Reaction of Isobutylene Carbonate with Secondary Amines. Observation of Kinetic and Thermodynamic Products

Constantine Sklavounos,* Irving M. Goldman, and Donald E. Kuhla

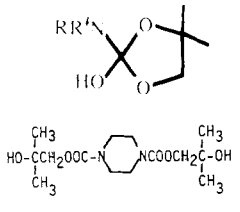
Chemical Process Research Department, Pfizer Inc., Central Research, Groton, Connecticut 06340

Received April 17, 1980

Unsymmetrical cyclic carbonates have been reported[1,2] to react with amines to give mixtures of the expected isomeric carbamates. Katzhendler and co-workers noted the effects of factors such as polarity and bulk of substituents on carbamate isomer distribution ratios but excluded the possibility of thermodynamic equilibration between the products under the reaction conditions.[2] We wish to report that the reaction of isobutylene carbonate (**1**, Scheme I) with secondary amines proceeds with initial formation of a kinetic product mixture (**2** and **3**) which indeed then undergoes equilibration to the thermodynamic product mixture comprised almost exclusively of **3**.

The reaction of isobutylene carbonate (**1**) with morpholine at 120 °C is illustrative as summarized in Table I. By use of a ^{1}H NMR assay to follow the rate of disappearance of starting materials and the appearance of products **2b** and **3b**, it was observed that a kinetic product mixture consisting of an excess of **2b** over **3b** was formed at the early stages of the reaction. As the reaction proceeded toward completion the **3b**/**2b** ratio increased to the thermodynamic equilibrium value of greater than 97:3. When the same reaction was run at 20 °C for 36 days, an approximately 50:50 mixture of **3b**/**2b** was obtained (also containing 20% starting materials). Compound **2b** was isolated from this mixture by column chromatography and shown to give **3b** in 98% yield when treated at room temperature in D_2O with excess morpholine. Equilibration of the product carbamates is therefore found to occur under both neat or aqueous reaction conditions similar to those employed by Katzhendler.[2] Both the aminolysis of **1** and the transformation of **2** to **3** appear to be most facile in polar protic solvents. For instance, in water[3] the reaction is complete (**1** completely consumed, **3**/**2** ratio of approximately 98:2) within 30 min at room temperature while in acetonitrile, Me_2SO, or excess amine (neat), considerably longer times or higher temperatures are necessary for completion.

The observation of a preponderance of **2** over **3** in the initial product mixture can be rationalized by invoking the intermediacy of a tetrahedral species such as **4**, with an



increased rate of bond cleavage to form primary alcohol, possibly resulting from the lower basicity of the primary alcohol and/or greater ease of protonation of the less hindered ether oxygen. The overall thermodynamic stability of **3** vs. **2** is thought to result from steric congestion of a tertiary over a primary carbamate.

Scheme I

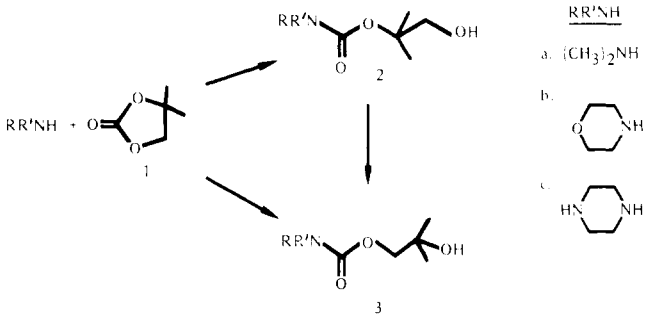


Table I. Monitoring of Reaction[a] of **1** with Morpholine at 130 °C

t, min	3b:2b	% unreacted **1**
15	40:60	76
45	57:43	52
180	80:20	35
330	90:10	21
1320	97:3	14

[a] Reaction conducted neat with equimolar amounts of starting materials.

This finding has provided an efficient synthesis of 2-hydroxy-2-methylpropyl piperazine-1-carboxylate (**3c**), a key intermediate in the preparation of important quinazoline antihypertensive agents,[4] from readily available starting materials.[5]

Experimental Section

General Methods. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers. The ^{13}C NMR spectra were obtained in the FFT mode on a Varian XL-100-15 (25 MHz) spectrometer equipped with a Nicolet Technology 1080 data system. Proton decoupling was provided by square-wave modulation[6] of the Varian gyroscope heteronuclear decoupler. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo by using either a water aspirator or a vacuum pump.

General Procedure for Preparation of Carbamates 3 in Water. To a solution of 0.1 mol of the appropriate amine in 36 mL of water was added 0.025 mol of isobutylene carbonate, and the mixture was stirred at ambient temperature for 30 min. The resulting solution was saturated with sodium chloride, and the product was extracted three times with 36-mL portions of methylene chloride. The organic layers were combined, dried ($MgSO_4$), and evaporated to give crude product which was then purified by either vacuum distillation or recrystallization (vide infra).

2-Hydroxy-2-methylpropyl (dimethylamino)formate (3a): yield 77.1%; bp 63–65 °C (0.2 mm); ^{1}H NMR (Me_4Si) δ_{CDCl_3} 1.25 (s, 6, *gem*-CH_3), 2.96 (s, 6, CH_3NCH_3), 3.96 (s, 2, CH_2); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 156.3 (C=O), 72.8 (CH_2), 69.3 (COH), 35.8 (CH_3NCH_3), 25.8 (*gem*-dimethyl).

Anal. Calcd for $C_7H_{15}NO_3$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.23; H, 9.24; N, 8.67.

2-Hydroxy-2-methylpropyl morpholine-1-carboxylate (3b): yield 75.2%; bp 128–130 °C (0.75 mm); ^{1}H NMR (Me_4Si) δ_{CDCl_3} 1.27 (s, 6, *gem*-CH_3), 3.57 (m, 8, morpholine protons), 3.97 (s, 2, CH_2); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 155.0 (C=O), 72.8 (CH_2), 69.3

(1) Baizer, M. M.; Clark, J. R.; Smith, E. *J. Org. Chem.* **1957**, *22*, 1706.
(2) Katzhendler, J.; Ringel, I.; Sarel, S. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2019.
(3) In this solvent 5–10% yield loss is realized due to competing hydrolysis of isobutylene carbonate.
(4) Hess, H.-J. U.S. Patent 3669968, 1972.
(5) Isobutylene carbonate may be obtained from the reaction of isobutylene oxide with carbon dioxide as described: Liehtenwalter, M.; Cooper, J. F. U.S. Patent 2773070; Depasquale, R. J. U.S. Patent 3748345; *J. Chem. Soc., Chem. Commun.* **1973**, 157.
(6) Grutzner, J. B.; Santini, R. E. *J. Magn. Reson.* **1975**, *19*, 1973.

0022-3263/80/1945-4239$01.00/0

(COH), 66.0 and 43.7 (morpholine C's), 25.9 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.12; H, 8.36; N, 7.19.

2-Hydroxy-2-methylpropyl piperazine-1-carboxylate (3c): yield 62.0%;[7] recrystallized from methyl isobutyl ketone/hexane or toluene; mp 80–81 °C; NMR (Me_4Si) δ_{CDCl_3} 1.23 (s, 6, *gem*-CH_3), 2.8 (m, 4, piperazine protons), 3.43 (m, 4, piperazine protons), 3.93 (s, 2, CH_2); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 155.0 (C=O), 72.7 (CH_2), 69.1 (COH), 44.4 and 45.2 (piperazine C), 26.0 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.49; H, 8.71; N, 13.55.

1,1-Dimethyl-2-hydroxyethyl Morpholine-1-carboxylate (2b). A mixture of 1.74 g (0.02 mol) of morpholine and 2.32 g (0.02 mol) of isobutylene carbonate was stirred at room temperature for 3 days. Analysis by NMR spectroscopy showed the mixture containing **2b** and **3b** in a 50:50 ratio and approximately 20% unreacted starting materials. The mixture was chromatographed on a silica gel column with 96:4 methylene chloride–methanol. Fractions found by TLC (silica gel, 8:2 methylene chloride–methanol, I_2 detection) to contain pure product were evaporated to dryness to give 0.96 g (23.6%) of **2b** as a yellow oil which crystallized on standing: mp 68–70 °C; ^1H NMR (Me_4Si) δ_{CDCl_3} 1.4 (s, 6, *gem*-CH_3), 3.3–3.8 (m, 10, morpholine and CH_2 protons), 4.43 (t, 1, OH); ^{13}C NMR (Me_4Si) δ_{CDCl_3} 155.2 (C=O), 83.7 (quaternary C), 69.4 (CH_2), 66.3 and 44.0 (morpholine C's), 23.6 (*gem*-dimethyl).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 52.95; H, 8.15; N, 6.89.

Conversion of 2b to 3b. To a solution of 35 mg of **2b** in 0.4 mL of D_2O in an NMR tube was added approximately 40 mg of morpholine, and the conversion of **2b** to **3b** was monitored by ^1H NMR. Within 20 min at ambient temperature the mixture contained **3b** and **2b** in a 98:2 ratio. Solutions of **2b** in D_2O or $CDCl_3$ containing no base were found to be stable at room temperature for at least 30 min.

Acknowledgment. We thank Dr. G. N. Chmurny for providing the ^{13}C NMR spectra.

Registry No. 1, 4437-69-8; **2a**, 74684-67-6; **2b**, 74684-68-7; **2c**, 73352-30-4; **3a**, 74684-69-8; **3b**, 74684-70-1; **3c**, 71649-29-1; morpholine, 110-91-8; dimethylamine, 124-40-3; piperazine, 110-85-0.

(7) Use of excess piperazine is necessary, in this case, to minimize yield loss due to formation of the diacylated piperazine compound.

A Novel Route for Functionalization of the Bridgehead C-2 Position of Benzomorphans[1]

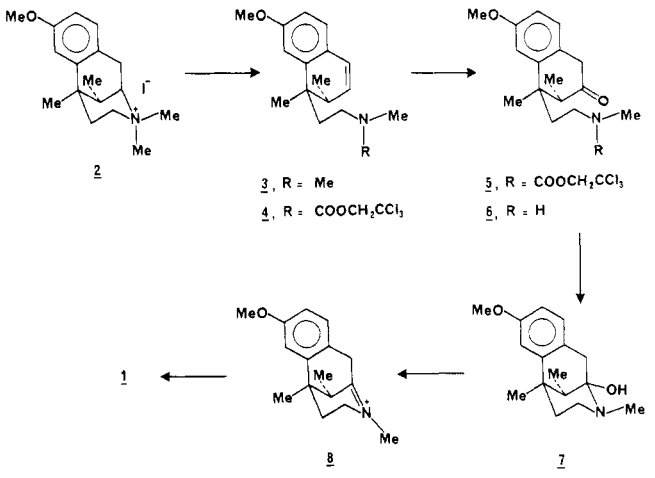
Kastooriranganathan Ramakrishnan and Philip S. Portoghese*

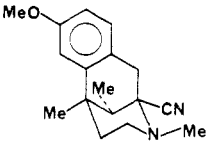
Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

Received May 13, 1980

Although hundreds of benzomorphans[1] containing substitution in different positions have been synthesized,[2,3] there is a noteworthy paucity of 2-substituted derivatives in this important class of compounds. The reason for this is the difficulty in creating a quaternary center at the C-2 position through conventional synthetic routes. In this report we describe a novel, practical approach to the attachment of a cyano group at this position, as exemplified by the synthesis of **1**.

Scheme I





1

The route to benzomorphan **1** is outlined in Scheme I. A key feature of the synthetic strategy involved the cyclization of tetralone **6** through an intramolecular Strecker-type reaction. In an effort to obtain **6** we subjected the quaternary compound **2** to a Hoffman elimination.[4] The dihydronaphthalene product (**3**) of this reaction was demethylated with trichloroethyl chloroformate[5] to afford the corresponding carbamate **4**, which was subsequently epoxidized with *m*-chloroperbenzoic acid. The product, which was a mixture of the epoxide and benzoate ester (arising from epoxide opening by nucleophilic attack of benzoate anion), was then subjected to acid-catalyzed rearrangement[6] to the ketone **5**.

When the amino group of **5** was deprotected with zinc and acetic acid, the anticipated intermediate **6** was not detected as a product. The infrared spectrum of the compound which was isolated possessed no carbonyl absorption and contained a peak at 3125 cm^{-1} which is attributable to OH. The spectral and analytical data suggest that the deprotected product is the carbinolamine **7**. The facility with which **7** forms is not surprising because there is ample precedent in the literature[7,8] for similar neighboring-group participation which leads to stable carbinolamine formation.

The target compound **1** was prepared in excellent yield by reacting **7** with KCN at pH 5.5. The reaction presumably occurs via the iminium intermediate **8**. Although **8** contains an sp^2-hybridized bridgehead carbon, such an intermediate would not violate Bredt's rule,[9] as the bicyclic system is large enough to accommodate a double bond at the bridgehead center.[8,10]

(1) Although the common name "benzomorphan" is used in our discussion, the numbering system of the chemical name, 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, is employed.

(2) D. C. Palmer and M. J. Strauss, *Chem. Rev.*, **77**, 1 (1977).

(3) J. Hellerbach, O. Schnider, H. Besendorf, B. Pellmont, N. B. Eddy, and E. L. May, "Synthetic Analgesics", Part II, Pergamon Press, New York, 1966.

(4) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(5) T. A. Montzka, J. D. Matiskella, and R. A. Partyka, *Tetrahedron Lett.*, 1325 (1974).

(6) J. G. Cannon, J. P. O'Donnell, J. R. Rosazza, and C. R. Hoppin, *J. Med. Chem.*, **7**, 565 (1974).

(7) M. G. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.*, **37**, 3489 (1972).

(8) H. O. Krabbenhoft, J. R. Wiseman, and C. B. Quinn, *J. Am. Chem. Soc.*, **96**, 258 (1974).

(9) G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, **12**, 464 (1973).

0022-3263/80/1945-4240$01.00/0