AN IMPROVED SYNTHESIS OF LABELLED DIBROMOCHLOROPROPANE

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Key words: Dibromochloropropane, tritium labelling.

SUMMARY

A continuous three-step micro-synthesis of 1,2-dibromo-3-chloropropane, labelled with tritium in position 1 and 2, is described. A specific activity of 10.8 Ci/mmol is obtained. The yield observed in the uninterrupted overall synthesis is appreciably lower than that in the controlled step-by-step synthesis.

INTRODUCTION

1,2-Dibromo-3-chloropropane (DBCP) has been used widely as fumigant by virtue of its effective nematocidal activity[1]. This compound is reported to have a potential to induce necrosis of the liver and kidney, atropy of the testes, reduction of the sperm cell number and development of abnormally formed sperms cells in rats[2,3]. Recent epidemiological studies, conducted at a chemical plant that manufactures DBCP, indicated that employees who had been exposed to this product showed oligospermia or azoospermia[4,5]. The potential reversibility of these testicular changes is still to be determined[6].

To our knowledge, the only published work related to labelled DBCP has recently appeared[7], describing the use of a C14-labelled product at a specific activity of 0.73 mCi/mmol and 94% radiochemical purity. The express need for a labelled compound at a very high specific activity induced us to attempt the synthesis of tritium-labelled dibromochloropropane.

0362-4803/81/121713-07$01.00

Received October 27, 1980

RESULTS AND DISCUSSION

The restricted experimental conditions when using tritium in synthesis, such as reduced pressure (vacuum manifold) or the limited quantities of tritium gas usually manipulated (10-100 Ci per experiment), determined the method of synthesis used. Each step was performed at optimal level, using hydrogen gas as reducing agent, in order to simulate reactions with tritium compounds. Then, the proposed synthesis was performed without disconnecting the reaction vessel from the manifold between each step. The technique used was essentially based on cryo-transfers from vessel to vessel under vacuum conditions. Ultimately, the synthesis was performed using tritium gas.
The first scheme(I) tried was as follows:

$$\underset{(1)}{HC\equiv C\text{-}CH_2Cl} \xrightarrow[\text{catalyst}]{H_2/T_2} \underset{(2)}{HCT{=}TC\text{-}CH_2Cl} \xrightarrow{Br_2} \underset{Br\ \ Br}{HCT\text{-}TC\text{-}CH_2Cl} \qquad (I)$$

based on the well known bromination of allyl chloride as used in the industrial production of DBCP[8].

The literature[9] emphasizes that the acetylenic group undergoes catalytic reduction on palladium with preference over all the other functional groups. This selectivity is not due to the rate of reduction but is due to the strong adsorption of the triple bond which enables the acetylene to displace all other functional groups from the catalyst. We based the controlled partial reduction of the propargyl chloride [step(1)] on the fact that selective hydrogenation of an acetylene to an olefin takes place more readily over a deactivated palladium catalyst at room temperature and atmospheric pressure[10]. This type of catalyst is generally deactivated by addition or adsorption of a base which, also, promotes the undesired dehalogenation. In spite of an expected advantage of the triple bond, the two reactions occurred simultaneously and scheme (I) had to be discarded.
The second scheme (II) attempted was the following:

$$\underset{(1)}{HC\equiv C\text{-}CH_2OH} \xrightarrow[\text{catalyst}]{H_2/T_2} \underset{(2)}{HCT{=}TC\text{-}CH_2OH} \xrightarrow[PPh_3]{CCl_4} \underset{(3)}{HCT{=}TC\text{-}CH_2Cl} \xrightarrow{Br_2} \underset{Br\ \ Br}{HCT\text{-}TC\text{-}CH_2Cl} \qquad (II)$$

Step (1):

The main difficulty in this step was to find the most suitable catalyst to perform the selective reduction from acetylene to olefin with the highest possible yield. The catalysts tried were RCTP*[12], 5% $Pd/BaSO_4$ poisoned with quinoline (Lindlar's catalyst)[11] and Pd/KOH[13]. In each experiment the reaction was stopped after the theoretical amount of hydrogen needed to perform the partial reduction was consumed.

Surprisingly, all the reactions resulted in a mixture of propargyl alcohol, allyl alcohol and propanol (as determined by g.l.c.), no matter which catalyst was used. Further attempts in which the catalyst/substrate ratio was decreased, slowing down the reaction rate appreciably, enabled us to reach the desired selective reduction and obtain only allyl alcohol in the product. After cryo-transfer, the yields of allyl alcohol were 42-52%, when using a 1:13 ratio of 5% $Pd/BaSO_4$ catalyst.

The choice of an appropriate solvent was an other factor which had to be determined. Because of its high boiling point and its similarity to alcohols, ethylene glycol was found to be the most suitable solvent. Experiments showed that the cryo-transfer after step (1) was performed without any ethylene glycol being carried over into the reaction vessel of step (2).

Step (2):

For the chlorination of allyl alcohol, we preferred the mild experimental conditions, in a neutral medium, with triphenyl phosphine and carbon tetrachloride instead of thionyl chloride. The former reaction is known to prevent allyl transposition[14,15]. The yield was very high (95%). The excess of carbon tetrachloride transferred into the vessel of step (3) remained inert in the subsequent reaction.

Step (3):

The reductive bromination of the double bond was easily performed. After removal of all the low boiling products by cryo-transfer and washing the remaining reaction mixture with methanol, the residual compound was identified as pure DBCP, by comparison with an authentic sample (as determined by t.l.c., g.l.c. and n.m.r.). The overall yield of steps (1) to (3) was 34.5%, based on propargyl alcohol.

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*Rhodium chloride tris(triphenylphosphine)

Overall synthesis:

The results obtained from the synthesis of DBCP by consecutive processing of the steps resulted in very low yields (3-5%) compared to the expected yield (29-35%). This fact may be possibly explained by the lack of control, particularly in the cryo-transfer after each step, where unreacted compounds are carried over and could interfere with the subsequent reactions. Indeed, the final crude product obtained was a mixture of compounds, including allyl alcohol and allyl chloride. These impurities were eliminated by repeated washes with methanol, followed by cryo-transfers of the solvent. Further attempts to increase the yield remained unsuccessful.

The tritiated synthesis led to a final pure product of low yield, with a specific activity of 10.8 Ci/mmol.

EXPERIMENTAL

The experiments were performed on a vacuum manifold, as previously described[16]. The vessels needed for each reaction step were previously charged with the reactants and / or the solvents, connected to the manifold, frozen, evacuated (10^{-2}mm Hg) and isolated from the system by a vacuum stopcock until used in the appropriate step of the reaction. The separate synthesis steps were performed using only hydrogen gas, while in the overall synthesis we used both hydrogen and tritium gas.

Proton magnetic resonance spectra were recorded with a Varian EM-360 spectrometer; gas chromatography was performed with Hewlett-Packard Model 7620A instrument by flame ionization detection (F.I.D.). Radiochemical purity was determined by radiochromatogram scanning of t.l.c. plates on Berthold Dunnschicht Scanner II, Model LB 2722; total and specific activity were measured on Packard Tri-Carb Liquid Scintillation spectrometer, Model 3375.

Allyl alcohol (step 1):

200 µl (3.46 mmol) of propargyl alcohol, dissolved in 1 ml of ethylene glycol, are added to 14.7 mg of 5% $Pd/BaSO_4$ and 20 µl of quinoline. The suspension is frozen (liquid N_2) and hydrogen introduced to an initial pressure of 450 mm Hg. The vessel is allowed to return to room temperature and the reaction mixture is vigorously stirred for 72 hours. The mixture is again frozen, the residual hydrogen evacuated and the allyl alcohol

formed is separated from the solvent by cryo-transfer to another vessel.
Yield: 42-52%, as determined by g.l.c. on 15% DEGS-stabil. on Crom.W. column, 60 cm; carrier gas He: 60 ml/min., inject. temp.: 210°C., F.I.D.: 250°C.; retention time (35°C.): propargyl alcohol: 8'18", allyl alcohol: 1'24", propanol: 1'06".

Allyl chloride (step 2):

100 µl (1.47 mmol) of allyl alcohol are added to a solution of 463 mg (1.77 mmol) of triphenylphosphine dissolved in 1 ml CCl_4. The solution is frozen, the vessel evacuated (10^{-2} mm Hg) for 10 minutes and then gently heated to 55°C for 5 hours with continuous stirring. A yellow precipitate appears with the beginning of the heating. The stirring is continued overnight at room temperature. At the end of the reaction, a thick slurry is obtained. The allyl chloride is separated and collected by cryo-transfer.
Yield: 95%, as determined by g.l.c. 1) on carbowax 20 M column, 200 cm, carrier gas He: 60 ml/min., inject. temp.: 210°C, F.I.D.: 250°C; retention time (55°C): allyl alcohol: 13'30", allyl chloride: 1'36"; 2) on 15% DEGS-stabil. on Crom.W.; retention time (35°C): allyl alcohol: 1'24", allyl chloride: 1'42".

1,2-Dibromo-3-chloropropane (step 3):

A solution of bromine in CCl_4 (1:10) is added dropwise to a solution of 0.5 ml (6.1 mmol) allyl chloride in 1 ml CCl_4. The solution is vigorously stirred and the addition is stopped when the colour of the solution remains stable. All in all, 0.8 ml of the bromine solution were added in the course of 3 hours. The residual bromine is evacuated and the reaction mixture is washed with three portions of 3 ml methanol which are removed by cryo-transfer. The residual oil obtained is pure DBCP.
Yield: 72%, as determined by g.l.c. on 15% DEGS-stabil. on Crom. W column; retention time (85°C): allyl chloride: 1'24", DBCP: 4'00", and t.l.c. detection (iodine spot) on analytical precoated silica-gel plates (Merck, 0.25 mm) in the solvent system: cyclohexane, ethyl acetate (9:1), R_f: 0.83. The n.m.r. spectrum of the final product was compared and found identical to an authentical sample.

Overall synthesis of 1,2-dibromo-3-chloropropane:

1. Using hydrogen gas:

Several experiments were performed as described when using tritium gas (see following paragraph). The crude product obtained was purified by repreated washes with methanol and cryo-transfers. Yield: 3-5% (g.l.c.).

2. Using tritium gas:

The reactants are prepared as for the synthesis of allyl alcohol. The suspension is frozen with liquid N_2 and 57 Ci (∿ 1 mmol) of gaseous tritium are introduced into the evacuated system, developing a pressure of about 450 mm Hg. The reaction vessel is allowed to return to room temperature and is vigorously stirred until most of the tritium reacted (41 Ci). To accelerate and to complete the reaction, hydrogen is then added (after freezing the suspension) and the reaction is stopped when the stoichiometric amount of tritium-hydrogen has reacted. The mixture is again frozen and the residual tritium-hydrogen is evacuated. When the vessel returns to ambient temperature, the mixture is transferred by cryo-sublimation to a connected vessel containing 443 mg of triphenylphosphine dissolved in 1 ml CCl_4. This vessel is isolated from the system by a vacuum stopcock, warmed to 55°C and the procedure follows that described in the synthesis of unlabelled allyl chloride. A yellow precipitate appears, as observed during the controlled step (2). At the end of the reaction, 100 µl of bromine diluted in 1 ml CCl_4 are cryo-transferred, in small portions, into the reaction vessel. After each partial transfer, the vessel is allowed to return to room temperature and the solution is vigorously stirred. The transfer is stopped after approximately 3 hours, when the colour of the solution remains stable. The reaction mixture is washed three time with 3 ml portions of methanol, to eliminate volatile by-products and labile tritium. After the last cryo-transfer of the solvent, a residual oil is obtained which is directly dissolved and made up to 1 ml in CCl_4. The solution is disconnected from the manifold and sampled for analytical controls. The analytical results were as follows:
chemical and radiochemical purity (g.l.c. and t.l.c.): > 98%;chemical yield (g.l.c.): 3.4%; radiochemical yield: 3.5% (1.44 Ci total radioactivity), on the base of 41 Ci tritium reacted; specific activity of final product: 10.8 Ci/mmol.

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