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Research Article

A rapid microwave assisted synthesis of [U-^{14}C]isosorbide and Dimethyl[U-^{14}C]isosorbide from D-[U-^{14}C]glucose

K. M. Mathew*, S. Ravi, D. Padmanabhan, V. K. P. Unny and N. Sivaprasad
Labelled Compounds Radiopharmaceuticals, Immunoassay, Labelled Compounds and Jonaki Board of Radiation and Isotope Technology, BARC Vashi Complex, Navi Mumbai 400705, India

Summary

[U-^{14}C]Isosorbide and [U-^{14}C]dimethyl isosorbide with a specific activity of 462 MBq/mmol was prepared from D-[U-^{14}C]glucose, in an overall yield of 79%, under microwave heating conditions. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: D-[U-^{14}C]glucose; [U-^{14}C]isosorbide; dimethyl[U-^{14}C]isosorbide

Introduction

Isosorbide is a key synthetic intermediate for the synthesis of (i) perfluoroalkylated monoesters used as new surfactants in biomedical application,[1] (ii) mono and dinitro isosorbide,[2] (iii) monobenzylated[3] and octylated isosorbide[4] (iv) chiral auxiliary for the asymmetric synthesis[5] and (v) dimethyl isosorbide.[6] The ^{14}C-labelled analogues of these compounds are required to study their mode of action and usefulness. For this purpose, a suitable method was developed for its preparation and the procedure was standardized using microwave heating technique.

In recent times, microwave (MW) induced organic reaction enhancement (MORE) chemistry has taken an undeniable place in chemical laboratory practice as a very effective method of activating reactions. Microwave heating is especially useful for reactions using radioisotopes because of its capability to bring about significant decrease in the reaction time which often results in substantial increase of the radiochemical yield. Examples of the use of this technology in organic synthesis are numerous.[7] Better yields of products are

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*Correspondence to: K. M. Mathew, Labelled Compounds Radiopharmaceuticals, Immunoassay, Labelled Compounds and Jonaki Board of Radiation and Isotope Technology, BARC Vashi Complex, Navi Mumbai 400705, India. Email: lcbrit@rediffmail.com

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obtained when compared to those obtained with conventional heating under the same conditions, in spite of similar profiles of rise in temperature.

Results and discussion

In our approach D-[U-^{14}C]glucose **1** was quantitatively converted to D-[U-^{14}C] sorbitol **2** by sodium borohydride reduction under microwave[†] (1300 W) heating for 2 min. Alternatively, D-[U-^{14}C]sorbitol was also prepared by simple mixing of D-[U-^{14}C]glucose with (10%) $NaBH_4$–alumina in solid state and heating the mixture in an alumina bath for 40 s using a domestic microwave oven (520 W). The product formation was confirmed by TLC and also by the absence of bands at $2725\,cm^{-1}$ and $1700\,cm^{-1}$ due to aldehydic group in IR spectra. Optical rotation values further confirmed the formation. The acid catalyzed dehydration of D-[U-^{14}C]sorbitol under microwave heating for 3 min yielded [U-^{14}C]isosorbide **3**. TLC (silica, ethyl acetate: methanol 5:1). R_f for D-sorbitol was found to be 0.25 and for isosorbide 0.5. Optical rotation was observed to be $[\alpha]_{D^{30}} + 44^\circ$ (H_2O) . This on methylation with methyl iodide in presence of a phase transfer catalyst tetrabutylammonium bromide (TBAB) under microwave (520 W) irradiation for 4 min (8 × 30 s) yielded [U-^{14}C] dimethyl isosorbide **4** in an overall yield of 79% starting from D-[U-^{14}C]glucose. TLC (silica, ethyl acetate: methanol 5:1). The R_f for dimethyl isosorbide was 0.8 and for isosorbide 0.5. Optical rotation was found to be $[\alpha]_{D^{30}} + 96^\circ$ (C2, $CHCl_3$). It was further confirmed by HPLC analysis and by comparison with the authentic sample. The results obtained were found to be in good agreement (dimethyl isosorbide eluted out at R_f 1.95 min, and isosorbide at 3.5 min) (Scheme 1).

Thus the microwave irradiation technique has been efficiently employed for the radiosynthesis of [U-^{14}C]dimethyl isosorbide **4** in an overall yield of 79% starting from D-[U-^{14}C]glucose.

Experimental

D-*[U-^{14}C]Sorbitol* (**2**). A mixture of D-[U-^{14}C]glucose **1** (0.2 mmol, 36 mg, specific activity 462 MBq/mmol), sodium borohydride (9.5 mg, 0.25 mmol), Dowex 1 × 8 anion exchange resin (10 mg, Cl^- form, 100–200 mesh) and THF (500 μl) was heated in a borosilicate glass tube using a domestic microwave oven (BPL make with different power setting) (1300 W,) for 2 min (4 × 30 s). The reaction mixture was then de-ionized by passing through a column containing a mixture of Dowex 1 × 8 (OH^-, 50–100 mesh) and Dowex 50 × 8 (H^+, 50–100 mesh). The eluate was rotary evaporated several times with

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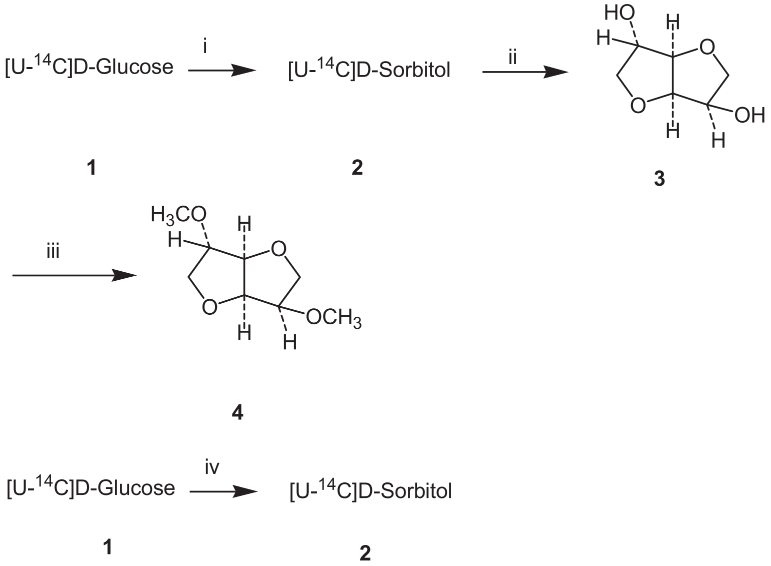
[†] The domestic microwave oven (LG make, model MS 257PL) with variable power setting was used through the experiment.



Scheme 1. (i) $NaBH_4$/Dowex 1 × 8, MW; (ii) H_2SO_4, Undecane, MW; (iii) CH_3I, KOH, TBAB, MW; (iv) Alumina-$NaBH_4$, MW

methanol to give D-[U-^{14}C]sorbitol in quantitative yield. The reaction mixture was analyzed by TLC followed by radiochromatogram scanning.

TLC (silica, isopropanol: benzene: water 20:1:1). R_f for D-glucose was found to be 0.5 and for D-sorbitol 0.35. Optical rotation was observed to be $[\alpha]_{D^{25}} - 2.2^\circ$ (H_2O) (Reported $[\alpha]_{D^{20}} - 2.0^\circ$ (H_2O))[8].

Alternate method

D-*[U-^{14}C]Sorbitol* (**2**). Freshly prepared $NaBH_4$–alumina[‡] (54 mg, 0.168 mmol $NaBH_4$) was thoroughly mixed with D-[U-^{14}C]-glucose (30 mg, 0.166 mmol, specific activity 462 MBq/mmol) in a test tube and placed in an alumina bath (see footnote ‡) inside the microwave oven (520 W) and irradiated for 40 s. Water was added to the reaction mixture and filtered. The filtrate was concentrated to give quantitative yield of D-[U-^{14}C]sorbitol. The reaction mixture was analyzed as above.

[U-^{14}C]Isosorbide (**3**). A mixture of D-[U-^{14}C]sorbitol **2** (34 mg, 0.2 mmol, specific activity 462 MBq/mmol), sulfuric acid (5 µl) and undecane (500 µl) was heated in a domestic microwave (1300 W) oven for 3 min (6 × 30 s). The reaction mixture was then de-ionized by passing through a column of anion

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[‡] 10% Sodium borohydride supported on alumina was prepared by mixing alumina (5 g) thoroughly with sodium borohydride (0.565 g) using a pestle and mortar. Alumina bath (50 g in 100 ml breaker) was used for the uniform heating of the reaction mixture, thereby preventing its charring.

exchange resin (Dowex 1 × 8, OH^-) and the eluate was concentrated under reduced pressure. It was purified by column chromatography (silica, ethyl acetate: methanol, 5:1). The product was analyzed by TLC followed by radiochromatogram scanning.

TLC (silica, ethyl acetate: methanol 5:1). R_f for D-sorbitol was found to be 0.25 and for isosorbide 0.5. Optical rotation $[\alpha]_{D^{25}} + 45^\circ$ (C3, H_2O) (reported value +44°).[8] Yield >80%.

[U-^{14}C]Dimethyl isosorbide (**4**). [U-^{14}C]Isosorbide (0.067 mmol, 9.78 mg, specific activity 462 MBq/mmol), methyl iodide (0.2 mmol,12.5 μl), TBAB (3 mg), powdered KOH (0.12 g, 0.23 mmol) and undecane (300 μl) were taken in a borosilicate glass ampoule and was sealed. The reaction mixture was then homogenized and submitted to microwave irradiation using a domestic microwave oven (520 W) for 6 min (30 s × 12). It was cooled to room temperature and the contents dissolved in methylene chloride. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The pure products were isolated by column chromatography (silica, ethyl acetate: methanol, 5:1) and analyzed by TLC (silica, ethyl acetate: methanol 5:1). R_f for dimethyl isosorbide was found to be 0.8 and for isosorbide 0.5. Optical rotation: $[\alpha]_{D^{30}} + 96^\circ$ (C2, $CHCl_3$).[§] Yield: 99%.

HPLC (mobile phase: acetonitrile, Column ODS (SS Exsil(SGE), 4 mm × 250 mm)5 μ, detector UV 210 nm, flow rate 1 ml/min). The retention time for dimethyl isosorbide and isosorbide was 1.95 and 3.5 min respectively.

The fraction corresponding to the dimethyl isosorbide was collected and assayed by liquid scintillation counter for radioactive content. (A product having radioactivity 10 000 dpm was injected and the fraction at R_t 1.95 contained 9870 dpm). Radiochemical purity was 98.70%.

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[§] The authentic sample was obtained from M/s Sigma-Aldrich Fine Chemicals.

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