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A Convenient, High-Yielding Preparation of 1,1,1-Trideuterioethane

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SUMMARY

Coupling of methyl-$^2H_3$ benzenesulphonate with the higher-order organocuprate dilithium methyl-2-thienylcyanocuprate results in a virtually quantitative yield of 1,1,1-trideuterioethane uncontaminated by other ethane species. Methyl-$^2H_3$ benzenesulphonate is prepared from perdeuterated methanol and benzenesulphonyl chloride in 65–70% yield.

Keywords: 1,1,1-trideuterioethane; dilithium methyl-2-thienylcyanocuprate; methyl-$^2H_3$ benzenesulphonate; coupling

Infrared spectroscopy of molecular, torsional transitions in symmetric rotors gave rise to a desire to study 1,1,1-trideuterioethane. A previous related study made use of commercially available labelled ethane (1). However, due to the nature of the transitions of interest, a large sample volume is required as demonstrated with a similar study of normal ethane (2). The large amount of material required, over two moles, and the prohibitive cost, the unknown purity of the commercial product, and the vagarity of delivery time led to the development of a procedure for a multigram synthesis and isolation of the desired deuterated material.

The following preparation of 1,1,1-trideuterioethane is convenient and high yielding with no contamination by the solvents used in the synthesis or by protiated ethane, methane, or undesired deuterated analogues. The deuterated precursor used in this synthesis is methyl-$^2H_3$ benzenesulphonate, prepared from commercially available perdeuterated methanol (>99.8% ^2H) and the corresponding sulphonyl chloride. Iodomethane was not used in this synthesis because of its disadvantageous volatility, instability, and toxicity (3). The protiated methyl component of the coupling is introduced by dilithium methyl-2-thienylcyanocuprate. The use of this higher-order cuprate is advantageous in that the coupling is rapid and high yielding, and the formation of normal ethane which can occur by metathesis of the reaction byproducts (e.g. methylcopper) from lower-order organometallics (4, 5) does not occur. The desired cuprate complex is prepared by the addition of one equivalent of methyllithium to a solution of lithium 2-thienylcyanocuprate, which is commercially available or is easily prepared (4, 6).

The preparation of the organometallic complex and the production of the 1,1,1-trideuterioethane were conveniently performed in a single one-litre flask attached to the manifold of traps depicted below. This system was used repeatedly on a 200 millimole scale. A

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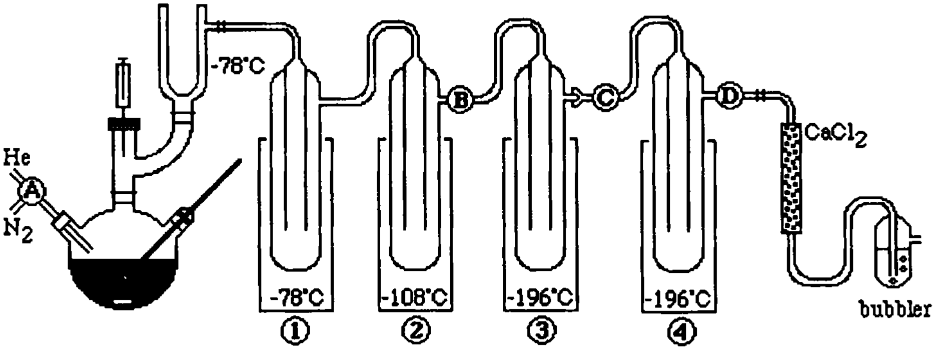
three-way stopcock, A, leading to a gas-inlet tube allows the use of either nitrogen or helium as an inert atmosphere over the reaction mixture. Nitrogen is used during the preparation of the cuprate complex, while helium is used as a carrier gas when sweeping the ethane into the isolation traps, since even a slight overpressure above one atmosphere will cause the nitrogen to condense in the trap system, creating a safety hazard. In addition, the ethane being produced will dissolve in the condensed nitrogen which results in a tedious and unnecessary separation.

A dry-ice condenser is used to return to the reaction mixture the significant quantity of solvent which is vaporized and co-distilled with the ethane during the exothermic coupling reaction. This condenser is followed by a dry-ice/acetone cooled trap, **1**, to prevent any uncondensed solvent from continuing into the system. Next a methanol/liquid nitrogen cooled trap, **2**, is used as a final precaution against any contamination of the ethane by solvents or butane (remaining from the preparation of the cuprate) which may be present in the gas stream. Traps **1** and **2** are equipped with ground glass joints to allow convenient cleaning in the event that any solvent is indeed condensed into them. However, these two traps were never found to contain any material if the dry-ice condenser was maintained constantly at -78°C.

The final two traps, **3** and **4**, are cooled in liquid nitrogen. It is necessary to ensure that these latter traps are of sufficient size to contain the ethane which is generated in this procedure without danger of the gas flow through the system being blocked. All of the ethane produced in the reaction is initially frozen in trap **3**. The last two traps may be isolated from the system and from each other by stopcocks **B**, **C**, and **D**. A ball joint between the two traps allows removal of trap **4**, which will eventually contain the final product, from the system. Traps **3** and **4** are of one-piece construction to minimize the possibility of the loss of material during the transfer of ethane from one trap to the other. A Tygon® tubing line fitted with a quick disconnect connector located after stopcock **D** leads *via* a calcium chloride-containing drying tube and a mineral oil-filled bubbler to the atmosphere.



The yields of the 1,1,1-trideuterioethane obtained were determined by mass measurement as well as by volume/pressure measurements of the product. The yields on the 200 millimole scale employed were consistently over 90%. This procedure allowed the rapid and convenient preparation of a highly pure product for approximately one tenth of the cost of material obtained from a commercial supplier.

EXPERIMENTAL

Gas chromatographic analysis of the methyl-$^2H_3$ benzenesulphonate was performed on a Hewlett-Packard 5830 gas chromatograph equipped with a 1.8m x 0.3 cm column packed with 3% OV-17. Mass spectral analysis of the methyl-$^2H_3$ benzenesulphonate was performed on a Kratos MS-50 mass spectrometer. Gas chromatography-mass spectrometry was carried out on a sample of 1,1,1-trideuterioethane using a Kratos MS-80 mass spectrometer coupled to a Carlo-Erba gas chromatograph equipped with a 30 m DB1 capillary column coated with a 5 μm film.

Methyl-$^2H_3$ benzenesulphonate: A 250-mL, round-bottom flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel was charged with 10 g (280 mmol) of perdeuterated methanol (>99.8% ^2H, MSD Isotopes) dissolved in 50 mL of tetrahydrofuran, and the solution was cooled to -5°C using an ice/salt bath. With stirring, 36 mL (280 mmol) of benzenesulphonyl chloride was added *via* the dropping funnel over 15 minutes. Then 44 mL of aqueous 25% sodium hydroxide (275 mmol), was added to the dropping funnel and subsequently added over one hour to the reaction solution at room temperature. The resulting two-phase slurry was stirred for five hours after which time the tetrahydrofuran was removed under reduced pressure. Extraction of the mixture with 2x40 mL of dichloromethane, drying of the organic phase over anhydrous magnesium sulphate and removal of the solvent yielded 36 g of crude product which by gas chromatographic analysis consisted of 85% methyl-$^2H_3$ benzenesulphonate and 15% unreacted benzenesulphonyl chloride. Vacuum distillation of the product gave recovered benzenesulphonyl chloride at 120°C (15 Torr) and methyl-$^2H_3$ benzenesulphonate at 144°C (15 Torr). Redistillation of the intermediate fractions gave a total yield of 28–32 g of pure product, representing a yield of 65–70%. Mass spectral analysis of the product indicated a total deuterium content of at least 99.8%

1,1,1-Trideuterioethane: A dry, one-litre, 3-necked round-bottom flask was equipped with a magnetic stirring bar, a gas inlet tube attached to a three-way stopcock, a thermometer, and a Claisen adapter fitted with a septum (see Figure). Initially, the reaction flask was not connected to the trap manifold, a stopper replacing the dry-ice condenser in the Claisen adapter. After the flask was flushed with nitrogen, 250 mL of tetrahydrofuran from a freshly opened bottle of anhydrous solvent and 17.6 mL (220 mmol) of thiophene were added to the reaction flask and the solution was cooled to -78°C. *n*-Butyllithium, 150 mL of a 1.4 M solution in hexanes (210 mmol), was added to the reaction mixture over 15 minutes *via* a syringe to produce a pale yellow solution.

After warming the reaction mixture slowly to 0°C, 18.8 g (210 mmol) of copper(I) cyanide was added in one portion to the reaction flask and stirring was continued until the solid had dissolved producing a turbid orange mixture which separated into two clear layers if left to stand. The reaction volume was reduced to approximately 250 mL by means of an aspirator to the Claisen adapter. The dissolved butane boils off first, evidenced by a froth of small bubbles, followed by the solvent. If commercially available (Aldrich Chemical Company, Inc.) lithium 2-thienylcyanocuprate is used, this solvent concentration should still be carried out in order to remove the butane (generated during the deprotonation of the thiophene) from the reaction mixture.

The use of the opaque, dark-brown commercial material resulted in no difference in the yield of ethane produced.

The reaction flask was then repressurized with nitrogen and 200 mL of anhydrous tetrahydrofuran was added to produce an orange to light brown solution. After cooling the reaction mixture to -78°C, 143 mL (200 mmol) of a 1.4 M solution of methyllithium in diethyl ether was added quickly and the reaction allowed to warm slowly to 0°C, yielding a pale yellow solution of dilithium methyl-2-thienylcyanocuprate. In some cases, the reagent precipitated, but the yield of the subsequent coupling reaction was unaffected.

After the reaction mixture was allowed to warm to room temperature, the dry-ice condenser was installed, the trap manifold connected and the entire system purged with helium. The dry-ice condenser was charged with a slurry of dry ice and acetone and the appropriate temperature baths (see discussion) were raised onto the traps, making sure that the helium flow was sufficient to maintain a positive pressure in the system.

While the temperature of the reaction mixture was maintained between 0–10°C, 31.4 mL (210 mmol) of methyl-$^2H_3$ benzenesulphonate was added very slowly *via* a pressure-equalizing dropping funnel. Ethane production was evidenced by an immediate increase in the gas flow and the refluxing of solvent from the tip of the dry-ice condenser. Following the addition of the methyl-$^2H_3$ benzenesulphonate, the temperature of the reaction mixture was allowed to rise to room temperature, stirring was slowed, and the gas inlet tube was lowered below the surface of the reaction mixture. Helium was gently bubbled through the reaction mixture in order to sweep the significant quantity of dissolved ethane into the trap manifold.

After three hours of gentle bubbling, the gas inlet tube was raised above the surface of the reaction mixture and the helium flow was stopped, while simultaneously closing stopcocks B and D. The ethane which had frozen in trap 3 was freeze-pumped into trap 4 by removing the liquid nitrogen bath from around the former trap and allowing the contents to warm. The ethane appeared in trap 3 as a white snow or a glassy solid which upon melting occupied a volume of approximately 10 mL. After a few moments the liquid ethane warmed and began to gently distill into trap 4. This transfer process required about 15 minutes. Stopcock C was then closed, the gas inlet A at the beginning of the system was opened to the atmosphere, and stopcock B was opened to release any internal pressure in the system. Trap 4 which contained the product was then disconnected from the system and the contents transferred to a storage line or cylinder. The total elapsed time to complete the reaction is typically about six hours.

Yields of the 1,1,1-trideuterioethane obtained were determined by mass measurement as well as by volume/pressure measurements of the product. The yields on the 200 millimole scale employed were consistently over 90%. No impurities were detectable in the product by capillary gas chromatographic analysis. Comparison of the mass spectra of the deuterated material and normal ethane confirmed that the isotopic purity of the product was greater than 99.5%.

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