

A HIGH YIELD SYNTHESIS OF  $^{13}\text{C}$  - AND  $^{14}\text{C}$  - LABELED DIETHYL CARBONATE

William R. Porter, Larry A. Spitznagle\*, and William F. Trager  
Department of Pharmaceutical Sciences, School of Pharmacy,  
University of Washington, Seattle, Washington 98195

Received on March 2, 1976

Revised on April 8, 1976

SUMMARY

Labeled silver carbonate was prepared from barium carbonate- $^{13}\text{C}$  or - $^{14}\text{C}$  and aqueous silver nitrate in 95 to 100% yield. Diethyl carbonate- $^{13}\text{C}$  or - $^{14}\text{C}$  was generated in 60 to 85% overall yield by treatment of labeled silver carbonate with ethyl iodide and tetraethylammonium iodide in dimethylformamide. The effects of alterations in reaction time, metal ion, solvent and catalyst were investigated.

Key words: Diethyl carbonate, carbon 13, carbon 14, silver carbonate

INTRODUCTION

Diethyl carbonate- $^{14}\text{C}$  has been successfully utilized in the specific labeling of various oral anticoagulant drugs derived from 4-hydroxycoumarin (1-3). The yield of diethyl carbonate obtained by the original workers (1) was reported to be 9 to 30% (4). An improved method was reported to yield 40% (4) but in our hands gave only 6%. Because the addition of carrier was required in order to isolate the product, neither of these procedures is satisfactory for the synthesis of  $^{13}\text{C}$  labeled coumarin derivatives or the corresponding  $^{14}\text{C}$ -labeled compounds with high specific activity.

---

\*Nuclear Medicine Department, University of Connecticut Health Center,  
Farmington, Connecticut 06032

## RESULTS AND DISCUSSION

Labeled silver carbonate was prepared by a modification of the method reported by Tsuyuki and Simamura (4). We found that a six-fold increase in the amount of silver nitrate employed consistently gave yields in excess of 95%.

The main drawback of all earlier work has been in the conversion of silver carbonate to diethyl carbonate by reaction with ethyl iodide. The reported isotopically labeled product has always been made in non-polar aprotic media (triethylamine, diethyl ether). A study by Japanese workers (5) showed that sodium or potassium carbonate could be converted to various alkyl carbonates in moderate yield by heating the alkali salt with an alkyl halide in dimethylformamide solvent at 150°. Recently, Monsanto chemists reported (6) a major breakthrough in the synthesis of esters by the  $S_N2$  displacement of halide with carboxylate. They found that quarternary ammonium salts of a wide variety of single and polyfunctional carboxylic acids were esterified in high (50-100%) yield by stirring with an alkyl halide in a polar aprotic solvent at room temperature for several hours. This method seemed eminently suitable for the synthesis of carbonate esters as well, and in fact was found to give consistently good yields (60-85%, based on barium carbonate) when silver carbonate, produced metathetically from barium carbonate, was treated with ethyl iodide in dimethylformamide saturated with tetraethylammonium iodide.

This procedure was altered to test the effect of different cations, solvents, and temperatures on the reaction (see EXPERIMENTAL). Best results were obtained with silver ion as the cation, dimethylformamide as the solvent, and a saturated solution of tetraethylammonium iodide as the catalyst.

We found it was unnecessary to distill the product in order to obtain it in a form suitable for subsequent reactions. Excess ethyl iodide was destroyed with triethylamine. A single extraction procedure involving partitioning between buffered aqueous saline solution and cyclohexane was found to separate the diethyl carbamate from the dimethylformamide. The cyclohexane solution, after drying, could be used without further purification. This procedure eliminates the necessity of adding carrier diethyl carbonate at the isolation stage and thereby avoids uncontrolled isotopic dilution of the product. Precisely controlled dilution, if

desired, is easily accomplished by adding weighed quantities of carrier barium carbonate to the starting material.

#### EXPERIMENTAL

Solvents and various reagents were commercially available from common sources and were used without further purification unless specified. The amount of non-radioactive diethyl carbonate present in various reaction mixtures was measured by gas-liquid chromatography. Analyses were performed on a Hewlett-Packard Model 5750 Research Gas Chromatograph equipped with a flame ionization detector. A 6 ft 10% Carbowax column was used for all analyses. Injector temperatures ranged from 270°-290°. Detector temperatures ranged from 280°-300°. Helium was used as the carrier gas at a 25-30 ml/min flow rate. Mixtures containing only volatile solvents were analyzed isothermally at 100° oven temperature. Mixtures containing substances of low volatility or dimethylformamide were analyzed using temperature programming: 110° for 4 min, 60°/min rise to 210°, then 210° for 2 min. Sample volume was 2  $\mu\text{l}$ . Under these conditions diethyl carbonate has a retention time of 2.7-2.9 min. A Beckman LS-230 scintillation counter was used for radioactivity determinations, while all determinations were made in 10 ml Aquasol (New England Nuclear).

Silver Carbonate- $^{13}\text{C}$ -Silver nitrate (20 g) was dissolved in 50 ml distilled water contained in a flask wrapped in aluminium foil to exclude light. Finely powdered barium carbonate- $^{13}\text{C}$  (1.97 g, 0.01mol, 90 atom %  $^{13}\text{C}$ , Stohler Isotope Chemicals) was added to the solution, the flask sealed with aluminium foil, and magnetically stirred overnight. The silver carbonate- $^{13}\text{C}$  was filtered and washed consecutively with three 10 ml portions of distilled water, acetone and anhydrous diethyl ether. The pale yellow precipitate was air dried and used immediately. All manipulations were conducted in the dark or in subdued indirect incandescent lighting. This procedure gave consistent yields of silver carbonate- $^{13}\text{C}$  in the 95-100% range.

Silver Carbonate- $^{14}\text{C}$ -Silver carbonate- $^{14}\text{C}$  was obtained from barium carbonate- $^{14}\text{C}$  (New England Nuclear) suitably diluted with carrier barium carbonate to give the desired molar specific activity by the procedure described above.

Diethyl Carbonate-<sup>13</sup>C-To dimethylformamide (10 ml, dried over Linde 3A Molecular Sieves) in a flask wrapped with aluminum foil to exclude light, was added ethyl iodide (5.0 ml, 0.0625 mol) and triethylamine (2.0 ml, 0.0143 mol, distilled from barium oxide). The mixture was allowed to stand about 20 min, or until crystals of tetraethylammonium iodide first began to precipitate. Silver carbonate-<sup>13</sup>C (0.009-0.010 mol, freshly prepared) was then added. The mixture was stirred in total darkness for 6-12 hr, protected by a guard tube packed with a layer of anhydrous calcium sulfate and a layer of soda-lime (to prevent contamination by atmospheric CO<sub>2</sub>). Additional triethylamine (6.8 ml, 0.0488 mol) was added, and stirring was continued 6-12 hr. Cyclohexane (20 ml, dried over sodium) was added, and stirring was continued an additional 2 hr. The mixture was filtered by suction under normal room illumination, and the precipitate was washed with small portions of dimethylformamide (7.0 ml total) and cyclohexane (20 ml total). The filtrate was mixed with phosphate buffer (10 ml, 0.1 M, pH 7.0) and a saturated solution of sodium chloride (10 ml). The mixture was again filtered by suction; the two-phase filtrate was recovered and the lower aqueous phase was discarded. The upper phase contained cyclohexane, diethyl carbonate, and traces of triethylamine and dimethylformamide. It was dried over sodium sulfate and used without further purification. The cyclohexane may be conveniently removed by azeotropic distillation from most reactions in which the diethyl carbonate stock solution might be employed. The yield of diethyl carbonate (based on barium carbonate) is consistently in the range 60-85%. A second cyclohexane extraction of the aqueous phase recovers little additional diethyl carbonate but significantly increases the levels of contaminants.

A sample of diethyl carbonate-<sup>13</sup>C was prepared from barium carbonate-<sup>13</sup>C (diluted to 46 atom % <sup>13</sup>C with carrier barium carbonate) and used to prepare phenprocoumon-2-<sup>13</sup>C by a modification of the procedure of Goding and West (1). The product was analysed by mass spectrometry and found to contain the calculated amount of <sup>13</sup>C.

Diethyl Carbonate-<sup>14</sup>C-Diethyl carbonate-<sup>14</sup>C was prepared from silver carbonate-<sup>14</sup>C by the procedure described above. A sample of diethyl carbonate -<sup>14</sup>C was used to prepare phenprocoumon-2-<sup>14</sup>C (1); the molar specific activity of the product

was identical within experimental error to that of the barium carbonate starting material.

Effect of the Metal Ion on the Yield-Mixtures of dimethylformamide (10 ml), triethylamine (10 ml) and ethyl iodide (5 ml) were allowed to stand until tetraethylammonium iodide first began to precipitate. Then to each mixture was added the carbonate salt (0.010 mol) of the following metal cations; lithium, sodium, potassium, cupric, silver, magnesium, calcium, strontium, barium, and zinc. The reaction mixtures were shaken in total darkness at 37° for 48 hr. Under these conditions only the silver, potassium, and sodium salts reacted, yielding respectively 72%, 2%, and < 1 % diethyl carbonate.

Effect of Solvent, Temperature, and Reaction Time on Yield-A repetition of the procedure of Tsuyuki and Simamura (4), in which ether is used as the solvent and no triethylamine is added gave, in our hands, only a 6% yield. A series of experiments was conducted in which silver carbonate (0.010 mol), ethyl iodide (5.0 ml) and triethylamine (0.3-2.0 ml) were mixed in the solvents (50 ml) listed below and stirred for the times and at the temperatures indicated:

<u>Solvent</u>	<u>Temperature</u>	<u>Time</u>	<u>Yield</u>
Diethyl ether	20°C	50 hr	25%
Benzene	reflux	20 hr	40%
Ethanol	reflux	70 hr	40-60%
Tetrahydrofuran	reflux	96 hr	Trace

Effect of Triethylamine-When diethyl carbonate is prepared in dimethylformamide solvent by the method described above, but the triethylamine is omitted from the reaction mixture, the yield is reduced to 35-45% overall. When the complete mixture, including triethylamine, is allowed to stand several hours prior to the addition of the silver carbonate, stirring becomes extremely difficult and the yield is reduced to 40-55%.

#### ACKNOWLEDGMENTS

The authors wish to thank the American Foundation for Pharmaceutical Education for financial support (to W.R.P.) and Dr. William Garland for perform-

ing the high resolution mass spectroscopic analysis.

#### REFERENCES

1. Goding L. and West B. - J. Med. Chem. 12: 517 (1968).
2. Goding L. - Ph.D. Thesis, pp. 30-31, Univ. New Mexico (1969).
3. Eisenhaurer H., Pepper J., Jaques L. and Spinks J. - Canad. J. Chem. 30: 245 (1952).
4. Tsuyuki T. and Simamura O. - J. Org. Chem. 23: 1079 (1958).
5. Fukui K., Yoneda S., Takayama H. and Kitano H. - Kogyo Kagaku Zasshi 63: 2146 (1960).
6. Wagenknecht J., Baizer M. and Chruma J. - Syn. Comm. 2: 215 (1972).