SYNTHESIS OF ^{13}C-LABELLED PROPYLENE OXIDE via ^{13}C-LABELLED 2-CHLOROPROPIONIC ACID AND 2-CHLOROPROPANOL

Ilan Pri-Bar and Ouri Buchman

Radiochemistry Department

Nuclear Research Centre-Negev
P.O. Box 9001, Beer-Sheva 84190, Israel

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SUMMARY

1-Methyl-[2-^{13}C]ethylene oxide (I) is prepared in a four-step synthesis, starting from [1-^{13}C]propionic acid. A method for an efficient α-chlorination of low carboxylic acids is developed, 2-chloropropionyl chloride being esterified without separation to give 72% of phenyl-2-chloro-[1-^{13}C]propionate. The ester is hydrogenated with $LiAlH_4$ to give 95% yield of 2-chloro-[1-^{13}C]propan-1-ol which is then subjected to alkaline dehydrochlorination, giving 35% yield of the isolated product (I). This micro-scale method is also suitable for syntheses of ^{14}C-labelled epoxides of low molecular weight.

INTRODUCTION

Recently the interest in novel syntheses for propylene oxide arose[1]. The use of deuterium labelling in an attempt to determine if methylene fragments cleaved symmetrically failed, due to the existence of an H-D scrambling[2]. A special interest in synthesis of isotopic labelled propylene oxide has arisen as the result of research in the fragmentation pattern of $[C_3H_6O]^+$ ions.

In this work, we want to introduce a new approach for the synthesis of propylene oxide, starting from propionic acid. The method is especially suited

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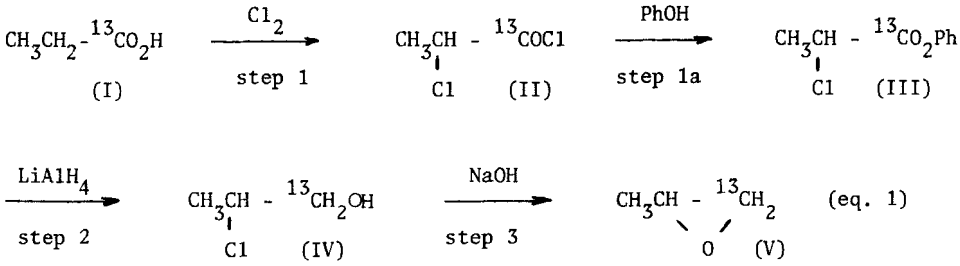
for a small scale preparation of ^{13}C- or ^{14}C-labelled propylene oxide. In this four-step synthesis no separation of intermediates was necessary and two of the steps were performed in a one-pot reaction.

Most of the published syntheses for epoxides[3,4] do not satisfy the following requirements: an easily available ^{13}C-labelled precursor; the formation of non volatile intermediates (to avoid losses by evaporation); a simple work-up procedure adapted to a mmole scale synthesis which is dictated by the price of isotopic labelled compounds. As a consequence of these requirements, direct oxidation of propylene[3] or dehydration of monotosylates of diols[4] are unsuitable as synthetic pathways.

RESULTS AND DISCUSSION

As the starting material, we chose [1-^{13}C]propionic acid (I) which is a non volatile precursor and is easily prepared by the Grignard reaction of $^{13}CO_2$ and ethylhalide in a procedure analogous to that described for the preparation of [1-^{14}C]propionic acid[5]. The following reaction sequence was outlined for the synthesis of ^{13}C-labelled propylene oxide (eq. 1):



The α-chlorination of carboxylic acids is discussed in a recent publication[6]; however, the adaptation of the methods described in the literature to a small scale chlorination of C_3- and C_4-carboxylic acids resulted in poor yields[7], due to the evaporation of the volatile acyl halides formed. Addition of a small amount of $POCl_3$ to the reaction mixture and performing the reaction in a sealed reaction vessel avoided these losses, since the reaction temperature was lowered to 60°C and no gas bubbling was involved.

The chlorination was selective at the α-position when the reaction was carried out in the dark, providing yields of 96% α-chloropropionyl chloride and 4% α-dichloropropionyl chloride.

The addition of $POCl_3$ also helped in the next step of the synthesis where it served as a promoter in the esterification of the α-chloroacid[8]. Thus, addition of phenol to the crude reaction mixture already containing the phosphoroxy chloride and the acylhalide (II) resulted in 72% yield of the phenyl ester (III). The phenol must be introduced after the chlorination is completed, otherwise the presence of phenol in the reaction mixture prevents chlorination. In such a case, a fast esterification with phenol occurs, which precludes the presence of an enol form necessary for the halogenation[9].

By preparing the phenyl propionate, a few advantages were obtained:

a) the weight of the product was doubled and resulted in a decrease of losses during the following work-up;
b) the ester was easily separated by ether extraction from the excess of phenol, the phosphoric acid derivatives and other water soluble intermediates;
c) the esters are more susceptible to LAH hydrogenation than the free acids[10].

The chlorhydrin (IV) was obtained by LAH hydrogenation together with an equimolar amount of phenol formed by hydrogenolysis of the phenyl ester (III). In order to avoid the decomposition of (IV), no attempt was made to wash out the phenol with an alkaline solution. Instead, the mixture was subjected to a controlled dehydrochlorination at 70°C. The vapors of the epoxide (V) formed under these conditions were trapped in a cold receiver, after being dried. The yields of dehydrochlorination are known to be quantitative for higher chlorhydrins[11]. However, due to the high volatility of propylene oxide, isolated yields were of the order of 35%.

EXPERIMENTAL

Commercially available reagents of synthesis grade were used without purification. [1-^{13}C] propionic acid (99% ^{13}C) was purchased from Cambridge

Isotope Lab. Inc., MA. The reactions were carried out in the absence of air. ^{1}H-NMR spectra were recorded on a EM 360 spectrometer (Varian).

Step 1 (Phenyl-2-chloropropionate (III))

Propionic acid (3 gr, 40 mmol) was introduced into a chlorination reactor consisting of a 1 liter glass bulb provided with stopcocked gas inlet and outlet and a magnetic stirring bar. Phosphorus oxychloride (3.3 gr, 20 mmol) was added and the mixture was cooled at -5°C while the reactor was flushed for 15 min. with chlorine gas. The reactor was then sealed and the reaction mixture was stirred for 18 h, at 60°C, in the dark. The reaction mixture was cooled in an ice bath and the HCl formed was released. A sample of the reaction mixture was checked by ^{1}H-NMR and was found to contain 96% of 2-chloropropionyl chloride and 4% of the 2,2-dichloropropionyl chloride. A solution of phenol (5.2 gr, 55 mmol) in benzene (1 mL) was introduced and the reactor was sealed again and heated to 60°C. The reaction mixture was stirred at this temperature for another 18 h. After cooling to -5°C, the excess pressure was released and the mixture was cautiously treated with 50 mL of Na_2CO_3 1M. The mixture was extracted with three 100 mL portions of ether. The organic phase was dried on $MgSO_4$ and the ether was evaporated. The product mixture was analyzed by ^{1}H-NMR and contained 4.9 gr (29 mmol, 72% yield) of (III) and 0.3 gr (1.8 mmol, 4% yield) of phenyl-2-chloropropionate.

^{1}H-NMR: 2-chloropropionyl chloride ($POCl_3$) (^{12}C compound) δ 1.57 (d, 3, J= 8 Hz)-CH_3; 4.60 (q, 1, J= 8 Hz)-CHCl; (^{13}C compound) δ 1.61 (A_3BX q, 3, J= 4 Hz)-CH_3; 4.55 (octate, 1)-CHCl;

phenyl-2-chloropropionate ($CDCl_3$) (^{12}C compound) δ 1.74 (d, 3, J= 8 Hz)-CH_3; 4.62 (t, 1, J= 8 Hz)-CHCl; 6.80-7.45 (broad s, 5)-C_6H_5; (^{13}C compound) δ 1.60 (A_3BX q, 3, J= 4 Hz)-CH_3; 4.55 (A_3BX octate, 1)-CHCl; 6.85-7.50 (broad s, 5)-C_6H_5.

Step 2 (2-Chloropropanol (IV))

Lithium aluminium hydride (2.1 gr, 55 mmol) was suspended in 100 mL of anhydrous ether by reflux under nitrogen atmosphere. The crude product of step 1 in 20 mL ether was introduced slowly into the reaction vessel, held at 0°C. The stirring was continued while the ice bath was removed, allowing the mixture to return to room temperature. After 1 h of stirring, hydrolysis was performed by slow addition of 5 mL of ice water followed by 30 mL of 30% H_2SO_4 solution. The organic product was extracted by three 100 mL portions of ether. The ether solution was dried ($MgSO_4$) and evaporated to give a mixture of 2.7 gr (28 mmol, 96% yield) of the halohydrin (IV) and 2.7 gr (29 mmol) of phenol.

^{1}H-NMR: (^{12}C compound) ($CDCl_3$) δ 1.49 (d, 3, J= 8 Hz)-CH_3; 3.63-3.72 (distorted t, 2)-CH_2O; 3.87-4.40 (m, 1)-CHCl; 5.08 (broad s, 1)-OH; (^{13}C compound) ($CDCl_3$) δ 1.40 (A_3BX t, 3)-CH_3; 3.85-4.45 (m, 1)-CHCl; 2.46 (broad d, 1) and 4.90 (broad d, 1)-CH_2-O-; 3.00-3.80 (broad s, 1)-OH.

Step 3 (Propylene oxide (V))

5 mL of aqueous solution of 4.8 gr (120 mmol) NaOH was warmed to 80°C in a two-neck reaction vessel provided with a dropping funnel and a magnetic stirrer. The vessel was connected to a drying tube, a coiled efficient cold trap and a receiver for the purified product, all connected in line. The receiver was protected from moisture by an additional drying tube. The crude product from step 2 was introduced slowly through the dropping funnel into the alkaline solution; the evolution of gas indicated the formation of volatile propylene oxide (V) which was collected by distillation through the drying tube filled with 3X Molecular Sieves, into the cold trap at -40°C. The reaction mixture was stirred for 5 h at 90°C to ensure the complete distillation of product (V). The distilled (V) was redistilled into a pre-weighed receiver by cooling the latter at -40°C and heating the cold trap to 60°C. Pure propylene oxide (0.6 gr, 10 mmol, 35% yield) was isolated and collected.

^{1}H-NMR: (^{12}C compound) ($CDCl_3$) δ 1.30 (d, 3, J= 8 Hz)-CH_3; 2.33-3.20 (m, 3)-$CHCH_2$;

(^{13}C compound) ($CDCl_3$) δ 0.97 (A_3BX t, 3, J= 8 Hz); 2.15-2.85 (broad m, 1)-CH_3-CH-O-; 0.60-1.70 (m, 1) and 3.05-4.15 (m, 1)-CH_2-O-.

The final product was also identified by G.C. and found identical to a commercial sample of propylene oxide. (column: Ø 1/8", 1.6 m., 10% diethyleneglycol succinate; He flow rate: 50 mL/min.; retention time at 40°C: 0.6 min.).

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