A Convenient Method for the Synthesis of Carbamate Esters from Amines and Tetraethylammonium Hydrogen Carbonate

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Organic carbamates represent an important class of compounds, largely employed in pharmacology (medical drugs), agriculture (pesticides, fungicides, herbicides), and chemical industry (intermediates of synthesis).[1] Their use as protective groups for the amine function of amino acids in peptide chemistry is also well-known.[2] Several attempts have been made to replace the classical syntheses, which involve the direct reaction of alcohols with phosgene or its derivative isocyanates, with new methodologies employing less toxic and dangerous reagents. Important results were obtained by means of both the homogeneous catalytic carbonylation of nitroaromatics[3] and the oxidative carbonylation of amines.[4] More recently carbon dioxide, a cheap and abundant reagent, has been proposed as a trouble-free starting material to replace phosgene.[5] The direct incorporation of carbon dioxide into amines, which leads to ionic carbamates, can be mediated by both metal and nonmetal species. These compounds behave as bidentate ions and, in the presence of an alkylating reagent, reactions of O-alkylation (formation of carbamic esters) and N-alkylation are both theoretically possible. In the case of metal−carbamates, electrophilic attack by alkylating reagents usually affords N-alkylation products.[6] Likewise, phosphocarbamates [$P(NR_2)_{3-x}(O_2CNR_2)_x$, obtained by insertion of CO_2 in the P−N bonds of aminophosphines] and alkylammonium carbamates (obtained by direct interaction of primary and secondary amines with CO_2)[7] react with alkyl halides mainly to give N-alkylation products.[6a,b] These results suggest that the transfer reaction of carbamate group from the intermediate ion pair to an alkylating reagent is strongly affected by the anion−cation interaction, which can depress the oxygen nucleophilicity. In fact, the alkylation of the carbamate anion provides the corresponding carbamates only in low to moderate yields and under drastic reaction conditions.[8] On the other hand, the addition of suitable crown ethers (capable of coordinating the cation) makes O-alkylation significantly competitive; the role of crown ethers in the synthesis of carbamic esters has been recently described.[5,9]

Recently, we investigated the synthesis of linear and cyclic carbamates by means of electrochemical procedures. In particular, we found that electrochemically activated carbon dioxide (by either direct reduction or by reaction with electrochemically generated superoxide ion) reacts, under mild reaction conditions, with several aliphatic and aromatic amines, as well as with *N*-acyl or *N*-alkoxycarbonyl alkylamines, affording the corresponding carbamates in high to excellent yields.[10] This reactivity is probably to be ascribed to tetraalkylammonium carbonate and peroxydicarbonate, which are formed as main products in the direct[11] or in the dioxygen-mediated[12] reduction of carbon dioxide, respectively. These considerations prompted us to investigate the reactivity of both tetraalkylammonium carbonates and hydrogen carbonates toward amines in order to develop a new class of carboxylating reagents.

Herein, we report a simple and safe methodology for the synthesis of linear and cyclic alkyl and aryl carbamates by reaction of amines with tetraethylammonium hydrogen carbonate (TEAHC). This compound was first used by Venturello[13a] in the synthesis of cyclic carbonates starting from the corresponding halohydrins.

TEAHC was simply obtained by saturating a methanol solution of commercially available tetraethylammonium hydroxide (TEAOH) with carbon dioxide.[13] The pale brown highly hygroscopic solid obtained after removal of the solvent was allowed to react, in acetonitrile at room temperature, with different amines **1** and alkylating

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(1) (a) Adams, P.; Baron, F. A. *Chem. Rev. (Washington, D.C.)* **1965**, *65*, 567. (b) Mateen, A.; Chapalamadugu, S., Kashar, B.; Batthi, A. R.; Chaudry, G. R. *Biol. Degrad. Biorem. Toxic. Chem.* **1994**, 198. (c) Wigfiled, Y. Y. *Food Sci. Technol. (N. Y.)* **1996**, *77* (Handbook of Food Analysis, vol. 2) 1501.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons, Inc.: New York, 1991; pp 315−348.

(3) (a) Ragaini, F.; Cenini, S.; Demartin, F. *J. Chem. Soc. Chem. Commun.* **1992**, 1467. (b) Ragaini, F.; Cenini, S. *Chim. Ind. (Milan)* **1996**, *18*, 421. (c) Tafesh, A. M.; Weiguny, J. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 2035. (d) Ragaini, F.; Cenini, S. *J. Mol. Catal. A Chem.* **1996**, *109*, 1. (e) Jakus, V.; Bojsova, E. *Collect, Czech. Chem. Commun.* **1992**, *57*, 1505. (f) Leconte, P.; Metz, F.; Mortreux, A.; Osborn, J. A.; Paul, F.; Petit, F.; Pillot, A. *J. Chem. Soc. Chem. Commun.* **1990**, *22*, 1616. (g) Bender, R.; Braunstein, P.; De Bellefon, C. D. M. *Polyhedron* **1988**, *7*, 2271. (h) Cenini, S.; Pizzotti, M.; Crotti, C.; Ragaini, F.; Porta, F. *J. Mol. Catal.* **1988**, *49*, 59.

(4) (a) Mulla, S. A. R.; Gupte, S. T.; Chaudhari, R. V. *J. Mol. Catal.* **1991**, *67*, L7. (b) Fukuoka, S.; Chono, M.; Kohno, M. *J. Org. Chem.* **1984**, *49*, 1458. (c) Fukuoka, S.; Chono, M.; Kohno, M. *J. Chem. Soc. Chem. Commun.* **1984**, 399. (d) Gupte, S. T.; Chaudhari R. V. *J. Catal.* **1988**, *114*, 246. (e) Abe, Y.; Nagao, Y.; Misono, T. *Chem. Express* **1988**, *3*, 727.

(5) (a) Aresta, M.; Quaranta, E. *Proceeding of the International Conference on Carbon Dioxide Utilization*, Bari; Italy 1993; pp 63−77. (b) Riley, D.; McGhee, W. D.; Waldman, T. *ACS Symp. Ser.* **1994**, *577*, 122. (c) Xanding, X.; Moulijn, J. A. *Energy Fuels* **1996**, *10*, 305. (d) Waldman, T. E.; McGhee W. D. *J. Chem. Soc. Chem. Commun.* **1994**, *957*. (e) McGhee, W. D.; Pan, Y.; Talley, J. J. *Tetrahedron Lett.* **1994**, *35*, 839.

(6) (a) Aresta, M.; Quaranta, E. *J. Chem. Soc., Dalton Trans.* **1992**, 1893. (b) Aresta, M.; Quaranta, E. *J. Org. Chem.* **1988**, *53*, 4153. (c) Belforte, A.; Calderazzo, F. *J. Chem. Soc., Dalton Trans.* **1989**, 1007.

(7) Schroth, W.; Schaedler, H. D.; Andersch, J. *Z. Chem.* **1989**, *29*, 129.

(8) (a) Yoshida, Y.; Ishii, S.; Watanabe, M.; Yamashita, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1534. (b) Hori, Y.; Nagano, T.; Nakao, S.; Fukuhara, T.; Taniguchi, H. *Chem. Express* **1986**, *1*, 224. (c) McGhee, W.; Riley, D. P.; Christ, M. E.; Christ, K. M. *Organometallics* **1993**, *12*, 1429.

(9) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**,*48*, 1515.

(10) (a) Casadei, M. A.; Inesi, A.; Micheletti Moracci, F.; Rossi, L. *Chem. Commun.* **1996**, 2575. (b) Casadei, M. A.; Micheletti Moracci, F.; Zappia, G.; Inesi, A.; Rossi, L. *J. Org. Chem.* **1997**, *62*, 6754 and references therein.

(11) (a) Ikeda, S.; Takagi, T.; Ito, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2517. (b) Gennaro, A.; Isse, A. A.; Severin, M. G.; Vianello, E.; Bhugun, I.; Savéant, J. M. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 3963 and references therein.

(12) Roberts, J. L., Jr.; Calderwood, T. S.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4667.

(13) (a) Venturello, C.; D'Aloisio, R. *Synthesis* **1985**, 33. (b) Aoyama, T.; Shina, E.; Ishikawa, J.; Sakurai, N. *Eur. Pat. Appl. EP* **1986**, 269, 949.

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Table 1. Reactivity of TEAHC with Different Amines and Alkylating Reagents

entry	R	R^1	R^2	X	yield[a]
1	C_6H_{11}	H	Et	Br	90
2	C_6H_{11}	H	*i*-Pr	Br	71
3	C_6H_{11}	H	*t*-Bu	Br	[b]
4	C_6H_{11}	H	Bn	Br	92
5	C_6H_{11}	H	Et	OTs	97
6	C_6H_{11}	H	Et	OCO_2Et	[b]
7	C_6H_{11}	H	Et	I	94
8	$PhCH_2$	H	Et	I	98
9	$Ph(CH_2)_3$	H	Et	I	94
10	Ph	H	Et	I	53
11	4-MeOPh	H	Et	I	76
12	$PhCH_2$	Me	Et	I	85
13	$CH_2{=}CHCH_2$	H	Et	I	80
14	Ph	Ph	Et	I	[b]

[a] Yields (%) refer to isolated carbamate except for entry 5 (GC yield). [b] Starting amines were recovered at the end of the reaction.

reagents. This procedure afforded the corresponding carbamates **2** in high to excellent yields (eq 1).

$$\underset{\mathbf{1}}{RR^1NH} \xrightarrow[2.\ R^2X]{1.\ Et_4NHCO_3} \underset{\mathbf{2}}{RR^1NCO_2R^2} + Et_4NX + H_2O \qquad (1)$$

The results are reported in Table 1. The yield of carbamate is affected by the nature of the alkylating reagent employed. Cyclohexylamine was used as model compound (entries 1−7). The corresponding carbamate was isolated in excellent yields when primary and benzylic halides were used (entries 1, 4, 7) and in good yield with isopropyl bromide (entry 2), while it was absent when a tertiary halide was employed (entry 3). Also, diethyl carbonate did not furnish the expected carbamate (entry 6). Ethyl tosylate was reactive, but the resulting carbamate needed to be separated from the unreacted starting tosylate present in the solution (entry 5).

The nucleophilicity of the amine represents another factor that modifies the reactivity and consequently the amount of carbamate obtained. Primary (entry 9), secondary (entry 12), benzylic (entry 8), and allylic (entry 13) amines all react in very good yields. Aromatic amines show a weaker reactivity compared to aliphatic ones. A moderate yield of carbamate (53%) results from the reaction of aniline (entry 10), while the reactivity is remarkably increased (76% yield of carbamate; entry 11) by the presence of an electron-donating group on the aromatic ring. The combination of steric and electronic effects completely inhibits the reaction; as a confirmation, diphenylamine turned out to be completely unreactive (entry 14).

When TEAHC was allowed to react with amines bearing a leaving group, a different reactivity was reported; cyclic carbamates were obtained as a result of an intramolecular nucleophilic substitution. Only moderate yields of oxazolidin-2-one and 1,3-oxazin-2-one were recovered from the corresponding *ω*-bromoethyl and propylamines, probably because of a competitive self-alkylation reaction of the substrate (Figure 1).

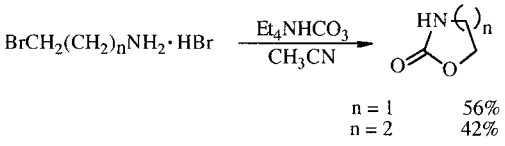

Figure 1. Reaction of TEAHC with amines bearing a leaving group.

Under our experimental conditions, the formation of tetraethylammonium carbamate can be supposed. Keeping in mind the previously noted difficulty in transferring carbamic ion into alkyl halide substrates, it follows that the presence of tetraethylammonium ion as counterion increases the nucleophilicity of oxygen, thus rendering the O-alkylation reaction prevalent with respect to the N-alkylation.

The reactivity of TEAHC toward a wide range of aromatic and aliphatic amines and alkylating reagents opens up the development of a novel, mild, and safe methodology for the synthesis of linear and cyclic carbamates. The mildness of the reaction conditions and the stability of reagent (if stored under argon TEAHC has a shelf life of several months), as well as its easy and cheap preparation, make this procedure a valuable alternative to the methodologies reported up to now.

Extension of this methodology to other classes of organic compounds is now under study.

Experimental Section

General. Amines were commercially available; purification by distillation or crystallization was carried out when necessary. Dry acetonitrile (Lab-scan, anhydroscan) was used as received. TEAHC was prepared as reported by Venturello[13a] starting from a methanol solution (25% w/w) of TEAOH (Fluka). The reagent was dried under vacuum for 24 h and then was stored under argon.

Reaction of Amines with TEAHC. General Procedure. Amine (1.0 mmol) was added to a stirred solution of TEAHC (1.5 mmol) in dry acetonitrile (15 mL). After 1 h, if necessary, a 5-fold excess of alkylating reagent was added and the reaction was stirred overnight. The progress of the reaction was monitored by TLC (silica gel, *n*-hexanes−ethyl acetate 7:3). Solvent was removed under reduced pressure and the residue extracted with ether. Flash chromatography, or simple filtration of the ethereal extracts, afforded the isolation of the carbamate. All the products were fully characterized by ^1H (200 MHz) and ^{13}C NMR (50.3 MHz), MS (EI, 70 eV; CI), melting point, and comparison with authentic samples,[10b] wherever possible.

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Supporting Information Available: ^1H and ^{13}C NMR of all the linear and cyclic carbamates obtained (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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