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Research Article

No-carrier added synthesis of ^{18}F-labelled nucleosides using Stille cross-coupling reactions with 4-[^{18}F]fluoroiodobenzene

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Summary

The radiosyntheses of 5-(4′-[^{18}F]fluorophenyl)-uridine **[^{18}F]-11** and 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine **[^{18}F]-12** are described. The 5-(4′-[^{18}F]fluoro-phenyl)-substituted nucleosides were prepared via a Stille cross-coupling reaction with 4-[^{18}F]fluoroiodobenzene followed by basic hydrolysis using 1 M potassium hydroxide. The Stille cross-coupling reaction was optimized by screening various palladium complexes, additives and solvents. By using optimized labelling conditions ($Pd_2(dba)_3$/CuI/$AsPh_3$ in DMF/dioxane (1:1), 20 min at 65°C), 550 MBq of [4-^{18}F]fluoroiodobenzene could be converted into 120 MBq (33%, decay-corrected) of 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine **[^{18}F]-12** within 40 min, including HPLC purification. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: Stille cross-coupling; 4-[^{18}F]fluoroiodobenzene; nucleosides; uridine

Introduction

The radiosyntheses of nucleosides has attracted significant interest over the last decade due to the central role that nucleosides and their phosphorylated derivatives play in biological systems. Thus, nucleoside tracers labelled with positron emitters such as ^{11}C, ^{18}F, ^{76}Br and ^{124}I have extensively been studied as markers for imaging proliferation of tumour cells, and for monitoring gene therapy and gene expression by means of positron emission tomography (PET).[1–9] Most examples of labelled nucleosides for PET have used ^{18}F as the radiolabel. The introduction of ^{18}F into the nucleosides has been accomplished either by direct fluorination with [^{18}F]fluoride of the acylochain or furanose

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sugar part of the intact nucleoside[10–12] or by the combination of the radiofluorinated furanose sugar part with a nucleobase.[1,4]

Transition metal-mediated C–C bond-forming reactions comprise an attractive alternative approach for the synthesis of nucleosides.[13,14] Such regioselective C–C bond formations are of great interest because they may provide a versatile route to various, potentially valuable nucleoside derivatives exhibiting a structural broad variety. The potential of transition metal-assisted reactions for the synthesis of nucleosides was recently reviewed by Agrofoglio[13] and Hocek.[14] In this connection, Samuelsson *et al.* described the synthesis of 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-[*methyl*-^{11}C]thymine ([^{11}C]FMAU) via a Pd-mediated Stille cross-coupling reaction with [^{11}C]methyl iodide.[15] This work represents the first application of a Pd-mediated reaction in the ^{11}C-labelling of a nucleoside. A former work by Conti *et al.*[16] has made use of an alkylation reaction with [^{11}C]methyl iodide to synthesize [^{11}C]FMAU.

The Stille reaction has been established in ^{11}C chemistry as an efficient labelling route for the regioselective introduction of [^{11}C]methyl groups on aromatic or vinylic substrates under mild reaction conditions.[17,18] However, there are only a few examples known utilizing a Stille reaction in ^{18}F chemistry.[19–21]

Recently, we have reported the synthesis of 4-[^{18}F]fluoroiodobenzene and its use in Sonogashira cross-coupling reactions.[22] Herein, we describe an improved method for the synthesis of 4-[^{18}F]fluoroiodobenzene and its application in Stille-cross coupling reactions to form 5-(4′-[^{18}F]fluorophenyl)-substituted nucleosides 5-(4′-[^{18}F]fluorophenyl)-uridine **[^{18}F]-11** and 5-(4′-[^{18}F]fluoro-phenyl)-2′-deoxy-uridine **[^{18}F]-12**.

Results and discussion

Synthesis of labelling precursors and reference compounds

The synthesis of the 5-tributylstannyl-2′,3′,5′-triacetyl-uridine **7** and 5-tributylstannyl-3′,5′-diacetyl-deoxyuridine **8** as labelling precursors, and 5-(4′-fluorophenyl)-uridine **11** and 5-(4′-fluorophenyl)-deoxyuridine **12** as reference compounds is depicted in Figure 1.

Acetylation of uridine **1** and deoxyuridine **2** was accomplished in high yields of 97 and 94%, respectively, according to a literature procedure.[23]

Compounds **3** and **4** were treated with ICl in refluxing CH_2Cl_2 to give 5-iodo nucleosides **5** and **6** in 92 and 85% yield after purification by flash chromatography. The organostannanes **7** and **8** serve as precursors for the subsequent Stille coupling with 4-fluoroiodobenzene and 4-[^{18}F]fluoroiodobenzene. For this purpose compounds **7** and **8** were prepared via a Pd-mediated cross-coupling reaction between 5-iodo nucleosides **5** and **6** and hexabutyldistan-

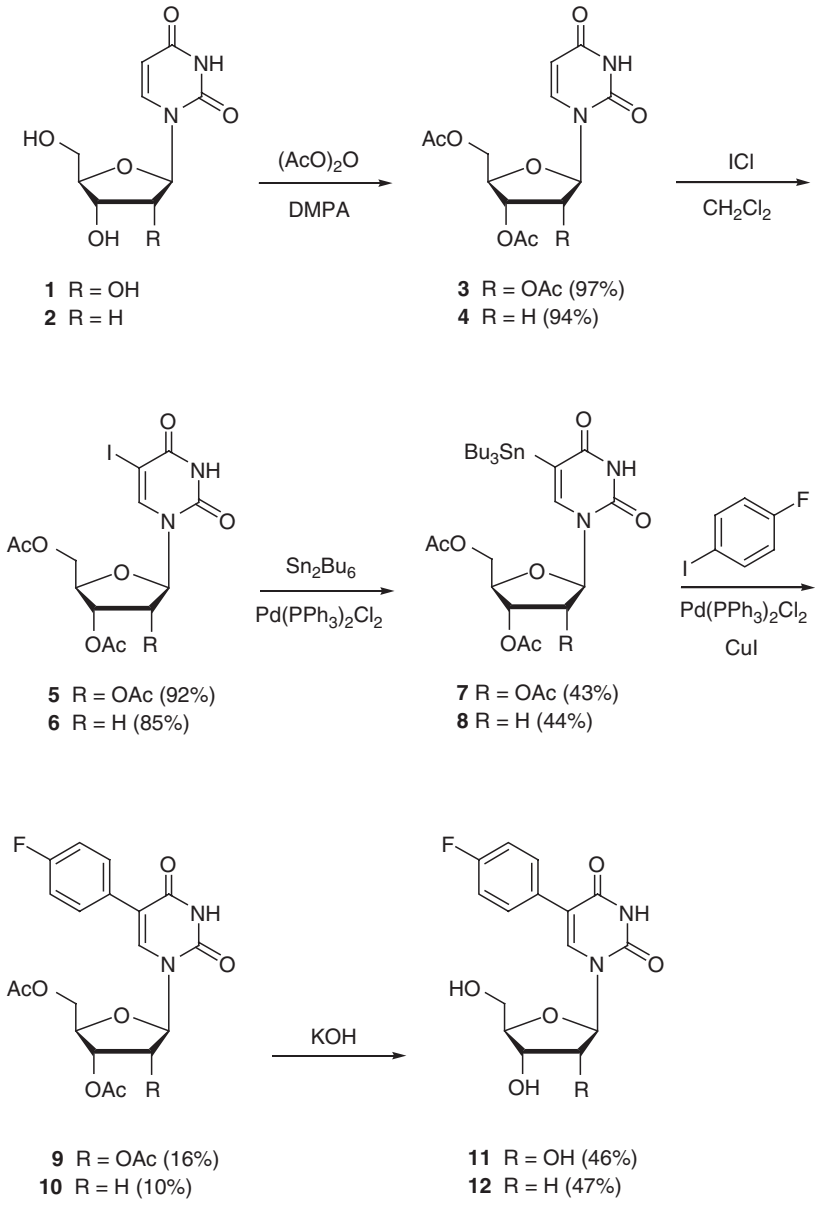

Figure 1. Synthesis of labelling precursors 7 and 8 and reference compounds 11 and 12

nane in yields of 43 and 44%, respectively. The use of 1,4-dioxane as the solvent proved to be superior to toluene as the solvent. However, subsequent Stille coupling of stannanes **7** and **8** with 4-fluoroiodobenzene gave the corresponding cross-coupled products **9** and **10** in only disappointing low yields of 16 and 10% after purification by flash chromatography. Copper iodide was used as an additive to increase the rate of the transmetallation step

in the catalytic cycle of the Stille reaction.[24] However, no further optimization of the reaction conditions was performed since sufficient amounts of compounds **9** and **10** could be obtained. Final cleavage of the acetyl protecting groups by treatment with 1 M KOH afforded reference compounds **11** and **12** in 46 and 47% yield, respectively.

Improved synthesis of 4-[^{18}F]fluoroiodobenzene

As it was shown previously, 4-[^{18}F]fluorohalobenzenes such as 4-[^{18}F]bromofluorobenzene and 4-[^{18}F]fluoroiodobenzene are versatile ^{18}F-labelling precursors for C–C bond forming reactions.[19–22,25] Our group has recently described the synthesis of 4-[^{18}F]fluoroiodobenzene via thermal decomposition of symmetrical 4,4′-diiododiphenyliodonium salts in the presence of [^{18}F]fluoride.[22] One major drawback of the procedure is the inevitable formation of 1,4-diiodobenzene as a side-product interfering subsequent cross-coupling reactions. Thus, we set up a modified synthesis to provide radiochemically and chemically pure 4-[^{18}F]fluoroiodobenzene. 4,4′-Diiododiphenyliodonium triflate proved to be the best labelling precursor to afford 4-[^{18}F]fluoroiodobenzene in 35–45% yield and high radiochemical purity (>95%) after a single solid phase extraction step. Moreover, 4,4′-diiododiphenyliodonium triflate as labelling precursor is readily soluble in DMF enabling the performance of the reaction in a remotely controlled synthesis module. Removal of 1,4-diiodobenzene was accomplished by elution 4-[^{18}F]fluoroiodobenzene from the solid-phase extraction (SPE) cartridge by means of 70% CH_3CN/H_2O. This procedure allows the selective elution of 4-[^{18}F]fluoroiodobenzene from the cartridge while 1,4-diiodobenzene is retained. The eluate was diluted with water and the resulting mixture was subjected to a second SPE-cartridge. 4-[^{18}F]Fluoroiodobenzene can finally be eluted from the second cartridge via a drying cartridge (Na_2SO_4) with THF or DMF, respectively. This modified protocol gives 4-[^{18}F]fluoroiodobenzene in high radiochemical purity >95 without 1,4-diiodobenzene contamination in decay-corrected radiochemical yields of 25–36% within 45 min after EOB.

Optimization of Stille cross-coupling reaction with 4-[^{18}F]fluoroiodobenzene

Stannane compound **7** was used for the optimization of the Stille cross-coupling reaction conditions with 4-[^{18}F]fluoroiodobenzene (Figure 2).

The radiochemical yields were determined by radio-HPLC of aliquots withdrawn from the reaction mixture representing the percentage of cross-coupled product **[^{18}F]-9** present in the reaction mixture.

It was shown that the radiochemical yields of Stille reactions with 4-[^{18}F]bromo-fluorobenzene strongly depend on the catalyst system (Pd-source and additives) and the solvent.[19–21] When 4-[^{18}F]bromofluorobenzene was

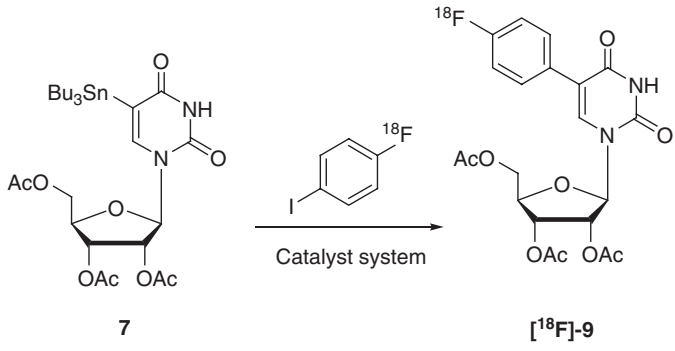

Figure 2. Stille reaction of stannane 7 with 4-[^{18}F]fluoroiodobenzene

used as a the coupling partner, reaction temperatures in the range of 110–130°C were necessary to achieve satisfactory radiochemical yields.[19–21] The use of the more reactive 4-[^{18}F]fluoroiodobenzene in terms of an accelerated oxidative addition of the aryl halide to the Pd-complex prompted us to lower the reaction temperature to have milder reaction conditions. Thus, all reactions were conducted at 65°C for 20 min. The effects of various Pd-sources ($Pd(PPh_3)_2Cl_2$, $Pd[PPh_3]_4$, $Pd_2(dba)_3$, $Pd(CH_3CN)_2Cl_2$, and $Pd(OAc)_2$) and additives like CuI, LiCl and $AsPh_3$ on the radiochemical yield were studied. The use of $AsPh_3$ in the coupling of stannanes with halides is known to increase the rate of the transmetallation of the stannane to Pd, which is thought to be the rate-determining step of the catalytic cycle.[26] The results of the Stille cross-coupling reaction of stannane **7** with 4-[^{18}F]fluoroiodobenzene are summarized in Table 1.

In a first set of reaction we studied the effect of several Pd(II) catalyst in the presence of CuI as additive and DMF/dioxane as the solvent on the radiochemical yield (entry 1–3). Best results were obtained when $Pd(PPh_3)_2Cl_2$ was used. Comparable radiochemical yields of 52% were found when Pd(0)-complex $Pd_2(dba)_3$ was used (entry 9). Moreover, Pd(0)-complex $Pd_2(dba)_3$ gives also better results in direct comparison with Pd(0)-complex $Pd[PPh_3]_4$ (entry 7 vs entry 8). The benefit of DMF/dioxane as the solvent was shown by comparison the radiochemical yields when the reaction was conducted in a mixture of THF/dioxane (entry 3 (50%) vs entry 4 (24%)). Compared to CuI, LiCl proved to be ineffective as an additive in the Stille reaction, since no product formation was found when stannane **7** was reacted with 4-[^{18}F]fluoroiodobenzene in THF/dioxane using $Pd(PPh_3)_2Cl_2$ as Pd-catalyst (entry 4 vs entry 5).

In an other set of reactions we tested the composition of the catalyst system $Pd_2(dba)_3$/CuI/$AsPh_3$ in DMF/dioxane on the radiochemical yield (entry 9–11). A combination of a 1:1:1 molar ratio of $Pd_2(dba)_3$/CuI/$AsPh_3$ gave the highest radiochemical yield of 69% (entry 10). The combination $Pd_2(dba)_3$/

Table 1. Reaction conditions for Stille cross-coupling of stannane 7 with 4-[^{18}F]fluoroiodobenzene[a]

Entry	Catalyst system[b]	Solvent[c]	Radiochemical yield[d] (%)
1	$Pd(CH_3CN)_2Cl_2$/CuI	DMF/dioxane	11
2	$Pd(OAc)_2$/CuI	DMF/dioxane	33
3	$Pd(PPh_3)_2Cl_2$/CuI	DMF/dioxane	50
4	$Pd(PPh_3)_2Cl_2$/CuI	THF/dioxane	24
5	$Pd(PPh_3)_2Cl_2$/LiCl	THF/dioxane	0
6	$Pd[PPh_3]_4$/CuI	THF/dioxane	15
7	$Pd[PPh_3]_4$	DMF/dioxane	3
8	$Pd_2(dba)_3$	DMF/dioxane	34
9	$Pd_2(dba)_3$/CuI	DMF/dioxane	52
10	$Pd_2(dba)_3$/CuI/$AsPh_3$	DMF/dioxane	69
11	$Pd_2(dba)_3$/$AsPh_3$	DMF/dioxane	21
12	$Pd_2(dba)_3$/CuI/$AsPh_3$	THF/dioxane	32
13	$Pd_2(dba)_3$/CuI/$AsPh_3$	DMF/dioxane	12[e]

[a] All reactions were conducted at 65°C for 20 min.
[b] Molar ratios of stannane 7/Pd-source/CuI/LiCl/$AsPh_3$: 1:1:2:10:1.
[c] Solvents in a 1:1 mixture.
[d] Radiochemical yield determined by radio-HPLC representing the percentage of radioactivity area of cross-coupled product [^{18}F]-9 related to the total radioactivity area.
[e] Reaction was carried out at 110°C.

CuI alone (entry 9) and $Pd_2(dba)_3$/$AsPh_3$ alone (entry 11) gave in both cases lower radiochemical yields of 52 and 21%, respectively. The importance of DMF/dioxane as the solvent of choice was demonstrated by direct comparison of the radiochemical yields obtained by using the optimal catalyst system ($Pd_2(dba)_3$/CuI/$AsPh_3$) in DMF/dioxane and THF/dioxane, being 69 and 32%, respectively (entry 10 vs entry 12). The beneficial effect to perform the reaction at lower reaction temperature (65°C) rather than at elevated temperatures (110–130°C) as reported for Stille reactions with 4-[^{18}F]bromofluorobenzene[19–21] is shown in entries 10 and 13. The radiochemical yield drops drastically to 12% when a higher reaction temperature of 110°C is used.

Using optimized reaction conditions ($Pd_2(dba)_3$/CuI/$AsPh_3$, DMF/dioxane, 65°C for 20 min) we performed a large-scale preparation of 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine **^{18}F-12** by the reaction of stannane **8** with 4-[^{18}F]fluoro-iodobenzene and subsequent basic hydrolysis by means of 1 M KOH. Similar reaction conditions were applied to the synthesis of compound **^{18}F-11** (Figure 3).

Thus, in a typical experiment 550 MBq of 4-[^{18}F]fluoroiodobenzene could be converted into 120 MBq (33%, decay-corrected, related to 4-[^{18}F]fluoro-iodobenzene) of 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine **^{18}F-12** within 40 min, including HPLC purification.

The radiochemical purity of the isolated product exceeded 95%. The radiopharmacological investigation of the new ^{18}F-labelled nucleosides **^{18}F-11** and **^{18}F-12** is currently in progress.

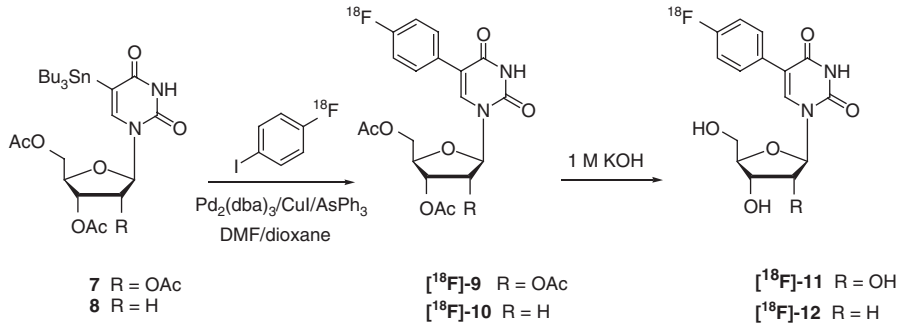

Figure 3. Synthesis of 5-(4′-[^{18}F]fluorophenyl)-uridine ^{18}F-11 and 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine ^{18}F-12

Conclusions

The convenient no-carrier added synthesis of 5-(4′-[^{18}F]fluorophenyl)-uridine ^{18}F-11 and 5-(4′-[^{18}F]fluorophenyl)-2′-deoxy-uridine **^{18}F-12** via a Stille cross-coupling reaction with 4-[^{18}F]fluoroiodobenzene has been developed. The synthesis of 4-[^{18}F]fluoroiodobenzene was further improved to provide the compound without contamination with 1,4-diiodobenzene. The easy access to radiochemical and chemical pure 4-[^{18}F]fluoroiodobenzene and the mild reaction conditions of the Stille reaction make this approach an interesting route for the no-carrier added synthesis of other 4-[^{18}F]fluorophenyl-containing radiotracers via a C–C bond formation.

Experimental

General

^{1}H-NMR and ^{19}F-NMR spectra were recorded on a Varian Inova-400 at 400 and 376 MHz, respectively. Chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale. Mass spectra were obtained on a Quattro/LC mass spectrometer (Micromass) by electrospray ionization. Flash chromatography was conducted according to Still *et al.*[27] using MERCK silica gel (mesh size 230–400 ASTM). Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plastic plates with visualization under UV (254 nm).

All chemicals were obtained from commercial suppliers of reagent grade and used without further purification. 2′,3′,5′-triacetyluridine **3** and 3′,5′-diacetyl-2′-deoxyuridine **4** were synthesized by the reaction of uridine **1** and 2′-deoxyuridine **2** with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) according to the literature.[23] 4,4′-Diiododiphenyliodonium triflate was prepared according to Wüst *et al.*[22]

Chemical synthesis

*General procedure for the synthesis of 5-iodo-uridines **5** and **6***. A solution of acetyl uridines **3** or **4** (4.1 mmol) in CH_2Cl_2 (50 ml) was refluxed with ICl (1.0 g, 6.15 mmol) for 8 h. The mixture was washed thoroughly with 1 M Na_2SO_3-solution and the organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (EtOAc) to give compounds **5** and **6** as white foams.

*5-iodo-2′,3′,5′-triacetyl-uridine **5***. Yield: 92%. ^{1}H-NMR (DMSO-d_6), δ 2.05 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 4.24 (m, 2 H, 5′-H), 4.33 (m, 1 H), 5.34 (m, 1 H), 5.45 (dd, $J = 6.2$ Hz, $J = 5.1$ Hz, 1 H), 5.87 (d, $J = 5.1$ Hz, 1 H), 8.18 (s, 1 H, 6-H), 11.84 (s, 1 H, NH). LRMS (ESI positive) 497 [M + H].

*5-iodo-3′,5′-diacetyl-2′desoxyuridine **6***. Yield: 85%. ^{1}H-NMR (DMSO-d_6), δ 2.06 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.30 (m, 1 H), 2.48 (m, 1 H), 4.19 (m, 1 H), 4.25 (m, 2 H), 5.18 (m, 1 H), 6.15 (dd, $J = 7.8$ Hz, $J = 5.9$ Hz, 1 H), 8.04 (s, 1 H, 6-H), 11.76 (s, 1 H, NH). LRMS (ESI positive) 461 [M + Na].

*General procedure for the synthesis of 5-tributylstannyl-uridines 7 and **8***. A solution of **5** or **6** (3.6 mmol), $Pd(PPh_3)_2Cl_2$ (125 mg, 0.16 mmol) and Sn_2Bu_6 (1.90 ml, 6.55 mmol) in dry 1,4-dioxane (30 ml) was refluxed for 24 h under nitrogen. The reaction mixture was filtered and the solvent was evaporated. The residue was purified by flash-chromatography (EtOAc) to afford compounds **7** or **8** as pale yellow oils.

5-Tributylstannyl-2′,3′,5′-triacetyl-uridine 7. Yield: 43%. ^{1}H-NMR (DMSO-d_6), δ 0.83 (t, $J = 7.3$ Hz, 9 H, CH_3), 0.97 (m, 6 H, CH_2), 1.26 (m, 6 H, CH_2), 1.46 (m, 6 H, CH_2), 2.02 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 4.20 (m, 2 H, 5′-H), 4.30 (dd, $J = 10.6$ Hz, $J = 2.3$ Hz, 1 H), 5.36 (m, 1 H), 5.52 (dd, $J = 6.2$ Hz, $J = 5.1$ Hz, 1 H), 5,87 (d, $J = 4.5$ Hz, 1 H), 7.31 (s, 1 H, 6-H), 11.31 (s, 1 H, NH). LRMS (ESI positive) 661 [M + H].

*5-Tributylstannyl-3′,5′-diacetyl-uridine **8***. Yield: 44%. ^{1}H-NMR (DMSO-d_6), δ 0.84 (t, $J = 7.3$ Hz, 9 H, CH_3), 0.98 (m, 6 H, CH_2), 1.28 (m, 6 H, CH_2), 1.47 (m, 6 H, CH_2), 2.03 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.31 (m, 1 H), 2.44 (m, 1 H), 4.19 (m, 1 H), 4.21 (m, 2 H), 5.18 (m, 1 H), 6.11 (dd, $J = 8.0$ Hz, $J = 6.2$ Hz, 1 H), 7.23 (s, 1 H, 6-H), 11.24 (s, 1 H, NH). LRMS (ESI positive) 602 [M + H].

*General procedure for the synthesis of 5-(4′-fluorophenyl)-substituted uridines **9** and **10***. A solution of tributylstannyl compounds **7** or **8** (1 mmol), $Pd(PPh_3)_2Cl_2$ (350 mg, 0.5 mmol), CuI (100 mg, 0.5 mmol) and 4-fluoroiodobenzene (450 mg, 2 mmol) in dry 1,4-dioxane (20 ml) was heated at 100°C for 24 h under a nitrogen atmosphere. The solvent was evaporated and the residue was purified by flash-chromatography (50% EtOAc/*n*-hexane).

5-(4′-Fluorophenyl)-2′,3′,5′-triacetyl-uridine ***9***. Yield: 16%. ^{1}H-NMR ($CDCl_3$), δ 2.11 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 4.21 (m, 1 H), 4.36 (m, 2 H), 4.38 (m, 1 H), 5.35 (m, 1 H), 5.40 (m, 1 H), 6.14 (m, 1 H), 7.09 (m, 2 H, Ar–H), 7.45 (m, 2 H, Ar–H), 7.70 (s, 1 H, 6-H), 8.82 (bs, 1 H, NH). ^{19}F-NMR ($CDCl_3$), δ −113.32 (m). LRMS (ESI positive) 487 [M + Na].

5-(4′-Fluorophenyl)-3′,5′-diacetyl-uridine ***10***. Yield: 10%. ^{1}H-NMR ($CDCl_3$), δ 1.87 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.21 (m, 1 H), 2.53 (m, 1 H), 4.27 (m, 1 H), 4.35 (m, 2 H), 5.21 (m, 1 H), 6.36 (m, 1 H), 7.07 (m, 2 H, Ar–H), 7.45 (m, 2 H, Ar–H) 7.62 (s, 1 H, 6-H), 8.86 (bs, 1 H, NH). ^{19}F-NMR ($CDCl_3$), δ −113.30 (m). LRMS (ESI positive) 407 [M + H].

General procedure for the synthesis of 5-(4′-fluorophenyl)-substituted uridines ***11*** *and* ***12***. A solution of 9 or 10 (120 µmol) and 0.5 M KOH (0.5 ml) in acetonitrile (3 ml) was stirred for 2 h at room temperature. The solvent was partially removed under reduced pressure and the residue was purified by flash-chromatography to yield compounds **11** or **12** as white solids.

5-(4′-Fluorophenyl)-uridine ***11***. Yield: 46%. Melting point: 156–158°C. ^{1}H-NMR (DMSO-d_6), δ 3.58 (dd, J = 11.9 Hz, J = 2.2 Hz, 1 H), 3.68 (m, 1 H), 3.88 (m, 1 H), 4.04 (t, J = 4.8 Hz, 1 H), 4.13 (m, 1 H), 5.84 (m, 1 H), 7.19 (m, 2 H, Ar–H), 7.56 (m, 2 H, Ar–H), 8.29 (s, 1 H, 6-H), 11.51 (bs, 1 H, NH). ^{19}F-NMR (DMSO-d_6), δ −115.53 (m). LRMS (ESI positive) 339 [M + H].

5-(4′-Fluorophenyl)-2′-desoxyuridine 12. Yield: 47%. Melting point: 198–201°C. ^{1}H-NMR (DMSO-d_6), δ 2.16 (m, 1 H), 2.24 (m, 1 H), 3.60 (m, 1 H), 3.80 (m, 1 H), 4.28 (m, 1 H), 5.13 (m, 1 H), 5.60 (d, J = 4.4 Hz, 1 H), 6.22 (t, J = 6.9 Hz, 1 H), 5.84 (m, 1 H, 1′-H), 7.21 (m, 2 H, Ar–H), 7.58 (m, 2 H, Ar–H), 8.20 (s, 1 H, 6-H), 11.51 (bs, 1 H, NH). ^{19}F-NMR (DMSO-d_6) δ -115.51 (m). LRMS (ESI positive) 345 [M + Na].

Radiochemical synthesis

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 by an automated nucleophilic fluorination module (Nuclear Interface, Münster) as described by Römer *et al.*[28]

HPLC analyses were carried out with a SUPELCOSIL LC-18S column (4.6 × 250 mm, 5 µm) using an indicated isocratic eluent (CH_3CN/H_2O) from a gradient pump L2500 (Merck, Hitachi) with a flow rate of 1 ml/min. The products were monitored by an UV detector L4500 (Merck, Hitachi) at 254 nm and by γ-detection with a scintillation detector GABI (X-RAYTEST). Semi-preparative HPLC was performed with a Merck LiChroCart 250-10

column using isocratic elution with CH_3CN/H_2O (50/50) at a flow rate of 4.0 ml/min.

Synthesis of 4-[^{18}F]fluoroiodobenzene

Cyclotron-produced [^{18}F]HF (3–4 GBq) was dried in the automated fluorination module according to Römer *et al.*[28] Then, 4,4′-diiododiphenyliodonium triflate (20 mg, 29.3 μmol) dissolved in DMF (0.7 ml) was added and the reaction mixture was heated at 140°C for 20 min. After cooling the reaction vessel to 50°C, water (8 ml) was added and the reaction mixture was passed through a LiChrolut RP18 cartridge (500 mg). The cartridge was washed with water (5 ml). 4-[^{18}F]Fluoroiodobenzene was eluted from the cartridge using 70% CH_3CN/H_2O (2.5 ml). The eluate was diluted with water (15 ml) and the resulting mixture was passed through a second LiChrolut RP18 cartridge (200 mg). 4-[^{18}F]Fluoroiodobenzene was finally eluted from the second cartridge via a drying cartridge (Na_2SO_4) with THF or DMF (1 ml), respectively. This procedure provides radiochemical and chemical pure 4-[^{18}F]Fluoroiodobenzene. Yield: 25–36% (decay-corrected). HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 5.6$ min.

Optimization of Stille reaction with 4-[^{18}F]fluoroiodobenzene

To a vial containing tin precursor **7** (5 mg, 7.6 μmol), palladium catalyst (7.5 μmol) and CuI (3 mg, 15 μmol) in dioxane (0.5 ml) was added 4-[^{18}F]fluoro-iodobenzene (25–75 MBq in 0.5 ml of THF or DMF). To some experiments $AsPh_3$ (3 mg, 7.5 μmol) or LiCl (3 mg, 71 μmol) was added. The sealed reaction vial was heated at 65°C for 20 min. 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]-9** related to the total radioactivity area.

5-(4′-[^{18}F]fluorophenyl)-2′,3′,5′-triacetyl-uridine ***[^{18}F]-9***. HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 3.5$ min.

Radiosynthesis of 5-(4′-[^{18}F]fluorophenyl)-uridine [***^{18}F*]-*11* *and 5-(4′-[^{18}F]fluorophenyl)-2′-desoxyuridine* [***^{18}F*]-*12* *using optimized Stille cross-coupling reaction conditions (analytical scale)*

To a vial containing tin precursors **7** or **8** (5 mg), $Pd_2(dba)_3$ (8 mg, 7.5 μmol), CuI (3 mg, 15 μmol) and $AsPh_3$ (3 mg, 7.5 μmol) in 0.5 ml of dioxane was added 4-[^{18}F]fluoroiodobenzene (50 MBq in 0.5 ml DMF). The sealed reaction vial was heated at 65°C for 20 min and aliquots (50 μl) were taken for radio-HPLC analysis.

5-(4′-[^{18}F]fluorophenyl)-2′,3′,5′-triacetyl-uridine ***[^{18}F]-9***. Yield: 69% (related to 4-[^{18}F]fluoroiodobenzene). HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 3.5$ min.

5-(4′-[^{18}F]fluorophenyl)-3′,5′-diacetyl-uridine ***[^{18}F]-10***. Yield: 61% (related to 4-[^{18}F]fluoroiodobenzene). HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 3.3$ min.

1 M KOH (0.5 ml) was added to the Stille cross-coupling reaction mixture and stirring was continued for 10 min at 65°C. The reaction mixture was filtered through a PTFE syringe filter and aliquots (50 µl) were take for radio-HPLC analysis.

5-(4′-[^{18}F]Fluorophenyl)-uridine ***[^{18}F]-11***. Yield: 100% (related to **[^{18}F]-9**). HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 2.8$ min.

5-(4′-[^{18}F]Fluorophenyl)-2′-desoxyuridine ***[^{18}F]-12***. Yield: 100% (related to **[^{18}F]-10**). HPLC-analysis: CH_3CN/H_2O (60/40), $t_R = 2.8$ min.

Preparation of 5-(4′-[^{18}F]fluorophenyl)-2′-desoxyuridine [***^{18}F*]-*12* *(large-scale preparation)*

To a vial containing stannane **8** (5 mg, 8.3 µmmol), $Pd_2(dba)_3$ (8 mg, 7.5 µmol), CuI (3 mg, 15 µmol) and $AsPh_3$ (3 mg, 7.5 µmol) in 0.5 ml of dioxane was added 4-[^{18}F]fluoroiodobenzene (550 MBq in 0.5 ml DMF). The sealed reaction vial was heated at 65°C for 20 min. One molar KOH (0.5 ml) was added to the Stille cross-coupling reaction mixture and stirring was continued for 10 min at 65°C. The reaction mixture was filtered through a PTFE syringe filter and the mixture was subjected onto a semi-preparative HPLC column. The fraction eluting at 5.5 min was collected. Yield: 120 MBq (33% decay-corrected, related to 4-[^{18}F]fluoroiodobenzene).

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