An Efficient Synthesis of Ethyne-1-^{13}C.

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SUMMARY

A synthesis of the title compound from $^{13}CO_2$ is described. The final step utilizes lithium hexamethyldisilazide as a base in the double dehydrobromination of 1,2-dibromoethane-1-^{13}C. Some alternative procedures are discussed.

Key words: Ethyne, Carbon Labelling, Dehydrobromination.

The widespread use of ethyne as a reagent, both in industry and academia, makes it a molecule of interest for mechanistic studies. The relative simplicity of ethyne has also prompted a large number of detailed spectroscopic investigations. In many cases, propyne will serve as an effective model for ethyne which contains a methyl group as a label. Alternatively, ethyne-1-^{2}H may be an appropiate choice to employ. In the event that neither of these molecules are suitable substrates[1], an efficient synthesis of ethyne-1-^{13}C is desirable.

The title compound had been previously the subject of a variety of spectroscopic probes (e.g. IR[2a], ^{1}H-NMR[2b]), but these studies were undertaken with mixtures of ethyne, ethyne-1-^{13}C and ethyne-1,2-$^{13}C_2$. Brown had published a synthesis of a doubly-labelled ethyne, ethyne-1-^{2}H,1-^{13}C.[3] While the synthesis might easily be adapted to the

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title compound, the yield suffers greatly in the last two reactions of an eleven step sequence so that the overall yield from $^{13}CO_2$ is less than five per cent.

Initial efforts were directed at a one-carbon-homologation of formaldehyde-^{13}C. However, attempts to convert formaldehyde to either 1,1-dibromoethene[4,5] or 1,1-dichloroethene[6] led to very low yields compared with higher homologs of formaldehyde e.g. hexanal.

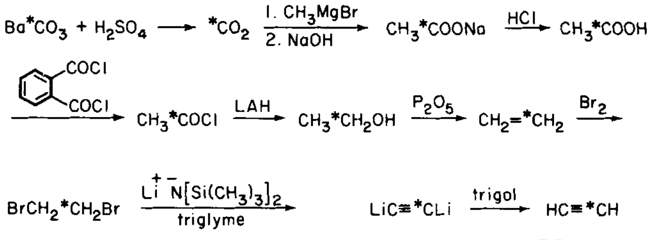
The lack of success in adding one-carbon units to formaldehyde prompted a more classical approach to the desired ethyne-1-^{13}C. The preparation of 1,2-dibromoethane-1-^{13}C had already been described in the literature.[7] It only remained to find an efficient means of double dehydrobromination.

A variety of bases were studied in order to optimize the production of ethyne. Included among these were n-butyl lithium, sodamide[8], methylsulfinyl carbanion[9] and lithium hexamethyldisilazide. All of these produced ethyne except n-butyl lithium; the respective yields from the other reagents were 59 %, 69 % and 86 % as measured by gas buret on reactions of 10 mmol scale. The ethyne-1-^{13}C obtained from lithium hexamethyldisilazide could be purified so that the only peaks in the mass spectrum corresponded to ethyne and nitrogen. The ^{1}H-NMR spectrum confirmed the identity of the gas.

The complete synthesis of the labelled acetylene is outlined in Scheme 1. The starting material in our synthesis was either commercial barium carbonate (90 % enrichment) or acetic acid-1-^{13}C. Sodium acetate-1-^{13}C was obtained in a 90 % yield by means of a methyl Grignard reaction with labelled carbon dioxide, generated by acidification of barium carbonate. Previous workers had determined that higher yields of ethanol were possible when acetic acid was converted to the acetyl

SCHEME I

Preparation of HC≡^{13}CH



55 % overall
64 % from $CH_3{}^*COOH$

chloride than if direct reduction of the acid was attempted.[10] A one-step procedure to prepare acetyl chloride directly from the acetate[11a] was tried in our laboratories, but found inferior to a two-step process in which acetic acid is first liberated from its salt before conversion to the acid chloride. The only purification of the acetic acid necessary is the removal of any excess hydrogen chloride employed in the acidification. Phthaloyl chloride is a convenient reagent for the preparation of the acid chloride[10] since the product may easily be distilled away from the reaction mixture. Lithium aluminum hydride reduction of the acetyl chloride leads to the labelled ethanol in yields slightly greater than 90 % based on the acetic acid.[10] The dehydration of ethanol-1-^{13}C was carried out at 180 °C over phosphorus pentaoxide. The product ethylene was never isolated, but rather was allowed to react with bromine at 0 °C on the vacuum line. Yield of 1,2-dibromoethane-1-^{13}C was 83 %.[7] At this stage, the 1,2-dibromoethane could be rigorously purified. Moreover, the extent of isotopic enrichment could be assayed by examination of the peak intensities in the parent region of the mass spectrum. In this manner, it was determined that no dilution of the label transpired over the course of the synthesis.

The synthesis of ethyne-1-^{13}C in this manner has several advantages. It utilizes the least expensive source of isotopically labelled carbon as a source for the label in the product. There is no loss of enrichment in the course of the synthesis. All the reactions proceed in high yield and may be undertaken with conventional nitrogen and vacuum-line apparatus. The labelled material may be rigorously purified, assayed and stored as the immediate precursor to ethyne-1-^{13}C, namely 1,2-dibromoethane-1-^{13}C. It is hoped that this synthesis will be useful to other chemists either in mechanistic studies or spectroscopic experiments where a high purity of the mono-labelled ethyne is required.

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Experimental.

General Procedure. All reactions were routinely carried out under an atmosphere of dry nitrogen with glassware oven-dried. Proton NMR spectra were recorded on a Varian EM-390 or UCB-250 spectrometer. The UCB-250 uses a Nicolet 1180 data system and has a Cryo Magnet Systems 5.7-T magnet. Mass spectral data were collected on an AEI-MS-12 (low resolution) or Dupont CEC 21-110B (high resolution) instrument by the Mass Spectral Service at the University of California, Berkeley.

Dehydrohalogenation of 1,2-dibromoethane with lithium hexamethyldisilazide. Hexamethyldisilazane (10 ml, 47 mmol.) was added to freshly distilled ethyl ether and cooled to -78 ^{o}C. n-Butyllithium (26.7 ml of a 1.5 M solution in hexane, 40.0 mmol.) was added dropwise and a white precipitate appeared. The solution was allowed to warm to room temperature while stirring and then the solvent was removed on a vacuum line. The resulting colorless lithium salt was stored under nitrogen. In precipitation of the salt, some ether was occluded. The exact ratio of ether to salt which was usually ~0.9:1 may be determined by integration in ^{1}H-NMR. The base (5.15 g, 22 mmol.) was added to a 3-neck flask. Freshly distilled triglyme (25 ml) was added through a syringe. A pressure-equalizing dropping funnel was fitted to one of the necks and loaded with an excess of triethylene glycol (5 ml, 37.5 mmol.). The base in solution was cooled to 0^{o} prior to the addition of 1,2-dibromoethane (0.43 ml, 5 mmol.). Within two minutes of completed addition, the lithium carbide precipitated from the solution. Triethylene glycol was used to protonate the carbide and was added dropwise. The evolution of gas corresponded to an 86 % yield of ethyne (96 ml, 4.3 mmol.).

If it was desirable to isolate the ethyne in a separate flask, then the entire system was evacuated by a series of freeze/thaw cycles after the formation of the carbide, but prior to protonation. Meanwhile a separate round bottom flask could be attached to the vacuum line and evacuated. The line was then isolated from the pump and the empty flask cooled with liquid nitrogen. The addition of the trigol to the carbide in solution allowed for the ethyne as well as any other volatile material to be condensed in the cold flask. The condensed material was subsequently allowed to warm to room temperature and then cooled to -78 °C. The -78 °C temperature provided a method to distill ethyne away from ether and hexamethyldisilazane which were also transferred during the ethyne production. In this manner, it was possible to obtain a ^{1}H-NMR and a mass spectrum which only had peaks corresponding to ethyne [m/e 26, (100.00)] and nitrogen [m/e 28, (14.27)].

Acetic acid-1-^{13}C. The details of the experimental procedure to convert labelled barium carbonate to acetic acid by use of a Grignard reaction have been reported elsewhere.[11b] It was found to be advantageous to use a large round bottom flask to facilitate the subsequent steam distillation necessary in work-up of the reaction (e.g. 300 ml 3-neck flask for 50 mmol. scale of Grignard). It was very important to thoroughly crush the barium carbonate in a mortar prior to reaction with sulfuric acid. Particular caution is necessary during the addition of the sulfuric acid to the barium carbonate to avoid displacing particles of barium carbonate. The ether fraction from steam distillation was extracted with water to obtain a small amount of acetic acid which could be combined with the water/acetic acid mixture obtained by steam distillation of the original mixture. The yield was determined by titration with standardized solutions of sodium hydroxide and was typically in the range of 88-92 %. Removal of the water allowed for isolation of the acetic acid-1-^{13}C as the sodium salt. Weight of this material agreed well with values calculated from the titration numbers.

Acetyl chloride-1-^{13}C. The synthesis utilized a two-step conversion from the sodium acetate which involved the re-formation of acetic acid by anhydrous hydrogen chloride followed by conversion to acetyl chloride. The procedure used was almost identical to that developed by Cox and Turner.[10] The major difference was the addition of several milliliters of octane to act as a chaser and facilitate the distillation of the acetyl chloride (b.p. 51 °C) from the phthaloyl dichloride (b.p. 281 °C). Distillation from the phthaloyl dichloride was continued until the distillate temperature reached 100 °C. The liquid in the trap was returned to the vacuum line to remove residual hydrogen chloride according to the method of Cox.[10] The combined yield of these operations led to ~90 % yield of acetyl chloride-1-^{13}C based on sodium acetate. Generally, the acetyl chloride was not isolated from any octane because the octane could serve the same purpose in the distillation of the ethanol to be generated in the next step.

Ethanol-1-^{13}C. The procedure used for this reaction was also similar to that employed by Cox and Turner.[10] Diglyme was purified by filtration through alumina followed by distillation from calcium hydride. 2-Phenoxyethanol was purchased from Eastman and distilled from calcium hydride. Reagents were usually added assuming a 95 % yield of the acetyl chloride. A molar equivalent of lithium aluminum hydride reagent (95 %) was added to the diglyme and the system was degassed by repeated freeze/thaw cycles. The acetyl chloride/octane solution was transferred under vacuum into the reaction flask which was cooled with liquid nitrogen. The reaction flask, still under vacuum, was warmed to 0 °C and the reducing solution was stirred at that temperature for about two hours. Nitrogen was admitted to the system and six equivalents of 2-phenoxyethanol were placed in an addition funnel above the reaction. The alcohol was added dropwise to the stirred reaction mixture. The addition funnel was then removed and replaced by a distillation apparatus with the receiving flask cooled to -78 °C. The reaction mixture was heated to 90^o and then to 100 °C for two hours. Some ethanol was collected during this period, but yields were improved by reducing the pressure and collecting all of the material which distilled at room temperature. When there was a precipitous increase in the temperature of the distillate (e.g. 25^o to 40^o), nitrogen was readmitted to the system. If necessary, the ethanol obtained in this manner could be subjected to a second distillation to separate it from the octane and any traces of higher boiling materials. Yield for this reaction was 97 % (10-30 mmol scale). The labelled compound, ethanol-1-^{13}C, exhibits a ^{1}H-NMR spectrum where J_{CH} = 139.5 Hz and $J_{CCH} \simeq 2$ Hz.

1,2-Dibromoethane-1-^{13}C. The synthesis of labelled dibromoethane was accomplished according to the procedure of Bak *et al.*[7] A minor change was used in that a Fischer-Porter bottle was employed for the dehydration of ethanol rather than a sealed ampule. The labelled ethylene was never isolated or characterized, but was immediately carried on to the product dibromoethane as described below.

Labelled ethanol (0.93 g, 20 mmol.) was attached to the vacuum line and degassed. Phosphorus pentoxide (25 g, 66 mmol.) was placed in the Fischer-Porter bottle. The bottle was also connected to the vacuum line and evacuated. Ethanol was transferred under vacuum into the Fischer-Porter bottle which was then isolated from the system. The bottle was heated in an oil bath to 180^{0} for ~5 h until there was no further increase in pressure. During this time, the phosphorus pentoxide had some tendency to turn brown and foam. Another round bottom flask with sufficient volume to hold all the ethylene to be produced was attached to the vacuum line. An equivalent amount of bromine (3.20 g, 20 mmol.) was placed in a round bottom flask with a stirring bar and the bromine solution was degassed, then stirred at 0 ^{o}C. The ethylene was distilled away from the P_2O_5 at -30 ^{o}C into the vacant flask. The flask containing ethylene was then warmed to room temperature. Ethylene was reacted by aliquots with the bromine still at 0 ^{o}C to avoid a violent reaction. When the great majority of the ethylene had reacted, the remainder of the ethylene was condensed into the bromine flask using a liquid nitrogen trap. The reaction mixture was then allowed to stir an additional ten minutes at 0 ^{o}C. Nitrogen was then admitted to the system. Excess bromine was removed by extracting into aqueous ferrous ammonium sulfate-pentane. The Fe(II) was found to be superior to sodium thiosulfate for this purpose. The pentane was then removed by distillation to obtain the labelled 1,2-dibromoethane in pure form. The ^{1}H-NMR of 1,2-dibromoethane has been previously examined in detail including the splitting pattern of the ^{13}C satellite peaks.[12] Our spectrum confirmed the J_{CH} as 156 Hz and agreed in other aspects with the reported spectra. The 1,2-dibromoethame-1-^{13}C also served as an assay for the extent of isotopic enrichment. There was no loss of label during the sequence of reactions.

Exact mass calculated for $^{12}C^{13}CH_4{}^{79}Br^{81}Br$: 188.8692; $^{12}C^{13}CH_4{}^{79}Br_2$: 186.8712; found: 188.8685; 186.8708.

Ethyne-1-^{13}C. The labelled 1,2-dibromoethane was reacted as described above with lithium hexamethyldisilazide. (See Dehydrohalogenation of 1,2-dibromoethane with lithium hexamethyl disilazide.).

Mass spectrum m/e (intensity): 27(M^+,100), 26(1.75)

NMR: J_{HH} = 9.54 Hz, J'_{CH} = 49.0 Hz, J_{CH} = 248.9 Hz

The ^{1}H-NMR spectrum agreed well with the values assigned earlier based on a mixture of unlabelled, mono-, and bis-labelled ethyne.[2b]

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