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Research Article

Synthesis of [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide and its application in alkylation reactions

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Summary

A method is presented for preparing [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide. The method utilizes methyl iodide and [^{11}C]carbon monoxide in a palladium-mediated carbonylation reaction to form a mixture of [1-^{11}C]acetic acid and [1-^{11}C]methyl acetate. The acetates are reduced to [1-^{11}C]ethanol and subsequently converted to [1-^{11}C]ethyl iodide. The synthesis time was 20 min and the decay-corrected radiochemical yield of [1-^{11}C]ethyl iodide was $55 \pm 5\%$. The position of the label was confirmed by ^{13}C-labelling and ^{13}C-NMR analysis. [1-^{11}C]Ethyl iodide was used in two model reactions, an *O*-alkylation and an *N*-alkylation. Starting with approximately 2.5 GBq of [^{11}C]carbon monoxide, the isolated decay-corrected radiochemical yields for the ester and the amine derivatives were $45 \pm 0.5\%$ and $25 \pm 2\%$, respectively, based on [^{11}C]carbon monoxide. Starting with 10 GBq of [^{11}C]carbon monoxide, 0.55 GBq of the labelled ester was isolated within 40 min with a specific radioactivity of 36 GBq/μmol. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: [1-^{11}C]ethyl iodide; [^{11}C]carbon monoxide; carbonylation

Introduction

The use of positron emission tomography (PET) in medical applications and in drug discovery[1] has stimulated the development of new labelling methods using ^{11}C ($\beta+$, $t1/2 = 20.3$ min). Alkylation on nitrogen, oxygen and sulphur nucleophiles has been an important synthetic method for the incorporation of ^{11}C into target molecules. [^{11}C]Methyl iodide[2–5] and [^{11}C]methyl triflate[6] have proven to be useful alkylating agents. Other labelled organohalides[7–12] such as [^{11}C]ethyl iodide, [^{11}C]propyl iodide and [^{11}C]aryl halides[13] have also been used in alkylation reactions although not as frequently as [^{11}C]methyl iodide.

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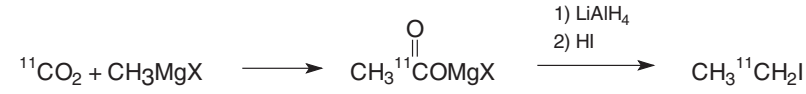
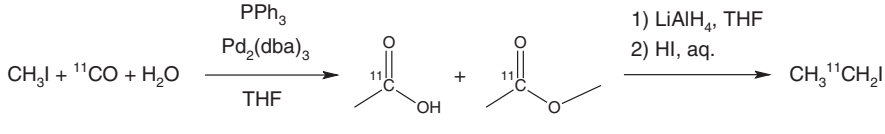
[1-^{11}C]Ethyl iodide has previously been prepared from [^{11}C]carbon dioxide and a methyl Grignard reagent according to Scheme 1.



Scheme 1. Synthesis of [1-^{11}C]ethyl iodide from [^{11}C]carbon dioxide and methyl Grignard reagent

Isotopic dilution originating from carbon dioxide in the environment is a potential drawback of the Grignard method. Careful preparation and handling of the Grignard reagent is required in order to maximize the specific radioactivity, which is of importance in many PET applications.

In recent work, [^{11}C]carbon monoxide has been applied in a variety of palladium mediated carbonylation reactions[14–18] producing products of high specific radioactivity. The low atmospheric concentration of carbon monoxide compared to carbon dioxide makes it advantageous to work with [^{11}C]carbon monoxide when aiming for high specific radioactivity. Thus, we wanted to investigate if [1-^{11}C]ethyl iodide could be synthesized from [^{11}C]carbon monoxide. Acetic acid, a viable intermediate in the synthesis of ethyl iodide, is produced at industrial scale from methanol and carbon monoxide. This can be done for example *via* the Monsanto process[19,20] where hydriodic acid and a polycarbonyl rhodium complex $[Rh(CO)_2I_2]^-$ are used as catalysts. More appropriate for our purpose was to use Pd^0-complexes which have been shown to promote the carbonylation of organohalides with carbon monoxide under mild conditions and at a low partial CO-pressure Scheme 2.[21–23]



Scheme 2. Synthesis of [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide

In this report, a three-step synthesis of [1-^{11}C]ethyl iodide is described together with the labelling of Etomidate and Lidocaine.

Results and discussion

The first step of the [1-^{11}C]ethyl iodide synthesis, i.e. the carbonylation reaction, was performed in a stainless steel micro-autoclave using the experimental set-up[24] shown in Figure 1. [^{11}C]Carbon dioxide was reduced to [^{11}C]carbon monoxide in a Zn-furnace, concentrated to a small volume and then transferred to a micro-autoclave.

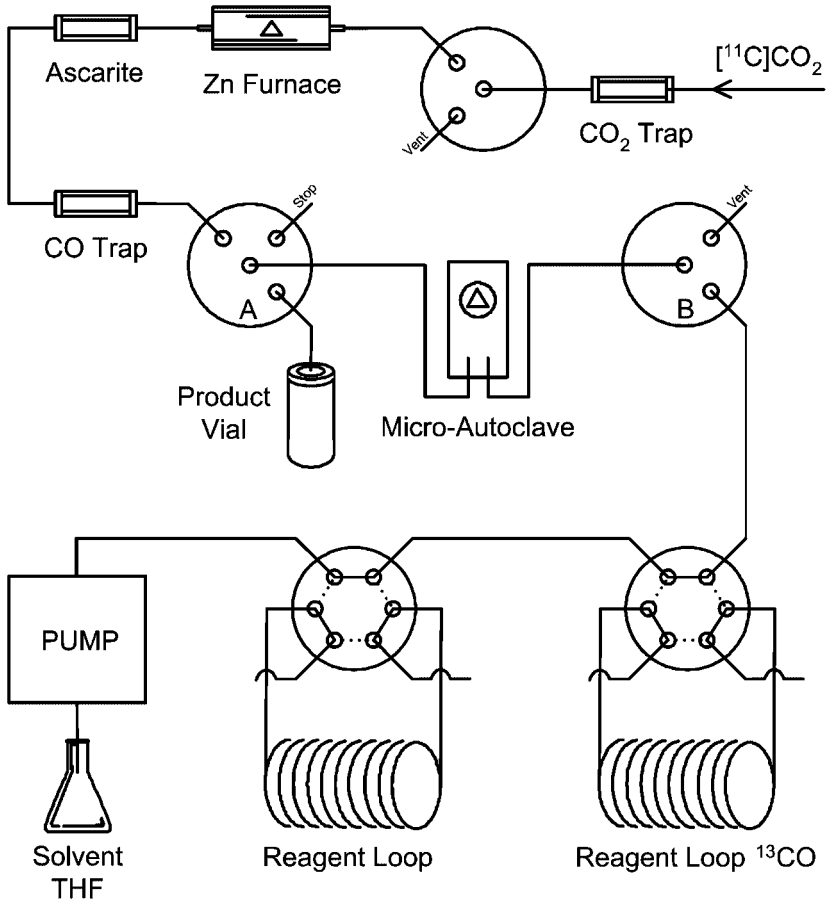


Figure 1. Schematic drawing of the experimental setup used in the carbonylation reactions

A solution of tris(dibenzylideneacetone)dipalladium(0), triphenylphosphine, methyl iodide and water in tetrahydrofuran was pumped into the micro-autoclave at a pressure of 6000 psi. The micro-autoclave was then heated and a mixture of [1-^{11}C]acetic acid and [1-^{11}C]methyl acetate was obtained. Methyl acetate was assumed to originate from the alkylation of the acetic acid with methyl iodide.

$Pd_2(dba)_3$ was used due to good air stability compared to other Pd^0-complexes and due to the ability to form complexes with PPh_3 that activate methyl iodide *via* oxidative addition. Six equivalents of PPh_3-ligands gave better reproducibility than 4 equivalents. Water was added to the carbonylation reaction to cleave off the acyl group formed by migratory insertion of [^{11}C]carbon monoxide into the methyl palladium bond. Lower radiochemical yield and low reproducibility was the result when no water was added. Hence,

it was preferred to have water present in the reaction. It seems to be beneficial to have a nucleophile present in the reaction mixture rather than directly transfer the palladium acyl-complex to the lithium aluminium hydride solution.

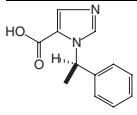
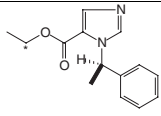
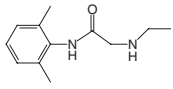
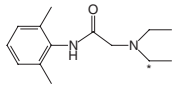
Some experiments were carried out using methanol instead of water in the carbonylation reaction. This resulted in slightly better yield but also in high amounts of methyl iodide in the final step of the synthesis. Considering the obvious competition between different alkyl halides in alkylation reactions and possible purification problems, it was desired to keep the formation of methyl iodide at the lowest possible level. Therefore we concluded that water was preferred rather than methanol as nucleophile in the carbonylation reaction.

Tetrahydrofuran was selected as the solvent in the carbonylation reaction since it facilitated good reaction conditions, both for the carbonylation reaction and the following reduction. Performing the carbonylation reaction at a lower temperature than 145°C resulted in lower radiochemical purity and yield of [1-^{11}C]ethyl iodide.

The reaction mixture was transferred from the micro-autoclave to a vial containing lithium aluminium hydride where the [1-^{11}C]acetates were reduced to [1-^{11}C]ethoxide. The conversion of [1-^{11}C]ethoxide to [1-^{11}C]ethyl iodide was performed by treatment with hydriodic acid. A closed reaction vial was used due to the volatility of [1-^{11}C]ethanol. In order to achieve good conversion of [1-^{11}C]ethoxide to [1-^{11}C]ethyl iodide it was important to thoroughly remove the tetrahydrofuran from the reaction mixture prior to the addition of the hydriodic acid. To avoid a sudden increase of pressure, the vial was cooled down to sub-zero temperature prior to the addition of the acid. The vial was heated at 120°C for 5 min during the conversion. After the reaction was completed, [1-^{11}C]ethyl iodide was transferred in a stream of nitrogen gas through a phosphorus pentoxide drying-tower to a vial containing dimethylformamide. The decay-corrected radiochemical yield of [1-^{11}C]ethyl iodide trapped in dimethylformamide was $55 \pm 5\%$ calculated from [^{11}C]CO.

Of the transferred radioactivity, [1-^{11}C]ethyl iodide accounted for 80–90% and the only by-product was [^{11}C]methyl iodide. [^{11}C]Methyl iodide was assumed to be derived from the reduction of [^{11}C]CO_2 and the subsequent iodination. Since an ascarite column efficiently trapped all unreduced CO_2 after the Zn-furnace, [^{11}C]CO_2 was assumed to be derived from the oxidation of [^{11}C]CO in the micro-autoclave. [^{11}C]CO_2 may be formed from [^{11}C]CO at the carbonylation conditions in the presence of Pd^{II} via the water-gas shift reaction[25] but also via the heterogeneous reaction with molecular oxygen on the stainless steel surface[26] of the micro-autoclave. The total amount of methyl iodide in the trap vessel typically ranged between 0.5–1.3 μmol. Most of the

Table 1.

Substrate	Product	Initial radioactivity ^{11}CO (GBq)	Yield[a] (%)	Product amount (nmol)	Specific radioactivity[b] (GBq/μmol)
		2.5 ± 0.5	45 ± 0.5	31 ± 6	8.4 ± 1.2
		7	25	15	22
		10	22	15	36
		2.2 ± 0.1	25 ± 2		

[a] Isolated decay-corrected radiochemical yield calculated from the initial amount of radioactivity used in the [1-^{11}C]ethyl iodide synthesis. When the reaction mixture was transferred from the micro-autoclave to the evacuated 2 ml vial containing lithium aluminium hydride, 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, e.g. ^{11}CO, could be determined.
[b] The radioactivity of the isolated product measured 40 min after start of carbonylation reaction.

unlabelled methyl iodide was probably derived from methoxide contained in the lithium aluminium hydride solution.

The labelled ethyl iodide was used in two model alkylation reactions, the synthesis of (R)-[*O*-ethyl-1-^{11}C]Etomidate and [*N*-ethyl-1-^{11}C]Lidocaine. The radiochemical yield and the specific radioactivity of the labelled compounds are presented in Table 1. The alkylation reactions were performed according to previously published methods.[7,8] The ethylated products were separated from the methylated by-products without difficulties using semi-preparative HPLC.

The isolated decay-corrected radiochemical yields of the ethylated products were calculated from the initial amount of radioactivity, e.g. ^{11}CO, and the radioactivity of the semi-preparative LC purified products. The specific radioactivity of the isolated (R)-[*O*-ethyl-1-^{11}C]Etomidate was determined from concentration measurements by HPLC. The standard curve was prepared using an unlabelled reference compound.

Conclusion

[1-^{11}C]Ethyl iodide was produced from [^{11}C]CO using a method which is feasible for automation. The radiochemical yield of [1-^{11}C]ethyl iodide was 55 ± 5%. Purified (R)-[*O*-ethyl-1-^{11}C]Etomidate was obtained within 40 min with a decay-corrected radiochemical yield of 45% from 2.5 GBq of ^{11}CO. When starting with 10 GBq of [^{11}C]CO, purified (R)-[*O*-ethyl-1-^{11}C]Etomidate was obtained in 40 min with a specific radioactivity of 36 GBq/μmol. [*N*-ethyl-1-^{11}C]Lidocaine was synthesized with 25% isolated decay-corrected radiochemical yield. The comparison with data published for (R)-[*O*-ethyl-1-^{11}C]Etomidate synthesized with the Grignard method[8] (6.4 GBq/μmol)

suggests that the new method give products with improved specific radioactivity. Work is in progress to expand this labelling methodology to include higher organoiodides.

Experimental

General

^{11}C was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using 17 MeV protons produced by a Scanditronix MC-17 Cyclotron at Uppsala Imanet AB. A target filled with nitrogen (AGA nitrogen 6.0) containing 0.05% oxygen (AGA oxygen 4.8) was used to produce the $[^{11}C]CO_2$. The carbonylation reactions were carried out using an experimental set-up described in detail elsewhere.[24] $[^{11}C]CO_2$ was reduced to $[^{11}C]CO$ by passage through a zinc furnace at 400°C, containing Merck zinc granules 14–50 mesh. Alltech silica gel 100/120 was used to trap and concentrate $[^{11}C]CO_2$ and $[^{11}C]CO$. Tetrahydrofuran (THF) was freshly distilled over sodium and benzophenone in a nitrogen atmosphere before use. The palladium complex was generated *in situ* from tris(dibenzylideneacetone)dipalladium and triphenylphosphine. All chemicals were purchased from Aldrich and used as received. The ^{13}C-NMR spectra were recorded using a Varian 400 MHz spectrometer. Analytical LC was performed on a Beckman system, equipped with a Beckman 126 pump, a Beckman 168 UV detector in series with a Bioscan β^+-flow count detector and a Waters Spherisorb S5 ODS1 column (250 × 4.6 mm). A Gilson 231 was used as auto injector. Semi-preparative LC was performed on a similar Beckman system equipped with a Genesis C18 120 4 µ column (250 × 10 mm). Mobile phase: A1) 0.05M ammonium formate pH 4.5; A2) 0.02M potassium dihydrogen phosphate pH 9.0; B1) acetonitrile; B2) acetonitrile/water 50/7; B3) methanol.

[1-^{11}C]Ethyliodide. Tris(dibenzylideneacetone)dipalladium(0) (0.80 mg, 0.87 µmol) and triphenylphosphine (2.7 mg, 10.3 µmol, 12 equivalent) were placed in a 0.8 ml vial equipped with a rubber septum. THF (360 µl) was added and the resulting solution was degassed with argon. Methyl iodide (1.2 µl, 19 µmol, 22 equivalent) and nanopure water (1.0 µl) was added. The solution was loaded into an injection valve loop and pumped into a 200 µl stainless steel micro-autoclave containing $[^{11}C]CO$. The micro-autoclave was heated for 5 min at 145°C. The reaction mixture was transferred to a 2 ml septum-equipped evacuated glass vial containing lithium aluminium hydride (100 µl, 1M). 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 the vial was heated for 5 min at 120°C. The vial was removed from the heating and while it was still warm [1-^{11}C]ethyl iodide was transferred in a stream of

nitrogen (20 ml/min) through a drying tower (phosphorus pentoxide desiccant) to a trapping vessel. Analytical LC was used to assess the identity and radiochemical purity. Mobile phase A1:B1 (50:50). Flow 1.0 ml min^{-1}. R.t. 8.7 min. Radiochemical yield of [1-^{11}C]ethyl iodide was $55 \pm 5\%$ with a radiochemical purity of $85 \pm 5\%$. [^{11}C]Methyl iodide was the only radiochemical by-product. R.t. 6.7 min.

(1-^{13}C)Ethyliodide. Tris(dibenzylideneacetone)dipalladium(0) (0.80 mg, 0.87 μmol) and triphenylphosphine (2.7 mg, 10.3 μmol, 12 equivalent) were placed in a 0.8 ml vial equipped with a rubber septum. THF (360 μl) was added and the resulting solution was degassed with argon. Methyl iodide (2.5 μl, 40 μmol, 22 equivalent) and nanopure water (1.0 μl) were added. The resulting solution was loaded into an injection valve loop. A second injection valve loop was filled with (^{13}C)CO (1 ml, 1 atm., 40 μmol). The reagents were pumped with THF into a 200 μl stainless steel micro-autoclave containing [^{11}C]CO. The micro-autoclave was heated for 15 min at 140°C. The reaction mixture was transferred to a 5 ml septum-equipped evacuated glass vial containing lithium aluminium hydride (150 μl, 1M). The vial was heated at 120°C for 2–3 min during the removal of THF under a stream of nitrogen. Then the vial was cooled to sub-zero temperature. Hydriodic acid (1.0 ml, 57 wt% in water) was added and the vial was heated for 10 min at 120°C. The vial was removed from the heating and while it was still warm the labelled ethyl iodide was transferred in a stream of nitrogen (20 ml/min) 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. (1-^{13}C)Ethyl iodide ^{13}C-NMR MHz ($CDCl_3$) δ: −0.79; (^{13}C)Methyl iodide ^{13}C-NMR MHz ($CDCl_3$) δ: −23.3.

(R)-[O-ethyl-1-^{11}C]Etomidate. In a 0.8 ml glass vial equipped with a rubber septum, (*R*)-3-(1-phenyl-ethyl)-3*H*-imidazole-4-carboxylic acid (1.2 mg, 5.5 μmol) was dissolved in dichloromethane (200 μl) at room temperature. Tetrabutylammonium hydroxide in methanol (4.8 μl, 1M, 4.8 μmol) was added. The vial was gently heated and the solvent was thoroughly removed under a stream of nitrogen gas. Dimethylformamide (300 μl) was added. [1-^{11}C]Ethyl iodide, prepared as described above, was transferred in a flow of nitrogen gas (20 ml/min) to the glass vial and bubbled through the solution. The vial was heated for 5 min at 120°C. The reaction mixture was injected onto a semi-preparative HPLC column and (R)-[*O*-ethyl-1-^{11}C]Etomidate was isolated. Mobile phase A1:B2 (52:48). Flow 4 ml min^{-1}. R.t 12.1 –13.5 min. Analytical LC was used to assess the identity and radiochemical purity. Mobile phase A1:B2 (45:55). Flow 1.5 ml min^{-1}. R.t. 8.4 min. Radiochemical purity >99%.

[N-ethyl-1-^{11}C]Lidocaine. In a 0.8 ml glass vial equipped with a rubber septum, des-ethyl Lidocaine (ethylaminoacet-2,6-xylidide) (2.2 mg, 11 μmol) was dissolved in 300 μl dimethylformamide. [1-^{11}C]Ethyl iodide prepared as described above was transferred in a flow of nitrogen gas (20 ml/min) to the glass vial and bubbled through the des-ethyl Lidocaine solution. The vial was heated at 130°C for 5 min.The reaction mixture was injected onto a semi-preparative HPLC column and [*N*-ethyl-1-^{11}C]Lidocaine was isolated. Mobile phase: A2:B3 (30:70). Flow 4 ml min^{-1}. R.t 10.3 – 11.9 min. Analytical LC was used to assess the identity and radiochemical purity. Mobile phase: A1:B3 (45:55). Flow 1.0 ml min^{-1}. R.t 10.2 min. Radiochemical purity >99%.

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