

Research Article

[¹¹C]Methanol production by a fast and mild aqueous-phase reduction of [¹¹C]formic acid with samarium diiodide

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Summary

The reduction of [¹¹C]carbon dioxide to [¹¹C]methanol with lithium aluminium hydride (LiAlH₄) and subsequent conversion into [¹¹C]methyl iodide is a standard way of producing the latter precursor for radiolabelling. However, it suffers from appreciable losses by incomplete reduction giving [¹¹C]formate. We show that samarium diiodide (SmI₂) can be used to improve the yield of [¹¹C]methanol by its ability to efficiently reduce [¹¹C]formate to [¹¹C]methanol. This can be done either by making [¹¹C]formate intentionally and treating it with SmI₂ or by treating the LiAlH₄-reduced [¹¹C]CO₂ with SmI₂. In the latter approach, sodium thiosulphate has a similar effect as SmI₂. Hydriodic acid was also shown to exert some reducing action on [¹¹C]formate too. [¹¹C]Carbonate is reduced to a small extent by SmI₂ under the mild conditions employed. In contrast to the very easy [¹¹C]formate reduction, SmI₂ had little effect on [¹¹C]acetate and practically no [¹¹C]ethanol could be produced. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: [¹¹C]formic acid; [¹¹C]acetic acid; [¹¹C]methanol; [¹¹C]ethanol; samarium diiodide

Introduction

Radiopharmaceutical chemistry with the short-lived radioisotope ¹¹C (half-life 20.4 min) rests for an important part on the methylating agent [¹¹C]methyl iodide^{1,2} and its derivative [¹¹C]methyl triflate.^{1,3–5} This radioactive building block is usually made by reduction of cyclotron-produced [¹¹C]carbon dioxide with lithium aluminium hydride (LiAlH₄) in tetrahydrofuran (THF) to [¹¹C]methanol, which, after hydrolysis of its organometallic complex, is then converted with hot aqueous hydriodic acid into [¹¹C]methyl iodide.² This

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robust method has been in practice successfully for many years.^{6–10} However, in our experience and in that of others, non-negligible quantities of radioactivity regularly stay behind in the reduction vial when distilling out the [¹¹C]methanol. For example, in an arbitrarily chosen series of five routine syntheses in our laboratory, this amount wildly varied between 18 and 47% (mean 27%) of the total starting radioactivity. Also, an average of 12% (6–19%) of total starting radioactivity remained in the hydriodic acid solution after [¹¹C]methyl iodide distillation. We identified these residues as [¹¹C]formate, resulting from incomplete reduction,¹¹ and then showed that [¹¹C]formate could be produced almost quantitatively from [¹¹C]carbon dioxide using the reducing agent lithium triethylhydroborate.¹²

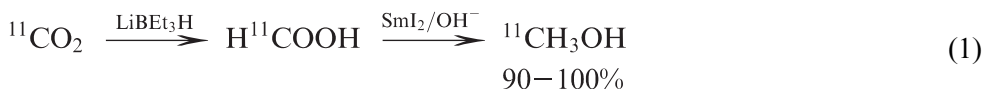
A number of higher ¹¹C-labelled alkyl iodides are available too, notably ethyl-, propyl-, butyl-, isobutyl-, and benzyl iodide,^{13–15} but these are less frequently used than [¹¹C]methyl iodide. Their synthesis proceeds via the reaction of [¹¹C]carbon dioxide with the appropriate Grignard reagent followed by reduction with LiAlH₄, at relatively high temperature, to the corresponding ¹¹C-labelled alcohol. Reaction with hydriodic acid gives the [¹¹C]alkyl iodide. An intrinsic problem of this method is the co-production of [¹¹C]methyl iodide from non-reacted [¹¹C]carbon dioxide in appreciable amounts. [¹¹C]methyl iodide is more reactive than the higher alkyl iodides and the resulting [¹¹C]methylation product has to be separated from the desired [¹¹C]alkylated product. Moreover, considerable amounts of non-radioactive methyl iodide are also formed, probably via methanol formed during the reduction step with LiAlH₄ from THF complexed with the Grignard.¹⁴ This non-labelled methyl iodide competes with the radiolabelled alkyl halide for the precursor. In an attempt to deal with these problems, a gaschromatographic purification of [¹¹C]ethyl iodide and [¹¹C]propyl iodide was proposed, however this complicated the procedure considerably.¹⁶ Recently, a synthesis of [¹¹C]ethyl iodide from [¹¹C]carbon monoxide and methyl iodide was described, however this method is also not free of labelled and unlabelled methyl iodide.¹⁷

Samarium diiodide (SmI₂) is a versatile one-electron reducing agent in organic chemistry. It has recently been shown to be able to reduce, in the presence of water and a base, a range of carboxylic acids to the corresponding alcohols under very mild conditions in extremely short reaction times.¹⁸ For example, benzoic acid was converted into benzyl alcohol by SmI₂ in aqueous sodium hydroxide at room temperature in 1 min. We reasoned that if [¹¹C]formic acid and [¹¹C]acetic acid could be reduced under the same conditions, which are very attractive for chemistry with short-lived ¹¹C, to [¹¹C]methanol and [¹¹C]ethanol, respectively, we might have a way of circumventing the various above-mentioned problems. An alternative strategy to deal with the incomplete reduction of [¹¹C]carbon dioxide to [¹¹C]methanol by LiAlH₄ could be the use, after the usual LiAlH₄ treatment, of an additional

reducing agent in the water for the hydrolysis step, such as sodium thiosulphate, sodium sulphite or again SmI₂, which could yet reduce the intermediate [¹¹C]formic acid to [¹¹C]methanol. In this context the question, that we have recently raised,¹¹ namely to what extent hydriodic acid plays a role in the overall reduction to [¹¹C]methanol, is relevant too. In the present paper we report on some preliminary results on these reactions and discuss their applicability in ¹¹C radiopharmaceutical chemistry.

Results and discussion

In their work on the reduction of carboxylic acids to the corresponding alcohols with SmI₂ in the presence of water and base, Kamochi and Kudo¹⁸ investigated benzoic acid and a number of aryl-, arylalkyl- and alkyl carboxylic acids. They reported that benzoic acid underwent a 92% conversion in 1 min at room temperature. The alkyl carboxylic acids gave lower yields than benzoic acid, but formic acid and acetic acid were not investigated. The shortest chain length in their series numbered five carbon atoms. Under our reaction conditions, that differ from those of the above authors notably by the low carboxylic acid concentration relative to the reagents, inherent in ¹¹C no-carrier-added chemistry, we found that [¹¹C]formic acid was reduced to [¹¹C]methanol equally well as the above benzoic acid, if not better (Equation (1)). [¹¹C]Formic acid was made almost quantitatively by bubbling no-carrier-added [¹¹C]carbon dioxide, contained



in helium vector gas, into lithium triethylborohydride (LiEt₃BH) in THF.¹² We tried two alternative sequences for treating the LiEt₃B–[¹¹C]formate complex:

- (1) Addition of SmI₂ (30 μmol) in THF followed by addition of aqueous NaOH (60 μmol).
- (2) Hydrolysis of the LiEt₃B–[¹¹C]formate complex with aqueous NaOH (60 μmol) followed by addition of SmI₂ (30 μmol) in THF.

After 1 min of reaction time, HPLC analysis of the mixture revealed in both cases a very high conversion into [¹¹C]methanol of more than 90% and sometimes up to 100%. When smaller amounts of NaOH and SmI₂ were used, the yields were lower. We found sequence 1 somewhat more reliable than sequence 2.

It has been suggested that this reduction reaction proceeds via a mechanism involving the carboxylate anion.¹⁸ Our [¹¹C]formic acid preparation as a LiEt₃B–[¹¹C]formate complex in an excess of LiEt₃BH/THF already provides upon hydrolysis an alkaline environment. Indeed, we found that the reduction

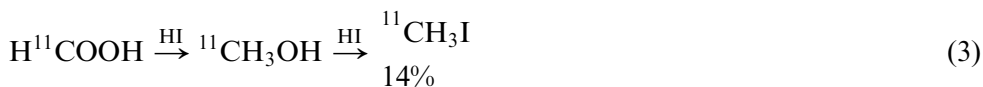
to [^{11}C]methanol also takes place when using just water instead of aqueous NaOH, but with a lower yield (64%). It was also possible (in sequence 2) to evaporate the THF after SmI_2 addition and before aqueous NaOH addition. This has the advantage of eliminating the THF in the case where one wants to distil out the [^{11}C]methanol for [^{11}C]formaldehyde synthesis, in which procedure THF can considerably lower the specific radioactivity by thermal decomposition.¹⁹ We were able to distil out [^{11}C]methanol in 83% yield.

We also investigated whether the SmI_2 reduction worked on an alkaline solution of [^{11}C]carbonate (Equation (2)). This turned out not to be a viable option under the conditions applied (room temperature, 1 min), although interestingly a conversion of 4% was achieved while no intermediate [^{11}C]formate could be detected. The latter observation is in line with our excellent [^{11}C]methanol yields when treating [^{11}C]formate with SmI_2/NaOH .



In order to see if [^{11}C]methanol, produced by SmI_2 reduction, could be easily converted into [^{11}C]methyl iodide, we took the crude reaction mixture, containing [^{11}C]methanol, up in hydriodic acid (57% in water), heated the mixture in a heating block at 170° and distilled the [^{11}C]methyl iodide out. Yields were at best a somewhat disappointing 54% relative to [^{11}C]formate. Apparently, in order to profit from the high [^{11}C]methanol yield, the latter has to be distilled out into aqueous HI.

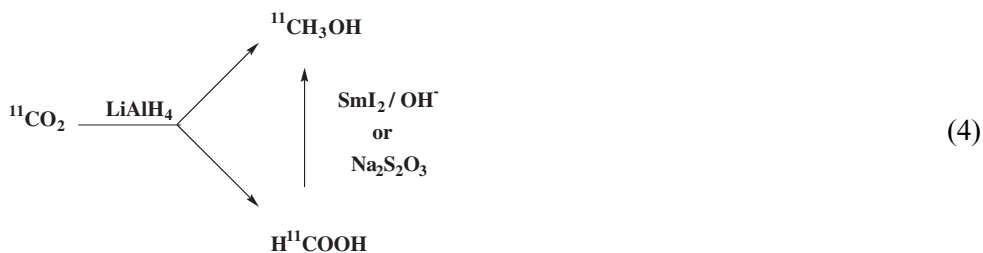
We have wondered to what extent hydriodic acid has a role in the overall reduction of [^{11}C]carbon dioxide into [^{11}C]methanol in the classical [^{11}C]methyl iodide synthesis.¹¹ To answer this question we treated [^{11}C]formate with hot hydriodic acid and were able to distil out up to 14% of [^{11}C]methyl iodide (Equation (3)). Thus we conclude that hydriodic acid probably plays a limited role in the overall reduction by taking care of a relatively small part of the [^{11}C]formate present after LiAlH_4 reduction of [^{11}C]carbon dioxide.



We conclude that the combination of LiEt_3BH and SmI_2 offers a superior reduction method of [^{11}C]carbon dioxide into [^{11}C]methanol compared to the traditional LiAlH_4 method. However, subsequent conversion into [^{11}C]methyl iodide was moderate and did not constitute an improvement relative to the classical method. Possibly, distillation of [^{11}C]methanol into preheated hydriodic acid will give better results, but this was not tried in the present work. It also has

to be noted that, from a practical point of view, SmI₂ has the important drawback of being very sensitive to air and moisture. Only solutions showing the characteristic deep-blue colour should be used. The quality of a stock solution after a first withdrawal of a small quantity tends to deteriorate quickly.

An alternative idea to overcome the problem of incomplete conversion of [¹¹C]carbon dioxide into [¹¹C]methanol by LiAlH₄ is the addition of some reducing agent to the water used in the hydrolysis step. The intermediate [¹¹C]formate would yet be reduced to [¹¹C]methanol just before and during the [¹¹C]methanol distillation step (Equation (4)).



Hydrolysis of the [¹¹C]methanolate/LiAlH₄ complex with aqueous NaOH followed by addition of SmI₂/THF resulted in an overall [¹¹C]methanol yield of 88%.

When applying the reducing agent sodium thiosulphate in diluted sulphuric acid, a very satisfactory 97% yield of [¹¹C]methanol was reached. However, some yellow solid had distilled over as well, which we believe was elemental sulphur which can be formed by disproportionation of thiosulphate to S and SO₂ in the acid milieu. When hydrolysis was performed with neutral aqueous sodium thiosulphate no sulphur was formed but a considerable amount of radioactivity could not be distilled out.

In contrast to the case of [¹¹C]formate, [¹¹C]acetate reduction to [¹¹C]ethanol with SmI₂ was unsuccessful (Equation (5)). We prepared [¹¹C]acetate by reaction of [¹¹C]carbon dioxide with methylmagnesium chloride in THF which was then treated in various ways. One approach consisted in the addition of SmI₂ in THF directly to the unhydrolyzed Grignard-[¹¹C]carbon dioxide adduct, followed



by aqueous sodium hydroxide. HPLC analysis of the mixture revealed an [¹¹C]ethanol yield of 2% only. The rest was unchanged [¹¹C]acetate. Subsequent heating and distillation (170°C heating block; helium stream) did not change this. Alternatively, no-carrier-added [¹¹C]acetate was produced with our routine synthesis apparatus²⁰ which delivers this product on an ion

exchange cartridge. Elution of this cartridge with SmI_2 in THF followed by aqueous sodium hydroxide dislodged 52% of the radioactivity which contained no $[^{11}\text{C}]$ ethanol. When the cartridge was eluted with aqueous sodium carbonate and the eluate was treated with SmI_2 in THF, no $[^{11}\text{C}]$ ethanol was found. Heating and distillation, as above, did not change this. The same SmI_2 treatment followed by addition of aqueous sodium hydroxide resulted in only a few percent of $[^{11}\text{C}]$ ethanol. Heating and distillation, as above, did not change this. Kamochi and Kudo¹⁸ reported that aliphatic acids were less reactive than aromatic ones. The shortest chain length attached to the carboxylic group that was investigated numbered five carbon atoms. We can add to their results that in the case of the one-carbon chain, the reaction does not work under our conditions while in the case of the zero-carbon chain length of formic acid, the results are excellent.

Experimental

SmI_2 (0.1 M in THF) was purchased from Aldrich, Fluka, or Strem Chemicals, France. All other chemicals were from Aldrich, France.

HPLC A: Column: Aminex HPX-87H (BioRad), 300 mm \times 7.8 mm; temperature: 44°C; mobile phase: 1 mM sulphuric acid in water; flow rate: 0.6 ml/min; detection: Geiger–Müller radiation detector and differential refractive-index detector; retention times (peak summits): formic acid: 13.9 min, acetic acid: 15.0 min, methanol: 19.5 min, ethanol: 21.8 min.

HPLC B: Column: Xterra MS C18, 7 μm , 300 mm \times 7.8 mm; temperature: ambient; mobile phase: MeOH/H₂O 1/1; flow rate: 5 ml/min; detection: Geiger–Müller radiation detector and UV-absorbance detector at 254 nm; retention times: formic acid: 2.0 min, methanol: 2.0 min, methyl iodide: 5.8 min.

$[^{11}\text{C}]$ Carbon dioxide

No-carrier-added $[^{11}\text{C}]$ carbon dioxide was produced using the nuclear reaction $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ by irradiation of a pressurized nitrogen gas target (20 bar) with a cyclotron-generated 18 MeV proton beam.² A current of 10 μA during 30 s gave rise to about 30 mCi (1.11 GBq) of radioactive carbon dioxide. After irradiation, the radioactive gas was released from the target holder through a drying column (20 mm \times 8 mm) filled with phosphorus pentoxide. The $[^{11}\text{C}]$ carbon dioxide was frozen out in a liquid-argon-cooled stainless-steel coil placed in a shielded hot cell. All further radioactivity manipulations were performed in the hot cell.

$[^{11}\text{C}]$ Formate

A conical reaction vial (1 ml), equipped with a septum holding an inlet and an outlet needle and containing a dry helium atmosphere, was charged with dry

THF (50 μl) and LiEt_3BH (1 M in THF, 10 μl) and cooled in an ethanol/ice mixture. No-carrier-added [^{11}C]carbon dioxide (see above) was released from the liquid-argon-cooled trap by warming up the latter to room temperature. A helium gas stream, dried by passage through a phosphorus pentoxide drying column (20 mm \times 8 mm), swept it along into the LiEt_3BH solution via the inlet needle. When the radioactivity accumulation in the vial, measured by a proximate ionization-chamber probe, had levelled, the reaction mixture, containing the LiEt_3B -[^{11}C]formate complex, was either hydrolyzed or treated with SmI_2 (see below). The formation of [^{11}C]formate was verified in separate experiments by way of HPLC, system A.

[^{11}C]Methanol via [^{11}C]formate using SmI_2

Method A: SmI_2 (0.1 M in THF, 300 μl) was added to the above LiEt_3B -[^{11}C]formate complex in THF, while briefly bubbling helium gas through the mixture via the inlet needle assured homogeneity. Immediately thereafter, aqueous NaOH (0.2 N, 300 μl) was added and the reaction vial was lifted out of the cooling bath and left to stand for 1 min. The reaction mixture, now containing [^{11}C]methanol, was either used as such for [^{11}C]methyl iodide synthesis or distilled out and swept along by a helium carrier gas stream and trapped in water at 0°C (2 \times 0.5 ml in series) for HPLC analysis (system A) and radiochemical yield determination.

Method B: As in method A, but with inversed order of aqueous NaOH and SmI_2 (THF) addition.

[^{11}C]Methyl iodide from [^{11}C]methanol produced from [^{11}C]formate

To the above alkaline solution of [^{11}C]methanol was added aqueous hydriodic acid (57%, 1 ml) which had been discoloured by treatment with some silver powder. The mixture was then transferred to a second vessel sitting in a heating block (170°C). After 2 min of heating, a helium gas stream was bubbled through, while heating was continued, carrying the formed [^{11}C]methyl iodide away. It was passed through a glass tube (70 mm \times 4 mm) filled with equal and separated quantities of phosphorus pentoxide and soda lime and finally bubbled into two vials in series each containing 0.5 ml of *N,N*-dimethylformamide (DMF), cooled in an ice/ethanol mixture. The radioactivity in all vials was measured for radiochemical yield determination and the contents were analyzed with HPLC, system B.

[^{11}C]Methyl iodide from [^{11}C]formate and hydriodic acid

LiEt_3B -[^{11}C]formate complex was produced as above. The THF was evaporated by using a helium stream while heating the vial in a heating block at 70°C. Hydriodic acid (57% in water, 1 ml) was added and the mixture was

transferred into a second vial, preheated in a heating block (170°C). The mixture was heated up in the heating block for 2 min. Then [^{11}C]methyl iodide was swept out of the solution with a helium stream (20 ml/min) into two vials in series, cooled in an ethanol/ice bath, each containing DMF (0.5 ml). Radioactivity was measured in all vials for radiochemical yield determination and the product was analyzed with HPLC, system B.

[^{11}C]Methanol from [^{11}C]carbon dioxide using LiAlH_4 and SmI_2

A conical reaction vial (1 ml), equipped with a septum, holding an inlet and an outlet needle and containing a dry helium atmosphere, was charged with dry THF (50 μl) and LiAlH_4 (1 M in THF, 5 μl) and cooled in an ethanol/ice mixture. No-carrier-added [^{11}C]carbon dioxide (see above) was released from the liquid-argon-cooled trap by warming up the latter to room temperature. A helium gas stream, dried by passage through a phosphorus pentoxide drying column (20 mm \times 8 mm), swept it along into the LiAlH_4 solution via the inlet needle. When the radioactivity accumulation in the vial, measured by a proximate ionization-chamber probe, had levelled, the vial was placed in a heating block (170°C) and the THF was evaporated with a helium stream. After cooling to ambient temperature the LiAlH_3 -[^{11}C]formate complex was treated with aqueous NaOH (0.2 N, 100 μl). A helium stream was set bubbling through (4 ml/min) and SmI_2 (0.1 M in THF, 100 μl) was added, the gas stream homogenizing the mixture. After 1 min at room temperature, the vial was placed in the heating block (170°C), and the gas flow was increased to 20 ml/min, distilling out the [^{11}C]methanol and bubbling into water cooled at 0°C (2 \times 0.5 ml in series). Radioactivity was measured in all vials for radiochemical yield determination and the contents of the water were analyzed with HPLC, system A.

[^{11}C]Methanol from [^{11}C]carbon dioxide using LiAlH_4 and sodium thiosulphate

The procedure is the same as the preceding one, replacing the aqueous NaOH and SmI_2 (THF) additions by a single addition of either acidic sodium thiosulphate (1 M in 2 M H_2SO_4 , freshly prepared: slight sulphur precipitation) or neutral aqueous sodium thiosulphate (1 M).

[^{11}C]Methanol from [^{11}C]carbonate and SmI_2

No-carrier-added [^{11}C]carbon dioxide (see above) was released from the liquid-argon-cooled trap by warming up the latter to room temperature. A helium gas stream (20 ml/min), dried by passage through a phosphorus pentoxide drying column (20 mm \times 8 mm), swept it along into aqueous NaOH (0.1 N, 100 μl) at room temperature. The gas stream was reduced to 4 ml/min

and SmI_2 (0.1 M in THF, 100 μl) was added while the gas stream was directed towards a vessel containing 1 ml of water at 0°C . After 1 min at room temperature, the mixture was placed in a heating block and the [^{11}C]methanol was distilled into the water (gas flow 50 ml/min). Radioactivity was measured in both vials for radiochemical yield determination and analyzed with HPLC, system A.

Attempted [^{11}C]ethanol synthesis from [^{11}C]acetate Method A

No-carrier-added [^{11}C]carbon dioxide (see above) was released from the liquid-argon-cooled trap by warming up the latter to room temperature. A helium gas stream, dried by passage through a phosphorus pentoxide drying column (20 mm \times 8 mm), swept it along into a solution of methylmagnesium chloride (15 μmol) in THF (100 μl) at room temperature. Two minutes after completion of radioactivity accumulation SmI_2 (30 μmol) in THF (300 μl) was added and mixed with the solution by briefly bubbling through some helium, followed by addition of aqueous NaOH (0.25 N, 300 μl). After 1 min at room temperature, radioactivity was measured and a sample was taken for HPLC analysis (system A). The mixture was then heated in a heating block (170°C) while sweeping out radioactivity with a helium stream into two vials in series, each containing 0.5 ml of water. Finally, the contents of these vials were analyzed by HPLC (system A).

Method B: No-carrier-added [^{11}C]acetate was produced using our routine [^{11}C]acetate synthesis apparatus²⁰ which delivers this product on an anion exchange cartridge (Chromfix[®] PS-OH). Instead of the habitual elution with citrate buffer, the radioactivity was eluted from the cartridge with aqueous Na_2CO_3 (0.2 N) in two fractions of 300 μl . One fraction was treated as such with SmI_2/THF (30 μmol , 300 μl) and to the other fraction was added NaOH (0.2 N, 300 μl) before treatment with SmI_2/THF (30 μmol , 300 μl). Alternatively, the cartridge was eluted with SmI_2/THF (30 μmol , 300 μl) and the eluate was treated with NaOH (0.2 N, 300 μl) for 1 min.

Conclusion

Samarium diiodide (SmI_2) can be used to improve the yield of [^{11}C]methanol by its ability to efficiently reduce [^{11}C]formate to [^{11}C]methanol. This can be done either by making [^{11}C]formate intentionally and treating it with SmI_2 or by treating the LiAlH_4 -reduced [^{11}C]carbon dioxide with SmI_2 . In the latter approach, sodium thiosulphate has a similar effect as SmI_2 . Hydriodic acid was shown to exert some reducing action on [^{11}C]formate too. [^{11}C]Carbonate is reduced to a small extent by SmI_2 under the very mild conditions employed. In contrast to the very easy [^{11}C]formate reduction, SmI_2 had very little effect on [^{11}C]acetate and practically no [^{11}C]ethanol could be produced.

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