

SYNTHESIS OF DEUTERIUM LABELLED 2,2-DIMETHOXYPROPANES

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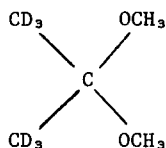
Summary

A method of preparing two 2,2-dimethoxypropanes-d₆ is described

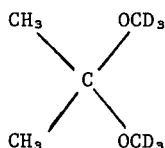
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Introduction

While investigating the gas-phase decomposition of oxonium ions (1), the need arose for 2,2-dimethoxypropane-1,1,1,3,3,3-d₆ [1] and 2,2-di(methoxy-d₃)-propane [2] as mechanistic probes. Since these labelled compounds have not been



1



2

previously reported, we undertook their synthesis. Our basic goal was to find a general procedure that was straightforward, gave high deuterium incorporation, utilized readily available deuterated reactants, and was applicable to milligram scale preparations.

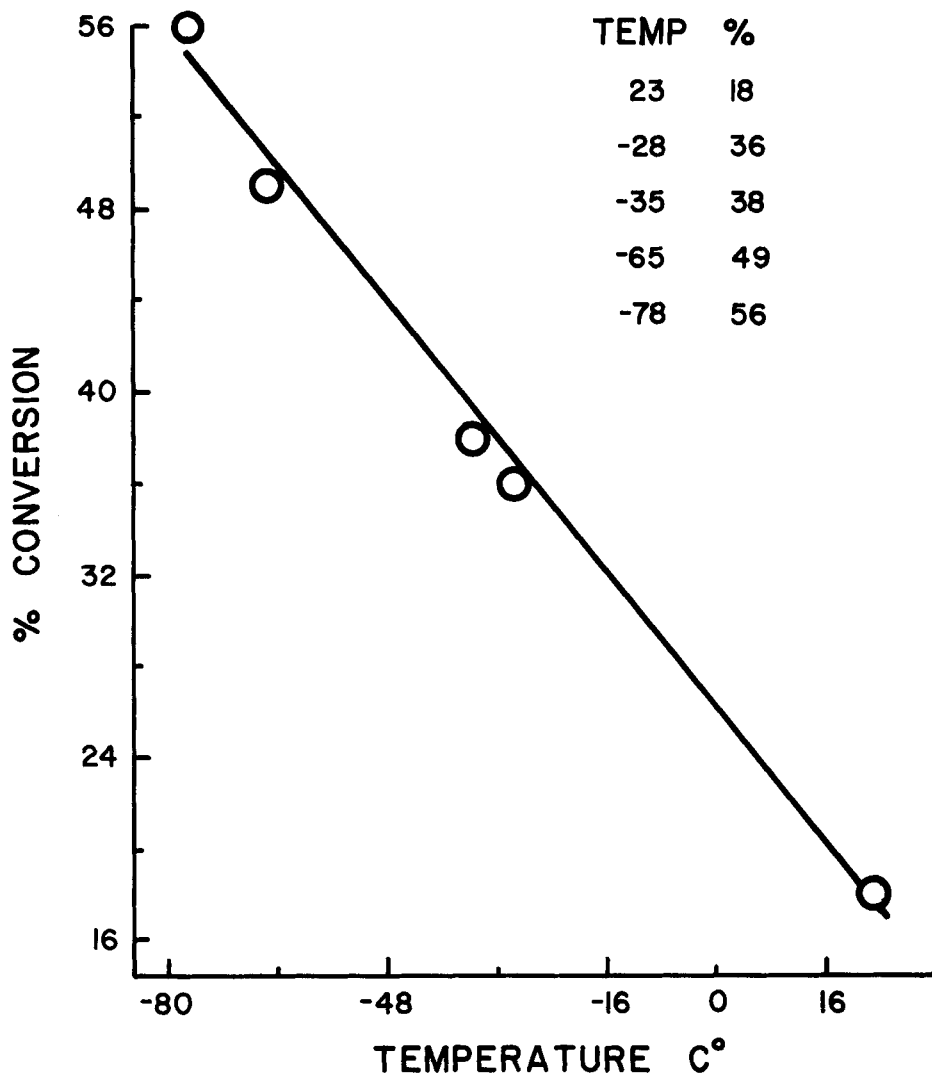
An examination of the literature did not provide a suitable synthesis: however, the techniques of resin acid-catalyzed ketal synthesis, developed by Lorette, *et al.* (2), appeared to lend themselves to modifications that would provide a suitable method. Lorette's method required the continuous flow of methanol:acetone (4:1) over a 3/4-in. glass column packed with Dowex 50 (H^+ form) followed by an 18 cm layer of basic Dowex 2 (OH^- form) at $-28^\circ C$. The reaction was treated with a 15% sodium hydroxide wash to remove unreacted reagents; conversions were typically 32%. While the method has merit for bulk synthesis, it would not be of use in small scale preparations with labelled reactants.

Discussion

The synthesis of Lorette, *et al.* (2) also demonstrated a marked increase in reaction yield as the temperature of the system was decreased from $24^\circ C$ to $-28^\circ C$. These results prompted a study to assess the effect of temperature on yield to determine optimum reaction conditions. A single reaction mixture was sampled at several different temperatures after reaching equilibrium with the results indicated in Figure 1. The improved yield at lower temperatures was obtained at the expense of an increase in time for the reaction to reach equilibrium (e.g., the reaction was complete in 30 min. at $-28^\circ C$ whereas 90 min. were required for the reactants to equilibrate at $-78^\circ C$). As a result of this study a temperature of $-78^\circ C$ was selected to perform our synthesis (lower temperatures would be more difficult to attain and would increase the yield by only 6% before the acetone freezes). Drying the resin under vacuum at $100^\circ C$ was found to further increase the yield by 4% at $-28^\circ C$ presumably by removing water from the system favoring ketal formation. The advantages of using a static, dried acid resin system at $-78^\circ C$ are clearly demonstrated in Table I.

Ketalization of acetone- d_6 using the static, low temperature conversion procedure required great care to remove any proton sources that might exchange with the labile deuterium atoms of acetone. The conversion at $-78^\circ C$ was 56%, and the isolated yield by preparative gas chromatography was 45%.

Figure 1: The Effect of Temperature on the Reaction of Methanol with Acetone in the Presence of a Cation Exchange Resin; the Percentage Conversion to Dimethoxypropane.



The synthesis of 2 did not require special precautions as the alkyl deuterium atoms of methanol are not readily exchanged. The acetone conversion at -78°C was 45%, and the isolated yield by preparative gas chromatography was 36%. This reduction in conversion reflects the change in molar ratios (Table I).

A variety of labelled ketals can be secured by this method using the appropriate ketones and alcohols. The temperature, reactant ratios, and dessicant action of the resin shift the reaction equilibrium sufficiently to make the reaction of synthetic interest.

Table I

<u>Ketone</u>	<u>Alcohol</u>	<u>Ratio</u> ^a	<u>System</u>	<u>Temperature, °C</u>	<u>Conversion %</u>
$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{-C-CH}_3 \end{array}$	CH_3OH	4:1	Flow	24	11 ^b
$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{-C-CH}_3 \end{array}$	CH_3OH	4:1	Flow	-28	32 ^b
$\begin{array}{c} \text{O} \\ \\ \text{CD}_3\text{-C-CD}_3 \end{array}$	CH_3OD	4.4:1 ^d	Static	-78	56 ^c
$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{-C-CH}_3 \end{array}$	CD_3OH	2.8:1 ^d	Static	-78	45 ^c

^aMole ratio of alcohol to ketone.

^bLorette, et al., J. Org. Chem., 24, 1731 (1959).

^cThis work.

^dThe selection of reactant ratios was a compromise between cost of reagents and yield of products.

Experimental

Prior to preparation of the ketals, all glassware was cleaned thoroughly with sulfuric acid/dichromate (Chromerge) then rinsed thoroughly with tap water, and finally distilled water. The glassware was then dried at 110°C for one hour under reduced pressure and allowed to cool in a dessicator. The sulfonic acid resin (Dowex 50W-X8, H^+ form) was cleaned by washing 20 g of resin once with 200 ml of methanol and then with three successive 200 ml portions of distilled

water. (The above treatment was found necessary to remove all colored impurities from the resin.) The resin was then packed in a glass column (45 cm x 2 cm) and washed with 1 M NaOH (Baker) until the effluent pH was above 9 (~2 column volumes), then dried at 100°C under reduced pressure for one hour.

The products were recovered from the pentane extracts by GC collection using a six foot (1/4") column packed with 10% UC-W98 on Chromosorb W under 50°C isothermal conditions. Mass spectral analyses of the isolated products were conducted on the Hewlett-Packard 5982A GC-MS system in the conventional and selected ion monitoring mode.

2,2-Dimethoxypropane-d₆ (1)--Three grams of dried resin (Na⁺ form) was equilibrated with D₂O [100 atom % D (Aldrich)] until no further swelling of the resin was noted and then packed into a glass column (40 cm x 0.5 cm) and washed with 15 ml of 1M D₂SO₄ [99.5+ atom % D (Aldrich) in D₂O, 100 atom % D (Aldrich)] and finally with 15 ml D₂O, 100 atom % D to remove any excess acid. The resin was subsequently dried at 100°C under reduced pressure for one hour and allowed to cool in a dessicator. To 3 g of this dried resin (D⁺ form) was added 1.5 ml (19 mmol) of acetone-d₆ [100 atom % D (Aldrich)] and 3.5 ml (84 mmol) of methyl alcohol-d [CH₃OD, 99.5+ atom % (Aldrich)] in a 15 ml glass vial. All transfer of resin and reagents was performed under a gentle stream of dry N₂ and the vial was flushed with dry N₂ before sealing it with a gas-tight silicon-rubber septum cap. The reaction mixture was allowed to equilibrate at room temperature with gentle agitation for 30 min. and then placed in a Dry Ice/acetone bath at -78°C for 90 min. The septum cap was then removed, and the product was extracted by adding 5 ml of pentane (Mallinkrodt) and 3 g of 15% KOH (w/v) that was ground to a fine powder after freezing in Dry Ice. The pentane layer was immediately drawn off and the reaction mixture was extracted with an additional 5 ml of pentane. Total ketone converted was 56%. Mass spectral analysis indicated 97 atom % D (99.5 mole % D) incorporation.

2,2-Di(methoxy-d₃)propane (2)--Three grams of dried resin (Na⁺ form) was equilibrated with distilled water until no further swelling of the resin was

noted and then packed into a glass column (40 cm x 0.5 cm). The resin was then washed with 15 ml of 1M H₂SO₄ and finally with 15 ml of distilled water prior to drying in an oven at 100°C under reduced pressure for 1 hr. The resin was then allowed to cool in a dessicator. To 3 g of this dried resin (H⁺ form) were added 1.5 ml (20 mmol) of acetone (Aldrich) and 2.5 ml (57 mmol) of methyl-d₃ alcohol [99+ atom % D (Stohler)]. The reaction was carried out and the product recovered as described previously. Total ketone converted was 45% (3). Mass spectral analysis indicated 99+ atom % D (~100 mole % D) incorporation.

NMR results obtained with a Varian EM-360 revealed a single peak at 1.48δ for Compound 1 and a single peak for Compound 2 at 3.28δ. This is in accordance with the spectrum of 2,2-dimethoxypropane (4).

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3. The reaction yield in this case was lower than the previous reaction because the stoichiometric excess of methanol was not as large.
4. The Aldrich Library of NMR Spectra, C. J. Pouchert and J. R. Campbell, Eds., 1974, Volume I, p. 140.