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Research Article

An efficient synthesis of sodium dimethylarsinate-^{14}C

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Summary

A short and efficient synthesis of sodium dimethylarsinate-^{14}C is described. Incorporation of the label has been achieved by methylation of methyldiiodoarsine with iodomethane-^{14}C. Product was precipitated and separated from sodium iodide by washing with acetone. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: iodomethane-^{14}C; methyldiiodoarsine; sodium dimethylarsinate-^{14}C

Introduction

Interest in the metabolism of inorganic arsenic in humans has recently increased because inorganic arsenic is a known human carcinogen[1] and because As_2O_3 is effective in the treatment of acute promyelocytic leukemia.[2] Ingestion of inorganic arsenate/arsenite by humans results in

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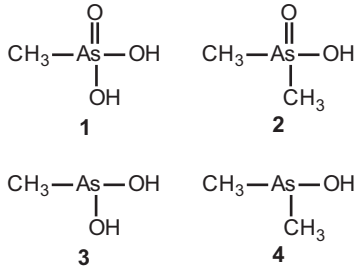
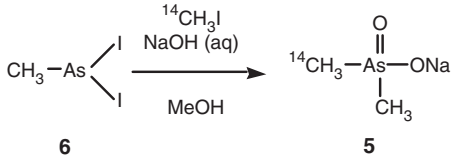
the excretion of arsenic in the urine. Of the total urinary arsenic, ~ 10% is inorganic arsenic, ~ 20% is monomethylarsonic acid (MMA^V, **1**) and about ~ 70% is dimethylarsinic acid (DMA^V, **2**).[3] Studies of urinary arsenic did not use analytical procedures specific enough to detect newly recognized arsenic species of the +3 oxidation state, such as monomethylarsonous acid (MMA^{III}, **3**) and dimethylarsinous acid (DMA^{III}, **4**).[4] Although in the past, the methylation of inorganic arsenic in the body was believed to be a detoxication process, this is no longer accepted by most investigators.[5] In addition, whether one or more of the arsenic species found in urine are carcinogenic is unknown. There has been considerable interest in the carcinogenic potential of DMA^V,[6] but only limited studies have been performed with radioactively labeled DMA^V-^{14}C.[7] Because of increasing concern about the importance of DMA^{III}, its distribution in the body, and its role in arsenic metabolism, we have synthesized DMA^V-^{14}C (**2**) as the sodium salt as depicted in the Scheme and described herein. This labeled compound will be used as a marker for various analytical chromatographic procedures and to study its metabolic distribution and fate in mammals, especially its possible conversion to DMA^{III}.



There are only two methods to prepare sodium dimethylarsinate (**5**) given in the literature. The first method involves treatment of methylarsine oxide[8] with sodium hydroxide and iodomethane. The disadvantage of this method is the tedious workup needed to isolate the product from sodium iodide, which is formed as a byproduct. In the second method methyldiiodoarsine (**6**)[9] is treated with sodium hydroxide and iodomethane to give a mixture of **5** and sodium iodide. However, **5** was not isolated in this procedure since it was used as an intermediate in the synthesis of dimethyliodoarsine.[9]

Results and discussion

Keeping the above facts in mind, we developed and executed the synthesis of sodium dimethylarsinate-^{14}C. We first optimized the synthesis of non-radioactive sodium dimethylarsinate on a micromolar scale. Thus, methyldiiodoarsine (**6**) was dissolved in methanol and was treated with an aqueous solution of sodium hydroxide at room temperature. Subsequently, iodomethane was added to the reaction mixture which was stirred vigorously for 72 h. Upon addition of acetone to the reaction mixture sodium dimethylarsinate (**5**) precipitated as a white solid. Acetone was used for two reasons. First, **5** would precipitate out since it is insoluble in acetone, and second, the product would be free of sodium iodide which is soluble in acetone. The liquid phase was decanted and the white solid was repeatedly washed with acetone and dried in air. The product was identified from its ^{1}H-NMR and mass spectra. The ^{1}H-NMR spectrum showed a peak at δ 1.51 corresponding to the methyl groups. The ESI(+) mass spectrum showed peaks at 139.0 and 160.9 corresponding to MH^+ and MNa^+ ions. The spectral features were identical with those of an authentic sample of **5** purchased from Aldrich Chemical Company. Likewise, sodium dimethylarsinate-^{14}C was prepared from **6** and iodomethane-^{14}C as described in the experimental section and depicted in scheme 1.



6 **5**

Scheme 1.

Experimental

Materials

Methyldiiodoarsine was prepared by a literature procedure.[10] Iodomethane-^{14}C was purchased as a methanolic solution (5 mCi, specific activity 54 mCi/mmol, in 50 μL of methanol) from American Radiolabeled Chemicals, Inc., USA.

Methods

^{1}H-NMR spectra were obtained at 500 MHz using a Bruker DRX-500 spectrometer and were referenced to residual HOD in D_2O solvent (4.70 ppm). Mass spectra were acquired using a Finnigan LCQ ion trap mass spectrometer equipped with an ESI source in positive ion mode. Samples were introduced with a syringe pump. The solvent system was 1:1 water:ethanol.

Sodium dimethylarsinate-^{14}C

To a solution of methyldiiodoarsine (**6**, 31.8 mg, 92.6 μmol) in methanol (100 μl) in a 1 dram vial was added 10 N NaOH (37 μL, 370 μmol) followed by iodomethane-^{14}C (5 mCi, specific activity 54 mCi/mmol, 92.6 μmol, in 50 μL of methanol). The vial was closed with a Teflon-lined screw cap and the mixture stirred vigorously for 72 h at room temperature. The reaction mixture was then transferred to a small culture tube. Acetone (8 mL) was added to precipitate a white solid. The liquid phase was decanted, fresh acetone was added, and the suspension was agitated using a vortex mixer, followed by centrifugation. This washing process was repeated two more times. The solid left after the final decantation was dried under vacuum. The yield of sodium dimethylarsinate-^{14}C was 11.3 mg (70 μmol, 76%, 3.81 mCi).

Conclusion

We have developed a facile and efficient synthesis of sodium dimethylarsinate-^{14}C starting from methyldiiodoarsine and iodomethane-^{14}C. To the best of our knowledge this is the first reported synthesis of sodium dimethylarsinate-^{14}C. The efficiency and conciseness of the procedure are its salient features.

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