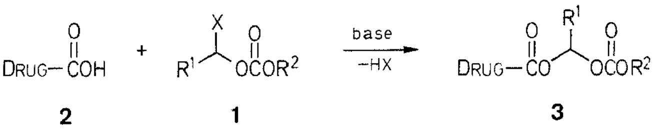
A Convenient New Route to 1-Haloalkyl Carbonates

Jean-Pierre Senet, Gérard Sennyey, Gary P. Wooden*

SNPE, Centre de Recherches du Bouchet, F-91710 Vert-le-Petit, France

Alkyl (or alkenyl or aryl) 1-haloalkyl carbonates are conveniently prepared by reaction of an aldehyde with an alkyl (or alkenyl or aryl) carbonohalidate (haloformate) in the presence of a catalyst.

In the past 15 years, there have been numerous publications and patents claiming applications of 1-haloalkyl carbonates (**1**) such as the synthesis of carbonofluoridates (fluoroformates),[1] pesticides,[2] protected amines,[3] and active esters.[4] However, for the most part, the 1-haloalkyl carbonates have been used to modify the acid function of certain types of drugs (**2**) according to the following scheme:



Among the many types of prodrugs **3** patented which use this method of protection, there are examples of antibiotics,[5,6] analgesics and antiinflammatory compounds,[7,8] antihypertensives,[9] and antifibrinolytically active drugs.[10]

Normally, simple 1-chloroalkyl carbonates (**1**, X = Cl) are prepared by reaction of the corresponding 1-chloroalkyl carbonochloridate (chloroformate)[11] ($R^1CHClOCOCl$) with an alcohol (R^2OH).[12] This method is very useful and gives good yields. Another older method of preparation involves the free-radical chlorination of carbonates.[13] However, as expected, this yields a mixture of products which requires separation by fractional distillation.

There are no examples of 1-fluoroalkyl carbonates (**1**, X = F) in the literature and the 1-bromoalkyl[14] and 1-iodoalkyl[6] carbonates have previously been prepared by halide exchange from the corresponding 1-chloroalkyl carbonates. With the continually increasing number of commercial and synthetic applications of 1-haloalkyl carbonates, we considered that a new route to a broader class of these compounds would be very useful. Our studies led to the discovery of a different method of preparation in which an aldehyde **4** is submitted to the reaction with a carbonohalidate (haloformate, **5**) in the presence of a catalyst:

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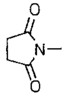
Table 1. Preparation of 1-Haloalkyl Carbonates (**1**)

Product **1**	R^1	X	R^2	Catalyst	Molecular Ratio **4** : **5** : Catalyst	Solvent[a]	Temperature (°C), Time (h)	Yield[b]	bp (°C)/Torr [mp (°C)]	Molecular Formula[c] or Lit. Data
a	CH_3	Cl	C_6H_5	pyridine	1.4 : 1.0 : 0.05	DCE	80, 5	71	67–68/0.15	101–104/3[16]
b	CCl_3	Cl	$CHClCH_3$	pyridine	1.0 : 1.0 : 0.09	DCE	83, 1	90	69–70/0.15	$C_5H_5Cl_5O_3$ (290.4)
				quinoline	1.08 : 1.0 : 0.05	DCE	83, 7	(89)[d]		
				1-methylimidazole	1.07 : 1.0 : 0.06	DCE	83, 11	(66)[d]		
				$PhNEt_2$	1.07 : 1.0 : 0.07	DCE	83, 11	(36)[d]		
				4,4'-bis(dimethylamino)benzophenone	1.05 : 1.0 : 0.06	DCE	83, 11	(83)[d]		
				$(n\text{-}C_6H_{13})_4NCl$	1.2 : 1.0 : 0.04	toluene	100, 6	87[d]		
				Bu_3P	1.06 : 1.0 : 0.05	DCE	83, 11	(72)[d]		
				Ⓟ$-CH_2PBu_3Cl$[e]	1.10 : 1.0 : 0.04	DCE	83, 11	(78)[d]		
				KCl/18-crown-6	1.05 : 1.0 : 0.16/0.17	DCE	83, 17	(57)[d]		
				no catalyst	1.05 : 1.0 : 0	DCE	83, 3	(0)[d]		
c	CH_3	Cl	$CHClCH_3$	pyridine	1.6 : 1.0 : 0.05	DCE	60, 4	49	67–72/9	$C_5H_8Cl_2O_3$ (187.0)
d	CCl_3	Cl	CH_2Cl	pyridine	1.1 : 1.0 : 0.04	DCE	80, 5	76	60–61/0.11	$C_4H_3Cl_5O_3$ (276.3)
e	C_6H_5	Cl	$C(CH_3)=CH_2$	pyridine	1.1 : 1.0 : 0.05	DCE	83, 20	67	92–96/0.2	$C_{11}H_{11}ClO_3$ (226.7)
f	CCl_3	Cl	$CHClCCl_3$	pyridine	1.6 : 1.0 : 0.06	DCE	80, 4	88	90–95/0.04 [63–64]	[64][17]
g	CCl_3	Cl	$CHClCH=CH_2$	$BzlNPr_3Cl$	1.1 : 1.0 : 0.06	DCE	80, 18	49	74–76/0.03	$C_6H_5Cl_5O_3$ (302.4)
h	CCl_3	Cl		pyridine	1.0 : 1.0 : 0.2	DCE	80, 1	40[d]	[108]	[108][4]
i	CH_3	Cl	$CH=CCl_2$	pyridine	1.5 : 1.0 : 0.05	DCE	80, 1.5	83	44–45/0.1	$C_5H_5Cl_3O_3$ (219.5)
j	$c\text{-}C_6H_{11}$	Br	CH_2CCl_3	5-ethyl-2-methylpyridine	1.08 : 1.0 : 0.05	DCE	83, 4	37[d]	117–120/0.04	$C_{10}H_{14}BrCl_3O_3$ (368.5)
k	CH_3	Br	C_6H_5	pyridine	1.5 : 1.0 : 0.03	DCE	83, 1	82	74–79/0.03	$C_9H_9BrO_3$ (245.1)
l	CH_3	I	C_6H_5	pyridine	1.6 : 1.0 : 0.05	DCE	70, 1.5	80	93–97/0.45 [59–61]	$C_9H_9IO_3$ (292.1)
m	CCl_3	F	C_6H_5	DMAP[a]	1.06 : 1.0 : 0.05	CH_3CN	82, 24	32	82–86/0.03	$C_9H_6Cl_3FO_3$[g] (287.5)
n	$(CH_3)_2CCl$	F	C_2H_5	KF/18-crown-6	1.0 : 1.4 : 0.63/0.13	–	55, 36	76[f]	60–63/2.5	$C_7H_{12}ClFO_3$ (198.6)
o	H	F	$(CH_2)_7CH_3$	KF/18-crown-6	2.4 : 1.0 : 1.0/0.13	CH_3CN	65, 2	76	82–85/2.5	$C_{10}H_{19}FO_3$ (206.3)
p	CCl_3	F	C_2H_5	KF/18-crown-6	1.0 : 1.3 : 1.5/0.09	CH_3CN	65, 20	72[f]	77–78/5	$C_5H_6Cl_3FO_3$ (239.5)

[a] DCE = 1,2-dichloroethane, DMAP = 4-dimethylaminopyridine.

[b] Yield of isolated product, based on **5**. Yield in parentheses determined by GLC.

[c] Satisfactory microanalyses obtained: C ±0.51, H ±0.07, Cl ±0.45, Br ±0.27, I ±0.23.

[d] Reaction conditions not optimized.

[e] Polystyrene-bonded tributylmethylphosphonium chloride cross-linked with 1% divinylbenzene (Fluka).

[f] Yield of isolated product, based on **4**.

[g] MS (70 eV): m/z = 290 (1%), 288 (2), 286 (2), 94 (100), 77 (84), 65 (61); recorded on a Riber-Nermag spectrometer.

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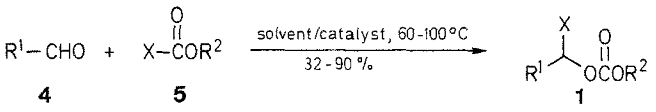
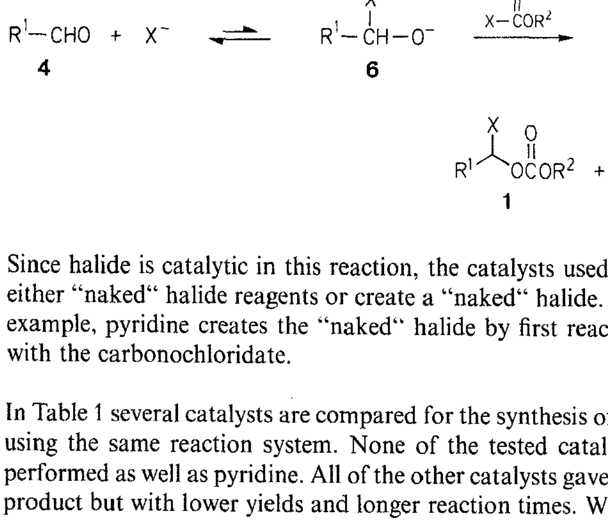


X = F, Cl, Br, I

A similar, but much less general procedure for the preparation of certain 1-chloroalkyl carbonates has been described,[15] but this normally requires a large excess of one of the starting materials and gives low yields. Our method complements the usual 1-chloroalkyl carbonate synthesis[11,12] by giving access to carbonates in which the alcohol (R^2OH) doesn't exist. It is also general enough to be used for the preparation of the 1-fluoroalkyl, 1-bromoalkyl, or 1-iodoalkyl carbonates (**1**, X = F, Br, or I).

This method is quite simple and generally gives good yields. In some cases, the reaction is reversible (**1** $\rightleftharpoons$ **4** + **5**), therefore the catalyst is usually eliminated by water washes before distillation of **1**. The only inconvenience in this method lies in the inability to prepare some products due to the instability of certain carbonohalidates **5** at 60–100 °C in the presence of the catalyst. For example, attempts to prepare **1** (with $R^1 = CH_3$, $R^2 = CH_2CH_3$, and X = Cl) in 1,2-dichloroethane at 60 °C with 0.05 equivalents of pyridine gave almost total decomposition of the carbonochloridate **5** and only a 6% yield. However, since products from less stable carbonohalidates are usually more easily prepared by one of the existing methods,[6,11,12] our procedure provides an alternate route to more complex and otherwise inaccessible 1-haloalkyl carbonates.

The mechanism of the formation of **1** probably involves the nucleophilic attack of halide on the aldehyde followed by attack of the intermediate **6** on the carbonohalidate **5**:



Since halide is catalytic in this reaction, the catalysts used are either "naked" halide reagents or create a "naked" halide. For example, pyridine creates the "naked" halide by first reacting with the carbonochloridate.

In Table 1 several catalysts are compared for the synthesis of **1b** using the same reaction system. None of the tested catalysts performed as well as pyridine. All of the other catalysts gave the product but with lower yields and longer reaction times. When the reaction was attempted without a catalyst, no product was formed.

For the preparation of the fluoro derivatives **1n, o, p**, different conditions were required to obtain good yields. Here, the best catalytic system found was the KF/18-crown-6 complex (Table 1). To avoid side reactions, only aldehydes without hydrogen at C-2 should be used in these cases.

In conclusion, the availability of compounds **1** by our new procedure coupled with the older procedures should open up new and promising applications for 1-haloalkyl carbonates.

Table 2. Spectral Data of Compounds **1**

1	IR (film)[a] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[b] δ, J(Hz)
a	1775	1.73 (d, 3H, $J = 6$); 6.37 (q, 1H, $J = 6$); 6.8–7.5 (m, 5H)
b	1780	1.86 (d, 3H, $J = 6$); 6.40 (q, 1H, $J = 6$); 6.64 (s, 1H)
c	1780	1.80 (d, 6H, $J = 6$); 6.35 & 6.40 (q, 2H, $J = 6$, diastereoisomers)
d	1785	5.73 (s, 2H); 6.60 (s, 1H)
e	1770, 1675	1.92 (s, 3H); 4.65 (s, 1H); 4.78 (s, 1H); 7.1–7.7 (m, 6H)
f	1792[c]	6.67 (s)
g	1782	5.2–6.5 (m, 3H); 6.68 (s, 1H); 6.72 (d, 1H, $J = 5$)
h	1760[c]	2.90 (s, 4H); 6.60 (s, 1H)
i	1782	1.86 (d, 3H, $J = 6$); 6.42 (q, 1H, $J = 6$); 7.46 (s, 1H)
j	1770	0.8–2.5 (m, 11H); 4.78 (s, 2H); 6.35 (d, 1H, $J = 5$)
k	1775	1.98 (d, 3H, $J = 6$); 6.56 (q, 1H, $J = 6$); 6.9–7.6 (m, 5H)
l	1772	2.30 (d, 3H, $J = 6$); 6.75 (q, 1H, $J = 6$); 7.0–7.6 (m, 5H)
m	1790	6.43 (d, $J = 53$); 7.0–7.6 (m, 5H)
n	1770	1.31 (t, 3H, $J = 7$); 1.57 (s, 6H); 4.21 (q, 2H, $J = 7$); 6.04 (d, 1H, $J = 55$)
o	1760	0.89 (t, 3H, $J = 6$); 1.30 (m, 14H); 4.12 (t, 2H, $J = 6$); 5.58 (d, 2H, $J = 52$)
p	1770	1.32 (t, 3H, $J = 7$); 4.30 (q, 2H, $J = 7$); 6.35 (d, 1H, $J = 54$)

[a] Recorded on a Beckman Acculab 4 spectrometer.
[b] 60 MHz NMR spectra recorded on a Varian EM 360 spectrometer.
[c] In CH_2Cl_2.

The commercially available aldehydes and carbonochloridates (chloroformates) were freshly distilled before use. 2-Chloro-2-methylpropanal,[18] the 1-chloroalkyl carbonochloridates,[11] isopropenyl carbonochloridate,[19] 2,2-dichlorovinyl carbonochloridate,[20] phenyl carbonoiodidate,[21] and the carbonofluoridates[22] were prepared according to literature procedures.

Carbonobromidates; General procedure:

A steady stream of anhydrous HBr is introduced into a solution of the appropriate carbonochloridate (140 mmol) and tetrabutylammonium bromide (1.0 g, 3 mmol) heated at 110 °C. After ~ 5 h, Br/Cl exchange is almost complete (monitored by GLC). The HBr stream is stopped and the product is isolated by careful fractional distillation under reduced pressure.

2,2,2-Trichloroethyl Carbonobromidate; yield: 89 %; bp 95–98°/35 Torr.

$C_3H_2Cl_3BrO_2$ (256.3)

IR (film): ν = 1780 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 4.86 (s).

Phenyl Carbonobromidate; yield: 91 %; bp 96 °C/20 Torr.

$C_7H_5BrO_2$ (201.0)

IR (film): ν = 1778 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 6.8–7.5 (m).

1-Chloroethyl Phenyl Carbonate (1a); Typical Procedure:

Pyridine (0.20 g, 2.5 mmol) is added to a stirred solution of phenyl carbonochloridate (8.0 g, 50 mmol) and acetaldehyde (3.2 g, 70 mmol) in 1,2-dichloroethane (30 mL). The solution is heated at 80 °C for 5 h, cooled to room temperature, and washed with H_2O (50 mL). The layers are separated and the aqueous phase is back-extracted with CH_2Cl_2 (50 mL). The organic phases are combined, dried ($MgSO_4$), and concentrated. The product **1a** is isolated by vacuum distillation; yield: 7.3 g (71 %); bp 67–68 °C/0.15 Torr.

1-Fluoromethyl Octyl Carbonate (1o); Typical Procedure:

A mixture of octyl carbonofluoridate (2.40 g, 14 mmol), KF (1.32 g, 14 mmol), and 18-crown-6 ether (0.47 g, 2.0 mmol) in CH_3CN (20 mL) is heated at 65 °C. In another reactor, paraformaldehyde (Aldrich; 1.00 g, 33 mmol) is heated with a heat gun to generate the gaseous monomer. The formaldehyde gas is bubbled into the first reactor

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through a heated tube which has its outlet below the surface of the liquid. After 2 h at 65 °C, the mixture is diluted with CH_2Cl_2 (50 mL), washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and vacuum distilled; yield: 2.1 g (76%); bp 82–85 °C/2.5 Torr.

The authors are grateful to Dr. Vu Dang and Prof. R. A. Olofson for the three KF/18-crown-6 results listed in Table 1.

Received: 18 August 1987; revised: 7 January 1988

(1) Piteau, M., Senet, J.-P., Wolf, P., Dang, V.A., Olofson, R.A. *Fr. Demande* 2571049 (1986), SNPE; *C.A.* **1987**, *106*, 4532.

(2) Theobald, H., Adolphi, H. *Ger. Offen.* 2628410 (1978), BASF AG; *C.A.* **1978**, *88*, 190080.

(3) Barcelo, G., Senet, J.-P., Sennyey, G. *J. Org. Chem.* **1985**, *50*, 3951.

(4) Jaouadi, M., Martinez, J., Castro, B., Barcelo, G., Sennyey, G., Senet, J.-P. *J. Org. Chem.* **1987**, *52*, 2364.

(5) Ekström, B.A., Sjöberg, B.O.H. *Ger. Offen.* 2144457 (1972), Astra Lakemedel AB; *C.A.* **1972**, *77*, 48452.

(6) Gregson, M. *Ger. Offen.* 2816873 (1978), Glaxo Laboratories Ltd.; *C.A.* **1979**, *90* 152209.

(7) Dorn, C.P. *Eur. Pat. Appl.* 82404 (1983), Merck & Co., Inc.; *C.A.* **1983**, *99*, 158031.

(8) Marfat, A. *Eur. Pat. Appl.* 147177 (1985), Pfizer Inc.; *C.A.* **1986**, *104*, 19596.

(9) Alexander, J., Shih, C. *US Patent* 4426391 (1984), Merck & Co., Inc.; *C.A.* **1984**, *100*, 175287.

(10) Svahn, C.M.E., Merenyi, F., Karlsson, L.E., Hanshoff, G. *Eur. Pat. Appl.* 79872 (1983), Kabi Vitrum AB; *C.A.* **1983**, *99*, 175264.

(11) Cagnon, G., Piteau, M., Senet, J.-P., Olofson, R.A., Martz, J.T. *Eur. Pat. Appl.* 40153 (1981), SNPE; *C.A.* **1982**, *96*, 142281.

(12) Barcelo, G., Senet, J.-P., Sennyey, G., Bensoam, J., Loffet, A. *Synthesis* **1986**, 627.

(13) Grignard, V., Rivat, G., Urbain, E. *C.R. Acad. Sci.* **1919**, *169*, 1143; *C.A.* **1920**, *14*, 739.

(14) Vaya, J., Kaspi, J., Ladkani, D., Salemnick, G., Schoenberger, C., Yellin, H., Cherkez, S. *Eur. Pat. Appl.* 108547 (1984), Orvet B.V.; *C.A.* **1984**, *101*, 130508.

(15) *Jpn. Patent* 60/72846 (1985), Mitsubishi Chem. Ind. Co., Ltd.; *C.A.* **1985**, *103*, 123021.
Susumu, J., Otomo, K., Tokunaga, H., Inayoshi, Y. *Jpn. Patent* 60/252449 (1985), Hodogaya Chemical Co., Ltd.; *C.A.* **1986**, *104*, 186006.

(16) Dang, V.A. *Ph. D. Thesis*, The Pennsylvania State University, 1986.

(17) *DRP* 121223 (1901), Bayer & Co.; *Chem. Zentralbl.* **1901**, *II*, 69.

(18) Stevens, C.L., Gillis, B.T. *J. Am. Chem. Soc.* **1957**, *79*, 3448.

(19) Malfroot, T., Piteau, M. *French Patent Applic.* 2421866 (1979), SNPE; *C.A.* **1980**, *93*, 7667.

(20) Bowman, M.P. *Ph. D. Thesis*, The Pennsylvania State University, 1986.

(21) Hoffmann, H.M.R., Iranshahi, L. *J. Org. Chem.* **1984**, *49*, 1174.

(22) Cuomo, J., Olofson, R.A. *J. Org. Chem.* **1979**, *44*, 1016.

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