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Synthesis of [4-^{18}F]-1-Bromo-4-fluorobenzene and its Use in Palladium-Promoted Cross-Coupling Reactions with Organostannanes

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A method of general interest for the introduction of a [4-^{18}F]fluorophenyl structure into highly functional molecules has been developed. [4-^{18}F]-1-Bromo-4-fluorobenzene **3** was obtained in a two-step reaction from [^{18}F]fluoride (in water solution) and 5-bromo-2-nitrobenzaldehyde **1** followed by a tris(triphenylphosphine)rhodium(I) chloride (PPh_3RhCl) catalysed decarbonylation in >70% isolated, decay-corrected radiochemical yield within 70 min. The precursor **3** was used in a number of palladium promoted cross-coupling reactions with organostannanes; for example, the reaction with tributylphenyltin gave [4-^{18}F]fluorobiphenyl in >90% decay-corrected radiochemical yield within 15 min.

Molecules labelled with positron-emitting, short-lived radionuclides can be used *in vivo* in studies of biological processes by positron emission tomography (PET). In order to extend the range of applications for PET, there is an increasing interest in developing synthetic methods for new tracers labelled with short-lived radionuclides such as ^{11}C, ^{18}F and ^{76}Br (half-lives of 20 min, 110 min and 16 h, respectively).

This report describes the development of a procedure to obtain a ^{18}F-labelled 4-fluorophenyl group. The procedures available for incorporating ^{18}F into a molecule are limited, especially when high specific radioactivity is demanded. Electrophilic fluorination reactions with ^{18}F yield products with low specific radioactivities in the range 0.5–37 GBq μmol^{-1}, while nucleophilic fluorination reactions often give products with specific activities from 50 to 370 GBq μmol^{-1}.[1] For that reason the nucleophilic fluorination reaction with [^{18}F]fluoride ions is often preferred over the electrophilic substitution reactions. Many of the compounds used in PET contain sensitive functional groups, which further restricts the choice of the synthetic pathway. To be useful in PET, the synthesis of a radiotracer, including purification, usually has to be completed within three half-lives of the radionuclide. Consequently, a general method for incorporation of the radionuclide demands fast and efficient reactions that can be performed on a small scale and under mild conditions.

Palladium-promoted cross-coupling reactions of vinyl triflates, aryl triflates, vinyl halides and aryl halides with organostannane compounds have been used successfully in carbon–carbon bond-forming reactions with a wide range of substrates containing sensitive functional groups.[2] In labelling reactions using short-lived radionuclides, palladium promoted cross-coupling reactions have been used to incorporate ^{11}C.[3] Recently a similar approach was presented for labelling with ^{18}F.[4]

The study described here was initiated in order to perform pharmacokinetic PET-studies in man with the ^{18}F-labelled derivative of the cholesterol-lowering agent fluvastatin[5,6] (Fig. 1). The labelling of fluvastatin might be performed with ^{11}C, however the short half-life of 20 min restricts the time-window available for use of this labelled tracer in PET-studies when the focus of the study is on regional pharmacokinetics of the drug. By

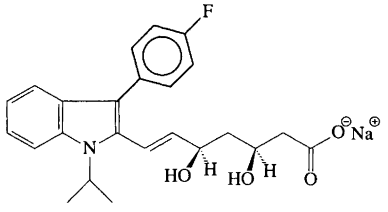

Fig. 1. Fluvastatin (one stereoisomer is shown).

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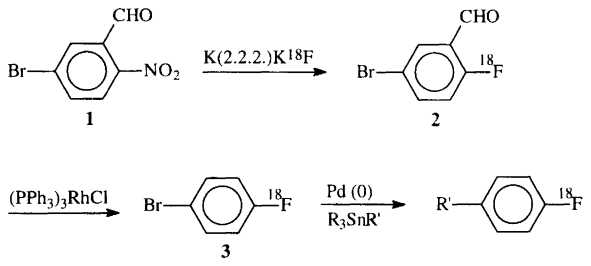
use of ^{18}F, the time-window can be substantially increased.

The fluorophenyl structure is found in fluvastatin, as well as in many other pharmaceutically active compounds, and this structure was considered an attractive model for incorporation of the ^{18}F label. It was also recognised that the coupling of ^{18}F-labelled aryl halides with organostannanes could be a general method for introduction of a [4-^{18}F]fluorophenyl structure into complex and highly functional target molecules.

In this paper, the synthesis of [4-^{18}F]-1-bromo-4-fluorobenzene **3**, a synthon for the [4-^{18}F]fluorophenyl group, and its use in palladium promoted cross-coupling reactions with some model organostannanes are reported. [4-^{18}F]-1-Bromo-4-fluorobenzene was synthesised via nucleophilic substitution of 5-bromo-2-nitrobenzaldehyde with fluoride ion, followed by decarbonylation of the intermediate **2** (Scheme1).



R=butyl, methyl R'=methyl, phenyl, vinyl, acetate and an indole derivative

Scheme. 1. Synthesis of [4-^{18}F]-1-bromo-4-fluorobenzene **3** and its use in palladium-promoted cross-coupling reactions.

Results and discussion

[4-^{18}F]-1-Bromo-4-fluorobenzene **3**. The introduction of ^{18}F into the phenyl ring had to proceed through the use of a nucleophilic [^{18}F]fluoride ion, as this is the only ^{18}F-labelled compound of high specific radioactivity that can be obtained by the use of a low energy cyclotron. In this work, [^{18}F]fluoride was produced by an $^{18}O(p, n)$ ^{18}F nuclear reaction, using ^{18}O-enriched water.

[4-^{18}F]Fluoroiodobenzene has previously been prepared via nucleophilic substitution of the corresponding triflate.[7] Unfortunately, however, the yield of ^{18}F-aryl halide obtained in this reaction was too low to be useful in this work. An alternative route to **3** was therefore considered. The well-established method of nucleophilic displacement of an activated nitro group by [^{18}F]fluoride, was applied.[1] The activating group employed was an aldehyde in an *ortho*-position to the nitro group. Decarbonylation[8] of the aldehyde with the use of tris(triphenylphosphine)rhodium(I) chloride [$RhCl(PPh_3)_3$] furnished **3** in >70% radiochemical yield calculated from [^{18}F]fluoride ion in water solution.

In the first reaction step, [^{18}F]fluoride was mixed with Kryptofix 2.2.2 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane, K[2.2.2.]) and potassium carbonate (K_2CO_3) to form a K[2.2.2.]–potassium [^{18}F]fluoride complex. The complex was reacted with 5-bromo-2-nitrobenzaldehyde **1** to give [2-^{18}F]-5-bromo-2-fluorobenzaldehyde **2** in 75–90%, decay-corrected radiochemical yield. By the use of an automated tracer production system (Synthia),[9] the decay-corrected radiochemical yield was 70–90% within 35 min counted from [^{18}F]fluoride.

In the second reaction step the following solvents, toluene, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dioxane and tetrahydrofuran (THF) were investigated. It was observed that the decarbonylation was most efficient in dioxane and **3** was obtained in >95% decay-corrected radiochemical yield from [2-^{18}F]-5-bromo-2-fluorobenzaldehyde.

In order to simplify the synthesis of **3** a 'one pot reaction' was developed. The time-consuming purification of [2-^{18}F]-5-bromo-2-fluorobenzaldehyde was not needed prior to decarbonylation when a solvent mixture of DMSO–dioxane (1:4) was selected. Decarbonylation of [2-^{18}F]-5-bromo-2-fluorobenzaldehyde using $RhCl(PPh_3)_3$ in a solvent mixture of DMSO–dioxane gave a total conversion of the aldehyde **2** into [4-^{18}F]-1-bromo-4-fluorobenzene within 20 min. The labelled compound **3** was purified by distillation and obtained in >70% decay-corrected radiochemical yield within 70 min counted from [^{18}F]fluoride in water solution.

[4-^{18}F]-1-Bromo-4-fluorobenzene in palladium-promoted coupling reactions with organostannanes. The palladium promoted cross-coupling reaction of [4-^{18}F]-1-bromo-4-fluorobenzene with several organostannanes was investigated, producing a number of different model compounds (Table 1).

Tributylphenylstannane was allowed to react with [4-^{18}F]-1-bromo-4-fluorobenzene of high specific radioactivity in a mixture of dioxane–DMSO (4:1) using tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] as catalyst. Reactions performed at temperatures ranging from 60 to 80 °C did not give any labelled product within 60 min. When the temperature was raised to 100 °C and to 120 °C, [4-^{18}F]fluorobiphenyl was formed within 60 min in radiochemical yields of 3% and 8% respectively. Changing the solvent to DMF, DMSO, toluene, THF or dioxane did not improve the radiochemical yield. When the catalyst used was tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) with triphenylarsine ($AsPh_3$) as the ligand, the radiochemical yield was significantly improved. After 50 min at 60 °C, [4-^{18}F]fluorobiphenyl was formed in 20% yield. This observation was in agreement with previous reports claiming that weaker electron donating ligands accelerate the cross-coupling reaction.[10] The reaction was performed at 60 °C in a number of different solvents; dioxane: DMF, DMSO–dioxane (1:4) and DMF–dioxane (1:1), and the yields of [4-^{18}F]fluorobiphenyl were constant at approximately 20%. When [4-^{18}F]-1-bromo-4-fluorobenzene was purified by distillation, substantial amounts of dioxane

Table 1. Reaction of [4-^{18}F]-1-bromo-4-fluorobenzene with organostannane compounds. Conditions: 25 μmol stannane, 5 μmol $Pd(PPh_3)_4$ (or 5 μmol Pd_2dba_3 and 10 μmol $AsPh_3$) in 1000–1400 μl solvent.

Reagent	Catalyst	*T*/°C	Solvent	*t*/min	Product	Radiochemical yield[a]/%
Bu_3SnPh	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	6	[4-^{18}F]-4-Fluorobiphenyl	40
Bu_3SnPh	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	15	[4-^{18}F]-4-Fluorobiphenyl	>90
Bu_3SnPh	$Pd(PPh_3)_4$	60	DMSO–dioxane	60	[4-^{18}F]-4-Fluorobiphenyl	0
Bu_3SnPh	$Pd(PPh_3)_4$	120	DMSO–dioxane	60	[4-^{18}F]-4-Fluorobiphenyl	8
$Bu_3SnCH{=}CH_2$	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	5	[4-^{18}F]-4-Fluorostyrene	
$Bu_3SnCH{=}CH_2$	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	30	[4-^{18}F]-4-Fluorostyrene	>80
$Bu_3SnOOCCH_3$	Pd_2dba_3, $AsPh_3$	120	Dioxane	10	[4-^{18}F]-4-Fluorophenyl acetate	>50
$Bu_3SnOOCCH_3$	Pd_2dba_3, $AsPh_3$	120	DMSO	10	[4-^{18}F]-4-Fluorophenyl acetate	60
$Bu_3SnOOCCH_3$	Pd_2dba_3, $AsPh_3$	120	DMF–dioxane	5	[4-^{18}F]-4-Fluorophenyl acetate	78
$Bu_3SnOOCCH_3$	$Pd(PPh_3)_4$	120	THF	10	[4-^{18}F]-4-Fluorophenyl acetate	0
$Bu_3SnOOCCH_3$	$Pd(PPh_3)_4$	120	Dioxane	10	[4-^{18}F]-4-Fluorophenyl acetate	0
Me_4Sn	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	30	[4-^{18}F]-4-Fluorotoluene	
1-isopropyl-2-methylindol-3-yl(tributyl)tin	Pd_2dba_3, $AsPh_3$	115	DMF–dioxane	15	1-Isopropyl-2-methyl-3-([4-^{18}F]-4-fluorophenyl)indole	15

[a] Determined by analytical HPLC of samples withdrawn from the reaction mixture.

co-distilled and were trapped in DMF together with the labelled product. The resulting solvent mixture of DMF–dioxane (1 : 1) was found suitable for the cross-coupling reaction. The outcome of the reaction was highly temperature dependent and when the temperature was raised to 115 °C [4-^{18}F]fluorobiphenyl was formed in 90% radiochemical yield within 15 min. Temperatures higher than 120 °C decreased the yield of [4-^{18}F]fluorobiphenyl probably due to decomposition of the palladium catalyst (Table 2).

When the reaction was run under the conditions described in Fig. 2, the radiochemical yield of [4-^{18}F]fluorobiphenyl increased for more than 150 min. The optimal reaction time was, however, not more than 45 min, owing to decay of the already formed product.[11]

In conclusion, it has been shown that the precursor [4-^{18}F]-1-bromo-4-fluorobenzene can be synthesised and used in palladium promoted cross-coupling reactions to produce ^{18}F-labelled compounds. The coupling reaction of aryl halides with organostannanes is compatible with a wide range of functional groups, and this ^{18}F-labelling synthesis may therefore be a general method for introduction of a [4-^{18}F]fluorophenyl structure into highly functional and sensitive molecules. The complete automation of a procedure to prepare [4-^{18}F]-1-bromo-4-fluorobenzene of high specific radioactivity from ^{18}F via this synthetic route is now under development.

Table 2. Radiochemical yields of [4-^{18}F]fluorobiphenyl. Conditions: 25 μmol tributyl(phenyl)tin, 5 μmol Pd_2dba_3 and 10 μmol $AsPh_3$ in 1400 μl DMF–dioxane for 45 min.

T/°C	Radiochemical yield (%)[a]
60	21
100	54
115	90
140	15

[a] Determined by analytical HPLC of samples withdrawn from the reaction mixture.

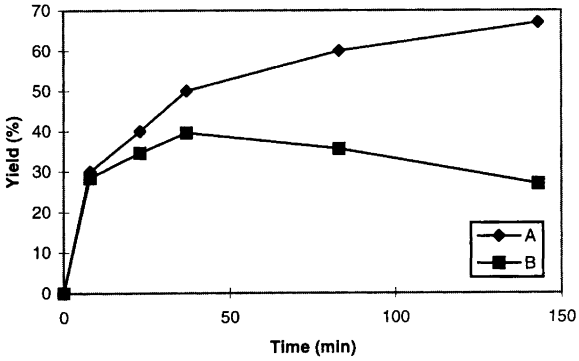


Fig. 2. Radiochemical yields of [4-^{18}F]fluorobiphenyl. A, determined by analytical HPLC of samples withdrawn from the reaction mixture; B, calculated from the yields of A with respect to the decay of ^{18}F. Conditions: 25 μmol stannane, 5 μmol Pd_2dba_3 and 10 μmol $AsPh_3$ in 1400 μl DMF–dioxane at 100 °C.

Experimental

General. The [^{18}F]fluoride was prepared by the $^{18}O(p, n)^{18}F$ nuclear reaction using enriched [^{18}O]water (20–95%), in a 1.2 ml silver target, and 17 MeV protons produced by the Scanditronix MC-17 Cyclotron at Uppsala University PET Centre. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer or a Varian Gemini (200 MHz) with [^{2}H]chloroform as the solvent. The LC–MS analyses were performed on a Fison VG Platform spectrometer or a Fison VG Quattro using a Beckman high pressure liquid chromatography (HPLC) system, and a Kromasil C18 5 μm column, 100 × 4.6 mm (i.d.). A CMA 240 autosampler (CMA Microdialysis, Sweden) was used for injection. Analytical HPLC was performed on a Beckman HPLC system equipped with a UV detector in series with a β^+-flow detector and a Beckman Ultrasphere ODS 5 μm column, 250 × 4.6 mm (i.d.). A Gilson 231 XL autosampler was used for injection. Mobile phases

were 0.05 M ammonium formate pH 3.5 (A), MeCN (B) and methanol [MeOH, (C)]. HPLC was performed at room temperature and detection at 254 nm. Thin layer chromatography (TLC) as well as radio-TLC was performed using Alugram Sil G/UV_{254} silica plates (Macherey–Nagel, Düren, Germany). The radioactive distribution by radio-TLC was quantified by storage-phosphorus autoradiography (Molecular Dynamics PhosphorImager®, Sunnyvale, CA, USA).

The following reagents and substances were of commercial grade and used as supplied (Aldrich and Lancaster): $Pd(PPh_3)_4$, $Pd_2(dba)_3$, triphenylphosphine (PPh_3), $AsPh_3$, $RhCl(PPh_3)_3$, bis(tributyltin), Bu_3SnPh, tetramethyltin, tributyltin acetate, vinyltributyltin, 3-bromobenzaldehyde, indole-2-carboxylic acid, 1-bromo-4-fluorobenzene, 2-methylindole, Kryptofix 2.2.2®.

Dry DMSO, MeCN and DMF were purchased in Sure-seal® bottles from Aldrich. Dioxane and THF was distilled from sodium, and kept under nitrogen in sealed bottles.

5-Bromo-2-nitrobenzaldehyde was synthesised, via nitration, from 3-bromobenzaldehyde according to the literature.[12]

1-Isopropyl-2-methyl-3yl(tributyl) tin.

1-Isopropyl-2-methylindole **4**. The alkylation of 2-methylindole was carried out according to the literature.[13] Purification was performed by flash chromatography[14] (silica gel, Millipore S. A. 60A) with diethyl ether and pentane (2:9) as eluents. The yield was 39% of 1-isopropyl-2-methylindole. ^1H NMR ($CDCl_3$): δ 1.65 (6 H, d, *J* 3.5 Hz), 2.48 (3 H, s), 4.60–4.79 (1 H, m), 6.24 (1 H, s), 7.03–7.19 (2 H, m), 7.47–7.59 (2 H, m). MS: *m/z* 174.3 $[M+H]^+$.

1-Isopropyl- 2-methyl-3-iodoindole **5**. Iodination of **4** was performed according to the literature[15] in 90% yield. ^1H NMR (CDCl3): δ 1.64 (6 H, d, *J* 3.5), 2.53 (3 H, s), 4.63–4.86 (1 H, m), 7.11–7.20 (2 H, m), 7.37–7.44 (2 H, m).

1-Isopropyl-2-methylindol-3-yl(tributyl) tin. Compound **5** was stannylated according to the literature[16] in 20% yield. ^1H NMR ($CDCl_3$): δ 0.82–1.7 (33 H, m), 2.45 (3 H, s), 4.57–4.76 (1 H, m), 7.09–7.18 (2 H, m), 7.41–7.55 (2 H, m).

Synthesis of [4-^{18}F]-1-bromo-4-fluorobenzene **3**.

Preparation of [^{18}F]potassium fluoride–Kryptofix®2.2.2. The aqueous [^{18}F]fluoride solution (0.2–1.0 ml) was added to a 4 ml septum equipped glass vessel, containing Kryptofix® 2.2.2, (13 mg, 34.7 μmol) and potassium carbonate (K_2CO_3) (2.6 mg, 18.8 μmol). The $[K/222]^+$ $^{18}F^-$ complex was dried by azeotropic distillation in a gentle stream of nitrogen with acetonitrile (MeCN, 3 × 1 ml) at 105 °C.

[2-^{18}F]-5-Bromo-4-fluorobenzaldehyde **2**. A solution of 5-bromo-2-nitrobenzaldehyde (4.9 mg, 21.3 μmol) in 1 ml DMSO was added to the $[K/222]^+$ $^{18}F^-$ complex and the solution was transferred to a 1 ml septum-equipped glass vessel. The solution was heated at 135 °C for 20 min. Purification was performed by solid phase extraction (SPE) as follows. The DMSO solution was diluted with 10 ml of water and passed through an activated (5 ml of methanol followed by 5 ml of water) C18 Sep-Pak® cartridge. The cartridge was washed with water (5 ml) and dried with air. [2-^{18}F]-5-bromo-4-fluorobenzaldehyde was eluted with pentane (5 ml) and dried by passage through a column containing potassium carbonate (K_2CO_3) and magnesium sulfate ($MgSO_4$) (1:1). The organic solvent was evaporated under a stream of nitrogen at 0 °C. The radiochemical yield (75–90%) was determined by radio-TLC using hexane–ether (50:50) as the eluent. Identification was by radio-TLC (R_f = 0.75) and analytical radio-HPLC: solvent A–B (20:80), isocratic elution, flow 1.0 ml min^{-1}, k' = 1.6.

[4-^{18}F]-1-Bromo-4-fluorobenzene **3**. [2-^{18}F]-5-Bromo-4-fluorobenzaldehyde **2** was dissolved in dioxane (1 ml, purged with argon) and transferred to a 1.5 ml septum-equipped glass vessel, and $RhCl(PPh_3)_3$ (20 mg, 21.6 μmol) was added. The mixture was heated at 140 °C for 20 min. [4-^{18}F]-1-Bromo-4-fluorobenzene was distilled in a gentle stream of nitrogen via a Teflon tube at 150–160 °C and trapped in the solvent of choice. The product **3** was obtained in 95% decay-corrected radiochemical yield from [2-^{18}F]-5-bromo-2-fluorobenzaldehyde **2**. The identity and the radiochemical purity of [4-^{18}F]-1-bromo-4-fluorobenzene were determined by radio-TLC (R_f = 0.77) and by analytical radio-HPLC: solvent A–B (20:80), isocratic elution, flow 1.0 ml min^{-1}, k' = 2.2.

One-pot synthesis of [4-^{18}F]-1-bromo-4-fluorobenzene **3**. This procedure was performed as above but with only 300 μl DMSO in the nucleophilic substitution step. The product obtained (**2**) from the first reaction step was used without purification in the decarbonylation step.

Palladium-promoted cross-coupled products. General procedure for reaction of [4-^{18}F]-1-bromo-4-fluorobenzene with organostannanes. A typical reaction procedure for the palladium promoted cross-coupling reaction is described below for [4-^{18}F]fluorobiphenyl.

[4-^{18}F]fluorobiphenyl. A solution of the purified [4-^{18}F]-1-bromo-4-fluorobenzene in 1000–1400 μl of DMF–dioxane (1:1) was transferred to a reaction vial containing 5.2 mg (5.7 μmol) $Pd_2(dba)_3$ and 6.1 mg (19.6 μmol) $AsPh_3$ and the reaction mixture was purged with nitrogen gas. After addition of 8 mg (21.8 μmol) Bu_3SnPh the reaction mixture was heated at 115 °C for 15 min. Samples were withdrawn from the reaction mixture and the radiochemical yield was determined by analytical radio-HPLC: solvent A–C (20:80), isocratic elution, flow 1.5 ml min^{-1}, k' = 3.7.

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