

SYNTHESES WITH STABLE ISOTOPES: SODIUM CYANIDE- ^{13}C

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SUMMARY

Sodium cyanide- ^{13}C has been prepared in 65-70% overall yield from carbon- ^{13}C monoxide in a three-step synthesis proceeding through isopropyl formate- ^{13}C and formamide- ^{13}C as intermediates. Several methods for the dehydration of formamide have been investigated.

INTRODUCTION

We have required sodium cyanide- ^{13}C in this Laboratory as a precursor for incorporating carbon-13 into other molecules. The methods [1] which have been utilized for preparing carbon-14 cyanide involve either (a) the high-temperature reaction between carbon dioxide or carbonate and ammonia, ammonium ion, or azide ion in the presence of metals such as sodium, potassium, and zinc or (b) the preparation and cleavage of nitriles such as phenylacetonitrile or triphenylacetonitrile. The carbon dioxide-ammonia-metal reactions did not look attractive for larger-scale preparations. The nitrile cleavage, while seemingly applicable to larger-scale reactions, seemed somewhat laborious. More recently, syntheses of isotopic cyanide from methane and ammonia [2] or elemental carbon and ammonia [3] have been reported.*

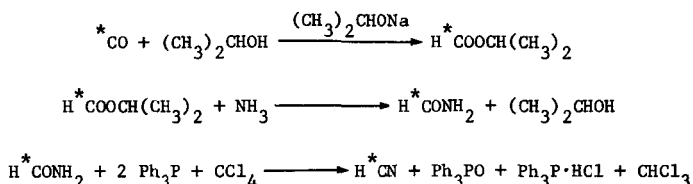
One synthetic pathway to sodium cyanide which appears not to have been applied to isotopic synthesis is the dehydration of formamide. Our investigations of this

* A synthesis of sodium cyanide- ^{13}C from methane- ^{13}C and ammonia has also been developed at this Laboratory and will be described in a future publication [4].

reaction have shown both *p*-toluenesulfonyl chloride in pyridine and triphenylphosphine-carbon tetrachloride to be suitable dehydration reagents. In addition, we are reporting a convenient two-step synthesis of formamide-¹³C from carbon-¹³C monoxide.

RESULTS AND DISCUSSION

The reaction sequence for the conversion of carbon-¹³C monoxide to hydrogen cyanide-¹³C is shown below:



The reaction used for preparing isopropyl formate-¹³C is actually a general reaction in which an equilibrium is established between carbon monoxide, an alcohol, and the corresponding alkyl formate in the presence of the appropriate metal alkoxide. We have prepared methyl and isopropyl formate in yields of approximately 90% under conditions (i.e., excess alcohol) which favor formation of the ester. Treatment of either of these crude reaction mixtures with ammonia yields formamide. Isopropyl formate was chosen because of its lower volatility and the expectation that the boiling point difference between ester and alcohol (being greater for isopropyl formate) would facilitate isolation of the pure ester. Subsequent work showed that fractionation of the ester-alcohol mixture (after deionization to prevent retrograde decomposition of the ester) gave an azeotropic mixture which was ca. 90% isopropyl formate and ca. 10% isopropyl alcohol.

The description of the carbon monoxide-isopropyl alcohol reaction presented in the experimental section utilizes a mechanically stirred autoclave, but we have found that a stainless steel gas-sampling cylinder equipped with an inlet valve and pressure gauge to be a suitable and, in some cases, preferable reaction vessel. The reaction is conveniently carried out by filling the cylinder to 80-85% of its volume with a sodium isopropoxide-isopropyl alcohol solution and repeatedly pressuring the cylinder with carbon monoxide until the desired uptake has been achieved. It has

also been observed that both the position of equilibrium and the time required to reach that equilibrium are profoundly affected by the presence of water, and so the formate reaction must be carried out under anhydrous conditions.

Ammonolysis of the crude isopropyl formate-¹³C reaction mixture yields formamide-¹³C. Prior removal of the sodium isopropoxide is not required and is probably not desirable since alkoxide is known to catalyze the reaction [5]. The ammonolysis, while potentially applicable to nitrogen-15 labeling (i.e., using limited ammonia), has not been extended to formamide-¹⁵N or formamide-¹³C-¹⁵N as yet.

There are numerous reagents for transforming amides into nitriles by dehydration. We investigated the reaction using phosphorus pentoxide in both toluene and pyridine solution, *p*-toluenesulfonyl chloride in pyridine solution, and triphenylphosphine-carbon tetrachloride. These results are summarized in Table 1. Attempts to dehydrate formamide using phosphorus pentoxide result in the formation of clumps of phosphorus pentoxide-phosphoric acid which are not dissipated by vigorous stirring.

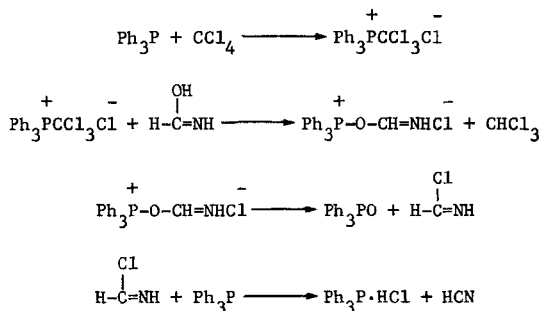
TABLE 1 -- Reagents for the Dehydration of Formamide.

Reagent	Yield (Range)	Yield (Average)
Phosphorus pentoxide-Toluene	50-65%	60%
Phosphorus pentoxide-Pyridine	50-55%	52%
<i>p</i> -Toluenesulfonyl chloride-Pyridine	60-80%	73%
Triphenylphosphine-Carbon tetrachloride	75-90%	83%

Entrapment of hydrogen cyanide in these clumps is probably responsible for the low yields obtained with phosphorus pentoxide. A single attempt to dehydrate formamide with acetic anhydride was unsuccessful. Also, the vapor-phase dehydration of formamide over alumina failed to give satisfactory results. *p*-Toluenesulfonyl chloride in pyridine solution [6] is an acceptable dehydration reagent, but consistently higher yields were obtained using triphenylphosphine-carbon tetrachloride [7].

The triphenylphosphine-carbon tetrachloride reagent is known to convert primary and secondary alcohols into alkyl chlorides [8,9]. From known phosphine chemistry

and the alkyl chloride reaction, the following steps can be formulated for the dehydration reaction:



The amino form of formamide and the iminohydrochloride of hydrogen cyanide have been used for convenience in the mechanism.

The overall conversion of carbon-¹³C monoxide to sodium cyanide-¹³C can be accomplished in yields of 65-70%. All of the reactions have been carried out on scales ranging from a few millimoles to a mole with little variation in yield.

EXPERIMENTAL

Materials and Methods--Carbon-¹³C monoxide was produced at this Laboratory (Los Alamos Scientific Laboratory Isotope Separation Facility, Group CNC-4). Ir spectra were recorded on a Perkin-Elmer 710 spectrophotometer using polystyrene calibration lines and are reported to the nearest 10 cm⁻¹, with natural abundance absorptions being given in parentheses. Proton-nmr spectra were recorded on a Perkin-Elmer R-24 60-MHz spectrometer using TMS as an internal standard.

Isopropyl Formate-¹³C--A mechanically stirred one-liter autoclave was charged with a sodium isopropoxide solution prepared by dissolving 1.0 g sodium metal in 380 cm³ of anhydrous isopropyl alcohol and sealed. Carbon-¹³C monoxide (ca. 90 mol % ¹³C, containing 7.3 mol % methane) was added to a total pressure of 6.00 MPa (870 psi, ca. 806 psi carbon-¹³C monoxide, 1.4 mol). After stirring for 48 hr at room temperature, the pressure had fallen to an equilibrium value of 0.83 MPa (120 psi, ca. 56 psi residual carbon-¹³C monoxide). After venting, the autoclave was drained to give 331 g of a solution containing isopropyl formate-¹³C, isopropyl alcohol, and sodium isopropoxide which was used directly in the preparation of formamide-¹³C.

Formamide- ^{13}C --The solution of isopropyl formate- ^{13}C , isopropyl alcohol, and sodium isopropoxide was transferred to a one-liter three-neck flask equipped with a magnetic stirrer, thermometer, Dry Ice condenser with drying tube, and an inverted 300-cm³ gas-sampling cylinder containing liquid ammonia (ca. 60 g). The solution was cooled to -70°C with a Dry Ice-ethanol bath, the liquid ammonia was added rapidly to the viscous solution, and the reaction mixture was allowed to slowly warm to -30°C . After stirring for 3 hr at -30°C , the Dry Ice condenser was replaced with a chilled-water condenser, and the mixture was stirred overnight at room temperature. The mixture was deionized by treatment with 30 g of anhydrous Dowex 50 (H^+) cation exchange resin [prepared by successive reduced-pressure evaporations of benzene from an anhydrous benzene-Dowex 50 (H^+) slurry] and filtered through a Celite pad. The filtrate was transferred to a distilling flask where most of the isopropyl alcohol was removed by distillation through a short fractionating column at atmospheric pressure. The remaining material was fractionated at reduced pressure to give 56 g (1.2 mol, 86% yield from carbon- ^{13}C monoxide) of formamide- ^{13}C ; bp $138\text{--}140^\circ\text{C}$ at 8.0 kPa (60 Torr); nmr (δ , DMSO- d_6) 8.0, $J_{\text{CH}} = 187$ Hz; ir 3370 (3370), 2870 (2880), 1650 (1680), 1590 (1600), 1390 (1400), 1290 (1310), 1040 (1050) cm^{-1} .

Sodium Cyanide- ^{13}C --A one-liter three-neck flask equipped with a magnetic stirrer, gas inlet tube, addition funnel, and condenser connected to a gas evolution trap containing 5 M sodium hydroxide solution (150 cm³) was charged with triphenylphosphine (131 g, 0.5 mol) and carbon tetrachloride (375 cm³). The reaction mixture was heated to 40°C with nitrogen flushing through the system, and a solution of formamide- ^{13}C (11.5 g, 0.25 mol, ca. 90 mol % ^{13}C) in anhydrous tetrahydrofuran (375 cm³) was added over a 2-hr period. A tan solid began to precipitate during the addition. The reaction was allowed to continue for 60 hr with nitrogen flushing through the system and the temperature maintained at $40\text{--}45^\circ\text{C}$. The contents of the sodium hydroxide trap were washed into a volumetric flask, and an aliquot was analyzed for cyanide by titration with silver nitrate solution to an iodide end point. The yield of sodium cyanide- ^{13}C was 0.20 mol (80%). The sodium cyanide- ^{13}C sodium hydroxide mixture was purified [10] by dropwise addition of the solution into 30% sulfuric acid and collection of the hydrogen cyanide- ^{13}C in a Dry Ice-isopropyl alcohol trap as the reaction flask was flushed with nitrogen. The solid hydrogen

cyanide- ^{13}C was dissolved in cold water and carefully neutralized with an equivalent amount of sodium hydroxide solution. The resulting sodium cyanide- ^{13}C solution was used directly or lyophilized to give solid sodium cyanide- ^{13}C ; ν 2020 (2070), 1450 (1450) cm^{-1} .

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