EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201500992

Solid-Supported Iodonium Salts for Fluorinations

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

Keywords: Solid-phase synthesis / Radiochemistry / Fluorine / Fluorination / Iodine / Hypervalent iodine

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 has been demonstrated. Furthermore, the production of new iodonium salt precursors for fluorination has been achieved by an alternative and improved method with respect 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 separate intermediates from reagents and solvents mechanically.[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 pharmacokinetics 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.[6] The use of diaryliodonium salts for the formation of ^{18}F-labelled aromatic compounds was first reported by Pike et al., who used both symmetrical and unsymmetrical diaryliodonium precursors.[7] If an unsymmetrical diaryliodonium salt is used, selective fluorination can be achieved by tuning the steric and electronic properties of the second aryl substituent.[8] 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 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.[10] Furthermore, a patent published by Carroll et al. shows the synthesis of diaryliodonium salt precursors for radiofluorination linked to an aminomethyl resin through amide linkages.[11]

Here 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.

[a] School of Chemistry, Cardiff University,
Main Building, Park Place, Cardiff CF10 3AT, UK
E-mail: wirth@cf.ac.uk
http://blogs.cardiff.ac.uk/wirth/
[b] School of Pharmacy and Pharmaceutical Sciences, Cardiff University,
Cardiff CF10 3NB, UK
[c] Wales Research & Diagnostic PET Imaging Centre (PETIC), School of Medicine, Cardiff University,
Cardiff CF14 4XN, UK

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500992.

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. Aminomethyl-functionalised polystyrene resin is used for coupling to carboxylic acids **1** and **2**(TFA) (Figure 1).

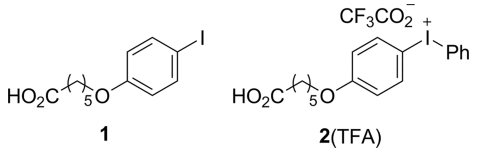


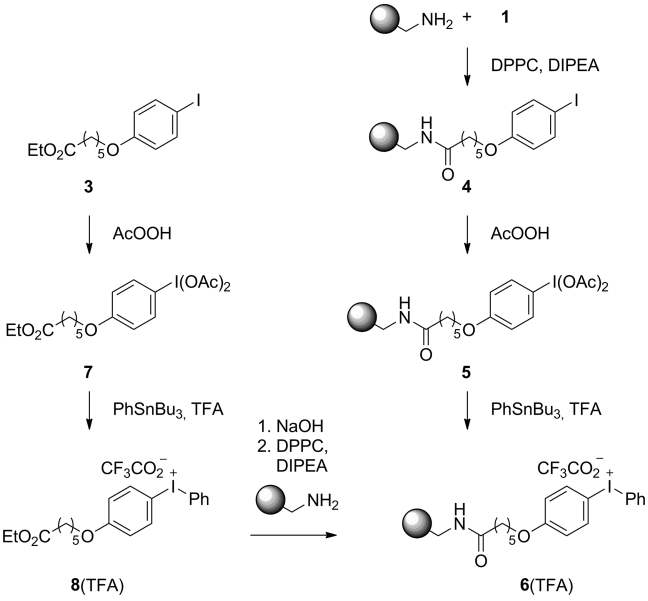
Figure 1. Iodoaryl-functionalised carboxylic acid **1**, for amide coupling followed by oxidation to the iodonium salt, and iodonium salt functionalised linker **2**(TFA), ready for amide coupling to the amine resin.

The two carboxylic acids **1** and **2**(TFA) provide the starting materials for two possible routes to the same resin-bound precursor. As shown in Scheme 1 on the right-hand 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-hand side), the iodonium salt **8**(TFA) is formed first and is then, after hydrolysis to **2**, bound through an amide linkage to the aminomethyl resin.

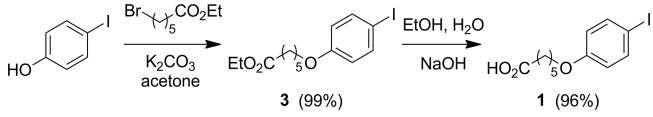
The right-hand route starting from **1** in Scheme 1 was chosen for initial investigations because a higher loading with regard to iodine was reported for this method by elemental analysis (11.59% I for right-hand route vs. 7.49% I for left-hand route).

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

However, the functionalisation of the aminomethyl resin with the linker **1** proved to be difficult. Only a low loading



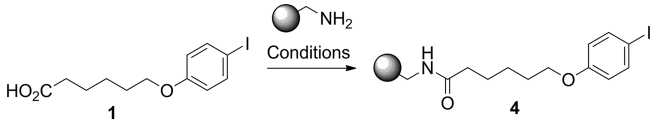
Scheme 1. Two routes for the synthesis of resin-bound iodonium salt **6** from **1** or **3** (DIPEA = diisopropylethylamine, DPPC = diphenylphosphoryl chloride, TFA = trifluoroacetic acid).



Scheme 2. Synthesis of iodoaryl linker **1**.

could be attained under the reported conditions, and reproducibility was a problem (Table 1, Entries 1–3). A number of different conditions were used to obtain higher loadings (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 unaccept-

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 the Supporting Information for details).

able and repeats of the experiment again gave inconsistencies in the observed loadings.

Increasing the equivalents of diisopropylethylamine did not change the loading (Entry 5). The use of anhydrous DMF as the solvent was also investigated because 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).

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

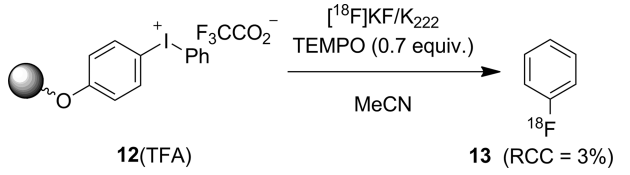
1 **9** (91%)

Scheme 3. Amide coupling between carboxylic acid **1** and aniline.

These results implied that complications had originated from the solid-supported amine, and a solution was achieved 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 under the optimised 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, after which addition of tri-*n*-butylphenyltin and TFA afforded the solid-supported diaryliodonium salt **12**(TFA) in quantitative yield.

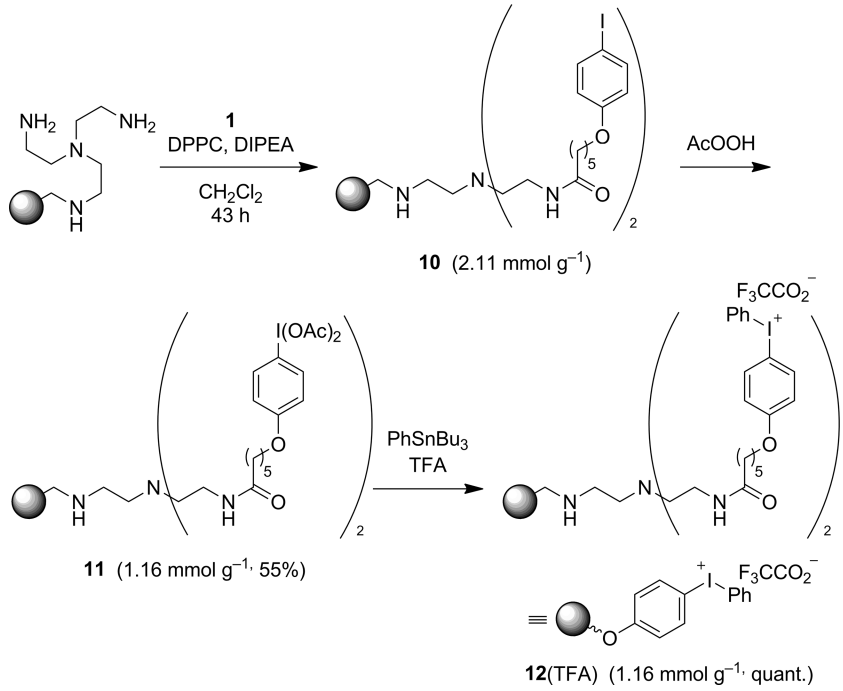
Fluorination of the solid-supported salt **12**(TFA) with no-carrier-added (n.c.a.) [^{18}F]fluoride produced [^{18}F]fluorobenzene (**13**, Scheme 5). TLC showed a radiochemical conversion (RCC) of 3%. Identity of the radiolabelled compound was confirmed by radio-HPLC and co-elution with a "cold" standard.



12(TFA) **13** (RCC = 3%)

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

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 by means of a simple cartridge purification. The reaction, however, was not as successful as reported for the unsupported TEMPO. The extra resin in the reaction mixture resulted in an increase in the amount of activity retained by the resin (12% with unsupported TEMPO, 19% with supported TEMPO), and radio-TLC showed a reduction in the radiochemical conversion to <1%. Further-



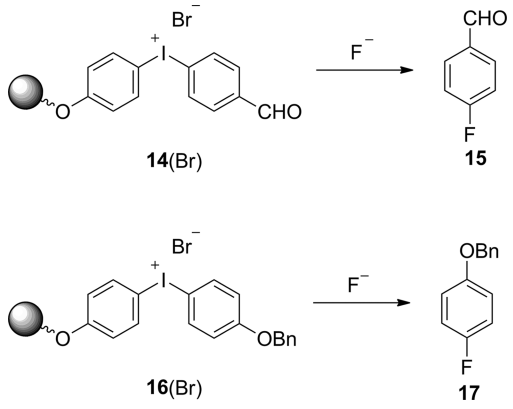
Scheme 4. Amide coupling between **1** and tris(2-aminoethyl)amine resin and synthesis of solid-supported iodonium salt **12**(TFA).

more, radio-HPLC analysis showed a significant increase in impurities (see the 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. The labelling is achieved under mild conditons by chemoselective oxime formation between an aminooxy-functionalised peptide and the [^{18}F]FBA.[12]

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

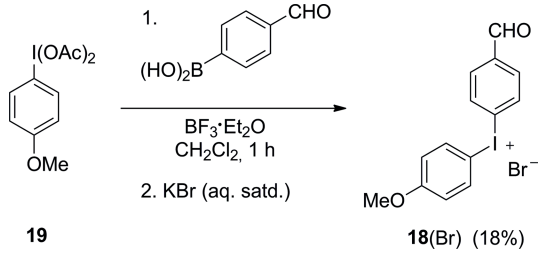


Scheme 6. Solid-supported precursors **14**(Br), for 4-fluorobenzaldehyde production, and **16**(Br), for 4-fluorophenol production.

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 produce **18**(Br) proceeded poorly. The initial conditions, with the diacetate **19** and a boron-trifluoride-catalysed reaction with the boronic acid, provided the iodonium salt **18**(Br) in poor yield. It should also be noted that the obtained iodonium salt could not be isolated with a high purity. Attempts to improve the yield by tuning the reaction conditions were unsuccessful (see the Supporting Information for a full Table of conditions used in attempts to improve the yield). This is presumably due to the electron-rich nature of the hypervalent iodine compound, because reaction with (diacetoxyiodo)benzene as described by Richarz et al.[14] proceeds well.

Arylstannanes can also be used in the synthesis of diaryliodoium salts[15] 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 4-methoxy Koser reagent, produced in situ under conditions adapted from those reported by Wirth et al.,[16] failed to produce the iodonium salt **18**(Br) (see the Supporting Information for all attempted conditions).

Attempts to produce the resin-bound precursor were also unsuccessful. The reaction gave a very small increase in the mass of the resin, thus suggesting a low level of conversion of the diacetate into the diaryliodonium salt. Fluorination of the supported precursor did not produce the desired fluorinated product, providing further evidence of the lack of success in forming the iodonium salt (see the 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 in order to investigate whether the linker moiety had any effect on the fluorination reaction (Figure 2).

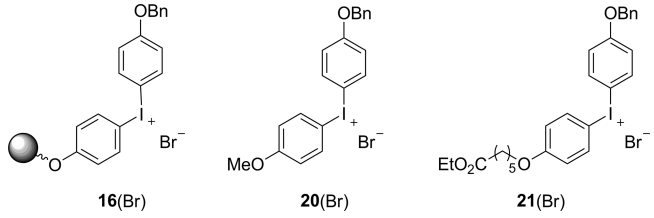
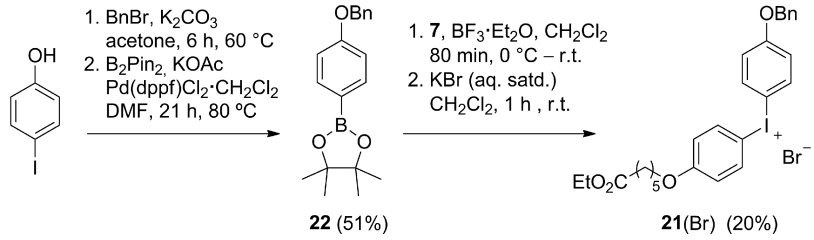


Figure 2. Precursors for [^{18}F]4-fluorobenzaldehyde production.

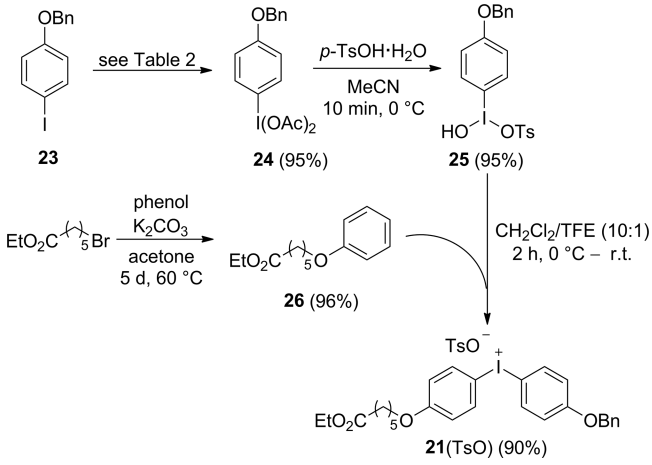
Iodonium salt **21**(Br) was synthesised first, in order to probe the reactivity of the linker moiety. Furthermore, subsequent transformation would provide a carboxylic acid for linkage to the aminomethyl resin.

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



Scheme 8. Synthesis of iodonium salt **21**(Br) via aryl BPin moiety **22**.

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.



Scheme 9. Synthesis of iodonium salt precursor **21**(TsO) via diacetate **24** (TFE = 2,2,2-trifluoroethanol).

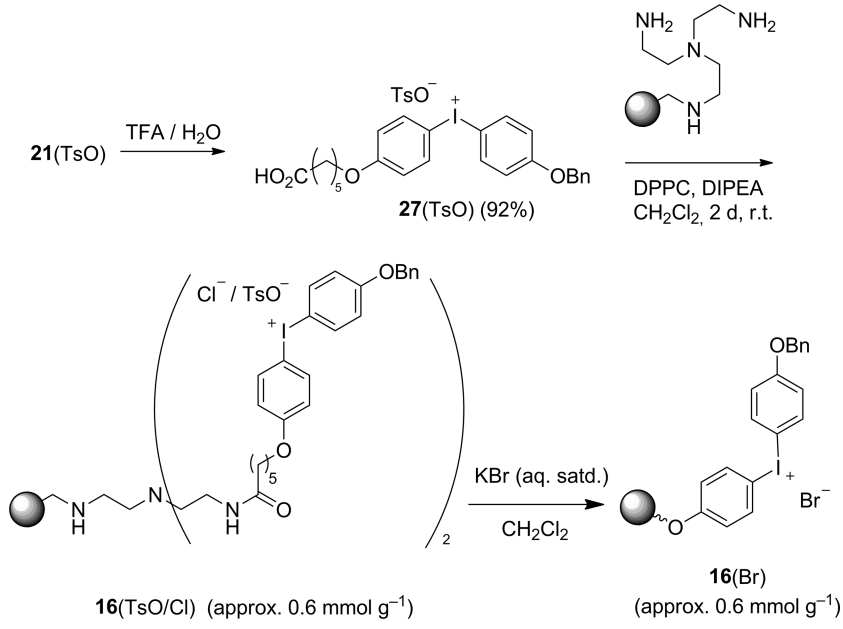
Optimisation for the oxidation of aryl iodide to diacetate **24** is shown in Table 2.

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	r.t.	0
4	Selectfluor®, AcOH, MeCN	5	r.t.	95

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.[17]

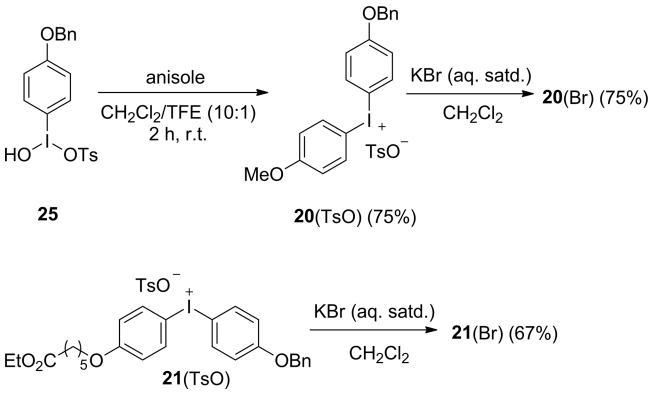
Conversion of the diacetate into the Koser reagent derivative **25** followed by treatment with electron-rich aromatic **26** gave the desired iodonium tosylate **21**(TsO) in good yields. The iodonium salt **21**(TsO) could then be hydrolysed with trifluoroacetic acid (TFA) in water to yield **27**(TsO). Interestingly, the tosylate counterion in acid **27**(TsO) was not exchanged to a trifluoroacetate counterion after the hydrolysis as confirmed by ^{1}H NMR spectroscopy. Coupling



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

to the solid support was achieved under the standard conditions to produce **16**(TsO/Cl), which was converted into **16**(Br) as shown in Scheme 10.

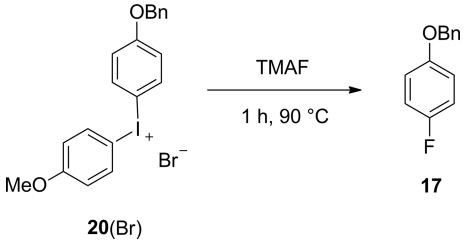
Synthesis of the solution-phase iodonium bromides was also successful (Scheme 11). Iodonium tosylate **20**(TsO) was produced by an analogous procedure for reaction with anisole. The isolated iodonium tosylates **20**(TsO) and **21**(TsO) were then converted into their corresponding iodonium bromides by washing with saturated aqueous 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 with iodonium salt **20**(Br) and tetramethylammonium fluoride (TMAF) as fluoride source (Table 3).

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

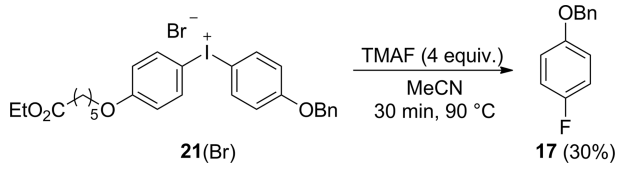


Entry	Solvent	Conc. of **20**(Br) [mol cm^{-3}]	TMAF [equiv.]	Yield[a] [%]
1	MeCN	5	1	13
2	DMF	5	1	7
3	DMSO	5	1	8
4	MeCN	2.5	1	5
5	MeCN	1.25	1	5
6	MeCN	5	2	20
7	MeCN	5	4	22

[a] Yields determined by GC analysis.

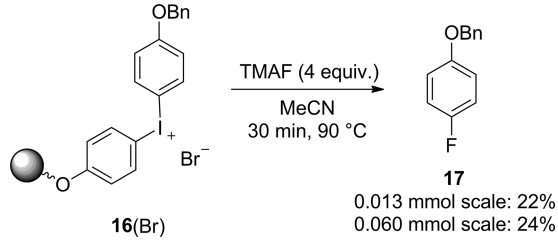
Optimal conditions were found by GC analysis of the reaction mixture subsequent to the thermal breakdown of the iodonium salt. Of the solvents tested, acetonitrile provided the best result, giving a 13% yield (Table 3, Entry 1). When the reaction was performed in DMF or DMSO, the yields obtained dropped 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, with use of 2 equiv. increasing the yield to 20% and use of 4 equiv. giving 22%.

Interestingly, when the fluorination reaction was performed with precursor **21**(Br) under optimised reaction conditions, the yields of the desired fluorinated product **17** were improved to 30% 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 equivalents used for the cold fluorination reactions means 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, because this is the application in which 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 represents a proof of concept for the production of valuable ^{18}F-labelled synthons/prosthetic groups by this method. Furthermore, the importance of the resin functionality has been demonstrated. Limitations of aminomethyl-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 through amide bond formation.

Production of a solid-supported precursor for *O*-benzyl-4-fluorophenol was achieved by an alternative approach to those previously reported. The method used 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 Functionalisation 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 diphenylphosphoryl chloride (0.31 g, 1.17 mmol, 1 equiv.). The reaction mixture was kept under agitation for 43 h. It was then filtered and washed thoroughly with CH_2Cl_2 (100 mL) and water in methanol (20%, 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 mixture was agitated at room temperature for 18 h, after which it 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*-butylphenyltin (128 mg, 0.348 mmol, 2 equiv.). The reaction mixture was agitated, trifluoroacetic acid (79 mg, 0.696 mmol, 4 equiv.) was added, and the mixture was 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 with Resin-Bound Iodonium Salt 12(TFA): [^{18}F]Fluoride, delivered from the cyclotron as an aqueous solution, was trapped on a pretreated 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, MeCN (0.3 mL), H_2O (0.3 mL), Kr-2.2.2 (22.8 mg), K_2CO_3 (8.4 mg)] 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 redissolved in acetonitrile and transferred 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 by 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 with $MgSO_4$. 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 = 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) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 ppm. Spectral data are in agreement with the literature.[18]

Procedure for the Formation of 4-Benzyloxy 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 subjected to high vacuum it decomposed to a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 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 ppm.

General Procedure for the Formation of Diaryliodonium Salts from 4-Benzyloxy 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 (anisole or **26**, 0.405 mmol, 1.01 equiv.). 2,2,2-Trifluoroethanol (TFE) (0.3 mL) was added to the solution and the reaction mixture 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 recrystallised from CH_2Cl_2 and Et_2O if necessary.

General Procedure for the Fluorination of Solution-Phase Iodonium Salt Precursors: In a glovebox, tetramethylammonium fluoride (TMAF) was added to a NMR tube, after which the tube was sealed with a rubber septum and removed from the glovebox. Iodonium salt precursor was dissolved in the appropriate dry deuterated solvent and added to the TMAF by injecting the solution through the septum that was equipped with . The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and allowed to cool 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 glovebox, tetramethylammonium fluoride (TMAF) was added to a reaction vessel containing supported iodonium salt **16**(Br), after which the tube was sealed with a rubber septum and removed from the glovebox. The appropriate dry deuterated solvent was added to the TMAF and precursor by injection through the septum that was equipped with a balloon filled with argon. The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and allowed to cool to room temperature. The reaction was monitored by ^{19}F NMR and GC.

Supporting Information (see footnote on the first page of this article): All synthetic methods including spectroscopic data and analytical data are included in the supporting information.

Acknowledgments

Support from the Schools of Chemistry, Pharmacy and Medicine of Cardiff University and from the Erasmus Exchange Program (grant to W. d. V.) is gratefully acknowledged. The authors thank the Engineering and Physical Sciences Research Council (EPSRC), National Mass Spectrometry Facility, Swansea, for mass spectrometric data.

[1] F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, Germany, **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; *Angew. Chem.* **2001**, *113*, 670.

[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; *Angew. Chem.* **2007**, *119*, 959; 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] a) M. S. Yusubov, Y. Svitich, M. S. Larkina, V. V. Zhdankin, *ARKIVOC* **2013**, *i*, 364–395; b) M. Tredwell, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 11426–11437; *Angew. Chem.* **2012**, *124*, 11590.

[7] V. W. Pike, F. I. Aigbirhio, *J. Chem. Soc., Chem. Commun.* **1995**, 2215–2216.

[8] J.-H. Chun, S. Lu, Y.-S. Lee, V. W. Pike, *J. Org. Chem.* **2010**, *75*, 3332–3338.

[9] a) B. Wang, J. W. Graskemper, L. Qin, S. G. DiMagno, *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083; *Angew. Chem.* **2010**, *122*, 4173; b) J. W. Graskemper, B. Wang, L. Qin, K. D. Neumann, S. G. DiMagno, *Org. Lett.* **2011**, *13*, 3158–3161.

[10] F. Brady, S. K. Luthra, E. G. Robins, WO2003002489 A2, **2004**.

[11] H. J. Wadsworth, D. A. Widdowson, E. Wilson, M. A. Carroll, WO2005061415 A1, **2004**.

[12] 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.

[13] a) U. Muehlhausen, J. Ermert, H. H. Coenen, *J. Labelled Compd. Radiopharm.* **2009**, *52*, 13–22; b) T. Stoll, J. Ermert, S. Oya, H. F. Kung, H. H. Coenen, *J. Labelled Compd. Radiopharm.* **2004**, *47*, 443–455.

[14] R. Richarz, P. Krapf, F. Zarrad, E. A. Urusova, B. Neumaier, B. D. Zlatopolskiy, *Org. Biomol. Chem.* **2014**, *12*, 8094–8099.

[15] E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070; *Angew. Chem.* **2009**, *121*, 9214.

[16] R. Edwards, A. D. Westwell, S. Daniels, T. Wirth, *Eur. J. Org. Chem.* **2015**, 625–630.

[17] T. L. Ross, J. Ermert, H. H. Coenen, *Molecules* **2011**, *16*, 7621–7626.

[18] T. L. Ross, J. Ermert, C. Hocke, H. H. Coenen, *J. Am. Chem. Soc.* **2007**, *129*, 8018–8025.

Received: July 27, 2015
Published Online: October 1, 2015

