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A Safe and Mild Synthesis of Organic Carbonates from Alkyl Halides and Tetrabutylammonium Alkyl Carbonates

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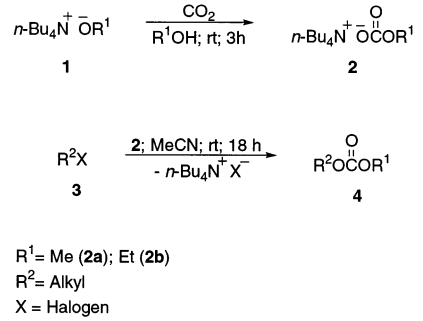
Abstract: A safe and mild procedure for the synthesis of mixed organic carbonates is described. Reaction of commercially available tetrabutylammonium methoxide and ethoxide with carbon dioxide yields the corresponding methyl and ethyl tetrabutylammonium carbonates (TBAMC and TBAEC). The reactions of these new compounds with several different alkyl halides give methyl and ethyl carbonates in high yields. The use of classic toxic and harmful chemicals such as phosgene and carbon monoxide is avoided.

Organic carbonates constitute an important and versatile class of substrates for a variety of industrial, synthetic, and medical applications. In particular, they are widely employed as solvents, intermediates, and protecting groups in the synthesis of several pharmaceuticals, plastics, lubricants, herbicides, and pesticides. Recently, great efforts have been made in order to find alternative and safe reagents to phosgene and carbon monoxide, traditionally utilized as first matters in industrial and laboratory synthesis of carbonates.[1,2] Among the different reagents, carbon dioxide represents a valuable and attractive choice because it is environmentally safe and economically inexpensive.

Our research group developed, in the last years, several different methods for the synthesis of linear and cyclic organic carbonates employing carbon dioxide derived reagents. In particular, tetraethylammonium peroxodicarbonate (TEAPC) and carbonate (TEAC) obtained by electrochemical methodologies were found to be suitable reagents in the carboxylation of alcohols to furnish carbonates.[3] Alternatively, we found that alcohols are successfully converted to carbonates when carbon dioxide was used combined with an electrochemically generated base in solutions containing tetralkylammonium cations.[4]

SCHEME 1. Preparation and Reaction of TBAMC and TBAEC with Alkyl Halides



In general, alkyl halides are not typical as starting materials for the synthesis of carbonates. The methods reported in the literature by Demlow[5] and Cella[6] consist of alkylation of alkali-metal carbonates and hydrogen carbonates performed by alkyl halides under phase-transfer catalysis (PTC) conditions at high temperature (100−150 °C). However, high reaction temperatures are frequently incompatible with remote functionalities eventually present in the substrate. In addition, the solubility of most metal carbonate salts in common organic solvents is negligible, and exotic and rather expensive alternative such as *N*-methyl-2-pyrrolidone or *N*,*N*-dimethylacetamide are used. Finally, when these methods are adopted, mixed dialkyl carbonates are obtained, only in poor reaction yields. With the aim to obtain carbonates from alkyl halides avoiding PTC, working under mild reaction conditions and with safe reagents, we proposed the synthesis of symmetrical carbonates as a results of a double nucleophilic substitution of alkyl halides by means of electrochemically generated TEAC.[7] Unfortunately, the presence of side reactions remarkably decrease the yield of carbonate in favor of alcohol formation.

Starting from the considerations reported above, we decided to develop a new methodology for the synthesis of organic carbonates, avoiding the drawbacks previously encountered. In particular, a novel mild and safe procedure for the synthesis of methyl and ethyl alkyl carbonates **4** by reaction of alkyl halides **3** with methyl and ethyl tetrabutylammonium carbonates (TBAMC and TBAEC respectively) **2** is reported (Scheme 1).

To our knowledge, there are not scientific works concerning the use of TBAMC and TBAEC as reagents for carboxylation reaction reported in the literature. These novel compounds are synthesized by the insertion reaction of carbon dioxide into tetrabutylammonium methoxide (TBAM) and ethoxide (TBAE), respectively. The reaction is simply performed by saturating with

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TABLE 1. Synthesis of Methyl and Ethyl Alkyl Carbonates 4 from Alkyl Halides and TBAMC 2a and TBAEC 2b, Respectively

entry	substrate	R^2	X	**3**/**2** ratio	*T* (°C)	time (h)	product and yield[a] (%)
1	**2a**	$Ph(CH_2)_3$	Br	1.25:1	25	18	**4a**, 67[b]
2	**2a**	$Ph(CH_2)_3$	Br	1:1.00	25	18	**4a**, 45
3	**2a**	$Ph(CH_2)_3$	Br	1:1.25	25	18	**4a**, 73
4	**2a**	$Ph(CH_2)_3$	Br	1:1.50	25	18	**4a**, 75
5	**2a**	$Ph(CH_2)_3$	Br	1:1.25	−25	18	**2a**, 95
6	**2a**	$Ph(CH_2)_3$	Br	1:1.25	0	18	**4a**, 47
7	**2a**	$Ph(CH_2)_3$	Br	1:1.25	80	4	**4a**, 81
8[c]	**2a**	$Ph(CH_2)_3$	Cl	1:1.25	25	40	**2a**, 94
9	**2a**	$PhCH_2$	Br	1:1.25	25	18	**4b**, 86
10	**2a**	$PhCH_2$	Br	1.30:1	25	18	**4b**, 84[b]
11	**2a**	$Ph(CH_2)_2$	Br	1:1.25	25	18	**4c**, 71
12	**2a**	$Ph(CH_3)CH$	Br	1:1.25	25	18	**4d**, 88
13	**2a**	$Ph_2CH(CH_2)_2$	Br	1:1.25	25	18	**4e**, 68
14	**2a**	$Ph(CH_2)_2$	I	1:1.25	25	18	**4c**, 60
15	**2b**	$PhCH_2$	Br	1:1.25	25	18	**4f**, 90
16	**2b**	$Ph(CH_2)_3$	Br	1:1.25	25	18	**4g**, 66
17	**2b**	$Ph(CH_2)_2$	Br	1:1.25	25	18	**4h**, 74
18	**2b**	$Ph(CH_3)CH$	Br	1:1.25	25	18	**4i**, 91

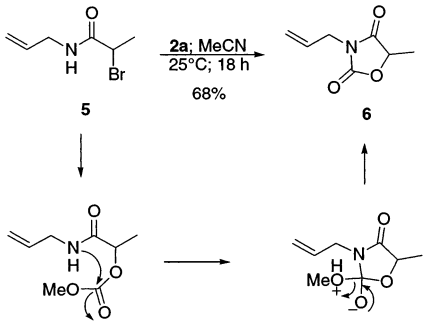
[a] Yields refer to isolated carbonate and are calculate on the amount of starting alkyl halide unless otherwise noted. [b] Yields calculated on starting tetrabutylammonium carbonate. [c] The presence of a catalytic amount of tetrabutylammonium iodide does not modify the course of the reaction.

carbon dioxide commercially available methanolic and ethanolic solution of TBAM and TBAE. Evaporation of the solvent yields a white or yellowish highly hygroscopic solid that is dried under vacuum. The solid thus obtained is keeped under argon in a desiccator and, if correctly stored, may be used for several months without loss in activity. The dialkyl carbonates are obtained after addition of the desired alkyl halides to a stirred solution of TBAMC or TBAEC in acetonitrile at room temperature for 18 h. Evaporation of the solvent and simple purification of the residue through a short pad of silica gel, to eliminate the tetrabutylammonium halides formed during the reaction, yields the desired carbonates (in some cases, flash column chromatography was required for purification). The reaction proceeds through a nucleophilic substitution of the halogen atom in the alkyl halide with the carbonate moiety. The tetrabutylammonium counterion (n-Bu_4N^+) if compared with the classical alkali-metal cations ensures a complete solubility of the carbonate in the organic solvent, thus making the carbonate anion naked and entirely available to induce nucleophilic substitution.

The results obtained in several experiments are reported in Table 1. Preliminary experiments were carried out to outline the best reaction conditions; (3-phenyl)-propyl bromide was used as the model compound (entries 1−7).

Since comparable reaction yields were obtained when an excess of alkylammonium carbonates or, in alternative, of alkyl halides was used (compare entries 1 and 3 or 9 and 10), it was preferred to carried out the reaction using an excess of carbonate to avoid, whenever possible, the chromatographic separation of the unreacted halide. An excess of **2** was necessary to obtain satisfactory yields; however, use of large carbonate excess did not further remarkably increase the reaction yields (entries 2−4). Concerning the reaction temperature, reaction kinetic at low temperature was particularly slow and resulted in a partial or total recover of the starting halides (entries 5 and 6). Although high temperatures seemed to slightly increase the product yield (entry 7), it was preferred to carry out the reaction at room temperature in such a way to preserve thermolabile groups eventually present in the molecule.

SCHEME 2. Synthesis of Malidone 6



The reaction was quite general and proceed without distinction when primary or secondary alkyl halides are used; alkyl chloride did not react in the reported reaction condition even if catalytic amount of tetrabutylammonium iodide were added to the reaction medium (entry 8).

To verify the potential synthetic application of the methodologies, the synthesis of malidone (3-allyl-5-methyloxazolidine-2,4-diones) **6**, a biologically active compound with interesting therapeutic properties,[8] was performed starting from α-bromoamide **5**. A cyclization reaction took place yielding the oxazolidin-2,4-dione **6** in good yield. This behavior could be explained by admitting a two-step reaction, the second step being a nucleophilic addition of the nitrogen atom to the carbonylic carbon of the carbonate followed by elimination of methanol (Scheme 2). This hypothetical reaction pathway was supported by the substantial recovery of starting materials in the reaction of benzylamine with TBAMC.

In summary, the method reported allows the synthesis of different methyl and ethyl alkyl carbonates in high yields using mild reaction conditions and safe reagents. The innocuous and cheap carbon dioxide is used as carboxylating agent in a formal two-step reaction comprising the synthesis of alkylammonium carbonates and the subsequent nucleophilic substitution reaction of the carbonate obtained with different alkyl halides. The method is susceptible of further improvements; in particular, we intend to study the reactivity of substrates having alkyl and aryl groups different than methyl ethyl and butyl, obtained by the reaction of tetralkylammonium alkoxides and aryl oxides containing different alkylammonium groups with carbon dioxide.

Experimental Section

Commercially available alkyl halides were used, except α-bromoamide **5**.[9] All the products were fully characterized by spectroscopic and elemental analysis and comparison with authentic samples (wherever possible) or data reported in the literature.

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General Procedure for the Synthesis of TBAMC or TBAEC. A commercial solution (50 mL) of TBAM (∼20% in MeOH) or TBAE (∼40% in EtOH) was bubbled with CO_2 at room temperature for 3 h. The solvent was then evaporated under reduced pressure, and the resulting slurry was kept under vacuum with vigorous stirring for 48 h yielding a white (TBAMC) or yellowish (TBAEC) solid that was stored under argon.

Tetrabutylammonium methyl carbonate **2a**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 1.00 (t, 12H, J = 6.1 Hz), 1.46 (sxt, 8H, J = 6.1 Hz), 1.55−1.80 (m, 8H), 3.30−3.45 (m, 8H), 3.51 (s, 3H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 13.71, 19.77, 24.05, 52.15, 58.73, 158.24; IR (KBr) 2940, 2880, 1670 cm^{-1}.

Tetrabutylammonium ethyl carbonate **2b**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 1.00 (t, 12H, J = 7.3 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.44 (sxt, 8H, J = 7.2 Hz), 1.55−1.80 (m, 8H), 3.30−3.55 (m, 8H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 13.72, 15.71, 19.77, 24.07, 58.72, 59.76, 157.92; IR (KBr) 2940, 2880, 1670 cm^{-1}.

General Procedure for the Synthesis of Carbonates. Alkyl halide (1.00 mmol) was added under argon to a stirred solution of TBAMC or TBAEC (1.25 mmol) in MeCN (10 mL) at room temperature. The mixture was stirred for 18 h at room temperature, and then the solvent was evaporated and the residue filtered through a short pad of silica gel (60−230 mesh) yielding the desired carbonate.

Benzyl methyl carbonate **4b**,[10] benzyl ethyl carbonate **4f**,[3a,10] ethyl (3-phenyl)propyl carbonate **4g**,[3a,11] ethyl (1-phenyl)ethyl carbonate **4i**,[3a] and 3-allyl-5-methyloxazolidine-2,4-diones **6**[9] are known compounds

Methyl 3-phenylpropyl carbonate **4a**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 1.85−2.10 (m, 2H), 2.64 (t, 2H, J = 7.3 Hz), 3.71 (s, 3H), 4.08 (t, 2H, J = 6.5 Hz), 7.05−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 30.25, 31.87, 54.70, 67.33, 126.05, 128.40, 128.46, 140.96, 155.82; GCMS *m*/*z* 119, 103, 91, 77, 65. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.30.

Methyl (2-phenyl)ethyl carbonate **4c**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 2.88 (t, 2H, J = 7.0 Hz), 3.65 (s, 3H), 4.24 (t, 2H, J = 7.1 Hz), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 35.05, 54.61, 68.30, 126.60, 128.48, 128.85, 137.17, 155.64; GCMS *m*/*z* 104, 91, 78, 65. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.62; H, 6.73.

Methyl (1-phenyl)ethyl carbonate **4d**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 1.48 (d, 3H, J = 6.6 Hz), 3.62 (s, 3H), 5.62 (q, 1H, J = 6.6 Hz), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 22.20, 54.48, 76.31, 125.91, 128.03, 128.45, 140.96, 155.04; GCMS *m*/*z* 180 (M^+), 148, 121, 104, 91 78. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.64; H, 6.73.

Methyl (3,3-diphenyl)propyl carbonate **4e**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 2.33 (q, 2H, J = 7.9 Hz), 3.66 (s, 3H), 3.9−4.1 (m, 2H + 1H), 7.0−7.4 (m, 10H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 34.25, 47.15, 54.70, 66.31, 126.45, 127.75, 128.59, 143.76, 155.68; GCMS *m*/*z* 195 ($M^+ - OCO_2CH_3$), 179, 167 (Ph_2CH), 152, 116, 91, 77. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.49; H, 6.73.

Ethyl (2-phenyl)ethyl carbonate **4h**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 1.20 (t, 3H, J = 7.1 Hz), 2.89 (t, 2H, J = 7.2 Hz), 4.09 (q, 2H, J = 7.1 Hz), 4.25 (t, 2H, J = 7.2 Hz), 7.00−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 14.21, 35.10, 63.87, 68.21, 126.60, 128.50, 128.88, 137.23, 155.06; GCMS *m*/*z* 104, 91, 78. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.99; H, 7.25.

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