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Research Article

Synthesis of [1-^{11}C]propyl and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide and their use in alkylation reactions

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Summary

A method to prepare [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide via a three step reaction sequence is presented. Palladium mediated formylation of ethene with [^{11}C]carbon monoxide and hydrogen gave [1-^{11}C]propionaldehyde and [1-^{11}C]propionic acid. The carbonylation products were reduced and subsequently converted to [1-^{11}C]propyl iodide. Labelled propyl iodide was obtained in 58 $\pm$ 4% decay corrected radiochemical yield and with a specific radioactivity of 270 $\pm$ 33 GBq/μmol within 15 min from approximately 12 GBq of [^{11}C]carbon monoxide. The position of the label was confirmed by ^{13}C-labelling and ^{13}C-NMR analysis. [1-^{11}C]Butyl iodide was obtained correspondingly from propene and approximately 8 GBq of [^{11}C]carbon monoxide, in 34 $\pm$ 2% decay corrected radiochemical yield and with a specific radioactivity of 146 $\pm$ 20 GBq/μmol. The alkyl iodides were used in model reactions to synthesize [*O*-propyl-1-^{11}C]propyl and [*O*-butyl-1-^{11}C]butyl benzoate. Propyl and butyl analogues of etomidate, a β-11-hydroxylase inhibitor, were also synthesized. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: [^{11}C]carbon monoxide; [1-^{11}C]propyl iodide; [1-^{11}C]butyl iodide; carbonylation; formylation; alkylation

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Introduction

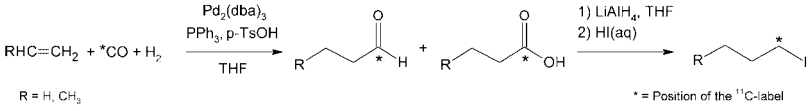
The use of positron emission tomography (PET) in medical applications and drug discovery[1–3] has stimulated the development of labelling methods and tracer molecules labelled with ^{11}C (β^+, $t_{1/2} = 20.3$ min) and other positron emitting radionuclides. The main radiolabelled building blocks for tracer synthesis, [^{11}C]methyl iodide[4–7] and [^{11}C]methyl triflate[8] have been used extensively in alkylation reactions with nitrogen and oxygen nucleophiles. Alkyl halides with longer alkyl chains prepared from Grignard reagents and [^{11}C]carbon dioxide, e.g. [1-^{11}C]ethyl iodide, [1-^{11}C]propyl iodide, [1-^{11}C]isopropyl iodide and [1-^{11}C]butyl iodide, have also been used but to lesser extent and are typically obtained with moderate to low specific radioactivity.[9–16] The possibility of fine-tuning tracer characteristics by using different alkyl groups have been an incentive to explore new synthetic methods for ^{11}C-labelled ethyl, propyl and butyl iodide that would give products with higher specific radioactivity. Recently a method to synthesize [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide was published which avoids reagents that potentially lead to isotopic dilution.[17] This method which utilized palladium mediated carbonylation of methyl iodide followed by reduction and iodination has now been modified in order to synthesize [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide. Ethene and propene were considered to be promising starting materials since carbonylation and formylation of olefins can be utilized in the synthesis of carboxylic acids, esters and aldehydes.[18–20] Carbonylation of olefins with [^{11}C]carbon monoxide has not been reported previously although various ^{11}C-carbonylation reactions have been explored.[21–28]

In this paper we describe the synthesis of [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide according to the method shown in Scheme 1.

[^{11}C]Carbon monoxide and hydrogen is used in palladium mediated formylation of ethene and propene to produce the corresponding [1-^{11}C]aldehydes and [1-^{11}C]carboxylic acids. The labelled carbonyl compounds were reduced and subsequently converted to the corresponding [1-^{11}C]alkyl iodides and then applied in the labelling of esters.

Results and discussion

The first step in the synthesis of [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide, i.e. the formation of the corresponding aldehyde and carboxylic acid, was



Scheme 1. Synthesis of [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide

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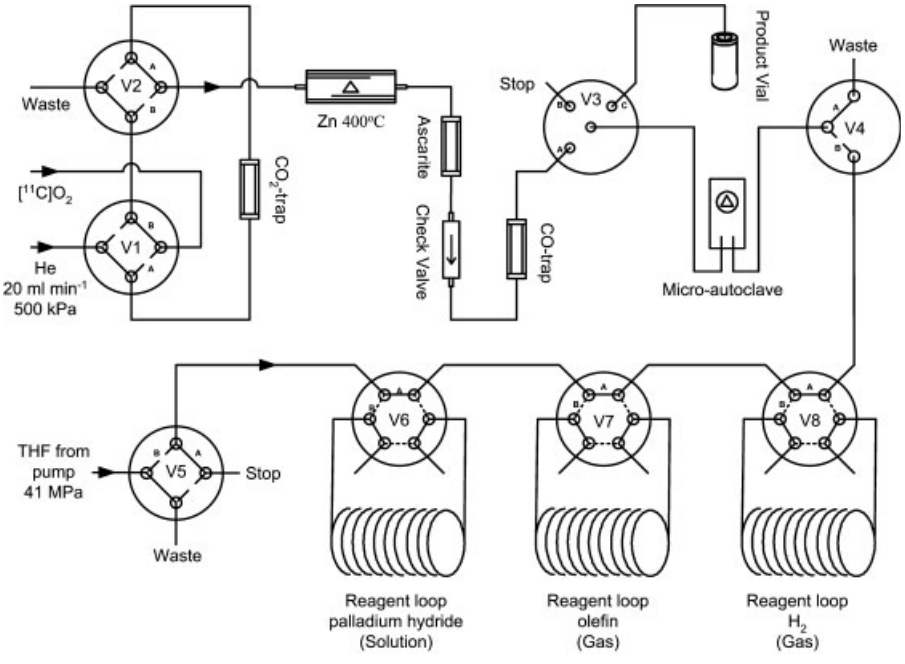

Figure 1. Schematic drawing of the experimental setup used in the carbonylation reactions

performed in a Teflon® coated micro-autoclave using the experimental set-up shown in Figure 1.[29] [^{11}C]Carbon monoxide was prepared via the reduction of [^{11}C]carbon dioxide over Zn at 400°C. It was concentrated to a small volume on silica at −196°C and then transferred to a 200 µl cylindrical reaction chamber, i.e. micro-autoclave, via an inlet at the bottom surface of the chamber.

A palladium hydride complex was generated in tetrahydrofuran (THF) by treatment of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) with triphenylphosphine (PPh_3) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH). $Pd_2(dba)_3$ was used because of its excellent air stability compared to some other Pd^0-complexes and due to the ability to form hydride complexes with PPh_3 and acid that activates olefins towards insertion into the palladium–hydride bond. The palladium hydride solution was transferred together with the olefin and hydrogen into the micro-autoclave via a second inlet at the bottom surface by use of a high-pressure pump (41 MPa). The high pressure inside the micro-autoclave secured an efficient trapping of [^{11}C]carbon monoxide in the reaction mixture due to a very small gas phase volume. Within the 3 min reaction time ^{11}C-labelled aldehyde was obtained as shown in Scheme 1. The corresponding labelled carboxylic acid was also obtained in approximately equal amount, most likely through nucleophilic attack of water

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on the acyl palladium intermediate. A change from the monohydrate *p*-TsOH to methyl sulfonic acid gave similar results. No desired product was obtained when hydrogen was used without sulfonic acid present. Acidic conditions without the addition of hydrogen resulted in the formation of labelled carboxylic acid but no aldehyde was observed. These observations may indicate that the aldehyde was formed via the insertion of the olefin into the palladium hydride, generated by *p*-TsOH, followed by the insertion of [^{11}C]carbon monoxide into the palladium carbon bond and finally by the reductive elimination induced by hydrogen.

The formylation reactions proceeded readily at a broad temperature range from room temperature to 70 and 60 °C was used throughout the experiments. Highest radiochemical yield for the formylation of ethene was obtained with 28 μmol of the olefin while the amount for propene was 170 μmol. Olefin and hydrogen was in used in 1:1 molar ratio. The identity of the labelled aldehydes were confirmed with analytical HPLC after derivatization with 2,4-dinitrophenylhydrazine.[30] The radiochemical purity of the propyl and butyl hydrazine derivatives was 47 and 28%, respectively.

The reaction mixture was transferred from the micro-autoclave to a vial containing lithium aluminium hydride (LAH) where the carbonyl compounds were reduced. Conversion to ^{11}C-labelled alkyl iodide was carried out using hydriodic acid similarly to previous procedures.[5] In order to obtain the labelled alkyl halide in good yield it was important to thoroughly remove the THF from the reaction mixture before the addition of the hydriodic acid. This was performed by flushing with nitrogen gas while heating the vial. The vial containing the dry alkoxide salt was cooled down to sub-zero temperature prior to the addition of the hydriodic acid to control the vigorous exothermic reaction. The vial was then heated for 5 min at 130 °C during iodination reaction. A closed reaction vessel was utilized to prevent the volatile alcohol from escaping. After 5 min the resulting labelled alkyl halide was distilled off and transferred in a stream of nitrogen gas through a drying tower (phosphorus pentoxide desiccant) to a vial containing dimethylformamide (DMF). The labelled alkyl halides were synthesized from [^{11}C]carbon monoxide within 15 min.

The decay-corrected radiochemical yield of [1-^{11}C]propyl iodide trapped in DMF was $58 \pm 4\%$ based on the amount [^{11}C]carbon monoxide in the autoclave at the start of the synthesis. [1-^{11}C]Propyl iodide accounted for $93 \pm 4\%$ of the transferred radioactivity. [1-^{11}C]Butyl iodide was obtained in $34 \pm 2\%$ yield and with a radiochemical purity of $79 \pm 9\%$. The only labelled by-product found was [^{11}C]methyl iodide which was assumed to be derived from the reoxidation of [^{11}C]carbon monoxide to [^{11}C]carbon dioxide in the micro-autoclave. This may occur through the Pd^{II} promoted water–gas shift reaction[18,31] or a heterogeneous reaction with oxygen on the surface of the

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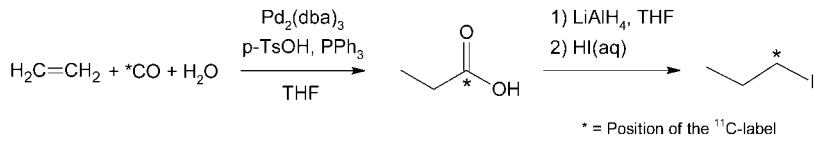

Scheme 2. Synthesis of [1-^{11}C]propyl iodide from [^{11}C]carbon monoxide, ethene and water

autoclave.[32] Zudin *et al* has reported inhibition of the water–gas shift reaction at acidic conditions by the addition of hydrogen.[33] Accordingly, when water was used instead of hydrogen as shown in Scheme 2, the radiochemical purity of [1-^{11}C]propyl iodide was significantly decreased from 93% to 75%.

The radiochemical yield decreased moderately from 58 to 52%. Contrary to when hydrogen was used, there was strong temperature dependence with a maximum radiochemical yield at 70°C. In the synthesis of the labelled alkyl halides, highest radiochemical yield and best reproducibility was achieved by using the formylation conditions. No labelled branched product was detected in the formylation of propene when PPh_3 was used. The regioselectivity was reduced when 1,3-bis-(diphenylphosphino)propane was utilized giving labelled n-butyl iodide and iso-butyl iodide in 10:1 ratio. The position of the radioactive label on [1-^{11}C]propyl iodide was confirmed with ^{13}C-NMR analysis after performing the synthesis with an isotope mixture of [^{11}C]/(^{11}C)carbon monoxide.

The labelled alkyl halides were used in the synthesis of [*O*-propyl-1-^{11}C]propyl benzoate **1**, [*O*-butyl-1-^{11}C]butyl benzoate **2**, [1-^{11}C]propyl 1-[(1*R*)-1-phenylethyl]-1*H*-imidazole-5-carboxylate **3** and [1-^{11}C]butyl 1-[(1*R*)-1-phenylethyl]-1*H*-imidazole-5-carboxylate **4**.

The specific radioactivity of the labelled benzoates and the isolated radiochemical yield of the labelled compounds are presented in Table 1. The alkylated products were obtained with >98% radiochemical purity after semi-preparative HPLC purification (Figure 2).

The specific radioactivity of the labelled alkyl halides were estimated by quantification of the corresponding labelled alkyl benzoates. The lowest isotopic dilution was achieved when the amount of LAH used in the reduction step was kept to a minimum without compromising the radiochemical yield. This was probably due to trace amounts of impurities in the commercially available stock solutions of LAH.

The temperature used in the evaporation of the THF prior to the addition of hydriodic acid influenced the specific radioactivity for [1-^{11}C]butyl iodide but not for [1-^{11}C]propyl iodide. Heating the vial at 120 °C rather than 60 °C during the evaporation resulted in a significant increase of the amount butyl iodide while there was a small change in the radiochemical yield. There is no

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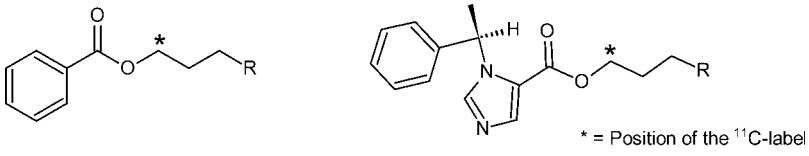
Table 1. Radiochemical yield, radiochemical purity and specific radioactivity

Entry	RCY[a] (%)	RCP[b] (%)	Product amount (nmol)	Specific radioactivity[c] (GBq/μmol)	Initial radioactivity ^{11}CO (GBq)
[1-^{11}C]Propyl iodide	58 ± 4[d] (14)[e]	93 ± 4%	—	270 ± 33[f] (3)	—
[1-^{11}C]Butyl iodide	34 ± 2[d] (13)	79 ± 9%	—	146 ± 20[f] (3)	—
1	52 ± 2[h] (6)	>98%	14 ± 1 (3)	162 ± 20 (3)	12.2 ± 0.7 (3)
2[g]	26 ± 1[h] (4)	>98%	7.8 ± 0.7 (3)	88 ± 12 (3)	8.1 ± 0.3 (3)
2[I]	29 ± 2[h] (4)	>98%	18 ± 5 (3)	26 ± 11 (3)	4.6 ± 0.6 (3)
3	37 ± 2[h] (2)	>98%	—	—	—
4	27 ± 2[h] (2)	>98%	—	—	—

[a] Decay-corrected radiochemical yield based on the initial amount of radioactivity at the start of the synthesis and the radioactivity of the isolated product. When the reaction mixture was transferred from the micro-autoclave to the evacuated 2 ml vial containing LAH, the radioactivity in the vial was measured. The radioactive residues left in the micro-autoclave were estimated to be less than 1%. Hence, the amount of initial radioactivity could be determined.
[b] Radiochemical purity assessed with analytical HPLC, defined as the percentage of the total radioactivity present in the specified chemical form.
[c] Specific radioactivity of the isolated product.
[d] Decay-corrected radiochemical yield of the alkyl halide transferred to the alkylation reaction.
[e] Number of experiments in brackets.
[f] Approximate value that was derived from the analysis of the corresponding labelled benzoic ester.
[g] Evaporation of THF at 60°C prior to the addition of the hydriodic acid.
[h] Decay-corrected radiochemical yield of the isolated product.
[i] Evaporation of THF at 120°C prior to the addition of the hydriodic acid.



1. R = H
2. R = CH_3
3. R = H
4. R = CH_3

Figure 2. Products obtained via alkylation with [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide

clear explanation for this observation. However, it may indicate that excessive heating of minute amounts of THF in the presence of the lithium/aluminium salt may have resulted in ring opening of THF and formation of butoxide. The treatment of the alkoxide with hydriodic acid would then give butyl iodide. Conventional ether cleavage of THF with hydriodic acid may be a less likely source of isotopic dilution since is should result in the formation of 1,4-diiodobutane.[34]

Conclusion

Ethene and propene are feasible starting material for the synthesis of [1-^{11}C]propyl iodide and [1-^{11}C]butyl iodide from [^{11}C]carbon monoxide.

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Formylation compared to hydroxycarbonylation gave higher radiochemical yield, increased the radiochemical purity and decreased the temperature dependence of the reaction. The syntheses performed using formylation conditions resulted in labelled aldehydes and carboxylic acids which were reduced and converted to alkyl iodides. [1-^{11}C]Propyl iodide and [1-^{11}C]butyl iodide, obtained in 58 ± 4% and 34 ± 2% yield, respectively, were used in the alkylation of benzoic acid. [*O*-propyl-1-^{11}C]propyl benzoate was isolated in 30 min with a specific radioactivity of 162 GBq/μmol from 12.2 GBq of [^{11}C]carbon monoxide. The decay-corrected radiochemical yield was 52%. [*O*-butyl-1-^{11}C]Butyl benzoate was isolated in 30 min with a specific radioactivity of 88 GBq/μmol from 8.1 GBq [^{11}C]carbon monoxide and with an decay corrected radiochemical yield of 26%. [1-^{11}C]Propyl and [1-^{11}C]butyl 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylate were synthesized and purified within 30 min from [^{11}C]carbon monoxide with a decay-corrected radiochemical yield of 30 and 27%, respectively. The labelled imidazole derivates are currently being investigated in preclinical experiments to evaluate their potential usefulness as tracers.

Experimental

General

^{11}C was prepared by the ^{14}N(p,α)^{11}C nuclear reaction using 17 MeV protons produced by a Scanditronix MC-17 Cyclotron at Uppsala Imanet AB and obtained as [^{11}C]carbon dioxide. The target gas used was nitrogen (AGA Nitrogen 6.0) containing 0.05% oxygen (AGA Oxygen 4.8). The carbonylation reactions were carried out in a 200 μl Teflon® coated micro-autoclave using the experimental set-up described in Figure 1 and the following procedure.[29]

[^{11}C]Carbon dioxide (approximately 1–10 nmol) was carried in a stream of nitrogen gas from the cyclotron to the CO_2-trap containing Alltech silica gel 100/120 at −196°C. The CO_2-trap was then flushed with helium gas at 20 ml min^{-1} for 1 min before it was warmed up and the [^{11}C]carbon dioxide was transferred in the gas stream through a quartz tube heated at 400 °C containing zinc granules (Merck 14–50 mesh). [^{11}C]Carbon dioxide was reduced to [^{11}C]carbon monoxide in the quartz tube. Any remaining trace of [^{11}C]carbon dioxide was subsequently removed by a column containing Ascarite®. [^{11}C]Carbon monoxide was transferred to the CO-trap where it was trapped on Alltech 100/120 silica gel (1 mg) at −196°C. The V3-valve connecting the CO-trap to the micro-autoclave was then switched to stop, giving rise to a pressure build-up of approximately 400–500 kPa by the helium carrier gas. The V4-valve was switched, connecting the autoclave to the injection valves. The CO-trap was heated to release the [^{11}C]carbon monoxide

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from the silica. By switching the V3-valve to the CO-trap, [^{11}C]carbon monoxide was transferred to the micro-autoclave by the pressure difference over the valve. After the transfer, the V3-valve was switched to stop. The reagents were then transferred from the reagent loops to the 200 µl micro-autoclave by the pressure of THF pumped at 41 MPa. After 3 min reaction time the mixture was transferred from the micro-autoclave to the product vial by the switching of the V3-valve.

THF was freshly distilled over sodium and benzophenone in a nitrogen atmosphere before use. The hydride palladium complex was generated *in situ* from $Pd_2(dba)_3$, *p*-TsOH and PPh_3. All chemicals were purchased from Aldrich/Fluka and used as received. The ^{13}C-NMR spectra were recorded using a Varian 400 MHz spectrometer. The identities of compounds **3** and **4** were assessed using a Waters Quattro Premier triple quadrupole mass spectrometer (Waters, Milford, MA, USA) with electrospray ionisation operated in positive mode. The identities of the remaining labelled compounds were determined with analytical HPLC using authentic samples as reference. The concentrations of compounds **1** and **2** were assessed with analytical HPLC. Analytical HPLC was performed on a Beckman system, equipped with a Beckman 126 pump, a Beckman 166 UV detector in series with a Bioscan β^+-flow count detector and a Beckman Ultrasphere ODS dp 5 µ column (250 × 4.6 mm). A Gilson 231 was used as auto injector. Purification with semi-preparative HPLC was performed on a similar Beckman system equipped with a Beckman Ultrasphere ODS dp 5 µ column (250 × 10 mm). Mobile phase: A) 0.05 M ammonium formate pH 3.5 B) acetonitrile.

Synthesis of [1-^{11}C]propyl iodide

$Pd_2(dba)_3$ (0.70 mg, 1.2 µmol), PPh_3 (2.7 mg, 10 µmol, 8.6 eq.) and *p*-TsOH (5.6 mg, 29 µmol, 24 Eq.) were placed in a 0.8 ml vial equipped with rubber septum. THF (600 µl) was added and the resulting solution was degassed with argon. The solution was loaded into an injection loop (200 µl). A second injection loop was loaded with ethene (0.7 ml, 100 kPa, 28 µmol). A third injection loop was loaded with hydrogen gas (0.7 ml, 100 kPa, 28 µmol). THF was pumped through all three injection loops and the reagents were pumped into a 200 µl Teflon® coated stainless steel micro-autoclave containing [^{11}C]carbon monoxide. The reagents were kept in the autoclave for 3 min at 60 °C. The reaction mixture was then transferred to a 2 ml septum-equipped evacuated glass vial containing LAH (100 µl, 1 M). The vial was heated at 120°C for 2–3 min during the removal of THF under a stream of nitrogen gas. Then the vial was cooled down to sub-zero temperature using liquid nitrogen. Hydriodic acid (1.0 ml, 57 wt% in water) was added and then the vial was heated for 5 min at 130°C. The vial was removed from the heat source and

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while it was still warm [1-^{11}C]propyl iodide was transferred in a stream of nitrogen (30 ml min^{-1}) through a drying tower (phosphorus pentoxide desiccant) to a vessel containing DMF (300 µl). Analytical HPLC was used to assess the identity and radiochemical purity. Mobile phase A:B (50:50). Flow 1.5 ml min^{-1}. [1-^{11}C]Propyl iodide: Rt 7.3 min; [^{11}C]methyl iodide: Rt 4.2 min

Synthesis of [1-^{11}C]propyl iodide utilizing water

The synthesis was performed as above with the following modifications. Water (1.0 µl) was added to the carbonylation reaction instead of using hydrogen gas. The micro-autoclave was heated for 3 min at 70 °C.

Synthesis of [1-^{11}C]butyl iodide

The synthesis was performed as for [1-^{11}C]propyl iodide with the following modifications. The second injection loop was loaded with propene (0.7 ml, 600 kPa, 170 µmol). The third injection loop was loaded with hydrogen gas (0.7 ml, 600 kPa, 170 µmol). The vial was heated at 60 °C for 3–4 min alternatively 120 °C for 2–3 min during the removal of THF under a stream of nitrogen gas. Analytical HPLC was used to assess the identity and radiochemical purity. Mobile phase A:B (35:65). Flow 1.5 ml min^{-1}. [1-^{11}C]Butyl iodide: Rt 7.1 min; [^{11}C]Methyl iodide: Rt 3.1 min.

Synthesis of (1-^{13}C)propyl iodide

$Pd_2(dba)_3$ (0.70 mg, 1.2 µmol), PPh_3 (2.7 mg, 10 µmol, 8.6 eq.) and *p*-TsOH (3.9 mg, 20.5 µmol, 17 eq.) were placed in a 0.8 ml vial equipped with a rubber septum. THF (450 µl) was added and the resulting solution was degassed with argon. The solution (200 µl) was loaded into an injection loop. A second injection loop was loaded with ethene (1.0 ml, 100 kPa). A third injection loop was loaded with hydrogen gas (0.7 ml, 100 kPa). A fourth injection loop was loaded with (^{13}C)carbon monoxide (0.7 ml, 100 kPa). The reagents were pumped with THF into a 200 µl Teflon® coated micro-autoclave containing [^{13}C]carbon monoxide. The micro-autoclave was heated for 15 min at 70 °C. The reaction mixture was then transferred to a 5 ml septa-equipped evacuated glass vial containing LAH (150 µl, 1 M). The vial was heated at 120 °C for 2–3 min during the removal of THF under a stream of nitrogen gas. Then the vial was cooled down to sub-zero temperature. Hydriodic acid (1.0 ml, 57 wt% in water) was added and then the vial was heated for 10 min at 130 °C. The vial was removed from the heating and while it was still warm the labelled propyl iodide was transferred in a stream of nitrogen (30 ml min^{-1}) through a drying tower (phosphorus pentoxide desiccant) and trapped in chloroform-d (0.8 ml) at −40°C. ^{13}C-NMR was used to assess the position of the ^{13}C-labelling.

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(1-^{13}C)Propyl iodide ^{13}C-NMR MHz ($CDCl_3$) δ: 9.87; (^{13}C)methyl iodide ^{13}C-NMR MHz ($CDCl_3$) δ: −23.2.

Characterization of [1-^{11}C]propionaldehyde and [1-^{11}C]butyraldehyde via derivatization with 2,4-dinitrophenylhydrazine

To a solution of 2,4-dinitrophenylhydrazine (1.2 mg, 6.2 μmol) and perchloric acid (10 μl) in acetonitrile (1 ml) was added a sample (10 μl) from the formylation reaction. Analytical HPLC was used to assess the identity and radiochemical purity. Propyl derivate: Mobile phase A:B (40:60). Flow 1.5 ml min^{-1}, Rt 8.68 min; Butyl derivate: Mobile phase A:B (30:70). Flow 1.5 ml min^{-1}, Rt 7.44 min.

[O-propyl/butyl-1-^{11}C]Propyl/Butyl benzoate (1/2)

In a 0.8 ml glass vial equipped with a rubber septum, benzoic acid (1.2 mg, 9.8 μmol) was dissolved in dichloromethane (200 μl) at room temperature. Tetrabutylammonium hydroxide in methanol (4.8 μl, 1 M, 4.8 μmol) was added. The solvent was removed under a stream of nitrogen. DMF (300 μl) was added. The labelled alkyl iodide was transferred to the DMF solution in a stream of nitrogen gas (30 ml min^{-1}) through a drying tower (phosphorus pentoxide desiccant. The vial was then heated for 5 min at 120 °C.

1. Semi-preparative HPLC mobile phase A:B (35:65). Flow 4 ml min^{-1}, Rt 9.4 min. Analytical HPLC was used to assess identity and radiochemical purity. Mobile phase A:B (40:60). Flow 1.0 ml min^{-1}, Rt 9.7 min.

2. Semi-preparative HPLC mobile phase A:B (25:75). Flow 4 ml min^{-1}, Rt 8.5 min. Analytical HPLC was used to assess the identity and radiochemical purity. Mobile phase A:B (35:65). Flow 1.0 ml min^{-1}, Rt 10.6 min.

[1-^{11}C]propyl/butyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate (3/4)

The synthesis was carried out by following the same procedure as for the labelling of the benzoates **1** and **2**. 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylic acid (1.2 mg, 5.5 μmol) was treated with tetrabutylammonium hydroxide in methanol (5.6 μl, 1 M, 5.6 μmol). The labelled alkyl iodide was transferred in a stream of nitrogen gas (30 ml min^{-1}) to the glass vial and bubbled through the solution. The vial was then heated for 5 min at 120°C.

3. Semi-preparative HPLC mobile phase A:B (34:66). Flow 4 ml min^{-1}, Rt 7.2 min. Analytical HPLC was used to assess the radiochemical purity. Mobile phase A:B (35:65). Flow 1.0 ml min^{-1}, Rt 5.8 min. LC-MS(ES+): m/z = 259.

4. Semi-preparative HPLC. Mobile phase A:B (28:72). Flow 4 ml min^{-1}, Rt 7.9 min. Analytical HPLC was used to assess the radiochemical purity. Mobile phase A:B (30:70). Flow 1.0 ml min^{-1}, Rt 6.1 min, LC-MS(ES+): m/z = 273.

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