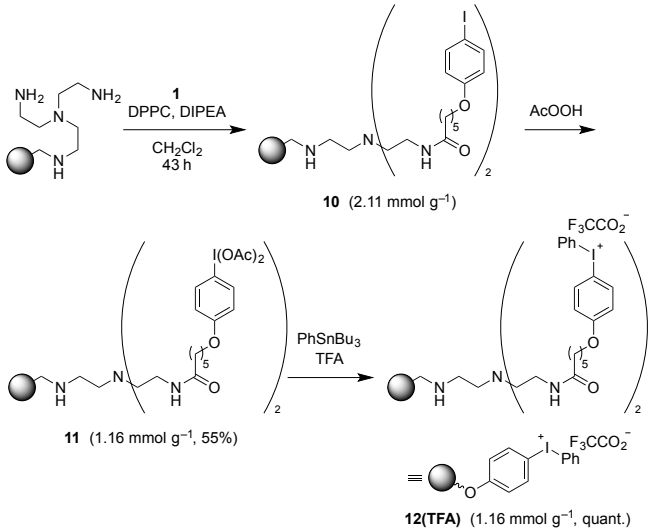
The poor results prompted a test reaction in which the amide linkage was performed between the 6-(4-iodophenoxy)hexanoic acid **1** and aniline to give **9** in excellent yield (Scheme 3).



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

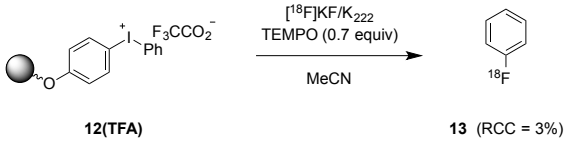
These results implied complications had originated from the solid-supported amine and a solution was realised by the use of a different resin. Coupling reactions with tris(aminoethyl) resin gave substantially higher loadings with both coupling agents (Table 1, entries 10 and 11). This suggested that 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.



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

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.



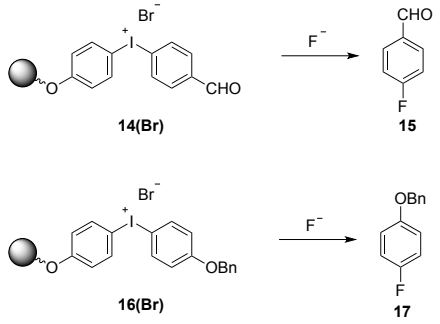
Scheme 5. 'Hot' fluorination of polymer-supported iodonium salt **12**.

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}F]4-fluorobenzaldehyde and [^{18}F]4-fluorophenol.

[^{18}F]4-fluorobenzaldehyde ([^{18}F]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}F]4-fluorophenol, is an important ^{18}F labelled synthon for the production of labelled molecules bearing the [^{18}F]4-fluorophenoxy 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(aminoethyl) resin were investigated (Scheme 6).

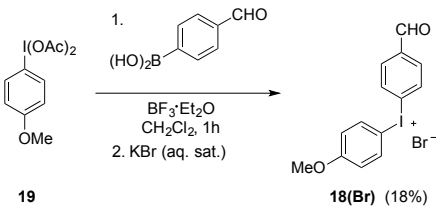


Scheme 6. Solid-supported precursors for 4-fluorobenzaldehyde production **14(Br)** and for for 4-fluorophenol production **16(Br)**.

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).



Scheme 7. Synthesis of solution phase [^{18}F]FBA precursor **18(Br)**.

However, the reaction to **18(Br)** proceeded poorly. The initial conditions using the diacetate **19** and a borontrifluoride-catalysed 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 diaryliodoium 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 inverstigate if the linker moiety had any effect on the fluorination reaction (Figure 2).

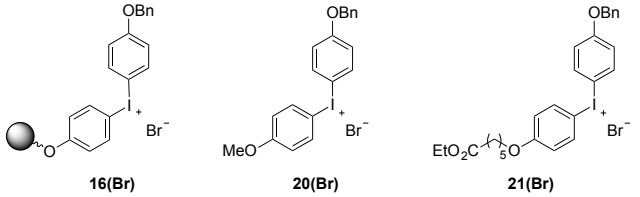
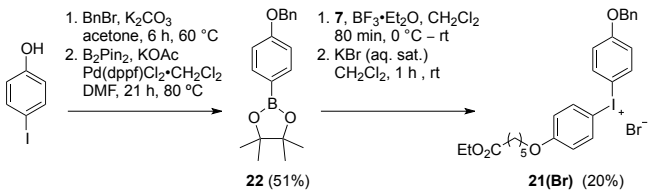


Figure 2. Precursors for [^{18}F]4-fluorobenzaldehyde production.

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.

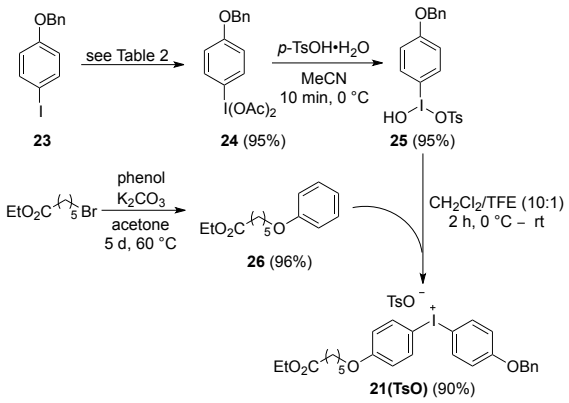
Firstly, aryl BPin moiety **22** was synthesised by benzyl protection of 4-iodophenol and subsequent coupling reaction with bis(pinocolato)diboron as shown in Scheme 8. Subsequent reaction with diacetate **7** produced the desired product **21(Br)** but with poor yields so an alternative approach was 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.[15]

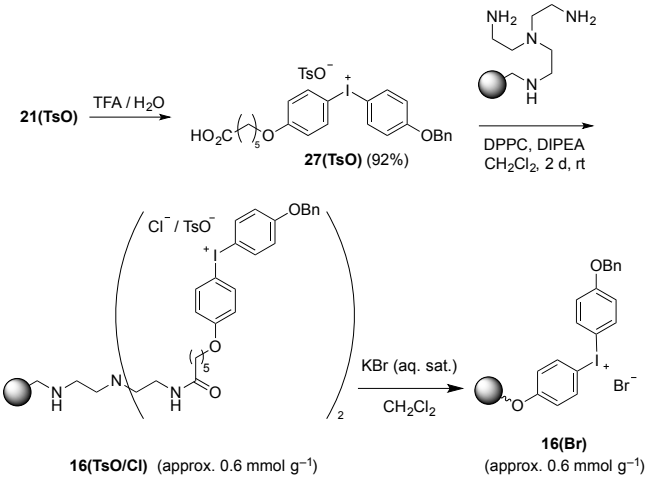


Scheme 9. Synthesis of iodonium salt precursor **21(TsO)** via diacetate **24**.

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

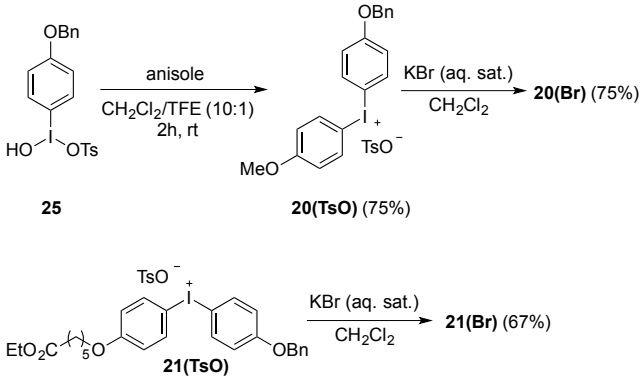
Entry	Reagents and Solvent	Time (h)	Temp. (°C)	Yield (%)
1	$NaIO_4$, NaOAc, AcOH, Ac_2O	2	120	Impure
2	$NaIO_4$, NaOAc, AcOH, Ac_2O	24	80	48
3	AcOOH, CH_2Cl_2	2	rt	0
4	Selectfluor®, AcOH, MeCN	5	rt	95

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 ^{1}H 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.



Scheme 10. Synthesis of solid-supported precursor **16(Br)**.

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).

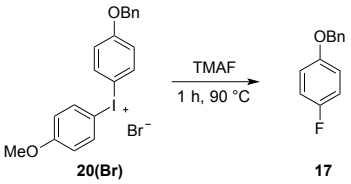


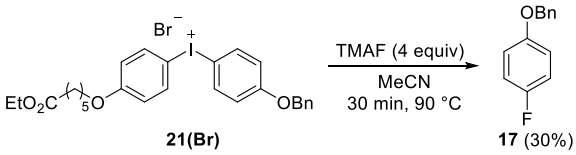
Table 3. Fluorination of solution phase iodonium salt **20(Br)**.

Entry	Solvent	Conc. of **20(Br)** (mol cm^{-3})	TMAF (equiv)	Yield (%)[a]
1	MeCN	5	1	13
2	DMF	5	1	7
3	DMSO	5	1	8
4	MeCN	2.5	1	5
5	MeCN	1.25	1	5
6	MeCN	5	2	20
7	MeCN	5	4	22

[a] Yields determined using GC analysis.

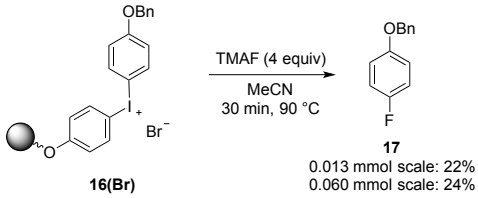
Optimal conditions were found using GC analysis of the reaction mixture subsequent to the thermal breakdown of the iodonium salt. Of the solvents tested acetonitrile provided the best result giving a 13% yield (Table 3, entry 1). When the reaction was performed in DMF or DMSO, the yields obtained dropped 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 [^{18}F]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 ^{19}F bearing aromatics as well as for the production of [^{18}F]fluorobenzene. The successful radiofluorination shows a proof of concept for the production of valuable ^{18}F 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. Adaption of this procedure for the incorporation of [^{18}F]fluoride could provide a suitable method for the production of valuable PET synthons.

Experimental Section

Procedure for the functionalization of tris(aminoethyl)amine resin.
Under argon tris(2-aminoethyl)amine-polymer resin (0.25 g, 0.88 mmol, 0.75 equiv) in freshly distilled CH_2Cl_2 (7 mL) was treated with 6-(4-iodophenoxy)hexanoic acid (0.39 g, 1.17 mmol, 1 equiv), diisopropylethylamine (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 CH_2Cl_2 (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-aminoethyl)amine-polymer resin amide (0.25 g, 0.52 mmol) in CH_2Cl_2 (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 CH_2Cl_2. 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, 0.174 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was cooled in a acetonitrile and dry ice bath to –41 °C and treated with tri-*n*-butylphenyl tin (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 CH_2Cl_2 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 9.97%, F 5.99%.

General procedure for n.c.a. [^{18}F]fluoride incorporation using resin bound iodonium salt 12(TFA).
[^{18}F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the ^{18}O enriched water. The [^{18}F]fluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) (0.3 mL MeCN, 0.3 mL H_2O, 22.8 mg Kr-2.2.2, 8.4 mg K_2CO_3) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 seconds. The residue was azeotropically dried twice with the addition of acetonitrile (2 × 1 mL). Distillation was achieved by heating at 120 °C under a flow of nitrogen for 440 seconds. The dried [^{18}F]KF•Kr222•K_2CO_3 salt was re-dissolved in acetonitrile and to a sealed vial containing the supported iodonium precursor **12(TFA)** (0.103 g, 0.12 mmol (1.16 mmol g^{-1}), 1.0 equiv) and TEMPO (6.56 mg, 0.042 mmol, 0.35 equiv). The reaction mixture was then heated at 90 °C for 15 min on a hot plate. The product solution was removed from the support by filtration. Analysis with radio TLC showed a RCC of 3%. Product identity was confirmed by radio HPLC.

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 acetonitrile was evaporated in vacuo and water was added to the residue before extraction with CH_2Cl_2. The combined organic layers were washed with water and dried over $MgSO_4$. Removal of the solvent gave the crude product as a yellow solid. Trituration with hexane gave the pure product as a colourless solid (2.13 g, 95%), m.p. 61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.04 - 7.97 (*m*, 2 H), 7.45 - 7.32 (*m*, 5 H), 7.07 - 7.03 (*m*, 2 H), 5.11 (s, 2 H), 2.00 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 176.5 (2 C), 161.4, 137.3 (2 C), 135.8, 128.9 (2 C), 128.6, 127.6 (2 C), 117.5 (2 C), 111.8, 70.5, 20.6. Spectral data are in agreement with literature.[16]

Procedure for the formation of 4-benyloxy Koser reagent 25.
Diacetate **24** (4.44 mmol, 1.0 equiv) was dissolved in MeCN (50 mL) and cooled to 0 °C before the addition of *p*-TsOH·H_2O (4.44 mmol, 1.0 equiv). The product began to precipitate immediately. After 10 min Et_2O was added to the slurry and the product was filtered off and washed with Et_2O. The pure product was dried under a flow of nitrogen to give the product as a pale yellow solid (2.09 g, 95%). The compound was stored under nitrogen at –20 °C. If the compound was submitted to high vacuum it decomposed to a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.27 – 8.23 (*m*, 2 H), 7.67 - 7.63 (*m*, 2 H), 7.44 - 7.39 (*m*, 2 H), 7.38 - 7.27 (*m*, 3 H), 7.24 - 7.16 (*m*, 4 H), 5.2 (s, 2 H), 2.32 (s, 4 H). ^{13}C NMR (100 MHz, MeOD) δ ppm: 164.7, 143.3, 141.8, 140.3, 137.4, 129.8 (2 C), 129.7 (2 C), 129.4, 128.8 (2 C), 126.9 (2 C), 119.3 (2 C), 71.6, 21.3.

General procedure for the formation of diaryliodonium salts from 4-benyloxy Koser reagent 25.
Koser reagent **25** (0.401 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (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 Et_2O. Filtration gives the iodonium salt which may be recrystallized from CH_2Cl_2 and Et_2O if necessary.

General procedure for the fluorination of solution phase iodonium salt precursors.
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 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 ^{19}F 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 **16(Br)** 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 hour before being removed and cooled to room temperature. The reaction was monitored by ^{19}F NMR and GC.

All synthetic methods including spectroscopic data and analytical data are included in the supporting information.

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

[1] F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**.
[2] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
[3] a) S. V Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195. b) S. Boldon, I. Stenhagen, J. Moore, S. Luthra, V. Gouverneur, *Synthesis* **2011**, 3929–3953. c) F. Guillier, D. Orain, M. Bradley, *Chem. Rev.* **2000**, *100*, 2091–2157. d) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679.
[4] a) L. J. Brown, D. R. Bouvet, S. Champion, A. M. Gibson, Y. Hu, A. Jackson, I. Khan, N. Ma, N. Millot, H. Wadsworth, R. C. D. Brown, *Angew. Chem. Int. Ed.* **2007**, *46*, 941–944. b) S. K. Luthra, F. Brady, H. J. Wadsworth, WO2003002489 A2, **2003**.
[5] P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn, *Br. J. Clin. Pharmacol.* **2012**, *73*, 175–186.
[6] V. W. Pike, F. I. Aigbirhio, *Chem. Commun.* **1995**, 2215-2216.
[7] a) B. Wang, J. W. Graskemper, L. Qin, S. G. DiMagno, *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083; b) J. W. Graskemper, B. Wang, L. Qin, K. D. Neumann, S. G. DiMagno, *Org. Lett.* **2011**, *13*, 3158–3161.
[8] F. Brady, S. K. Luthra, E. G. Robins, WO2003002489 A2, **2004**.
[9] H. J. Wadsworth, D. A. Widdowson, E. Wilson, M. A. Carroll, WO2005061415 A1, **2004**.
[10] T. Poethko, M. Schottelius, G. Thumshim, U. Hersel, M. Herz, G. Henriksen, H. Kessler, M. Schwaiger, H. J. Wester, *J. Nucl. Med.* **2004**, *45*, 892–902.
[11] a) U. Muehlhausen, J. Ermert, H. H. Coenen, *J. Labelled Comp. Radiopharm.* **2009**, *52*, 13–22. b) T. Stoll, J. Ermert, S. Oya, H. F. Kung, H. H. Coenen, *J. Labelled Comp. Radiopharm.* **2004**, *47*, 443–455.

[12] R. Richarz, P. Krapf, F. Zarrad, E. A. Urusova, B. Neumaier, B. D. Zlatopolskiy, *Org. Biomol. Chem.* **2014**, *12*, 8094–8099.
[13] E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070.
[14] R. Edwards, A. D. Westwell, S. Daniels, T. Wirth, *Eur. J. Org. Chem.* **2015**, 625–630.
[15] T. L. Ross, J. Ermert, H. H. Coenen, *Molecules* **2011**, *16*, 7621–7626.
[16] T. L. Ross, J. Ermert, C. Hocke, H. H. Coenen, *J. Am. Chem. Soc.* **2007**, *129*, 8018–8025.

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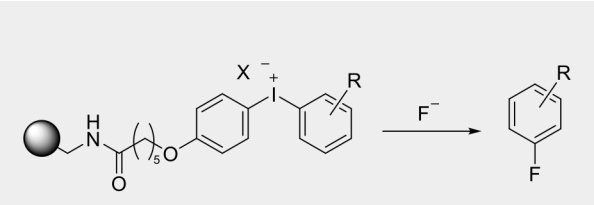

The preparation of solid-supported iodonium salt precursors has been investigated and their utility in the synthesis of fluoroarenes has been established. The successful radiofluorination of a simple solid-supported precursor shows the suitability of the method for the production of useful PET synthons.

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Solid-Supported Iodonium Salts for Fluorinations