Radiosynthesis of 1-iodo-2-[^{11}C]methylpropane and 2-methyl-1-[^{11}C]propanol and its application for alkylation reactions and C-C bond formation.

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Abstract

The multitude of biologically active compounds requires the availability of a broad spectrum of radiolabeled synthons for the development of positron emission tomography (PET) tracers. The aim of this study was to synthesize 1-iodo-2-[^{11}C]methylpropane and 2-methyl-1-[^{11}C]propanol and investigate the use of these reagents in further radiosynthesis reactions. 2-methyl-1-[^{11}C]propanol was obtained with an average radiochemical yield of 46 ± 6% d.c. and used with fluorobenzene as starting material. High conversion rates of 85 ± 4 % d.c. could be observed with HPLC, but large precursor amounts (32 mg, 333 µmol) were needed. 1-iodo-2-[^{11}C]methylpropane was synthesized with a radiochemical yield of 25 ± 7 % d.c.

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and with a radiochemical purity of 78 ± 7 % d.c. The labelling agent 1-iodo-2-[^{11}C]methylpropane was coupled to thiophenol, phenol and phenylmagnesium bromide. Average radiochemical conversions of 83 % d.c. for thiophenol, 40 % d.c. for phenol and 60 % d.c. for phenylmagnesium bromide were obtained. In addition, **[**^{11}C]2-methyl-1-propyl phenyl sulfide was isolated with a radiochemical yield of 5 ± 1 % d.c. and a molar activity of 346 ± 113 GBq/µmol at end of synthesis. Altogether, the syntheses of 1-iodo-2-[^{11}C]methylpropane and 2-methyl-1-[^{11}C]propanol was achieved and applied as proof of their applicability.

Words: 196

Introduction

Positron emission tomography (PET) is a powerful imaging tool, which is used in drug development, clinical research and patient care to study molecular processes *in vivo*.[1] Future progress of this technique is strongly dependent on the development of novel PET tracers. Carbon is one of the main elements in organic and biologically active molecules, and replacing carbon-12 by carbon-11 does not change the physicochemical properties nor the biological profile. Carbon-11 labelled methyl iodide is one of the most frequently used synthons for the synthesis of PET radiotracers.[2] This is based on the fact that methylation reactions are relatively simple and because many biologically active compounds contain a methyl group that can be introduced at a late stage through a radiolabelling reaction with [^{11}C]methyl iodide.[1-3] However, when the lead structure does not possess a methyl group, other carbon-11 containing precursors have to be used for radiosynthesis of the tracer.

Therefore, multiple alternative alkylation agents have been developed such as [^{11}C]benzyl iodide [4-8], 1-[^{11}C]-ethyl iodide [9-11], 1-[^{11}C]-propyl iodide [9,11-13], 1-[^{11}C]-butyl iodide

[9,11], 2-[^{11}C]-iodopropane [10,12] and 1-iodo-2-[^{11}C]methylpropane.[11] These synthons have been prepared from cyclotron produced [^{11}C]CO_2 via Grignard reactions [4-7,11] or from [^{11}C]CO carbonylation reactions.[9] So far, *N*- and *O*-alkylation reactions and [^{11}C]carbon-carbon bond formation based on alkylation of the α-C-atom of amino acetates have been performed by using these alternative synthons. Interestingly, no palladium catalysed couplings like Stille reaction or Suzuki reaction have been reported to date, although these reactions are frequently applied for the radiolabeling reagent [^{11}C]methyl iodide.[14,15] We were interested in the synthesis of 1-iodo-2-[^{11}C]methylpropane as 2-methylpropane is an important functional group in medicinal chemistry and drug development, e.g. for cyclooxygenase-2 (COX-2) inhibitors (figure 1).[16] Radiosynthesis of 1-iodo-2-[^{11}C]methylpropane has been reported by Långström et al. with a decay corrected radiochemical yield of 20% and a radiochemical purity of 65% for 1-iodo-2-[^{11}C]methylpropane [11]. In addition, no molar activity has been reported which is an important parameter in the application of a PET tracer. Therefore, the aim of this study was to improve the synthesis of 1-iodo-2-[^{11}C]methylpropane and 2-methyl-1-[^{11}C]propanol (Scheme 1) and to investigate whether these synthons are suited for late stage radiolabelling reactions. Therefore, we thoroughly investigated the stability of 1-iodo-2-[^{11}C]methylpropane and 2-methyl-1-[^{11}C]propanol and optimized the reaction parameters with these reagents for *O*- and *S*-alkylation model reactions as well as for model carbon-carbon-bond formations (Scheme 2). This study resulted in two synthons that can be reliably be produced and applied in late-stage radiolabelling reactions for PET tracer development.

Experimental

General

Chemicals were obtained from commercial sources and used without further purification. Solvents were purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands) and Biosolve (Valkenswaard, The Netherlands). Tetrahydrofuran (THF) was first distilled from $LiAlH_4$ and then stored over 3 Å molecular sieves. Dimethylsulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (MeCN), aceton and 1-Methyl-2-pyrrolidinone (NMP) were dried over 3 Å molecular sieves. Silicon stoppers (20 mm, 27235-U) were obtained from Sigma-Aldrich (Zwijndrecht, The Netherlands). 10 mL vials (N611568) were obtained from Covidien (Dublin, Ireland) and crimp-caps (20 mm, 98805) were purchased from Grace (Breda, The Netherlands). All reactions were performed at room temperature (RT) and under nitrogen unless otherwise mentioned. Reactions were monitored by thin layer chromatography on pre-coated silica 60 F254 aluminium plates (Merck, Darmstadt, Germany). Spots were visualized by UV light 254 nm. Evaporation of solvents was performed under reduced pressure at 40 °C using a rotary evaporator (Rotavapor ® R II, Flawil, Switzerland), Flash column chromatography was performed on a Büchi (Flawil, Switzerland), Sepacore system (comprising a C-620 control unit, C-660 fraction collector, two C-601 gradient pumps and a C-640 UV detector) equiped with Büchi Sepacore pre-packed flash columns. NMR spectrometry was performed on a Bruker Avance 500 (500.23 MHz for ^{1}H and 125.78 MHz for ^{13}C) with chemical shifts (δ) reported in parts per million (ppm) relative to the solvent ($CDCl_3$, ^{1}H 7.26 ppm, ^{13}C 77.16 ppm). Purity and molar activity were determined by analytical isocratic HPLC on a Jasco (Easton, MD, USA) PU-1580 station with a Altima C-18 5 µm (4.6 x 100 mm) column (Grace, Breda, The Netherlands) using a buffer (4 mmol of sodium formate in water and 4 % DMF) / MeCN (3/7, HPLC method **A** or 2/8, method **B**, *v/v*) as mobile phase at a flow rate of 1 mL/min, a Jasco UV-2075 Plus UV detector (254 nm)

and a NaI radioactivity detector (Raytest, Straubenhardt, Germany). Chromatograms were acquired with Raytest GINA Star software (version 5.8)

Analytical HPLC of the [^{11}C]2-methylpropanoic acid and 2-methyl-1-[^{11}C]propanol were performed on a Jasco (Easton, MD, USA) PU-1580 station with a Reprogel H^+ column 9 µm (4.6 x 100 mm) column (Dr. Maisch, Ammerbuch-Entringen, Germany) using 9 mmol sulphuric acid in water at a flow rate of 0.5 mL/min (HPLC method **C**), a Jasco UV-2075 Plus UV detector (254 nm), a Jasco RI-2031 detector and a NaI radioactivity detector (Raytest, Straubenhardt, Germany). Chromatograms were acquired with Raytest GINA Star software (version 5.8)

Semi-preparative HPLC was performed on a Jasco (Easton, MD, USA) UV-2087 Plus station with a Luna C-18 5 µm (10 x 250 mm) column (Phenomenex, Utrecht, The Netherlands) using a buffer (4 mmol of sodium formate in water and 4 % DMF) / MeCN (3.5/6.5, HPLC method **D**, *v/v*) as mobile phase at a flow rate of 8 mL/min, a Jasco UV-2075 Plus UV detector (254 nm) and a homemade NaI radioactivity detector. Chromatograms were acquired with Jasco ChromNAV CFR software (version 1.14.01).

Analytical GC of the 2-methyl-1-[^{11}C]propanol and [^{11}C]2-methylprop-1-ene was performed on a Thermo Scientific trace ultra (Thermo Scientific, The Netherlands) with a thermal conductivity detector (Thermo Scientific, The Netherlands), HP-PLOT U column 0,32 mm x 30 m (Phenomenex, Utrecht, The Netherlands) and a NaI 588I radiodetector (Teledyne isotopes, Huntsville, United States). The following program was used: Oven temperature 50 ºC (1 min) and 15 ºC/min to 170 ºC (10 min), inlet temperature 200 ºC, split ratio 50:1 and flow 3 mL/min. 1 µL of the corresponding sample and 1 µL of air were injected. Chromatograms were acquired with Raytest GINA Star software (version 5.01)

Radiochemistry was performed with our in-house build synthesis modules equipped with a VIK-202 ionization-chamber (Comecer, Joure, The Netherlands).[17] The radiochemical

yields were corrected from the starting amount of [^{11}C]CO_2. The HPLC chromatograms were corrected for decay to obtain decay corrected radiochemical purities and decay corrected radiochemical conversions.

Synthesis

2-methyl-1-propyl phenyl sulfide 6

2-methylpropane-1-thiol (4.17 mmol, 376 mg, 316 µL) was added to a suspension of NaH (4.17 mmol, 100 mg) in NMP (5.4 mL) and the mixture was stirred for 10 min. This freshly prepared solution was added to a solution of fluorobenzene (2.08 mmol, 200 mg, 195 µL) in NMP (13.5 mL). The reaction was stirred at 100 °C overnight. Water and ethyl acetate were added, the aqueous layer was separated and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography eluting with ethylacetate/hexane (1:2, *v:v*). 2-methyl-1-propyl phenyl sulfide was obtained as a clear oil in 47 % yield (147 mg, 0.979 mmol). ^{1}H NMR ($CDCl_3$) δ 7.35 (m, *J*=5.00 Hz, 2 H, CH_{Ar}), 7.29 (t, *J*=7.50 Hz, 2 H, CH_{Ar}), 7.18 (t, *J*=7.00 Hz, 1 H, CH_{Ar}), 2.83 (d, *J*=5.40 Hz, 2 H, PhS$\underline{CH_2}$), 1.85 - 1.95 (m, 1 H, $\underline{CH}(CH_3)_2$), 1.06 (d, *J*=5.70 Hz, 6 H, $CH(\underline{CH_3})_2$) ppm; ^{13}C NMR ($CDCl_3$), δ 137.09 (S$\underline{CH_{Ar}}$), 128.53 (3 x CH_{Ar}), 125.27 (2 x CH_{Ar}), 42.24 (PhO$\underline{CH_2}$), 27.95 ($\underline{CH}(CH_3)_2$), 21.77 ($CH(\underline{CH_3})_2$) ppm.

2-methylpropoxybenzene 8

2-methyl-propan-1-ol (5.40 mmol, 400 mg, 498 µL) was added to a suspension of NaH (5.40 mmol, 130 mg) in NMP (5.4 mL) and the mixture was stirred for 10 min. This freshly prepared solution was added to a solution of fluorobenzene (2.70 mmol, 259 mg, 253 µL) in NMP (13.5 mL). The reaction was stirred at 100 °C overnight. Water and ethyl acetate were added, the aqueous layer was separated and the organic layer was washed with water, dried

over Na_2SO_4, filtered and concentrated. 2-methylpropoxybenzene was obtained as a clear oil in 70.3 % yield (285 mg, 1.90 mmol) ^{1}H NMR ($CDCl_3$) δ 7.30 (t, *J*=7.30 Hz, 2 H, CH_{Ar}), 6.90 - 7.00 (m, 3 H, CH_{Ar}), 3.74 (d, *J*=3.80 Hz, 2 H, PhO$\underline{CH_2}$), 2.02 - 2.16 (m, 1 H, $\underline{CH}(CH_3)_2$), 1.05 (d, *J*=3.80 Hz, 6 H, $CH(\underline{CH_3})_2$) ppm; ^{13}C NMR ($CDCl_3$) δ 159.19 (O$\underline{CH_{Ar}}$), 129.35 (2 x CH_{Ar}), 120.36 (CH_{Ar}), 114.45 (2 x CH_{Ar}), 74.28 (PhO$\underline{CH_2}$), 28.28 ($\underline{CH}(CH_3)_2$), 19.31 ($CH(\underline{CH_3})_2$)

Radiosynthesis

Preparation of isopropylmagnesium chloride solution (4M)

A 10 mL vial was dried in the oven at 150 °C and was capped with a silicone stopper. The vial was purged with argon and cooled to room temperature. Isopropylmagnesium chloride (2 mmol, 1 mL, 2 M) was added to the capped vial. The solution was concentrated under vacuum until all the THF was evaporated and a brown/white solid was obtained. Dry THF (0.5 mL) was added to the vial and the solid was dissolved.

[^{11}C]2-methylpropanoic acid [^{11}C]**2**

A reaction vial was purged with helium and charged with isopropylmagnesium chloride in THF (600 µmol, 150 µL, 4M). [^{11}C]CO_2 was produced by the ^{14}N (p,α)^{11}C nuclear reaction performed in a 0.5 % O_2/N_2 gas mixture using an IBA Cyclone 18/9 cyclotron (IBA, Louvain-la-neuve, Belgium). The [^{11}C]CO_2 was transferred from the target and trapped in a stainless steel loop dispensed in liquid N_2. At 25 °C, the [^{11}C]CO_2 was transferred with a He flow of 10 mL/min into the reaction vessel until the trapped amount of radioactivity was constant (~2 min). The reaction mixture was quenched with water and analyzed with HPLC method **C**. t_R = 12.9 min

2-methyl-1-[^{11}C]propanol [^{11}C]**3**

[^{11}C]**2** was synthesised as described above and instead of adding water, $LiAlH_4$ (100 µmol, 100 µL, 1M) was added and the temperature was increased to 130 °C. At 130 °C, the helium flow was increased to 25 mL/min and the THF was evaporated (~2 min). The reaction mixture was cooled to room temperature, quenched with water and analyzed with HPLC method **C**. t_R = 18.9 min

1-iodo-2-[^{11}C]methylpropane [^{11}C]**4**

[^{11}C]**3** was synthesised as described above and instead of adding water, the reaction mixture was cooled to 25 °C and HI (4.55 mmol, 600 µL, 57 %) was added. The temperature of the reaction mixture was increased to 150 °C for 5 min. Product 1-iodo-2-[^{11}C]methylpropane was distilled by a helium flow of 25 mL/min into a second reaction vessel containing 250-500 µL of DMSO (25 °C), DMF (0 °C) or THF (0 °C). 1-iodo-2-[^{11}C]methylpropane was obtained in a decay-corrected radiochemical yield of 25 ± 7 % (n = 10) calculated from [^{11}C]CO_2 with a purity of 78 ± 7 % (n = 10) and an overall synthesis time of approximately 14 min. The identity of the product was confirmed with analytical HPLC method **B** by co-injection of 1-iodo-2-methylpropane , t_R = 9.3 min.

[^{11}C]2-methyl-1-propyl phenyl sulfide [^{11}C]**6; optimization reactions**

A reaction vessel was loaded with DMSO (100 µL), thiophenol (12 µmol, 1.3 mg, 1.2 µL) and K_2CO_3 (30 µmol, 4.2 mg). 1-iodo-2-[^{11}C]methylpropane was synthesized as described above and trapped in a reaction vessel with DMSO (500 µL) at 25 °C. 100 µL of this stock solution was transferred via a syringe to the reaction vessel. The reaction mixture was stirred for 5 min at 25 °C. The identity of the product was confirmed with analytical HPLC method **B** by co-injection of 2-methyl-1-propyl phenyl sulfide, t_R = 9.2 min.

[^{11}C]2-methyl-1-propyl phenyl sulfide [^{11}C]**6; full synthesis with $LiAlH_4$**

A reaction vessel was loaded with DMSO (400 µL), thiophenol (12 µmol, 2.6 mg, 2.4 µL) and K_2CO_3 (60 µmol, 8.4 mg). 1-iodo-2-[^{11}C]methylpropane was synthesized as described above. The 1-iodo-2-[^{11}C]methylpropane was trapped in the reaction mixture at 25 °C. The reaction mixture was stirred for 5 min at 25 °C followed by dilution of the reaction mixture with 1.0 mL of HPLC eluents. The crude product was purified by semi-preparative HPLC method **D**. t_R = 12.7. A radiochemical yield, decay corrected from the starting amount of [^{11}C]CO_2 (end of cyclotron bombardment) of [^{11}C]CO_2 in 11 ± 2% (n = 3) with a radiochemical purity of > 98 % was obtained in 41 min. The identity of the product was confirmed with analytical HPLC method **B** by co-injection of 2-methyl-1-propyl phenyl sulfide, t_R = 9.2 min

[^{11}C]2-methyl-1-propyl phenyl sulfide [^{11}C]**6; full synthesis with $LiBH_4$**

A reaction vessel was loaded with DMSO (400 µL), thiophenol (12 µmol, 2.6 mg, 2.4 µL) and K_2CO_3 (60 µmol, 8.4 mg). 1-iodo-2-[^{11}C]methylpropane was synthesized as described above but instead of using $LiAlH_4$, $LiBH_4$ (200 µmol, 100 µL, 2M) was used. The 1-iodo-2-[^{11}C]methylpropane was trapped in the reaction mixture at 25 °C. The reaction mixture was stirred for 5 min at 25 °C followed by dilution of the reaction mixture with 1.0 mL of HPLC eluents. The crude product was purified by semi-preparative HPLC method **D**. t_R = 12.7. A radiochemical yield, decay corrected from the starting amount of [^{11}C]CO_2 (end of cyclotron bombardment) of [^{11}C]CO_2 in 5 ± 1 % (n = 4) with a molar activity of 346 ± 113 GBq/µmol and a radiochemical purity of > 98 % was obtained in 41 min. The identity of the product was confirmed with analytical HPLC method **B** by co-injection of 2-methyl-1-propyl phenyl sulfide, t_R = 9.2 min

[^{11}C]2-methylpropoxybenzene [^{11}C]**8 (Approach A)**

A reaction vessel was loaded with DMSO (100 µL), phenol (90 µmol, 8.5 mg) and K_2CO_3 (60 µmol, 8.3 mg). 1-iodo-2-[^{11}C]methylpropane was synthesized as described above and trapped in a reaction vessel with DMSO (500 µL) at 25 °C. 100 µL of this stock solution was transferred via a syringe to the reaction vessel. The reaction mixture was stirred for 5 min at 130 °C. The identity of the product was confirmed with analytical HPLC method **A** by co-injection of 2-methylpropoxybenzene**,** t_R = 13.5 min.

[^{11}C]2-methylpropoxybenzene [^{11}C]**8 (Approach B)**

A reaction vessel was loaded with DMSO (100 µL), fluorobenzene (0.33 mmol, 32 mg, 31 µL) and NaH (0.40 mmol, 9.6 mg). 2-methyl-1-[^{11}C]propanol was synthesized as described above. The reaction mixture was quenched with HCl in diethyl ether (0.7 mmol, 350 µL, 2 M) or dioxane (1.4 mmol, 350 µL, 4 M), glycerol 400 µL and water 400 µL. The reaction mixture was heated to 150 °C and the activity was trapped in a reaction vessel with DMSO (500 µL) at 25 °C. Drying columns were prepared with a diameter of 1.0 cm and a length of 1.5 cm in 3 mL tubes (Sopachem, Nazareth, Belgium). A distillation tube of 10 cm with a diameter of 1-2 mm was used (Vygon, Valkenswaard, The Netherlands). 100 µL of this stock solution was transferred via a syringe to another the reaction vessel. The reaction mixture was stirred for 10 min at 130 °C. The identity of the product was confirmed with analytical HPLC method **A** by co-injection of 2-methylpropoxybenzene, t_R = 13.5 min.

1-phenyl-2-[^{11}C]methylpropane [^{11}C]**11**

A reaction vessel was dried, loaded with argon and cooled to room temperature. $Co(acac)_3$ (25 µmol, 8.9 mg), TMEDA (0.30 mmol, 28 mg, 37 µL) and THF (150 µL) were added. The

1-iodo-2-[^{11}C]methylpropane was synthesized as described above and trapped in the reaction vessel at 0 °C. The reaction mixture was cooled to -20 °C and phenylmagnesium bromide (50 µmol, 9.1 mg, 50 µL, 1 M) was added. The reaction mixture was heated to 0 °C and stirred for 10 min. The identity of the product was confirmed with analytical HPLC method **B** by co-injection of 1-phenyl-2-methylpropane , t_R = 12.1 min.

Results and Discussion

Synthesis of 1-iodo-2-[^{11}C]methylpropane

1-iodo-2-[^{11}C]methylpropane was synthesized in a three-steps one-pot procedure. The first step was the formation of [^{11}C]2-methylpropanoic acid in a Grignard reaction, by bubbling cyclotron produced [^{11}C]CO_2 through an isopropylmagnesium chloride (**1**, Table 1) solution. A trapping efficiency of more than 95% was obtained by passing [^{11}C]CO_2 with a flow of 10 mL/min through a solution of isopropylmagnesium chloride in tetrahydrofurane (THF). Different concentrations of isopropylmagnesium chloride were investigated to obtain the highest possible conversion, as measured by high-performance liquid chromatography (HPLC). Increasing the concentration of **1** from 2 M to 4 M resulted in a radiochemical conversion increase to 82 ± 1 % d.c. instead of 67 ± 5 % d.c., calculated from the starting amount of [^{11}C]CO_2 (table 1, entry 1-3, 6). Increasing the temperature or the reaction time did not improve the radiochemical conversion (table 1, entry 4 and 5).

The reduction of [^{11}C]2-methylpropanoic acid to 2-methyl-1-[^{11}C]propanol was performed with 1.0 M $LiAlH_4$. The THF was removed with a helium flow of 25 ml/min at 130 °C and resulted in a quantitative conversion of [^{11}C]2-methylpropanoic acid to 2-methyl-1-[^{11}C]propanol (Figure 2). The third step, formation of the 1-iodo-2-[^{11}C]methylpropane**,** turned out to be the most challenging one since the addition of hydriodic acid was performed at temperatures below 60 °C, otherwise the volatile intermediate 2-methyl-1-[^{11}C]propanol

would evaporate prior to the iodination reaction. The mixture was then heated, observing the highest radiochemical conversions (Graph 1) after 5 minutes reaction at either 150 or 180 °C (59 ± 3 and 59 ± 1 % d.c., respectively). When heating the reaction mixture for 5 min at a temperature of 130 °C, a radiochemical conversion of only 30 ± 13 % d.c. was observed. The possible rearrangement of the 1-iodo-2-[^{11}C]methylpropane to 2-iodo-3-[^{11}C]butane did not occur according to HPLC analysis. In addition, the potential side-product [^{11}C]2-methylprop-1-ene deriving from a β-hydrogen elimination of the iodide, was not observed on radio gas chromatography as well. Finally, purification of 1-iodo-2-[^{11}C]methylpropane was performed by distillation of the reaction mixture through a sicapent/NaOH column into a second reaction vial containing DMSO, DMF or THF as solvents. A radiochemical yield of 25 ± 7 % d.c. could be achieved, obtaining 1-iodo-2-[^{11}C]methylpropane with a radiochemical purity of 78 ± 7 % d.c. (n = 10) calculated from the starting amount of [^{11}C]CO_2 (Figure 3) in 14 minutes time. The stability of 1-iodo-2-[^{11}C]methylpropane (Table 2) was determined at different temperatures, with different bases and for 5 min, as this might influence the application and use of this reagent in further radiochemical reactions. Strong bases like TBAOH and NaOH (aq, 0.06 M) could decompose of 1-iodo-2-[^{11}C]methylpropane into 2-methyl-1-[^{11}C]propanol and [^{11}C]2-methylprop-1-ene at room temperature. On the other hand, 1-iodo-2-[^{11}C]methylpropane was stable in the presence of a milder base like K_2CO_3 (aq, 0.06 M) at temperatures ranging from 25 to 80 °C. However, decomposition of 1-iodo-2-[^{11}C]methylpropane was observed, even in the presence of these milder bases at higher temperatures of 100 °C or higher. The water content of the reaction mixtures was kept constant, as it can induce decomposition of 1-iodo-2-[^{11}C]methylpropane into [^{11}C]2-methylprop-1-ene and 2-methyl-1-[^{11}C]propanol.

[^{11}C]2-methyl-1-propyl phenyl sulfide synthesis by alkylation

To determine whether 1-iodo-2-[^{11}C]methylpropane can be used for the synthesis of PET tracers, three model reactions were performed. Two alkylation reactions using thiophenol and phenol as precursors were investigated. Furthermore, an unprecedented cobalt assisted cross-coupling reaction using phenylmagnesium bromide as precursor was investigated. [18]

For the synthesis of [^{11}C]**6** a high average radiochemical conversion of 83 % d.c. (Table 3, Entry 1-3) was observed when using 2.5 equivalents of crystalline K_2CO_3, even at room temperature for 5 minutes. When aqueous K_2CO_3 (0.06 M) was used, the formation of 2-methyl-1-[^{11}C]propanol as side product increased, while unreacted 1-iodo-2-[^{11}C]methylpropane was still present (Table 3, Entry 5), resulting in an average lower radiochemical conversions of [^{11}C]**6** of 34 % d.c. after 5 minutes. When using one equivalent of crystalline K_2CO_3, only 51 % d.cof product [^{11}C]**6** was formed, the remainder being 1-iodo-2-[^{11}C]methylpropane.

Optimized conditions were used to purify [^{11}C]**6** by semi-preparative HPLC. [^{11}C]**6** could be isolated with a radiochemical yield of 11 ± 2 % d.c. (n = 3) . However, a large UV impurity, which could not be separated from [^{11}C]**6**, was observed in the formulated product. To overcome this problem, 2.0 M $LiBH_4$ in THF instead of 1.0 M of $LiAlH_4$ as reductant was used successfully. A radiochemical yield of 5 ± 1 % d.c. (n = 4) and with a molar activity of 346 ± 113 GBq/µmol at end of synthesis was obtained.

[^{11}C]2-methylpropoxybenzene by an alkylation reaction (Approach A)

The model reaction of phenol with 1-iodo-2-[^{11}C]methylpropane resulted in a moderate average radiochemical conversion of 40 % d.c., applying the same reaction conditions as those used for the formation of [^{11}C]**6** (Table 4, Entry 18). In order to optimize the reaction conditions to improve the radiochemical conversion towards [^{11}C]**8**, different parameters were thoroughly investigated including, solvent, temperature, amount of different bases and

precursor amount. Unfortunately, none of these opmization conditions improved the radiochemical conversion (Table 4). Decomposition of 1-iodo-2-[^{11}C]methylpropane in [^{11}C]2-methylprop-1-ene occurred, in which [^{11}C]**8** and [^{11}C]2-methylprop-1-ene were formed in a 1:1 ratio (Figure 4). An explanation for the lower conversion to the desired product when using phenol as precursor could be that phenylthiolate anions have a higher nucleophilicity towards1-iodo-2-[^{11}C]methylpropane resulting in faster reaction kinetics.

Synthesis of 2-methyl-1-[^{11}C]propanol

The synthesis of 2-methyl-1-[^{11}C]propanol was initiated in the same manner as the synthesis of 1-iodo-2-[^{11}C]methylpropane, but instead of adding hydriodic acid after the reduction reaction of [^{11}C]2-methylpropanoic acid towards 2-methyl-1-[^{11}C]propanol, different quenching solvents were added to distill the alcohol out of the reaction mixture at 150 °C.

In the past, multiple quenching solvents have been used to distill alcohols out of the reaction mixture as purification method for carbon-11 labelled alcohols.[19,20] Several methods were investigate here as well, but all proved to be unsuccessful, e.g. hydrolysis with hydrogen chloride in diethyl ether or dioxane did not facilitate the evaporation of 2-methyl-1-[^{11}C]propanol because all radioactivity remained in the first reaction vial. Glycerol worked well as quenching solvent to release the 2-methyl-1-[^{11}C]propanol, but its very high viscosity made practical application of this solvent impossible (Table 5, Entry 1 and 2). In addition to this, alcoholic compounds from the glycerol were observed in the second reaction vessel as impurity. Most of the radioactivity was transferred to the second reaction vessel by using water. In that case, however, a drying column is needed to remove water from the distillate, as the presence of too much water is unfavourable for most of the follow-up reactions with 2-methyl-1-[^{11}C]propanol. Therefore, different drying columns were investigated, loaded with either $CaSO_4$, $MgSO_4$, K_2CO_3, Na_2SO_4 or CaO. Most of the columns that were used resulted

in trapping of the majority of the 2-methyl-1-[^{11}C]propanol, resulting in great losses of activity. Nevertheless, when Na_2SO_4 or CaO were used as drying agents, 2-methyl-1-[^{11}C]propanol could be obtained in isolated radiochemical yields of 33 ± 9 % d.c. and 46 ± 6 % d.c., respectively.

Synthesis of [^{11}C]2-methylpropoxybenzene by a nucleophilic aromatic substitution reaction (Approach B)

The synthesis of [^{11}C]**8** could also be accomplished by a nucleophilic aromatic substitution reaction with fluorobenzene (Table 6) in DMSO at 130 °C for 10 minutes. Entries 1 to 5 in table 6 show the radiochemical conversion from 2-methyl-1-[^{11}C]propanol to [^{11}C]**8** when distillation was performed with glycerol or water and CaO as a drying agent. The highest radiochemical conversion 85 ± 4 d.c.% was obtained when using large amounts of fluorobenzene (32 mg, 332 μmol). These high amounts were necessary, as side reactions with unidentified alcoholic compounds occurred.

Synthesis of 1-phenyl-2-[^{11}C]methylpropane

We were also interested in exploring the possiblity to perfomrd C-C cross coupling reactions with 1-iodo-2-[^{11}C]methylpropane. This is in general a challenging reaction since the neighbouring hydrogen of 1-iodo-2-[^{11}C]methylpropane can give β-hydrogen-elimination, resulting in a non-reactive side product. It has been described that for non-activated alkyl halides this competing β-hydrogen elimination is often proceeding faster than the coupling of the reagents to obtain the desired product. [21] Nevertheless, this cross-coupling reaction was investigated with good results. The desired product [^{11}C]**11** was successfully formed form 1-iodo-2-[^{11}C]methylpropane as labelling reagent and phenylmagnesium bromide as precursor, by employing a cobalt assisted carbon-carbon bond formation reaction, with $Co(acac)_3$ or

$CoCl_2$ and tetramethylethylenediamine (TMEDA) as base. Reaction of 1-iodo-2-[^{11}C]methylpropane and phenylmagnesium bromide afforded [^{11}C]**11**, with $Co(acac)_3$ outperforming $CoCl_2$, and β-hydogen elimination was observed. An optimized procedure was reported by Cahiez et al. by using non-radioactive 2-iodobutane, 2-bromobutane and phenylmagnesium bromide as starting materials. [18] In the present study, however, using Cobalt(III)acetylacetonate/ TMEDA in a 1:1 molar ratio in THF at 0 °C for 10 minutes did not result in any product formation (Table 7, Entry 4). Increasing the amount of TMEDA gave a average radiochemical conversion of 60 % d.c. (Table 7, Entry 3). Changing the Cobalt(III)acetylacetonate to Cobalt(II)chloride resulted in only an average radiochemical conversion of 37 % d.c. of product [^{11}C]**11** (Table 7, Entry 2) as half of the 1-iodo-2-[^{11}C]methylpropane did not react with the phenylmagnesium bromide, and increasing the reaction temperature did not result in any product formation (Table 7, Entry 1). To our knowledge this reaction and formation of a C-C bond has never been described within the field of radiochemistry.

Conclusion

In this study we described the improved radiosynthesis of 1-iodo-2-[^{11}C]methylpropane and of 2-methyl-1-[^{11}C]propanol. Furthermore, to demonstrate the added value of these reagents for PET tracer development, these synthons were successfully applied in [^{11}C]etherification, [^{11}C]alkylation and [^{11}C]cross-coupling reactions, demonstrating the versatile opportunities with these synthons in radiochemistry. The obtained products displayed high molar activity, which is particularly important for PET receptor sfdtudies. These two radiolabelled synthons provide the opportunity to develop novel PET tracers which have been inaccessible so far.

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Conflict of interest

The authors did not report any conflict of interest

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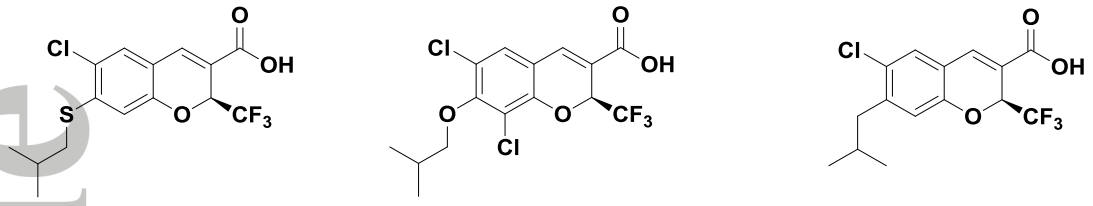
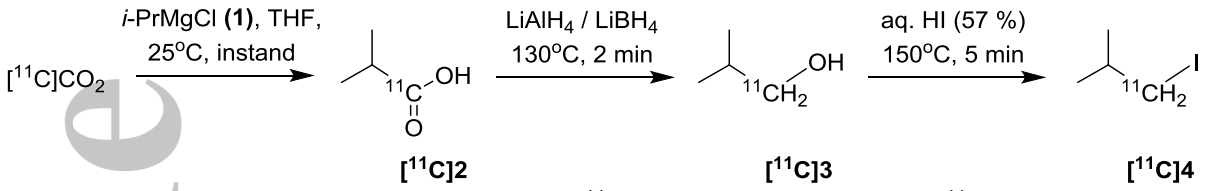
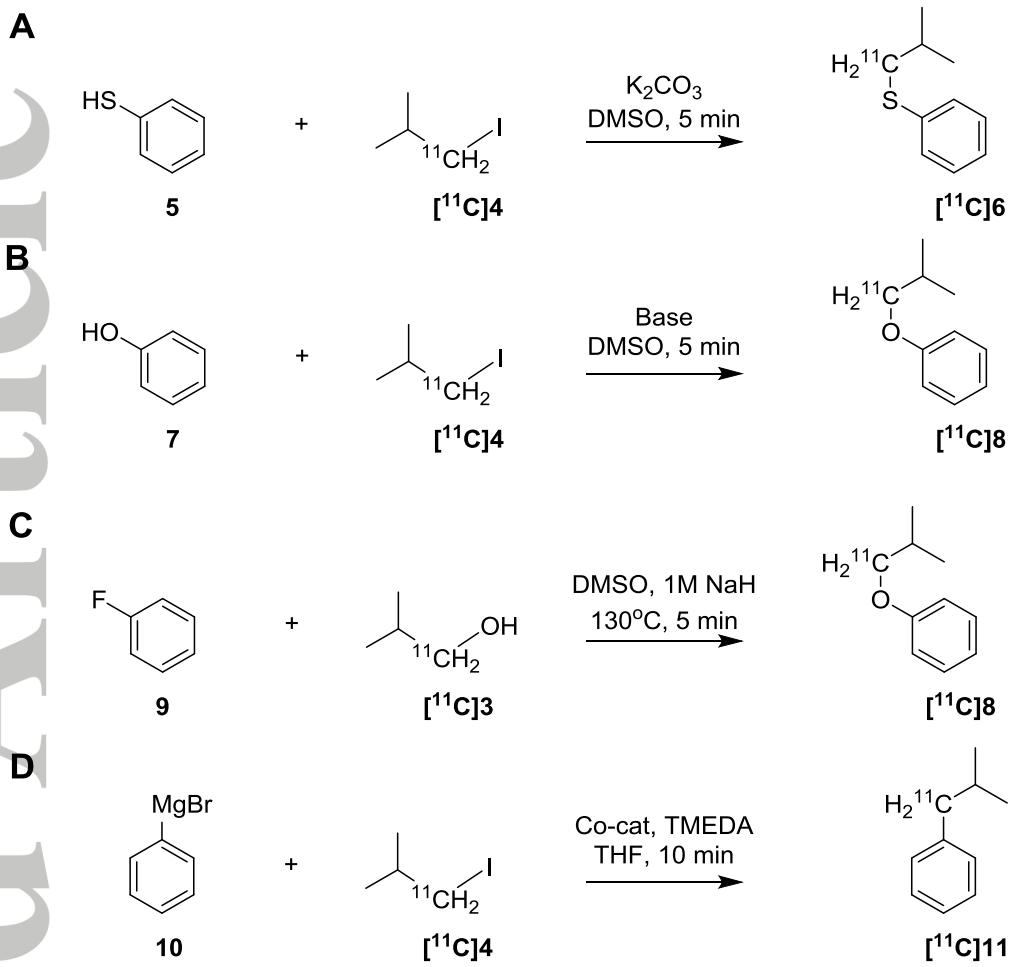


Figure 1: Described COX-2 inhibitors that allow potential radiolabeling with 1-iodo-2-[^{11}C]methylpropane for PET tracer development.



Scheme 1: Radiosynthesis of 2-methyl-1-[^{11}C]propanol and 1-iodo-2-[^{11}C]methylpropane

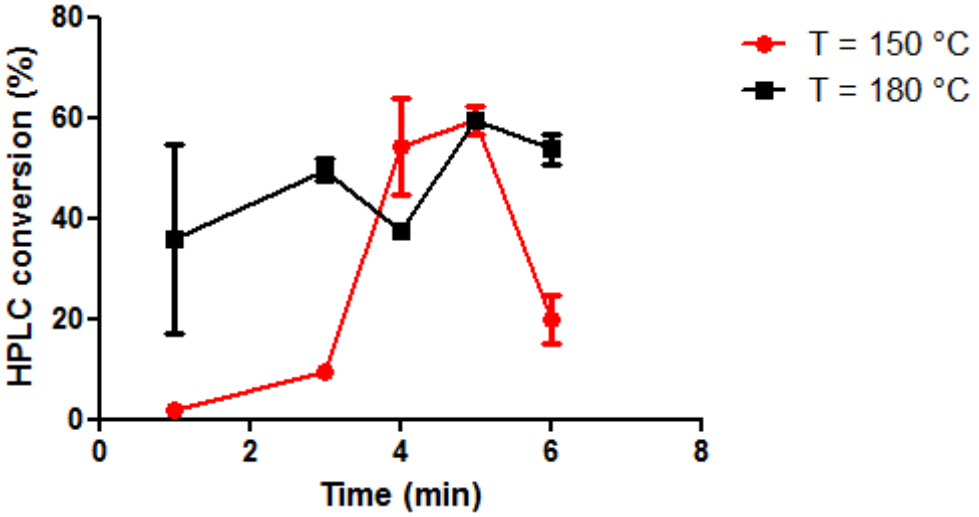


Scheme 2: Model reactions for the application of 2-methyl-1-[^{11}C]propanol and 1-iodo-2-[^{11}C]methylpropane for PET tracer development: **(A)** alkylation of thiols; **(B)** alkylation of alcohols; **(C)** alkylation of the 2-methyl-1-[^{11}C]propanol; **(D)** Cobalt catalyzed cross-coupling reaction.

Table 1: Optimization to synthesize [^{11}C]2-methylpropanoic acid

Entry	isopropylMgCl **1** (M)	isopropylMgCl **1** (µmol)	Reaction time (min)	RCC[a] (% d.c. ± SD)	n
1	0.5	75	0	56 ± 5	3
2	1.0	150	0	64 ± 8	3
3	2.0	300	0	67 ± 5	3
4	2.0	300	1	67 ± 5	3
5	2.0	300	2	68, 72	2
6	4.0	600	0	82 ± 1	4

[a] RCC = radiochemical conversions based on the HPLC chromatograms



Graph 1: Yield of 1-iodo-2-[^{11}C]methylpropane as a function of time at 150 °C and 180 °C (n = 3), determined by radio-HPLC analysis of the crude product.

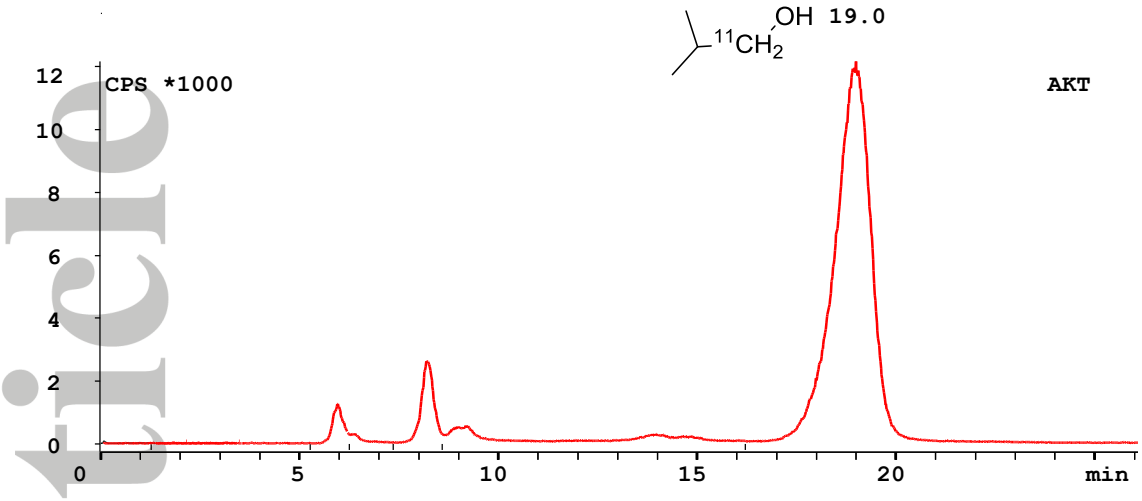


Figure 2: radioHPLC of 2-methyl-1-[^{11}C]propanol of the crude reaction mixture(HPLC eluens method C).

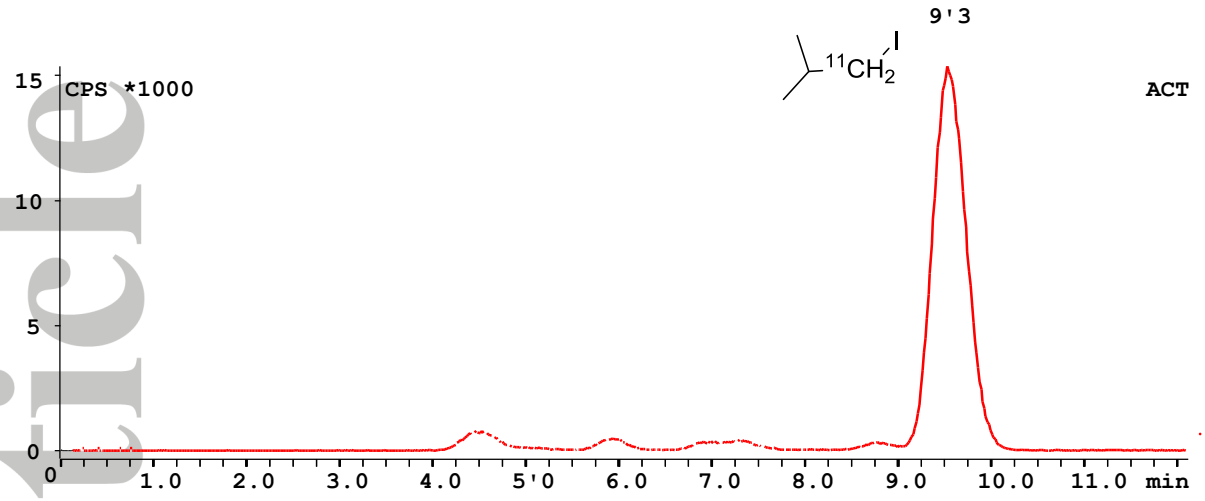


Figure 3: radioHPLC chromatogram of 1-iodo-2-[^{11}C]methylpropane (HPLC eluens method B)

Table 2: Stability test of 1-iodo-2-[^{11}C]methylpropane under different conditions after 5 minutes

Entry	Base[a]	Base (M)	Temp (°C)	purity of [^{11}C]**4**[b] (% d.c.)
1	TBAOH	0.06	25	0, 0
2	NaOH (aq)	0.06	25	53, 27
3	K_2CO_3 (aq)	0.06	25	100, 98
4	K_2CO_3 (aq)	0.06	80	98, 95
5	K_2CO_3 (aq)	0.06	100	88, 86
6	K_2CO_3 (aq)	0.06	130	24, 16

[a] 3 µL of a 4.1 M K_2CO_3 or NaOH solution were added.
[b] The results were corrected for the radiochemical purity.

Table 3: Optimization for thiol alkylation reactions with 1-iodo-2-[^{11}C]methylpropane to obtain [^{11}C]**6**

Entry	**5** (M)	**5** (mg)	K_2CO_3[a] (M)	K_2CO_3 (mg)	Temp (°C)	RCC (% d.c.)
1	0.45	9.9	0.30 (s)	8.3	130	84, 85
2	0.06	1.3	0.15 (s)	4.2	80	83, 83
3	0.06	1.3	0.15 (s)	4.2	25	82, 84
4	0.06	1.3	0.06 (s)	1.7	25	82, 20
5	0.06	1.3	0.06 (aq)	1.7	25	49, 18

[a] In Entry 1-4 K_2CO_3 was added to the reaction vessel as a crystalline base. In Entry 5, 3 µL of a 4.1 M K_2CO_3 solution was added to the reaction vessel.

Table 4: Optimization for alcohol alkylation reactions with 1-iodo-2-[^{11}C]methylpropane to obtain [^{11}C]**8.**

Entry	**7** (M)	Base[a]	Base (M)	Temp (°C)	RCC (% d.c.)
1	0.06	K_2CO_3 (s)	0.15	80	34, 33
2	0.06	K_2CO_3 (s)	0.15	80	-[b]
3	0.06	K_2CO_3 (s)	0.15	55	-[c]
4	0.06	K_2CO_3 (aq)	0.12	100	7, 23
5	0.06	K_2CO_3 (aq)	0.06	100	24, 21
6	0.06	K_2CO_3 (aq)	0.03	100	27, 26
7	0.06	K_2CO_3 (aq)	0.06	130	25, 24
8	0.06	K_2CO_3 (aq)	0.06	80	15, 18
9	0.06	K_2CO_3 (aq)	0.06	25	-
10	0.06	K_2CO_3 (aq)	0.06	100	13, 17[d]
11	0.06	NaOH (aq)	0.06	130	36, 30
12	0.06	KOH (aq)	0.06	130	29, 29
13	0.06	NaH (aq)	0.06	130	27, 21
14	0.06	Cs_2CO_3 (aq)	0.06	130	27, 29
15	0.06	LiHMDS	0.06	75	30, 30
16	0.06	K_2CO_3 (sat)	0.06	130	19, 27
17	0.90	K_2CO_3 (s)	0.30	130	37, 43
18	0.45	K_2CO_3 (s)	0.30	130	35, 45

[a] Bases were dissolved in water and 3 µL thereof was used
[b] Reaction was performed in MeCN
[c] Reaction was performed in Aceton
[d] Reaction was performed in DMF

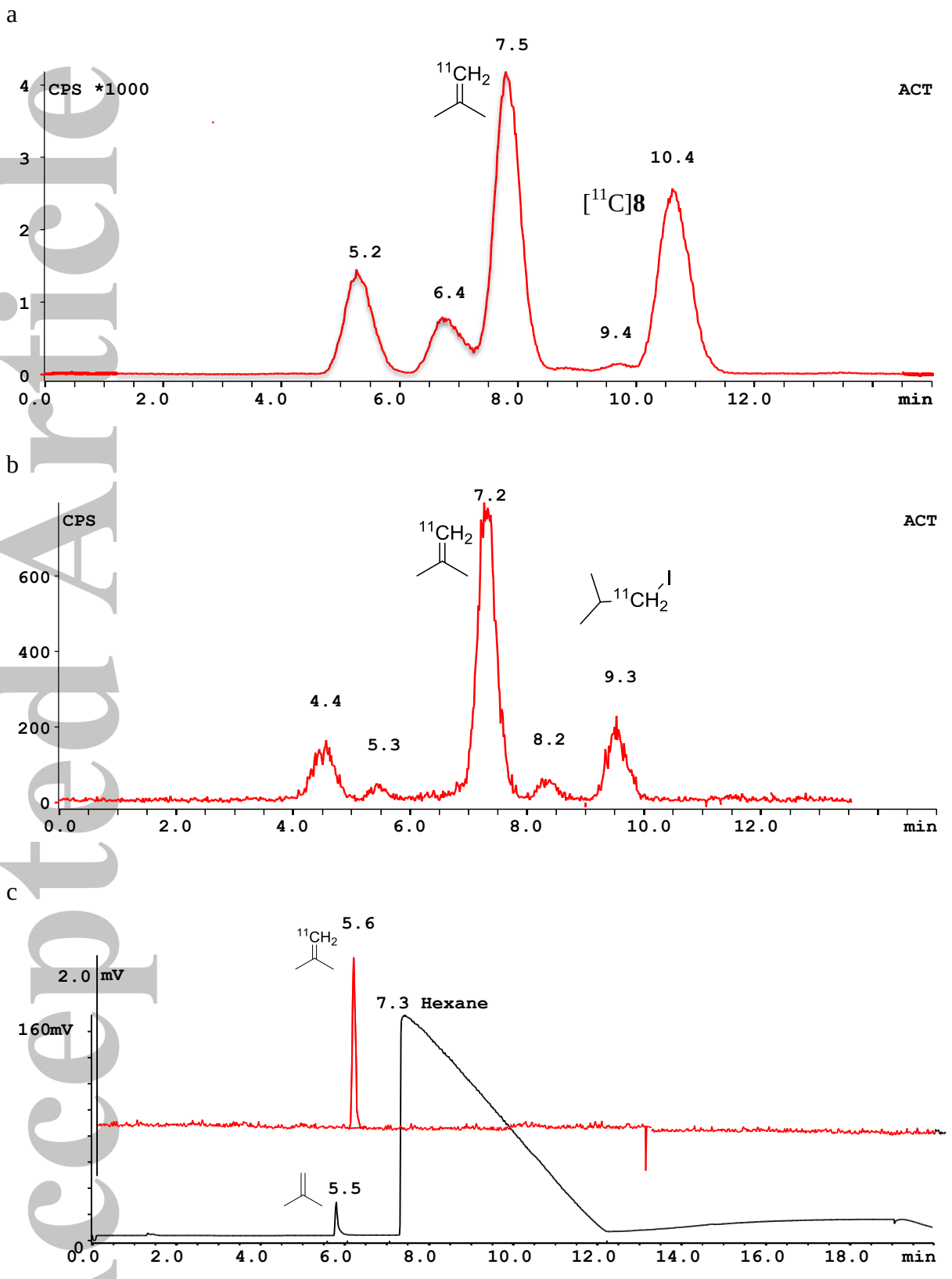


Figure 4: a) radioHPLC-chromatogram of [^{11}C]**8** entry 18, table 4, (HPLC eluens method B)**.** b) radioHPLC chromatogram of [^{11}C]2-methylprop-1-ene, generated by adding 10 mg of NaH to 1-iodo-2-[^{11}C]methylpropane. Reaction was done at 130 °C for 5 min in 200 µL DMSO. (HPLC eluens method B) c) Spiked GC-chromatogram of [^{11}C]2-methylprop-1-ene generated similar as described in b.

Table 5: Synthesis of 2-methyl-1-[^{11}C]propanol

Entry	Quenching solvent	Temp[a] (°C)	Drying agent	radiochemical yield (% d.c. ± SD)	n
1	Glycerol	80	-	55 ± 21	19
2	Glycerol/DMSO	80	-	57 ± 12	20
3	Water/DMSO	80	Na_2SO_4	33 ± 9	7
4	Water	80	CaO	46 ± 6	10

[a] Temperature at which the quenching solvent was added

Table 6: Optimization for alkylation of 2-methyl-1-[^{11}C]propanol to obtain [^{11}C]**8**

Entry	**9** (M)	RCC (% d.c. ± SD)	n
1	1.65	85 ± 4	4
2	0.83	82, 85	2
3	0.43	65	2
4	0.32	61 ± 15	3
5	0.21	50, 46	2
6	0.83	72, 41	2
7	0.43	49, 33	2
8	0.06	23, 11	2
9	0.06	3, 3[a]	2

[a] 0.3 M NaH was used

Entry 1-5: 400 µL of DMSO was used and distillation of 2-methyl-1-[^{11}C]propanol was performed with glycerol

Entry 6-9: 200 µL of DMSO was used and the distillation of 2-methyl-1-[^{11}C]propanol was performed with water and CaO as drying column

Table 7: Optimization of the Co-catalyzed cross-coupling with 1-iodo-2-[^{11}C]methylpropane to obtain [^{11}C]**11**

Entry	Catalyst	Catalyst (M)	**10** (M)	TMEDA (M)	Temp (°C)	RCC (% d.c.)	n
1	$CoCl_2$	0.10	0.25	1.24	25	-	1
2	$CoCl_2$	0.10	0.25	1.24	0	36, 38	2
3	$Co(acac)_3$	0.10	0.25	1.24	0	59, 61	2
4	$Co(acac)_3$	0.10	0.25	0.10	0	-	2