Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 12

S-Adenosyl-L-(1-^{14}C)-homocysteine

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SUMMARY

S-Adenosyl-L-(1-^{14}C)-homocysteine (3) was prepared from commercially available L-(1-^{14}C)-methionine (1) by conversion first to S-benzyl-L-(1-^{14}C)-homocysteine (2), which upon treatment with sodium in liquid ammonia gave the disodium salt of L-(1-^{14}C)-homocysteine. Reaction of this sodium salt with 5'-O-tosyladenosine gave 3.

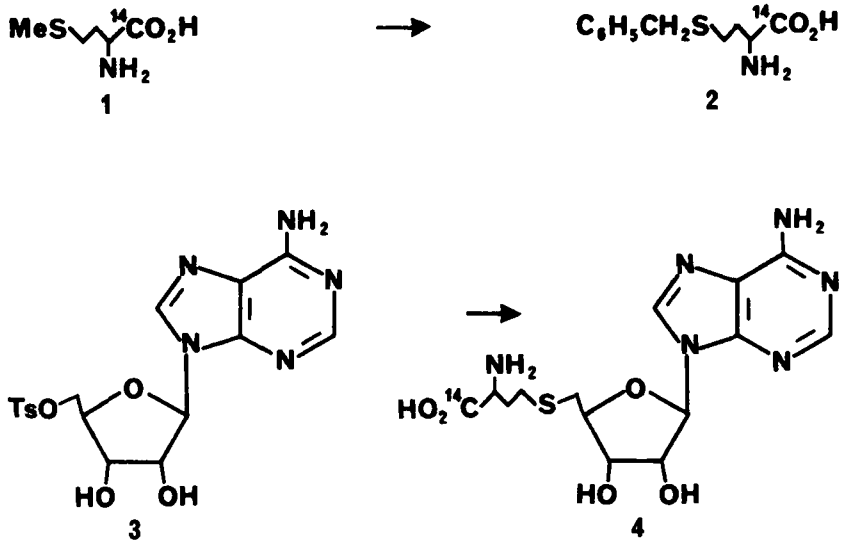
Key words: L-(1-^{14}C)-Methionine, S-Benzyl-L-(1-^{14}C)-homocysteine, S-Adenosyl-L-(1-^{14}C)-homocysteine, Labeled Nucleoside.

INTRODUCTION

S-Adenosylmethionine is known to be a methyl donor in many reactions of physiological importance, and S-adenosylhomocysteine is a by-product of these methyl transfer reactions.[1] Since labeled S-adenosylhomocysteine (4) was needed for studies on the biochemistry of S-adenosylmethionine, we have developed a simple synthesis of this compound from commercially available L-(1-^{14}C)methionine (1). This compound (1) was converted to S-benzyl-L-(1-^{14}C)-homocysteine (2) by the adaptation of a literature procedure.[2] Debenzylation of 2 was carried out with sodium in liquid ammonia to give the disodium salt of L-homocysteine, which was allowed to react with 5'-O-tosyladenosine (3). The resulting S-adenosyl-L-(1-^{14}C)-homocysteine (4) was purified by ion exchange chromatography to give a product that was chromatographically homogeneous and 99% radiochemically pure.

0362-4803/87/121517-03$05.00

Received June 2, 1986
Revised March 31, 1987



EXPERIMENTAL

S-Adenosyl-L-(1-^{14}C)-homocysteine (4)

A solution of 68.1 mg (0.46 mmol, 23.5 mCi) of L-(1-^{14}C)-methionine (1) (Research Products International Corp.) in 10 mL of 0.01 N HCl solution was diluted with 135 mg (0.90 mmol) of L-methionine (total 1.36 mmol) and lyopholized. A solution of the resulting solid in 10 mL of concentrated HCl and benzyl chloride (1.27 g, 1.16 mL, 10.0 mmol) was refluxed for 24 h. An aliquot examined by TLC (Silica gel G-F254, 250 μ layer) developed in CH_3CN-1N NH_4OH (13:7) showed traces of L-methionine (R_f 0.61), S-benzyl-L-homocysteine (R_f 0.75) as the major component, and a small amount of L-homocystine (R_f 0.30). The solution was evaporated to dryness in vacuo. The residue was partitioned between 1N HCl and ether. The aqueous layer was washed with ether and evaporated to dryness in vacuo. An aqueous solution of the residue was brought to pH 8-9 (pHydrion paper) with concentrated NH_4OH and evaporated to dryness in vacuo. The white solid residue was triturated with ethanol and the ethanol removed by evaporation in vacuo. The white residue of crude S-benzyl-L-(1-^{14}C)-homocysteine (2) was dried in vacuo for 20 h and used in the next step without further purification.

A stirred solution of this residue in 50 mL of liquid ammonia was treated with metallic sodium in small portions until the blue color persisted for 15 min. before it was dispelled with ammonium chloride. To the solution was added 421 mg (1.00 mmol) of 5'-O-tosyladenosine (Aldrich Chemical Company). Stirring of the mixture was discontinued as soon as a solution was obtained. Evaporation of the ammonia was adjusted to take about 4 h. The residue was evacuated on the rotary evaporator to remove last traces of ammonia. A solution of the residue in 1N HCl (about 5 mL) was purified on an ion exchange column [100 mL of Dowex 50-WX4(NH_4)$^+$, 50-100 mesh]. The column was eluted initially with water and then 1N NH_4OH. Evaporation of the ammonia eluate gave 274 mg of crude 4. A portion of this material (112 mg) was recolumned as above and eluted with water, 0.01 N NH_4OH, and then 0.05 N NH_4OH to obtain the product. Fractions of 15 mL were collected and examined for radiochemical purity. The fractions of greater than 99% radiochemical purity were pooled and lyopholized to give a white solid: yield 54 mg. This material was TLC homogeneous (R_f 0.49) [Silica gel GF 254, 250 μ thickness developed in CH_3CN-1N NH_4OH (13:7)] and greater than 99% radiochemically pure by scans of the thin-layer plate with a Packard radiochromatogram scanner, Model 7201 (specific activity 31.9 μCi/mg or 1.72 mCi total).

REFERENCES

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2. Armstrong, M. D.-Biochem. Prep. 5: 91 (1957).