ARTICLE

OBC
www.rsc.org/obc

Synthesis of ^{18}F-labelled cyclooxygenase-2 (COX-2) inhibitors *via* Stille reaction with 4-[^{18}F]fluoroiodobenzene as radiotracers for positron emission tomography (PET)

Frank R. Wüst,*[a] Aileen Höhne[a] and Peter Metz[b]

[a] *Institute of Bioinorganic and Radiopharmaceutical Chemistry, FZ-Rossendorf, PF 51 01 19, D-01314, Dresden, Germany. E-mail: f.wuest@fz-rossendorf.de; Fax: +493512602951; Tel: +493512602760*

[b] *Institute of Organic Chemistry, Technical University Dresden, Bergstraße 66, D-01069, Dresden, Germany. E-mail: peter.metz@chemie.tu-dresden.de; Fax: +4935146333162; Tel: +4935146337006*

Received 20th August 2004, Accepted 15th November 2004
First published as an Advance Article on the web 22nd December 2004

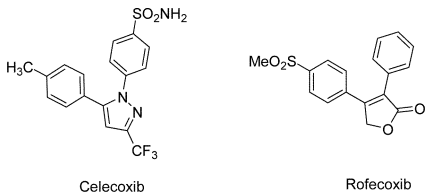
The Stille reaction with 4-[^{18}F]fluoroiodobenzene as a novel approach for the synthesis of radiotracers for monitoring COX-2 expression by means of PET has been developed. Optimized reaction conditions were elaborated by screening of various catalyst systems and solvents. By using optimized reaction conditions ^{18}F-labelled COX-2 inhibitors **[^{18}F]-5** and **[^{18}F]-13** could be obtained in radiochemical yields of up to 94% and 68%, respectively, based upon 4-[^{18}F]fluoroiodobenzene.

Introduction

Positron emission tomography (PET) is a medical imaging technique using compounds labelled with short-lived positron emitting radioisotopes, also termed as radiotracers, for quantitative investigations of molecular and cellular transport processes *in vivo*.[1] Thus, in combination with appropriately labelled radiotracers, PET offers exceptional possibilities to study physiology, metabolism, pharmacokinetics and modes of action of novel and established drugs.[2] For this purpose ^{11}C and ^{18}F are the most useful positron emitters, which have half-lives measured in minutes, being 20.4 min and 109.6 min, respectively. Consequently, time dominates all aspects of PET, and organic chemistry with ^{11}C and ^{18}F differs significantly from conventional chemistry. In this connection syntheses involving short-lived positron emitting radionuclides require fast and efficient reactions due to short half-lives. Moreover, use of submicromolar amounts of radiolabelled compounds, as typically found in the synthesis of PET radiotracers, results in an extraordinary stoichiometrical relation between labelled and unlabelled reagents. Therefore, one has to develop an appropriate radiosynthesis route considering the short half-life and the submicromolar amounts of compounds labelled with short-lived positron emitters such as ^{11}C and ^{18}F. The special features encountered in organic chemistry with the short-lived positron emitters ^{11}C and ^{18}F have extensively been reviewed recently.[3]

In the last decade especially palladium-mediated carbon–carbon bond forming reactions have proven to be very useful for the synthesis of a wide variety of ^{11}C-labelled radiotracers.[4] However, only a few attempts have been made to adopt the recent advances in palladium-mediated reactions to the synthesis of ^{18}F-labelled radiotracers.[5] Palladium-mediated carbon–carbon or carbon–heteroatom bond forming reactions with organic halides suggest the use of ^{18}F-labelled aryl halides (*e.g.* 4-[^{18}F]fluoroiodobenzene) as ideally suited coupling partners. This approach can be regarded as a general method for the mild and efficient introduction of a 4-[^{18}F]fluorophenyl group into a wide variety of potential PET radiotracers. Moreover, the 4-fluorophenyl group is recognized as a common structural component found in many fluorinated drugs. The beneficial effect of a fluoroaryl group in drug design and development with regard to drug metabolism, *in vivo* activity and stability has been reviewed recently.[6] Also, a hydrogen atom often can be replaced bioisosterically with a fluorine atom.

The development of COX inhibitors labelled with short-lived positron emitters is currently a major focus of pharmaceutical research.[7] Cyclooxygenases control the complex conversion of arachidonic acid to prostaglandins and thromboxanes, which trigger as autocrine and paracrine chemical messengers many physiological and pathophysiological responses.[8] The COXs exists in two distinct isoforms—a constitutive form (COX-1) and an inducible form (COX-2). The COX-1 enzyme is responsible for maintaining homeostasis (gastric and renal integrity) whereas COX-2 induces inflammatory conditions. Besides being associated with inflammation and pain, it is well documented that especially COX-2 is overexpressed in many human cancer entities. Although a large variety of COX-2 inhibitors, such as celecoxib and rofecoxib (Scheme 1), are among the most widely used therapeutics for the treatment of pain and inflammation, their exact biological pathway still remains uncertain.



Celecoxib Rofecoxib

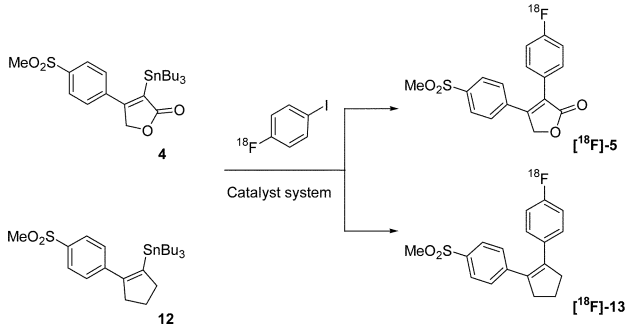
Scheme 1 Selective COX-2 inhibitors.

Therefore, the development and *in vivo* investigation of appropriately ^{18}F- or ^{11}C-labelled COX inhibitors would provide pharmacological data, which may help to understand their physiological actions and metabolic pathways. To date only a few attempts have been reported on the radiolabelling of COX-2 inhibitors as radiotracers for PET. Therein, the radiolabelling was accomplished *via* nucleophilic aromatic substitution with [^{18}F]fluoride or methylation with [^{11}C]MeI.[9] However, the approaches involving [^{18}F]fluoride are restricted to aromatic rings, which are sufficiently activated by the presence of electron-withdrawing groups.

DOI: 10.1039/b412871k

On the other hand COX-2 inhibitors often represent 1,2-diarylhetero- or carbocycles.[10] This typical structural motif suggests the selective introduction of a 4-[^{18}F]fluorophenyl group *via* transition metal-mediated carbon–carbon bond forming reactions such as the Stille reaction.

In this paper we describe the synthesis of two selective COX-2 inhibitors **[^{18}F]-5** and **[^{18}F]-13** *via* Stille reaction with 4-[^{18}F]fluoroiodobenzene as a novel approach for the synthesis of radiotracers for monitoring COX-2 expression by means of PET (Scheme 2). The radiolabelled COX-2 inhibitors differ in their core structure, being a 2(5*H*)furanone unit (compound **[^{18}F]-5**) and a cyclopentene ring (compound **[^{18}F]-13**), respectively. The reaction conditions were optimized by extensive screening of various catalyst systems and solvents.

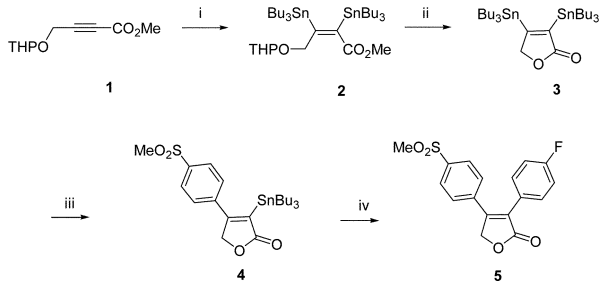


Scheme 2 Synthetic route for the preparation of ^{18}F-labelled COX-2 inhibitors **[^{18}F]-5** and **[^{18}F]-13**.

Results and discussion

Synthesis of labelling precursor 4 and reference compound 5 containing a 2(5*H*)furanone core

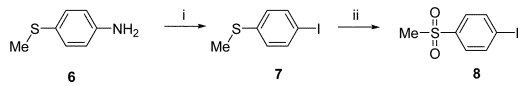
The synthesis of 2(5*H*)furanone-based compounds **4** and **5** is depicted in Scheme 3.



Scheme 3 *Reaction conditions*: (i) Sn_2Bu_6, $PdCl_2(PPh_3)_2$, THF, rt; (ii) DOWEX 50W-X4, MeOH, 50 °C; (iii) $Pd_2(dba)_3$, $AsPh_3$, CuI, 1-iodo-4-methanesulfonylbenzene **8**, THF, 50 °C; (iv) $PdCl_2(PPh_3)_2$, CuI, 4-fluoroiodobenzene, DMF, 50 °C.

Methyl propynoate **1** was subjected to a bis-stannylation reaction with hexabutylditin according to a literature procedure to give the desired bis-stannylated methyl enoate **2** in 75% yield.[11] A THP-ether deprotection/lactone cyclization reaction step by means of a cation exchange resin afforded compound **3** (83% yield) as a colourless oil. Stille reaction of bis-stannylated compound **3** with 1-iodo-4-methanesulfonylbenzene **8** gave labelling precursor **4** in 27% yield. The Stille reaction of **8** with bis-stannylated compound **3** exclusively gave the desired 3-(tributylstannyl)-4-aryl-2(5*H*)furanone regioisomer **4**. This observation is consistent with reports in the literature describing analogous reactions.[11] Moreover, 2D nuclear Overhauser effect spectroscopy (NOESY) of compound **4** revealed a correlation between aromatic protons at 7.50 ppm with methylene protons at 5.17 ppm, which confirms the specified regiochemistry. Compound **4** was further used for a second Stille reaction with 4-fluoroiodobenzene as the coupling partner to provide reference compound **5** in a very good yield of 88%.

The synthesis of 1-iodo-4-methanesulfonylbenzene **8** was accomplished by conversion of 4-methylthioaniline **6** into the corresponding iodo compound **7** employing a Sandmeyer analogous reaction (Scheme 4).[12]

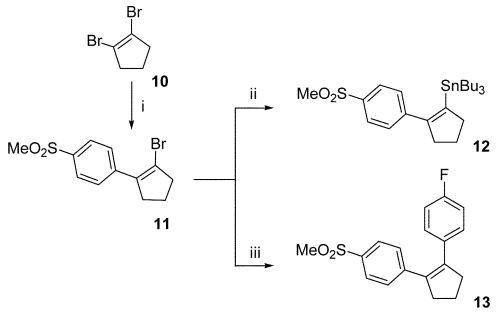


Scheme 4 *Reaction conditions*: (i) 1. $NaNO_2$, HCl, 0 °C, 2. KI, 80 °C; (ii) oxone, MeOH–H_2O.

Treatment of the intermediate diazonium salt generated from **6** with KI gave thioether **7**, which was oxidized to sulfone **8** by means of oxone in 58% total yield for both steps.

Synthesis of labelling precursor 12 and reference compound 13 containing a cyclopentene core

A different synthetic route was chosen for the preparation of labelling precursor **12** and reference compound **13**, which is illustrated in Scheme 5.

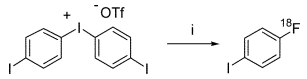


Scheme 5 *Reaction conditions*: (i) $PdCl_2(PPh_3)_2$, DMF, Cs_2CO_3, 4-(methanesulfonyl)phenylboronic acid, 100 °C; (ii) Sn_2Bu_6, $PdCl_2(PPh_3)_2$, dioxane, reflux; (iii) $Pd(PPh_3)_4$, toluene, EtOH, 2 M Na_2CO_3, 4-fluorophenylboronic acid, reflux.

Application of a Suzuki–Stille and Suzuki–Suzuki reaction sequence starting from commercially available 1,2-dibromocyclopentene **10** provided labelling precursor **12** and reference compound **13**, respectively. The synthesis was modified with respect to the literature procedure.[13] It was found that compound **11** could prepared in a single step starting from 4-(methanesulfonyl)phenylboronic acid as the coupling partner in the Suzuki cross-coupling reaction. Moreover, performance of the reaction in DMF proved to be superior to the reported solvent system toluene–EtOH–2 M Na_2CO_3. A two-fold excess of 1,2-dibromocyclopentene **10** was treated with 4-(methanesulfonyl)phenylboronic acid in a first Suzuki cross-coupling step to minimize the formation of symmetrically bis-arylated product. Thus, compound **11** could be obtained in a single step in 45% yield. A second Suzuki cross-coupling reaction between compound **11** and 4-fluorophenylboronic acid gave reference compound **13** in 69% yield. The required stannane labelling precursor **12** was prepared *via* a Pd-catalyzed cross-coupling reaction between monobromide **11** and hexabutylditin in 45% yield.

Optimization of the Stille cross-coupling reaction between stannane 4 and 4-[^{18}F]fluoroiodobenzene

Stannane **4** was used for the optimization of the Stille cross-coupling reaction conditions with 4-[^{18}F]fluoroiodobenzene, which was prepared *via* thermal decomposition of 4,4′-diiododiphenyliodonium triflate in the presence of [^{18}F]fluoride as reported recently (Scheme 6).[5c,d,f]



Scheme 6 *Reaction conditions*: (i) [^{18}F]KF, K_{222}, K_2CO_3, DMF, 120 °C.

The reaction conditions were optimized by screening several catalyst systems (palladium complex/co-ligand/additive), solvents, reaction temperatures and reaction times. The radiochemical yields (RCY) were determined by radio-HPLC of aliquots taken from the reaction mixture representing the percentage of cross-coupled product present in the reaction mixture. The results are summarized in Table 1.

In a first set of reactions (entries 1–6) the influence of different solvents on the radiochemical yield was studied by using the catalyst system $Pd_2(dba)_3/AsPh_3/CuI$. This catalyst system has already successfully been applied in the Stille reaction of stannylated nucleosides with 4-[^{18}F]fluoroiodobenzene.[5a]

The data show that in pure solvents, regardless of the different polarity (DMF, THF or toluene), only low radiochemical yields of up to 20% (entry 3) could be obtained, while most of the 4-[^{18}F]fluoroiodobenzene remained unreacted in the reaction mixture. When DMF was used as the solvent (entries 1 and 2), no effect of the reaction temperature (65 °C *vs.* 115 °C) on the radiochemical yield could be observed. In contrast, performance of the cross-coupling reaction at an elevated reaction temperature (115 °C *vs.* 65 °C) resulted in a significantly lower radiochemical yield when THF was the solvent (entry 3 *vs.* entry 4). The lowest radiochemical yields of 5% and 4%, respectively, were observed with toluene as the solvent (entries 5 and 6).

These findings led us to the use of several solvent mixtures in another set of reactions (entries 7–11). Also the effect of reaction temperature on the radiochemical yield was studied. The performance of the cross-coupling reaction in 1 : 1 mixtures of DMF–THF or DMF–toluene at 65 °C gave the desired product in 50% and 85% radiochemical yield, respectively (entries 7 and 11). Application of higher reaction temperatures led to the formation of non-determined side-products, which reduced the radiochemical yield of product **[^{18}F]-5** (entry 8). This tendency was also observed in DMF–dioxane as the solvent, although radiochemical yields were much lower compared to the results obtained by using DMF–THF or DMF–toluene as the solvents (entries 9 and 10). So far, these results suggested the use of DMF–toluene as the solvent system of choice and 65 °C as the preferred reaction temperature. Further optimization attempts were aimed at the variation of the used co-ligands, being triphenylarsine, tri-*o*-tolylphosphine and tri-2-furylphosphine (TFP), respectively (entries 11–13). The use of tri-*o*-tolylphosphine and tri-2-furylphosphine resulted in a further increase of radiochemical yield, reaching 93% (entry 12) and 98% (entry 13), respectively. Utilization of tri-2-furylphosphine as co-ligand in the Stille reaction is known to increase the rate of the transmetallation step of the stannane to palladium, which is thought to be the rate-determining step of the catalytic cycle.[14] Moreover, compared to other co-ligands that are commonly used in Stille cross-coupling reactions the formed catalyst species are remarkably stable when tri-2-furylphosphine is used.

However, in our experiments tri-2-furylphosphine was always co-eluted as a chemical impurity along with ^{18}F-labelled compound **[^{18}F]-5** as monitored by HPLC analysis. Complete removal of the tri-2-furylphosphine ligand from the HPLC fraction containing compound **[^{18}F]-5** was not possible even by testing different eluents.[15] This drawback may limit the use of tri-2-furylphosphine as co-ligand in the radiosynthesis of ^{18}F-labelled compounds *via* Stille reaction, since the corresponding radiotracers should be of pharmaceutical quality, which also implies a sufficient chemical purity.

The beneficial effect of tri-*o*-tolylphosphine on the radiochemical yield (entry 12) is mainly governed by steric effects, which are thought to be responsible for an acceleration of the reaction rate.[14]

The use of $Pd(PPh_3)_4$ as palladium complex diminished the radiochemical yield to 40% and 27% (entries 14 and 15). The lower radiochemical yields can be explained by the lower air stability of $Pd(PPh_3)_4$ compared to the more air-stable $Pd_2(dba)_3$, since the radiosynthesis was carried out without an inert gas atmosphere.

Thus, for the Stille cross-coupling of stannane **4** with 4-[^{18}F]fluoroiodobenzene, reaction conditions according to entry 12 turned out to be most suitable with respect to the efficient radiosynthesis of ^{18}F-labelled COX-2 inhibitor **[^{18}F]-5** as radiotracer for PET. Optimized reaction conditions (according to entry 12) were also applied to the synthesis of ^{18}F-labelled COX-2 inhibitor **[^{18}F]-13**, and this compound could be obtained in 68% radiochemical yield based upon 4-[^{18}F]fluoroiodobenzene.

Conclusions

In conclusion, we have developed a convenient method for radiolabelling of two COX-2 inhibitors with the short-lived positron emitter ^{18}F *via* carbon–carbon bond formation with 4-[^{18}F]fluoroiodobenzene. This approach represents an alternative route to the published methods involving nucleophilic aromatic substitution with [^{18}F]fluoride. Moreover, this novel method will also be applicable to structurally related COX-2 inhibitors bearing a 4-[^{18}F]fluorophenyl-substituted 1,2-diarylhetero- or carbocycle motif. The radiopharmacological evaluation of the

Table 1 Stille cross-coupling reaction of 4-[^{18}F]fluoroiodobenzene with stannane **4**[a]

Entry	Catalyst system	Solvent[b]	Temperature/°C	Reaction time/min	RCY (%)
1	$Pd_2(dba)_3/AsPh_3/CuI$	DMF	65	20	7
2	$Pd_2(dba)_3/AsPh_3/CuI$	DMF	115	30	10
3	$Pd_2(dba)_3/AsPh_3/CuI$	THF	65	20	20
4	$Pd_2(dba)_3/AsPh_3/CuI$	THF	115	30	9
5	$Pd_2(dba)_3/AsPh_3/CuI$	toluene	100	10	5
6	$Pd_2(dba)_3/AsPh_3/CuI$	toluene	100	20	4
7	$Pd_2(dba)_3/AsPh_3/CuI$	DMF–THF	65	20	50
8	$Pd_2(dba)_3/AsPh_3/CuI$	DMF–THF	115	30	3
9	$Pd_2(dba)_3/AsPh_3/CuI$	DMF–dioxane	65	20	8
10	$Pd_2(dba)_3/AsPh_3/CuI$	DMF–dioxane	90	30	0.2
11	$Pd_2(dba)_3/AsPh_3/CuI$	DMF–toluene	65	20	85
12	$Pd_2(dba)_3/P(o\text{-tol})_3/CuI$	DMF–toluene	65	20	93
13	$Pd_2(dba)_3$/TFP/CuI	DMF–toluene	65	20	98
14	$Pd(PPh_3)_4/AsPh_3/CuI$	DMF–toluene	65	20	40
15	$Pd(PPh_3)_4/P(o\text{-tol})_3/CuI$	DMF–toluene	65	20	27

[a] Molar ratios of stannane/Pd complex/co-ligand/CuI: 1 : 2 : 1.5 : 2. [b] Mixed solvents in a 1:1 mixture

^{18}F-labelled COX-2 inhibitors **[^{18}F]-5** and **[^{18}F]-13** for imaging COX-2 expression *in vivo* by means of PET is currently in progress.

Experimental

General

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Varian Inova-400 at 400 MHz, 100 MHz and 376 MHz, respectively. Chemical shifts (δ) were determined relative to the solvent and converted to the TMS scale. Melting points were determined on a Cambridge Instruments Galen™ III melting point apparatus and are uncorrected. Mass spectra were obtained on a Quattro/LC mass spectrometer (Micromass) by electrospray ionisation. Flash chromatography was conducted using MERCK silica gel (mesh size 230–400 ASTM). Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 aluminium plates, with visualization under UV light (254 nm). All chemicals were obtained from commercial suppliers (reagent grade) and used without further purification. 4-(Tetrahydropyran-2-yloxy)but-2-ynoic acid methyl ester **1**,[11] 4-(tetrahydropyran-2-yloxy)-2,3-bis-tributylstannanylbut-2-enoic acid methyl ester **2**,[11] 3,4-bis-tributylstannanyl-5*H*-furan-2-one **3**[11] and 4-methylthioiodobenzene **7**[12] were prepared according to literature procedures.

Chemical syntheses

4-(4-Methanesulfonylphenyl)-3-tributylstannanyl-5*H*-furan-2-one (4). 1-Iodo-4-methanesulfonylbenzene **8** (282 mg, 1.0 mmol), 3,4-bis-tributylstannanyl-5*H*-furan-2-one **3**, CuI (15.5 mg, 80 μmol), $AsPh_3$ (24.5 mg, 80 μmol) and $Pd_2(dba)_3$ (18.2 mg, 20 μmol) were dissolved in dry THF (7 ml). The reaction mixture was stirred at 50 °C overnight under nitrogen. The volume of the solution was concentrated to ~3 ml and loaded to a flash chromatography column. Elution with 80% Et_2O–petrol ether gave compound **4** (144 mg, 27%) as a colourless oil. R_f (80% Et_2O–petrol ether): 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78–1.48 (m, 27 H, $SnBu_3$), 3.07 (s, 3H, CH_3), 5.06 (m, 2H, CH_2), 7.53 and 8.02 (2d of AA′BB′ system, J = 8.5 Hz, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.5, 13.5, 27.1, 28.8, 44.4, 73.8, 125.4, 127.9, 133.8, 139.3, 141.9, 171.4, 177.9. LRMS (ESI positive): 471.0 [M − Bu].

3-(4-Fluorophenyl)-4-(4-methanesulfonylphenyl)-5*H*-furan-2-one (5). 4-Fluoroiodobenzene (57 μl, 0.5 mmol), 4-(4-methanesulfonylphenyl)-3-tributylstannanyl-5*H*-furan-2-one **4** (132 mg, 0.25 mmol), CuI (3.8 mg, 20 μmol), and $PdCl_2(PPh_3)_2$ (3.5 mg, 5.0 μmol) were stirred in dry DMF (10 ml) at 50 °C overnight under nitrogen. The volume of the solution was concentrated to ~3 ml and loaded to a flash chromatography column, which was eluted with 50% EtOAc–petrol ether to give 73 mg (88%) of compound **5** as a brownish solid. Mp 170–171 °C, R_f (50% EtOAc–petrol ether): 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.07 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 7.08 (m, 2H, Ar-H), 7.39 (m, 2 H, Ar-H), 7.50 and 7.93 (2d of AA′BB′ system, J = 8.3 Hz, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.2, 70.4, 116.1 (d, ^{2}J(C–F) = 21.7 Hz), 125.0 (d, ^{4}J(C–F) = 3.1 Hz), 127.8, 128.2, 128.4, 131.1 (d, ^{3}J(C–F) = 8.3 Hz), 153.5, 142.0, 136.1, 163.2 (d, ^{1}J(C–F) = 250.4 Hz), 172.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −110.8 (m). LRMS (ESI positive): 333.2 [M + H].

1-Iodo-4-methanesulfonylbenzene (8). 4-Methylthioiodobenzene **7** was prepared by adapting the procedure reported in the literature starting from 4-methylthioaniline **6** (3.1 ml, 25 mmol).[12] Crude **7** in a 1 : 1 mixture of THF–MeOH (100 ml) was treated with oxone (15.4 g, 25 mmol) in water (50 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was re-dissolved in EtOAc. After flash chromatography (30% EtOAc–petrol ether) the product was isolated as a colourless solid (4.1 g, 58%). Mp 116–118 °C (Lit. 117–118 °C),[12] R_f (30% EtOAc–petrol ether): 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (s, 3H, CH_3), 7.66 and 7.94 (2d of AA′BB′ system, J = 7.8 Hz, 4H, Ar-H).

1-(2-Bromocyclopent-1-enyl)-4-methanesulfonylbenzene (11). A solution of 1,2-dibromocyclopentene **10** (500 mg, 2.2 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), Cs_2CO_3 (1.08 g, 3.3 mmol) and 4-(methanesulfonyl)phenylboronic acid (220 mg, 1.1 mmol) in dry DMF (10 ml) was heated under nitrogen at 100 °C overnight. After the addition of water (25 ml) the solution was extracted with EtOAc. The solvent was evaporated and the residue was purified by flash chromatography (50% EtOAc–petrol ether) to afford 150 mg (45%, based upon 4-(methylsulfonyl)phenylboronic acid) of compound **11** as a solid. Mp 105–106 °C (Lit. 103.2–103.8 °C),[13a] R_f (30% EtOAc–petrol ether): 0.4; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (quint., J = 7.6 Hz, 2H, CH_2), 2.77 (t, J = 7.6 Hz, 2H, CH_2), 2.88 (t, J = 7.6 Hz, 2H, CH_2), 3.05 (s, 3H, CH_3), 7.76 and 7.90 (2d of AA′BB′ system, J = 8.4 Hz, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8, 35.9, 42.6, 44.4, 120.3, 127.1, 128.2, 136.8, 138.2, 141.4.

Tributyl-[2-(4-methanesulfonylphenyl)cyclopent-1-enyl]stannane (12). A solution of 1-(2-bromocyclopent-1-enyl)-4-methanesulfonylbenzene **11** (300 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 50.0 μmol) and Sn_2Bu_6 (0.5 ml, 1.00 mmol) in dioxane (10 ml) was heated under reflux for 16 h under a nitrogen atmosphere. The solvent was evaporated, and product **12** was isolated as a colourless oil by flash chromatography (20% EtOAc–petrol ether). Yield: 230 mg (45%). R_f (20% EtOAc–petrol ether): 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75–1.39 (m, 27H, $SnBu_3$), 1.99 (quint., J = 7.5 Hz, 2H, CH_2), 2.65, (m, 2H, CH_2), 2.77 (m, 2H, CH_2), 3.04 (s, 3H, CH_3), 7.43 and 7.86 (2d of AA′BB′ system, J = 8.5 Hz, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1, 13.6, 24.8, 27.3, 29.1, 38.1, 42.3, 44.6, 127.1, 127.7, 138.3, 146.1, 147.2, 151.4. LRMS (ESI positive): 535.3 [M + Na].

1-Fluoro-4-(2-(4-(methanesulfonyl)phenyl)cyclopent-1-enyl)-benzene (13). To a solution of compound **11** (100 mg, 0.33 mmol) and 4-fluorophenylboronic acid (56 mg, 0.4 mmol) in a solvent mixture containing of toluene (2 ml), ethanol (2 ml) and 2 M Na_2CO_3 (2 ml) was added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol). The mixture was refluxed overnight and then concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc–petrol ether) to afford 72 mg (69%) of compound **13** as a solid. Mp 146–147 °C, R_f (50% EtOAc–petrol ether): 0.6; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.09 (quint., J = 7.3 Hz, 2H, CH_2), 2.91 (t, J = 7.3 Hz, 4H, CH_2), 3.04 (s, 3H, CH_3), 6.93 (m, 2H, Ar-H), 7.10 (m, 2H, Ar-H), 7.32 and 7.76 (2d of AA′BB′ system, J = 8.2 Hz, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0, 38.6, 39.5, 44.4, 115.4 (d, ^{2}J(C–F) = 21.6 Hz), 127.2, 128.9, 129.7 (d, ^{3}J(C–F) = 8.0 Hz), 133.5 (d, ^{4}J(C–F) = 3.2 Hz), 135.6, 138.1, 140.4, 144.0, 161.9 (d, ^{1}J(C–F) = 245.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −114.8 (m).

Radiosyntheses

No-carrier added aqueous [^{18}F]fluoride ion was produced in a IBA CYCLONE 18/9 cyclotron by irradiation of [^{18}O]H_2O *via* the ^{18}O(p,n)^{18}F nuclear reaction. Resolubilization of the aqueous [^{18}F]fluoride was accomplished with Kryptofix® 2.2.2 and K_2CO_3. The radiosynthesis of 4-[^{18}F]fluoroiodobenzene was accomplished in an automated nucleophilic fluorination module (Nuclear Interface, Münster) as described by Wüst and Kniess.[5d]

HPLC analyses were carried out with a SUPELCOSIL LC-18S column (4.6 × 250 mm, 5 μm) using an indicated isocratic eluent (CH_3CN–0.1 M ammonium formate) from a gradient pump L2500 (Merck, Hitachi) with a flow rate of 1 ml min^{-1}. The products were monitored by a UV detector L4500

(Merck, Hitachi) at 254 nm and by γ-detection with a scintillation detector GABI (X-RAYTEST).

Optimisation of the Stille reaction with 4-[^{18}F]fluoroiodobenzene. To a vial containing stannane **4** (4 mg, 7.5 μmol), palladium complex (15 μmol), co-ligand (12 μmol) and CuI (3 mg, 15 μmol) in 0.5 ml of a solvent (DMF, THF, dioxane or toluene) was added 4-[^{18}F]fluoroiodobenzene (30–125 MBq in 0.5 ml of DMF, THF, dioxane or toluene). The sealed reaction vial was heated at 65 °C, 90 °C, 100 °C or 115 °C. After the indicated reaction times (see Table 1) aliquots (50 μl) were taken and after dilution with acetonitrile the samples were subjected to radio-HPLC analysis. The reaction yield was determined from the radio-HPLC chromatogram representing the percentage of radioactivity area of cross-coupled product **[^{18}F]-5** related to the total radioactivity area.

3-(4-[^{18}F]Fluoro-phenyl)-4-(4-methanesulfonylphenyl)-5*H*-furan-2-one ([^{18}F]-5). HPLC analysis: CH_3CN–0.1 M ammonium formate (60 : 40), $t_R = 4.5$ min.

Radiosynthesis of 1-[^{18}F]fluoro-4-(2-(4-(methanesulfonyl)-phenyl)cyclopent-1-enyl)benzene ([^{18}F]-13) using optimised reaction conditions. To a vial containing labelling precursor **12** (5 mg, 10 μmol), $Pd_2(dba)_3$ (18 mg, 20 μmol), tri-*o*-tolylphosphine (4.5 mg, 15 μmol) and CuI (3 mg, 20 μmol) in DMF (0.5 ml) was added 4-[^{18}F]fluoroiodobenzene (35 MBq in 0.5 ml toluene). The sealed reaction vial was heated at 65 °C for 20 min and aliquots (20 μl) were taken for radio-HPLC analysis after dilution with acetonitrile.

1-[^{18}F]Fluoro-4-(2-(4-(methylsulfonyl)phenyl)cyclopent-1-enyl)-benzene ([^{18}F]-13). HPLC analysis: CH_3CN–0.1 M ammonium formate (60 : 40), $t_R = 13.5$ min.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (to F. W.) is gratefully acknowledged. The authors wish to thank S. Preusche for radioisotope production, and H. Kasper and T. Krauss for technical assistance.

References

1 (*a*) M. E. Phelps, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 1484; (*b*) M. E. Phelps, *J. Nucl. Med.*, 2000, **41**, 661; (*c*) T. F. Massoud and S. S. Gambhir, *Gene. Dev.*, 2003, **17**, 545; (*d*) A. M. J. Paans, A. van Waarde, P. H. Elsinga, A. T. M. Willemsen and W. Vaalburg, *Methods*, 2002, **27**, 195; (*e*) T. J. McCarthy, S. W. Schwarz and M. J. Welch, *J. Chem. Educ.*, 1994, **71**, 830; (*f*) J. Czernin and M. J. Phelps, *Annu. Rev. Med.*, 2002, **53**, 89; (*g*) J. S. Fowler and A. P. Wolf, *Acc. Chem. Res.*, 1997, **30**, 181.

2 (*a*) W. C. Eckelman, *Nucl. Med. Biol.*, 2002, **29**, 777; (*b*) H. D. Burns, T. G. Hamil, W.-s. Eng, B. Francis, C. Fioravanti and R. E. Gibson, *Curr. Opin. Chem. Biol.*, 1999, **3**, 388; (*c*) J. S. Fowler, N. D. Volkov, G.-J. Wang, Y.-S. Ding and S. L. Dewey, *J. Nucl. Med.*, 1999, **40**, 1154; (*d*) A. M. J. Paans and W. Vaalburg, *Curr. Pharm. Des.*, 2000, **6**, 1583; (*e*) M. T. Klimas, *Mol. Imaging Biol.*, 2002, **4**, 311; (*f*) R. E. Gibson, H. D. Burns, T. G. Hamil, W.-s. Eng, B. Francis and C. Ryan, *Curr. Pharm. Des.*, 2000, **6**, 973; (*g*) D. Maclean, J. P. Northrop, H. C. Padgett and J. C. Walsh, *Mol. Imaging Biol.*, 2003, **5**, 304.

3 (*a*) P. H. Elsinga, *Methods*, 2002, **27**, 208; (*b*) V. W. Pike, *Drug Inf. J.*, 1997, **31**, 997; (*c*) B. Langström, T. Kihlberg, M. Bergström, G. Antoni, M. Björkman, B. H. Forngren, P. Hartvig, K. Markides, U. Yngve and M. Ögren, *Acta Chem. Scand.*, 1999, **53**, 651.

4 (*a*) M. Björkman, H. Doi, B. Resul, M. Suzuki, R. Noyori, Y. Watanabe and B. Langström, *J. Labelled Compd. Radiopharm.*, 2000, **43**, 1327; (*b*) T. Kihlberg and B. Langström, *J. Org. Chem.*, 1999, **64**, 9210; (*c*) T. Kihlberg, F. Karimi and B. Langström, *J. Org. Chem.*, 2002, **67**, 3687; (*d*) F. Karimi and B. Langström, *J. Labelled Compd. Radiopharm.*, 2002, **45**, 423; (*e*) E. D. Hostetler, S. Fallis, T. J. McCarthy, M. J. Welch and J. A. Katzenellenbogen, *J. Org. Chem.*, 1998, **63**, 1348; (*f*) L. Samuelsson and B. Langström, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 263; (*g*) M. Björkman and B. Langström, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3031; (*h*) O. Rahman, T. Kihlberg and B. Langström, *Eur. J. Org. Chem.*, 2004, 474; (*i*) F. Wüst, J. Zessin and B. Johannsen, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 333.

5 (*a*) L. Allain-Barbier, M. C. Lasne, C. Perrio-Huard, B. Moreau and L. Barrè, *Acta Chem. Scand.*, 1998, **52**, 480; (*b*) T. Forngren, Y. Andersson, B. Lamm and B. Langström, *Acta Chem. Scand.*, 1998, **52**, 475; (*c*) F. Wüst and T. Kniess, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 699; (*d*) F. Wüst and T. Kniess, *J. Labelled Compd. Radiopharm.*, 2004, **47**, 457; (*e*) E. Marriere, J. Rouden, V. Tadino and M.-C. Lasne, *Org. Lett.*, 2000, **2**, 1121; (*f*) A. Shah, V. W. Pike and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2043.

6 P. K. Park, N. R. Kitteringham and P. M. O'Neill, *Annu. Rev. Pharmacol. Toxicol.*, 2001, **41**, 443.

7 (*a*) G. Dannhardt and W. Kiefer, *Eur. J. Med. Chem.*, 2001, **36**, 109; (*b*) L. J. Marnett and A. S. Kalgutar, *Trends Pharmacol. Sci.*, 1999, **20**, 465; (*c*) H. R. Herschman, J. J. Talley and R. DuBois, *Mol. Imaging Biol.*, 2003, **5**, 286; (*d*) X.-C. Xu, *Anticancer Drugs*, 2002, **13**, 127; (*e*) K. Brune and B. Hinz, *Scand. J. Rheumatol.*, 2004, **33**, 1; (*f*) S. Tacconelli, M. L. Capone and P. Patrignani, *Curr. Pharm. Des.*, 2004, **10**, 589.

8 L. J. Marnett, *Curr. Opin. Chem. Biol.*, 2000, **4**, 545.

9 (*a*) T. J. McCarthy, A. U. Sheriff, M. J. Graneto, J. J. Talley and M. J. Welch, *J. Nucl. Med.*, 2002, **43**, 117; (*b*) E. F. deVries, A. Van Waarde, A. R. Buursma and W. Vaalburg, *J. Nucl. Med.*, 2003, **44**, 1700; (*c*) J. S. D. Kumar, M. D. Underwood, J. Prabhakaran, R. V. Parsey, V. Ramin, V. Arango, V. J. Majo, N. R. Norman, A. R. Cooper, J. Arcement, R. L. Van Heertum, J. J. Mann, presented at 228th ACS National Meeting, New York, NY, USA, September 7–11, 2003; (*d*) J. S. D. Kumar, J. Prabhakaran, M. D. Underwood, R. V. Parsey, V. Arango, V. J. Majo, presented at 226th ACS National Meeting, Philadelphia, PA, USA, August 22–26, 2004.

10 R. Garg, A. Kurup, S. B. Mekapati and C. Hansch, *Chem. Rev.*, 2003, **103**, 703.

11 (*a*) N. B. Carter, R. Mabon, A. M. E. Richecœur and J. B. Sweeney, *Tetrahedron*, 2002, **58**, 9117; (*b*) T. N. Mitchell, A. Amamria, H. Killing and D. Rutschow, *J. Organomet. Chem.*, 1986, **304**, 257; (*c*) R. Mabon, A. M. E. Richecœur and J. B. Sweeney, *J. Org. Chem.*, 1999, **64**, 328.

12 (*a*) H. Lumbroso and R. Passerini, *Bull. Soc. Chim. Fr.*, 1955, 1179; (*b*) H. Lumbroso and R. Passerini, *Bull. Soc. Chim. Fr.*, 1957, 311.

13 (*a*) J. J. Li, G. D. Anderson, E. G. Burton, J. N. Cogburn, J. T. Collins, J. D. Garland, S. A. Gregory, H. Huang, P. C. Isakson, C. M. Koboldt, E. W. Logusch, M. B. Norton, W. E. Perkins, E. J. Reinhard, K. Seibert, A. W. Veenhuizen, Y. Zhang and D. B. Reitz, *J. Med. Chem.*, 1995, **38**, 4570; (*b*) D. B. Reitz, J. J. Li, M. B. Norton, E. J. Reinhard, J. T. Collins, G. D. Anderson, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert and P. C. Isakson, *J. Med. Chem.*, 1994, **37**, 3878.

14 V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585.

15 The following eluents were tested: CH_3CN–0.1 M ammonium formate (60 : 40), (50 : 50), (45 : 55); CH_3CN–water (50 : 50), (40 : 60); EtOH–water (30 : 70); CH_3CN–0.1% TFA (50 : 50).