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Research Article

A practical laboratory route to the synthesis of trideuteriomethyl-[^{13}C] iodide

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Summary

A practical synthetic laboratory route for the synthesis of trideuteriomethyl-[^{13}C] iodide ($^{13}CD_3I$) (from tetradeuterio-[^{13}C]-methanol and hydriodic acid) is described. We comment on the experimental protocol, and the use of water as an 'additive' to improve the synthetic yield. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: Deuterium; Carbon-13 and Trideuterio-[^{13}C]-methyl iodide

The incorporation of a multi-[D, ^{13}C]-labelled methyl substituents within an organic molecule is very well documented.[1] The most common strategy has relied on carbon–carbon bond forming processes involving direct addition of the labelled methyl group motif.[2] This methodology has been conducted in two ways; through the use of a nucleophilic labelled methyl source,[3] such as a Grignard reagent[4] (e.g. $^{13}CH_3MgI$) or by using the complementary electrophilic source, such as an alkyl halide (e.g. $^{13}CH_3I$).[5] In practise, both strategies can rely on the use of the same alkyl halide starting precursor. A pivotal component of this methodology is in the synthesis of the required labelled methyl iodide, which is generally synthesized from the corresponding alcohol.[6]

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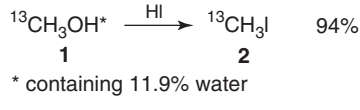
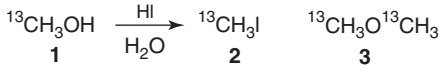
Methyl iodide is one of the more challenging alkyl halides to synthesise due to its volatile and electrophilic nature. Unlabelled methyl iodide is relatively inexpensive and is available in multi-kilogram quantities. Many of these available protocols are understandably large scale due to readily available cheap starting precursors. However, when dealing with high value isotopically labelled systems, such as tetradeuterio-[^{13}C]-methanol ($^{13}CD_3OD$), the situation is different; the reactions are generally performed on a smaller scale, and must be reproducible.

We now report a reliable and experimentally simple synthetic protocol for the synthesis of [^{13}C]-methyl iodide ($^{13}CH_3I$) **2** and trideuterio-[^{13}C]-methyl iodide ($^{13}CD_3I$) **5** derived from [^{13}C]-methanol **1** and tetradeuterio-[^{13}C]-methanol **4**, respectively, by simple addition of hydriodic acid (HI). We had initially attempted to synthesize the slightly cheaper variant, [^{13}C]-methyl iodide **2** using Ott's previously reported protocol;[8] by addition of a solution of [^{13}C]-methanol **1** containing 11.9% water to a cooled hydriodic acid solution (57% solution in water), followed by heating for 4 h (by raising the temperature to initially 70°C), then up to 85°C (for several hours) and collecting the distillate, [^{13}C]-methyl iodide **2** in 94% yield using a dry ice cooled trap (Scheme 1). However, we found following this protocol with spectroscopically pure [^{13}C]-labelled methanol **1** (99.9% purity) and hydriodic acid (99.99% purity, 57 wt % in water) gave very little [^{13}C]-methyl iodide **2** (yield $<5\%$ – Scheme 2: Entry 1) and no recovered



Scheme 1.



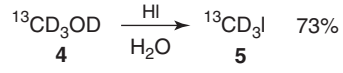
Entry	H_2O	Yield
1	0 wt %	<5%
2	50 wt %	70%
3	60 wt %	74%
4	80 wt %	76%
5	100 wt %	85%

Scheme 2.

[^{13}C]-methanol **1** (determined by ^{1}H and ^{13}C NMR spectroscopy) (Scheme 2). We believe this suggests that under our slightly modified conditions, the reaction must evidently proceed *via* formation of the unwanted and much more volatile dimethyl-[^{13}C] ether **3** (b.p. -25°C). Formation of dimethyl ether under related acidic conditions is well documented.[8] It is particularly interesting to note that Ott's specified[9] the use of a solution of [^{13}C]-methanol which contained 11.9% water. We were unsure about the reason why the water content in the solution of [^{13}C]-methanol **1** was specified so accurately (approximately 16 mol%), when considering the amount of water present within the aqueous solution of hydriodic acid (57 wt % in water).

We were surprised to find that the success of this reaction did hinge on an additional amount of water being added. We probed this procedure by pre-adding water to a fresh solution of [^{13}C]-labelled methanol **1** (50–100 wt% – Scheme 2: entries 2–5) and repeating Ott's original procedure. The additional water is crucial for the outcome of this reaction; in short, the more present, the better the overall yield of [^{13}C]-methyl iodide **2** (Scheme 2). The unaccounted loss of [^{13}C]-methanol is presumably due to competitive formation of volatile dimethyl-[^{13}C] ether **3**. We next investigated the synthesis of the more valuable trideuterio-[^{13}C]-methyl iodide **5** using our optimized procedure; addition of tetradeuteriomethyl-[^{13}C]-methanol **4** (Scheme 3) to a solution of 100 wt% of water, followed by the addition of a solution of hydriodic acid (57% in water) gave the required trideuterio-[^{13}C]-methyl iodide **5** in 73% yield (after distillation). The product was pure–determined by ^{13}C NMR spectroscopy, and was subsequently stored in a sealed ampoule over a copper shot. This sample was shown to be stable and the purity remained constant over the course of a year.[9]

In conclusion, we have probed the synthesis of [^{13}C]-methyl iodide **2** (derived from [^{13}C]-methanol **1** and hydriodic acid) and have shown that the reaction is dependent on the additional presence of water within the reaction mixture. We have extended this protocol by synthesizing the more valuable trideuterio-[^{13}C]-methyl iodide **5** in 73% yield from tetradeuterio-[^{13}C]-methanol **4**. The effect of adding water to the reaction mixture to promote formation of labelled methyl iodide is



Scheme 3.

complex. We presume the presence of water lowers the relative rate of formation of dimethyl ether **3**, by a combination of lowering the relative concentration of methanol and by making the hydriodic acid solution less dehydrating.

Previous attempts at synthesizing [^{13}C]-methyl iodide using related procedures have shown a variety of yields, ranging from 62% to 94%.[10] This variation in yield may be due to the volatility of dimethyl-[^{13}C]-iodide,[7] but more than likely is a result of competitive dimethyl-[^{13}C]-ether formation due to the quality of hydriodic acid used. This side reaction appears to have been kept to a minimum within the synthesis of short-lived [^{11}C]-methyl iodide[11] by continuous removal using a carrier gas (typically N_2)[12] or by conducting the reaction on a pre-adsorbed Al_2O_3-hydriodic acid column.[13] Alternatively, preparation using a phosphorus/iodine method has been documented, but the apparatus and procedure have been shown to be more complex.[14]

Procedure for the synthesis of trideuterio-[^{13}C]-methyl iodide **5**: Water (5.0 g, 5.0 ml, 0.27 mol) was added to a stirred solution of tetradeuterio-[^{13}C]-methanol **4** (5 g, 4.2 ml, 0.135 mol) in a 100 ml single neck round bottom flask. Hydriodic acid (50 ml, 99.99% purity, 57 wt% in water) was slowly added, and a micro-distillation apparatus fitted. The resulting solution was heated to 40°C and stirred for 2 h. The temperature of the reaction mixture was increased gradually by 5°C every 30 min until the temperature of the oil bath reached 80°C. At this point trideuterio-[^{13}C]-methyl iodide was collected using a 50 ml round bottom flask which was permanently cooled to −84°C using an ethyl acetate–liquid nitrogen bath. The temperature of the reaction mixture (inside the vessel) remained at 40°C. This distillation procedure was carried out (over 6–8 h) under a sealed nitrogen atmosphere using a balloon of nitrogen to give the trideuterio-[^{13}C]-methyl iodide **5** (14.3 g, 73%) as a colourless liquid.

Procedure for the synthesis of [^{13}C]-methyl iodide **2**: In the same way as above, [^{13}C]-methanol **1** (5 g, 4.8 ml, 0.151 mol), water (5 g, 5 ml, 0.27 mol) and hydriodic acid (50 ml, 99.99% purity, 57 wt% in water) gave, after distillation [^{13}C]-methyl iodide **2** (18.4 g, 85%) as a colourless liquid.

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