Synthesis of [^{2}H]-Diethoxymethane as a Convenient Source of a [^{2}H]-Methylene Unit

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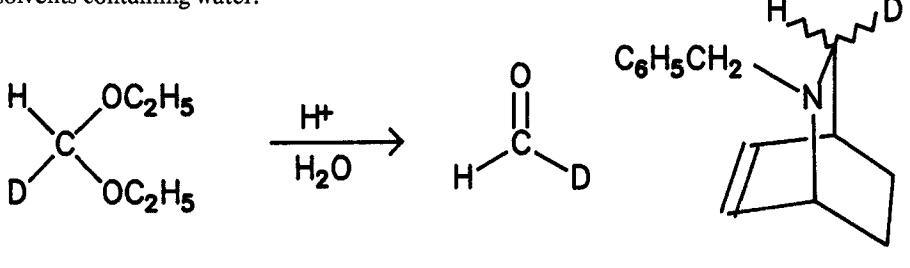
SUMMARY

[^{2}H]-Diethoxymethane is prepared in one step from triethylorthoformate. Its usefulness as a precursor to [^{2}H]-formaldehyde is shown by the Diels Alder synthesis of a monolabelled bicyclic amine. The title compound should also be useful in the syntheses of other labelled compounds in which [^{2}H]-formaldehyde is a required reagent.

KEY WORDS: [^{2}H]-diethoxymethane, [^{2}H]-formaldehyde, [^{2}H]-labelled amines.

INTRODUCTION

Formaldehyde is widely used in synthesis and is typically introduced as a formalin solution or as paraformaldehyde.(1) However, methylene acetals hydrolyze to formaldehyde(2) in an acid catalyzed reaction and thus [^{2}H]-diethoxymethane, **1**, will supply [^{2}H]-formaldehyde, **2**, in solvents containing water.



1 **2** **3**

In the course of our investigation of deuterium isotope effects in amines,(3) it became necessary to develop a convenient synthetic route for the preparation of specifically monolabelled amines, for example, 3-[^{2}H]-2-benzyl-2-azabicyclo[2.2.2]oct-5-ene, **3**. The un-

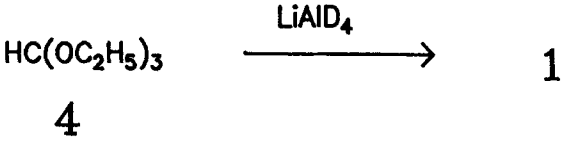
0362–4803/90/030307–04$05.00

Received August 24, 1989
Revised September 13, 1989

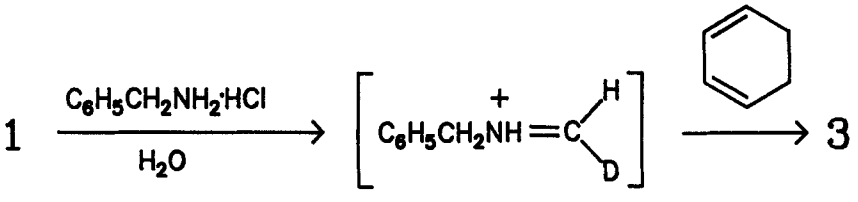
labelled bicyclic amine is available via a Diels Alder reaction utilizing paraformaldehyde or formalin.[4] Substituting a source of **2** would lead to the desired labelled product. While [^{2}H]-paraformaldehyde is commercially available,[5] it is costly. Anet recently reported the synthesis of [^{2}H]-paraformaldehyde in four steps with an overall yield of 25%,[6] and his method has been followed successfully in our laboratory. However, we have also found it possible to use **1** as an *in situ* source of **2** in the Diels Alder reaction mentioned above. This provides a shorter, more efficient route to introduce a singly labelled methylene unit.

DISCUSSION

Reduction of an orthoester by lithium aluminum hydride results in acetal formation.[7] This reaction allows a one-step preparation of a precursor of **2** in the form of a labelled acetal. [^{2}H]-Diethoxymethane, **1**, is easily prepared in 53% yield (98 atom % D, proton NMR analysis) via the lithium aluminum deuteride reduction of triethylorthoformate, **4**. While the reduction yield is modest, the single step is a great advantage, resulting in a doubling in the yield of an effective [^{2}H]-formaldehyde reagent compared to the Anet procedure. In addition, the length of time in preparing the reagent is considerably shortened.



Hydrolysis of acetals occurs at a fast enough rate under mildly acidic conditions that **1** serves satisfactorily as a source of **2** at about pH 5. Simply the presence of benzylamine hydrochloride in water allows hydrolysis of **1** to **2** and subsequent formation of an iminium ion, which then reacts in the presence of 1,3-cyclohexadiene to give the Diels Alder adduct **3**.



It should be possible to substitute [^{2}H]-diethoxymethane in other synthetic schemes requiring a source of [^{2}H]-formaldehyde. The only limitation should be the need for a protic solvent and neutral or acidic conditions. For example, introduction of labelled methylenedioxy

units in carbohydrate chemistry would be feasible,[8] or synthesis of other labelled amines via Mannich reactions. The ease of preparation and purification of **1**, and the ease of removal of the other hydrolysis product, ethanol, make **1** a convenient substitute for [^{2}H]-formaldehyde.

EXPERIMENTAL

[^{2}H]-Diethoxymethane (**1**): To a flame dried 3-neck flask equipped with a stopper, condenser (fitted with drying tube and nitrogen inlet), pressure equalizing addition funnel and magnetic stir bar is added 4.20 g (100 mmol) lithium aluminum deuteride (CIL, 98 atom % D) and 125 mL of dry ether. While stirring, 10.0 g (67.5 mmol) triethylorthoformate (**4**) (dried over 3 A molecular sieves) in 10 mL dry ether is added via the addition funnel over a period of 5 min. The funnel is replaced by a stopper and the mixture is refluxed for 24 h. The flask is allowed to cool and the drying tube is removed. Via the condenser, 20 mL of ether (previously shaken with water) is added in 1 mL portions and this is followed by the dropwise addition of water (20 mL) until the excess reducing agent is destroyed. Sodium hydroxide solution (12 M, 10 mL) is added and the mixture is stirred until the metal hydroxides have solidified. The solution is decanted and the solids are washed with ether (3 x 10 mL). All ether solutions are combined, dried ($MgSO_4$), and filtered, and the ether is removed by careful distillation to minimize loss of product through evaporation. Sodium (1.60 g, 69.6 mmol) is added to the remaining liquid and the mixture is refluxed under nitrogen for 4 h to remove residual ethanol. The distillation is resumed and product (**1**) is collected as a clear liquid, bp 88 ^{o}C, 3.75 g (35.7 mmol, 53%, 98 atom % D). ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 1.22 ppm (t, 6H, CH_3), 3.60 (q, 4H, CH_2), 4.66 (t, J_{HD} 1.0 Hz, CHD). ^{13}C NMR (75.4 MHz, $CDCl_3$/TMS): δ_C 15.05 ppm (CH_3), 62.93 (CH_2), 94.39 (t, J_{CD} 24.5 Hz, CHD).

3-[^{2}H]-2-benzyl-2-azabicyclo[2.2.2]oct-5-ene (**3**): Benzylamine hydrochloride (2.33 g, 16.3 mmol) is added to a 50 mL pyrex screw cap bottle along with 5 mL of water and stirred until dissolved. Addition of 1,3-cyclohexadiene (1.00 g, 12.5 mmol) is followed by adding **1** (1.70 g, 16.2 mmol). The bottle is capped, placed in an oil bath, and the mixture is stirred for 42 h at 60 ^{o}C. After cooling to room temperature, the bottle is opened, and 5 mL water is added, followed by 2 mL of conc. HCl. The mixture is washed with ether (5 x 5 mL), and 5 g of KOH is added in 0.5 g portions with cooling after each addition. The organic layer is extracted into ether (3 x 20 mL). The ether extracts are combined and washed with 5 mL satd. NaCl solution, dried ($MgSO_4$), and filtered, and the solvent is removed at reduced pressure. The remaining brown liquid is distilled to give (0.79 g, 3.9 mmol, 32% based on cyclohexadiene) of the

product as a colorless liquid (bp 130-155 °C/10 mm). ^{1}H NMR[9] (300 MHz, $CDCl_3$/TMS): δ 1.15-2.01 (m, 4H), 1.97 and 2.98 (m, 1H, CHD), 2.48 (m, 1H, CHD-CH), 3.33 (m, 1H, N-CH), 3.48 (ABq, J = 13.2 Hz, Ph-CH_2), 6.26 (m, 1H, C=CH), 6.42 (m, 1H, C=CH), 7.19-7.36 (m, 5H, C_6H_5). ^{13}C NMR[9] (75.4 MHz, $CDCl_3$/TMS): δ_C 22.09 (C7), 26.80 and 26.82 (C8), 30.82 (C4), 51.19 (C1), 55.14 (t, J_{CD} 21.3 Hz, C3), 62.01 and 62.08 ($PhCH_2$), 126.65, 128.10, 128.82 and 139.86 (C_6H_5), 131.79 and 131.76 (C5), 133.41 (C6).

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8. For example, dimethoxymethane has been used in the formation of methylene acetals of polyhydroxy compounds via an acid-catalyzed exchange: Hanessian S., Lavallee P. and Pernet A.G.-*Carbohydr. Res.* **26**: 258 (1973).

9. NMR spectra reflect the presence of two isotopomers, with the deuterium syn and anti to the double bond.

10. Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.