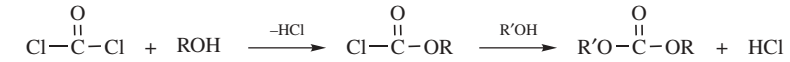
CHLOROFORMATES AND CARBONATES

1. Introduction

Discovered by Dumas in 1833 (1), the reaction of phosgene (carbonic dichloride [75-44-5]) with alcohols gives two classes of compounds, carbonic esters and carbonochloridic esters, commonly referred to as carbonates and chloroformates. The carbonic acid esters (carbonates), ROC(O)OR, are the diesters of carbonic acid [463-79-6]. The carbonochloridic esters, also referred to as chloroformates or chlorocarbonates, ClC(O)OR, are esters of hypothetical chloroformic acid [463-73-0], ClCOOH.

The reaction proceeds in stages, first producing a carbonochloridic ester (chloroformate), and then a carbonic acid diester (carbonate). When a different alcohol is used for the second stage, a mixed radical or unsymmetrical carbonate is produced.



An extensive review of the chemistry of chloroformates was published in 1972 (2,3). Over the last 30 years, in excess of 20,000 articles were published on the chemistry and uses of chloroformates and carbonates. Recent interest in chloroformates and carbonates as carbonylating agents has been enhanced due to the increased concern over phosgene transportation and handling. This article briefly reviews important events regarding these materials, especially those related to technology.

2. Chloroformates

In earlier literature, carbonochloridic esters are referred to as chloroformates or chlorocarbonates because of the structural parallel with formic acid [64-18-6], chloroformic acid, and carbonic acid. Before 1972, chloroformates were indexed in *Chemical Abstracts, Eighth Collective Index*, under formic acid, chloroesters; whereas, in the *Ninth Collective Index* (Dec. 1990), they are referred to as carbonochloridic acid esters. Table 1 lists the common names of commercially available carbonochloridates or chloroformates, the CAS Registry Numbers, and the formulas.

Table 1. **Commercial Chloroformates (Carbonochloridates)**

Ester	CAS Registry number	Formula
methyl	[79-22-1]	$ClCOOCH_3$
chloromethyl	[22128-62-7]	$ClCOOCH_2Cl$
ethyl	[541-41-3]	$ClCOOC_2H_5$
1-chloroethyl	[50893-53-3]	$ClCOOCHClCH_3$
2-chloroethyl	[627-11-2]	$ClCOOCH_2CH_2Cl$
2,2,2-trichloroethyl	[17341-93-4]	$ClCOOCH_2CCl_3$
vinyl	[5130-24-5]	$ClCOOCH{=}CH_2$
isopropyl	[108-23-6]	$ClCOOCH(CH_3)_2$
n-propyl	[109-61-5]	$ClCOOCH_2CH_2CH_3$
3-chloropropyl	[628-11-5]	$ClCOOCH_2CH_2CH_2Cl$
allyl	[2937-50-0]	$ClCOOCH_2CH{=}CH_2$
methallyl	[42068-70-2]	$ClCOOCH_2(CH_3)C{=}CH_2$
n-butyl	[592-34-7]	$ClCOOCH_2CH_2CH_2CH_3$
sec-butyl	[17462-58-7]	$ClCOOCH(CH_3)CH_2CH_3$
isobutyl	[543-27-1]	$ClCOOCH_2CH(CH_3)_2$
isoamyl	[628-50-2]	$ClCOOCH_2CH_2CH(CH_3)_2$
n-pentyl	[638-41-5]	$ClCOOCH_2CH_2CH_2CH_2CH_3$
cyclopentyl	[50715-28-1]	$ClCOOC_5H_9$
4-*tert*-butyl cyclohexyl	[42125-46-2]	$ClCOOC_6H_{10}C(CH_3)_3$
2-ethylhexyl	[24468-13-1]	$ClCOOCH_2CH(C_2H_5)(CH_2)_3CH_3$
2-octyl	[15586-11-5]	$ClCOOCH(CH_3)(CH_2)_5CH_3$
n-decyl	[55488-51-2]	$ClCOOCH_2(CH_2)_8CH_3$
dodecyl	[24460-74-0]	$ClCOOCH_2(CH_2)_{10}CH_3$
myristyl	[56677-60-2]	$ClCOOCH_2(CH_2)_{12}CH_3$
cetyl	[26272-90-2]	$ClCOOCH_2(CH_2)_{14}CH_3$
octadecyl	[51637-93-5]	$ClCOOCH_2(CH_2)_{16}CH_3$
2-methoxyethyl	[628-12-6]	$ClCOOCH_2CH_2OCH_3$
2-phenoxyethyl	[34743-87-8]	$ClCOOCH_2CH_2OC_6H_5$
phenyl	[1885-14-9]	$ClCOOC_6H_5$
p-nitrophenyl	[7693-46-1]	$ClCOOC_6H_4NO_2$
benzyl	[501-53-1]	$ClCOOCH_2C_6H_5$
p-nitrobenzyl	[4457-32-3]	$ClCOOCH_2C_6H_4NO_2$
4-cumylphenyl	[82914-10-4]	$ClCOOC_6H_4C(CH_3)_2C_6H_5$
9-fluorenylmethyl	[28920-43-6]	$ClCOOCH_2C_{13}H_9$
1-naphthyl	[3759-61-3]	$ClCOOC_{10}H_7$
cholesterol	[7144-08-3]	$ClCOOC_{28}H_{45}$
ethylene bis	[124-05-0]	$ClCOOCH_2CH_2OOCCl$
diethylene glycol bis	[106-75-2]	$ClCOOCH_2CH_2OCH_2CH_2OOCCl$
1,6-hexanediol bis	[2916-20-3]	$ClCOO(CH_2)_6OOCCl$
bisphenol A bis	[2024-88-6]	$ClCOOC_6H_4C(CH_3)_2C_6H_4OOCCl$

2.1. Physical Properties. In general, carbonochloridates or chloroformates are clear, colorless liquids with low freezing points and relatively high boiling points ($>100^{\circ}C$). They are soluble in most organic solvents, but insoluble in water, although they do hydrolyze in water. The lower chloroformates, eg, methyl and ethyl chloroformates, hydrolyze rapidly in water at room temperature, whereas the higher chloroformates, eg, 2-ethylhexyl or aromatic chloroformates, hydrolyze slowly in water at room temperature (4). The physical properties of the most widely used chloroformate esters are given in Table 2 (2).

Table 2. **Physical Properties of Selected Chloroformates**

Chloroformate	Mol wt	Sp gr, d^{20}_4	Refractive index n^{20}_D	Flash point, °C		Viscosity, mPa·s (=cP), 20°C	Bp, °C at		
				TOC[a]	TCC[b]		2.67 kPa[c]	13.3 kPa[c]	101.3 kPac
methyl	94.5	1.250	1.3864	24.4	17.8				71
ethyl	108.53	1.138	1.3950	27.8	18.3				94
isopropyl	122.55	1.078	1.3974	27.8	23.3	0.65		47	105
n-propyl	122.55	1.091	1.4045	34.4		0.80	25.3	57.5	112.4
allyl	120.5	1.1394	1.4223	27.8	31.1	0.71	25	57	
n-butyl	136.58	1.0585	1.4106	52.2	46.0	0.888	44	77.6	
sec-butyl	136.58	1.0493	1.4560	35.6	38.0	0.897	36	69	
isobutyl	136.58	1.0477	1.4079	39.5	34.4	0.88	39	71	
2-ethylhexyl	192.7	0.9914	1.4307		86.0	1.774	98	137	
n-decyl	220.7	0.9732	1.4400	118.3	120.2	3.00	122	159	
phenyl	156.57	1.2475	1.5115		77.0	1.882	83.5	121	185
benzyl	170.6	1.2166	1.5175	80.0	107.9	2.57	103	123	152
ethylene bis	186.98	1.4704	1.4512	134.0	126.0	4.78	108	137	
diethylene glycol bis	231.0	1.388	1.4550	160.0	182.2	8.76	148	180	

[a] Tag open cup.
[b] Tag closed cup.
[c] To convert kPa to mm Hg, multiply by 7.50.

2.2. Chemical Properties. Chloroformates are reactive intermediates that combine acid chloride and ester functions. They undergo many reactions similar to those of acid chlorides; however, the rates are usually slower (5–9). Those containing smaller organic (hydrocarbon) substituents react faster than those containing large organic (hydrocarbon) substituents (4). Reactions of chloroformates and other acid chlorides proceed faster and with better yields when means are employed to remove or capture HCl as it is formed. Classical acid scavengers include alkali hydroxides or tertiary amines, which act as stoichiometric acid acceptors rather than as true catalysts.

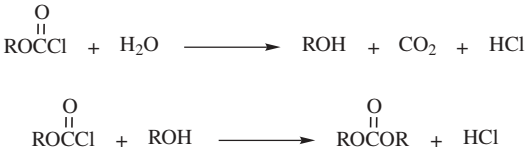
Stability. The ester moiety determines thermal stability generally in the following order of decreasing stability: aryl > primary alkyl > secondary alkyl > tertiary alkyl. In terms of mechanistic chemistry the chloroformates that produce stable carbonium ions on thermal decomposition, eg, benzyl, isopropyl, or tertiary butyl, are unstable (10) and can cause increased pressure in closed containers. Thus iron, zinc, and aluminum chlorides, ie, Lewis acids and metal oxides, catalyze decomposition of chloroformates and therefore the chloroformates should be handled in the absence of metals. Chloroformate purification and decolorizing with charcoal is generally avoided due to the tendency to undergo rapid decarboxylation (11), which could lead to a dangerous overpressurization of the reactor vessel. Alkyl chloroformates can be purified easily by distilling in glass vessels, but secondary or benzylic chloroformates have to be distilled under high vacuum in glass vessels. Tertiary chloroformates are too unstable to distill, even under high vacuum. In some situations the instability of chloroformates can be utilized to generate other chemical species. For example, Lewis acid induced decarboxylation of aromatic chloroformates provide access to chloro and fluoro aromatics (12,13).

Chloroformate decomposition can also be initiated by substances that either posses, or can generate (via reaction with the chloroformate), an ionic organic halide. The net product of an unbranched aliphatic radical is an alkyl chloride, while a substituted radical often loses HCl to produce the olefin. The ionic halide degradation is catalytic and the reaction accelerated by heat. Examples of decarboxylation catalysts include tertiary amines such as pyridine or quinoline (14), formamides (15,16), quaternary ammonium or phosphonium halides (17–19), ureas (20), and inorganic oxides (21). In an example, the ionic chloride of a quaternary amine initiates an S_N2 attack on the alpha carbon of the ester to induce decarboxylation and regeneration of the ionic halide. Controlled decarboxylation of chloroformates has been documented as an efficient means to generate alkyl halides (22–24).

$$ClCOOCH_2CH_2R \xrightarrow[\text{amine}]{\text{tertiary}} ClCH_2CH_2R + CO_2$$

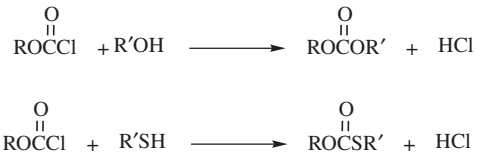
Reactions with Oxygen Moieties. Hydroxylic Compounds. Chloroformates on reaction with water give the parent hydroxy compound, HCl, and CO_2 as well as the symmetrical carbonate formed by the reaction of the hydroxy

compound with chloroformate.



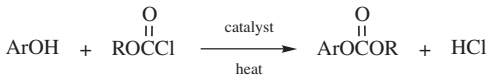
Alkali Metal Hydroxides. Addition of base to aqueous chloroformates catalyzes hydrolysis to yield the parent hydroxy compound (25). However, the use of a stoichiometric amount of alkali metal hydroxides can lead to the symmetrical carbonate, especially from aryl chloroformates (26,27).

Aliphatic Alcohols and Thiols. Aliphatic alcohols on reaction with chloroformates give carbonates and hydrogen chloride. Frequently, the reaction proceeds at room temperature without a catalyst or hydrogen chloride acceptor. However, faster reactions and better yields are obtained in the presence of alkali metals or their hydroxides, or tertiary amines. Reactions of chloroformates with thiols yield monothiolocarbonates (28).



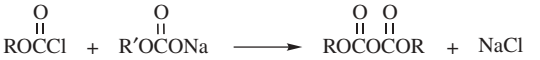
Heterocylic Alcohols. Their reactions with chloroformates lead to carbonates. Thus furan- and tetrahydrofuran-derived alcohols give the corresponding carbonates in 75% yield (29). Inorganic bases and tertiary amines as acid acceptors increase the rate and yield in this reaction.

Phenols. Phenols are unreactive toward chloroformates at room temperature and at elevated temperatures the yields of carbonates are relatively poor (<10%) in the absence of catalysis or quantitative HCl scavengers. Many catalysts have been claimed in the patent literature leading to high yields of carbonates from phenol and chloroformates. Alternate systems include biphasic systems that employ alkali bases and phase transfer catalysts (30). The use of catalyst or an alkali base is even more essential in the reaction of phenols and aryl chloroformates. Among the catalysts claimed are amphoteric metals or their halides (31), magnesium halides (32), activated carbon (33), titanium oxide (34), magnesium or manganese (35), secondary or tertiary amines such as imidazole (36,37), pyridine, quinoline, picoline (38–40), heterocyclic basic compounds (41) and carbonamides, thiocarbonamides, phosphoroamides, and sulfonamides (42).

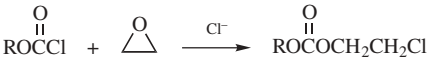


Carboxylic Acids. The reaction product of chloroformates and carboxylic acids is a mixed carboxylic–carbonic anhydride. The intermediate mixed anhydrides are very active acylating agents (43–45), but these agents may be isolated in cold temperatures for producing useful products (46). More often the anhydride is a transient intermediate that leads to the formation of a mixture of ester, carbonate and anhydride. The pathway is strongly dependent upon the anhydride itself and the choice of catalyst (47–50).

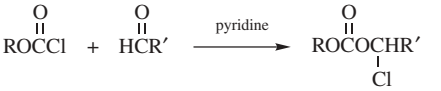
Pyrocarbonates or dicarbonates (anhydrides of carbonic acids) have been prepared from the alkali salt of the carbonate as shown (51,52). Modifications include the direct reaction of chloroformate with alkali metal hydroxide in the presence of a phase-transfer catalyst (53–57). Pyrocarbonates are useful as intermediates and protecting groups as well as effective radical scavengers, where they have established utility as polymer stabilizers and as preservatives in beverages such as wine and fruit juices (56,58).



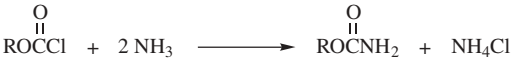
Epoxides. Epoxy compounds react with chloroformates to yield β-chloro-substituted carbonates. Ring opening is catalyzed with Lewis acids or sources of chloride anions (49,59,60).



Aldehydes. Aldehydes react with chloroformates in the presence of catalytic pyridine to yield 1-chloro carbonate esters. The reaction is highly dependant upon the stability of the chloroformate to the reaction conditions. The esters are useful intermediates for pharmaceuticals and insecticides (61–64).

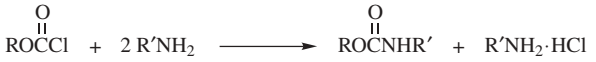


Reactions with Nitrogen Compounds. The reaction with ammonia is the classical method for preparing primary carbamates. Excess ammonia is used as an acid acceptor to remove the HCl formed (see CARBAMIC ACID).



Amines. Primary and secondary aliphatic amines also yield carbamates in the presence of excess amine or other acid acceptors such as inorganic bases under conditions analogous to those used in the Schotten-Baumann reaction

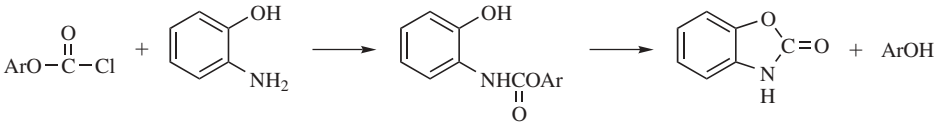
(65). Aromatic primary and secondary amines and heterocyclic amines react similarly, although slowly.



Tertiary amines give crystalline quaternary ammonium compounds (66,67). The acyl ammonium salts provide activation of the carbonyl species and are potential precursors to secondary amines via dealkylation chemistry.

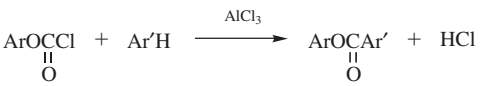
Amino Alcohols. Reaction of chloroformate is much more rapid at the amino group than at the hydroxyl group (5–9). Thus the hydroxy carbamates, which can be cyclized with base to yield 2-oxazolidones, can be selectively prepared (68). Nonionic detergents may be prepared from poly[(ethylene glycol) bis(chloroformates)] and long-chain tertiary amino alcohols (69).

Aminophenols. Reaction of chloroformate with aminophenols (qv) also takes place at the more reactive amino group selectively. Thus *o*-aminophenol [95-55-6] gives benzoxazolone [59-49-4] by cyclization of the intermediate carbamate (70).

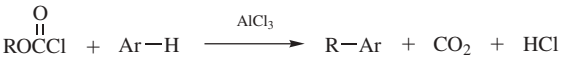


Amino Acids. Chloroformates play a most important role for the protection of the amino group of amino acids (qv) during peptide synthesis (71,72). The protective carbamate formed by the reaction of benzyl chloroformate and amino acid (73) can be cleaved by hydrogenolysis to free the amine after the carboxyl group has reacted further. The selectivity of the amino groups toward chloroformates results in amino-protected amino acids with the other reactive groups unprotected (74,75). Methods for the preparation of protected amino acids generally involve a pH stat procedure. These processes have been developed on an industrial scale (76–78). A wide variety of chloroformates have been used that give various carbamates that are stable or cleaved under different conditions.

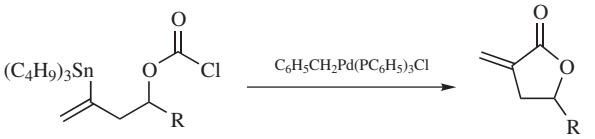
Acylation. Aryl chloroformates are good acylating agents, reacting with aromatic hydrocarbons under Friedel-Crafts conditions to give the expected aryl esters of the aromatic (Ar) acid (79).



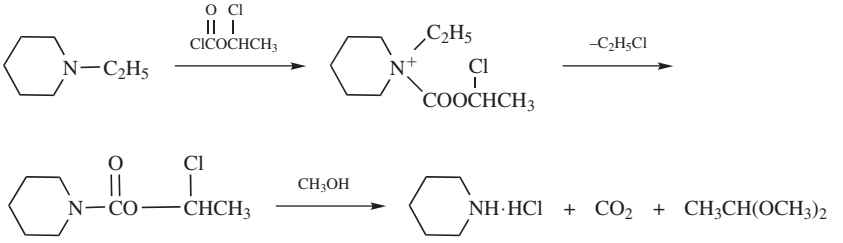
However, with aliphatic chloroformates under similar conditions, alkylation takes place (80).



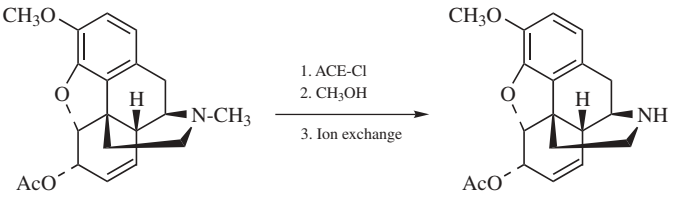
Chloroformates have also been shown to undergo inter and intramolecular Pd-catalyzed cross-coupling reactions with acetylenes and aryl- and vinylorganotins (81–83).



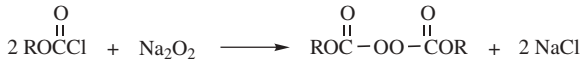
Dealkylation. Chloroformates such as vinyl chloroformates (84) are used to dealkylate tertiary amines. Chloroformates are superior to the typical Von Braun reagent, cyanogen bromide, because of increased selectivity producing cleaner products and higher yields. Other chloroformates such as allyl, ethyl, methyl, phenyl, and trichloroethyl have also been used in dealkylation reactions. Although the dealkylation reaction using chloroformates is mostly carried out on tertiary amines, dealkylation of oxygen or sulfur centers, ie, ethers or thioethers, can also be achieved. Commercially available α-Chloroethyl chloroformate [50893-53-3] (ACE-Cl) (85–87) is superior to all previously used chloroformates for the dealkylation reaction.



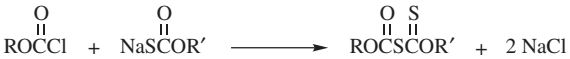
ACE-Cl has the advantage that the conditions required for ACE removal are much milder, thus expanding the list of functionalities allowed in the amine to be dealkylated. The potential significance of this process in drug congener preparation has been outlined (87–91).



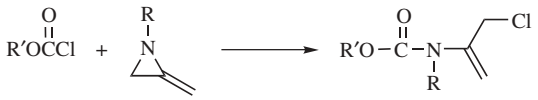
Miscellaneous Reactions. The reaction of chloroformates with hydrogen peroxide or metal peroxides results in the formation of peroxydicarbonates that are used as free-radical initiators of polymerization of vinyl chloride, ethylene, and other unsaturated monomers (92,93).



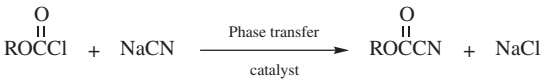
The reaction of chloroformates with sodium xanthates results in the formation of alkyl xanthogen formates that are useful as flotation agents in extraction of metals from their ores (94).



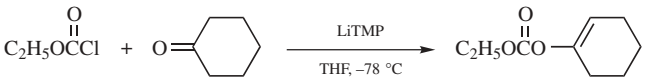
Methyleneaziridines undergo nucleophilic ring opening in the presence of alkyl chloroformates to generate enamide products (95).



Alkyl Chloroformates react with HCN in the presence of a tertiary amine, or with cyanide salts under phase-transfer conditions, to give cyanoformate esters. The esters are useful building blocks in pharmaceutical preparations (96–99).



The reaction of chloroformates with aldehyde and ketone enolates has been shown as a selective route to enol carbonates (100–103).



2.3. Manufacture. The reaction of phosgene with alcohols or phenols has been thoroughly discussed (2). In general, the availability of a chloroformate is limited only by access to the particular alcohol.

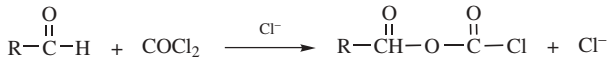
Most alkyl chloroformates, especially those of low molecular weight alcohols, are prepared by the reaction of liquid anhydrous alcohols with molar excess of dry, chlorine-free phosgene at low temperature. Corrosion-resistant reactors, lines, pumps, and valves are required. Materials of construction include glass, porcelain, Hastelloy C, Teflon-lined steel, or chemically impregnated carbon on

steel such as Karbate. Temperatures are kept at 0–10°C for the lower alcohols and may rise to 60°C for the higher aliphatic alcohols. Hydrogen chloride is evolved as the reaction proceeds and is then absorbed in a tower after recovering excess phosgene. The reactions are most often run in batch reactors, although some of the high volume chloroformates are produced in cascade-type continuous reactors (104–107) in either cocurrent or countercurrent flow (108,109). The continuous reactors also ensure excess of phosgene at all times since both reactants are added simultaneously, thus minimizing dialkylcarbonate side products. Phenols react with phosgene with difficulty and usually require higher temperature and lead to a fair amount of diaryl carbonate as a side product. Many different catalysts have been used to reduce the reaction temperature and the carbonate side products (110–115).

Unreacted phosgene is removed from the crude chloroformates by vacuum stripping or gas purging. Chloroformates of lower primary alcohols are distillable; however, heavy-metal contamination and charcoal purification should be avoided. As stated earlier, chloroformates generating a stable carbonium ion on decomposition, i.e. secondary or tertiary chloroformates or benzylic chloroformates, are especially unstable in the presence of heavy metals and more specifically Lewis acids and, hence, should be distilled at as low a temperature and high vacuum as possible. The yields of primary chloroformates are usually well above 90%. The secondary chloroformates give yields of 80–90%.

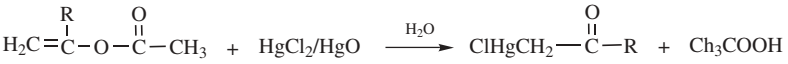
Commercial processes are usually run neat, although solvents such as chloroform, toluene, dioxane, or tetrahydrofuran (THF) are sometimes used to dissolve the starting alcohol or the product chloroformate as may be necessary. Chloroformates of phenols and arylene bisphenols are also made in aqueous base solution, often employing a phase transfer catalyst, pH control, and CH_2Cl_2 as the second phase (116–120). In special cases, chloroformates are prepared solely in cold water (121). In other cases, efficiencies have been improved by utilizing pressure or vacuum in either a solvent and solvent-less process (122,123).

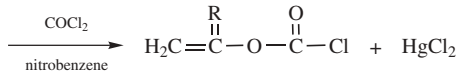
Certain precursor alcohols to chloroformates are synthetically inaccessible. As such, unique synthetic methods have been developed gain access to these materials. For instance, 1-chloroalkyl chloroformates have been synthesized by the reaction of aldehydes with phosgene in the presence of a source of ionic chloride (85,86,124–126). The reaction has been extended to include glyoxylate derived chloroformates (127). Alternatively, chloroalkyl chloroformates can be generated by free radical chlorination of simple alkyl chloroformates, followed by purification (126,128,129).



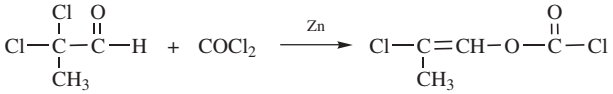
The synthesis of alkenyl chloroformates has proven to be very challenging both commercially and environmentally. Vinyl chloroformate can be made by the gas-phase pyrolysis of the bis(chloroformate) of ethylene glycol, however, the reaction suffers from low yield due to side reactions (130,131). Direct routes from phosgene and base derived enolates have been entirely unsuccessful. A successful and seemingly viable alternative using mercurials as enolate equivalents

is hindered by ecological concerns (132–134).



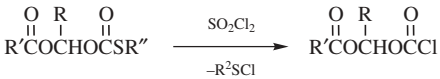


In special cases, vinyl chloroformates have been made by treating α-chloro or bromo aldehydes or ketones with zinc dust and phosgene (135). The reaction is limited to aldehydes and ketones that do not contain α-hydrogen.



Chloroformates have also been generated by the reaction of alcohols with trichloromethyl chloroformate or bis trichloromethyl carbonate (di- and triphosgene, respectively). In the reaction with an alcohol, both reagents serve as chloroformylating agents, and are in effect, a liquid or solid equivalent of phosgene.

A sulfuryl chloride initiated fragmentation of alkyl carbonothioates illustrates a unique indirect entry to synthetically challenging α-substituted acyloxy chloroformates (136), useful in the manufacture of prodrugs (137).



2.4. Shipping and Storage. Chloroformates are shipped in nonreturnable 208-L (55-gal) polyethylene drums with carbon steel overpacks or high density polyethylene drums. For bulk shipments, insulated stainless steel tank containers and trucks provide secure protection. Bulk equipment is specially lined for protection from corrosion. Tank truck and rail car quantities are shipped using equipment dedicated for these types of products. Materials such as isopropyl chloroformate, benzyl chloroformate, and *sec*-butyl chloroformate that require refrigeration are precooled when shipped in bulk containers. Bulk shipments that are pre-cooled must proceed to the destination without layover. Drum shipments of IPCF, BCF, and SBCF must be shipped in refrigerated containers. Many of the chloroformates are only shipped in truckload shipments. The U.S. Department of Transportation (DOT) Hazardous Materials Regulations control the shipments of chloroformates, as described in Table 3.

Chloroformates should be stored in a cool, dry atmosphere, preferably refrigerated, especially for prolonged storage. Drums must be stored out of direct sunlight. Chloroformate transfers to storage tanks or reactors should be made through a closed system, using stainless steel, nickel, glass or Hastelloy pumps, lines, and valves. Contact with iron oxides should be avoided.

Table 3. **Department of Transportation Regulations for Chloroformate Shipment**

Type	DOT hazard class	Subsidiary risk 1	Subsidiary risk 2	Tank truck	Refrigeration
allyl chloroformate	toxic-inhalation hazard	flammable	corrosive	yes[a]	required
benzyl chloroformate	corrosive			yes[a]	required
diethylene glycol bis(chloroformate)	not regulated			yes	needed to pre-serve assay[b]
ethyl chloroformate	toxic-inhalation hazard	flammable	corrosive	[a]	
2-ethylhexyl chloroformate	toxic	corrosive		yes[a]	
hexanediol bischloroformate	not regulated			yes[a]	
isobutyl chloroformate	toxic-inhalation hazard	flammable	corrosive	yes[a]	
isopropyl chloroformate	corrosive	flammable	corrosive	yes[a]	required
methyl chloroformate	toxic-inhalation hazard	flammable	corrosive	yes[a]	
n-propyl chloroformate	toxic-inhalation hazard	flammable	corrosive	yes[a]	
phenyl chloroformate	toxic	corrosive		yes[a]	
sec-butyl chloroformate	toxic-inhalation hazard	flammable	corrosive	yes[a]	required
4-*tert*-butyl chloroformate	toxic			no	required

[a] Bulk shipments can be made in DOT-approved IMO containers.
[b] Only for shipments through the tropics.

Table 4. **Typical Specifications of Commercial Chloroformates**

Assay	Value
purity, %	98
phosgene, %	<0.1
iron, ppm	<5
acidity as HCl, %	<0.1
alcohol or phenol, %	<2

2.5. Economic Aspects. Most chloroformate production is used captively and production figures are not available. The prices are also not published, but can be obtained by contacting United States and other worldwide producers, such as PPG Industries, Inc., BASF, SNPE, and Hodogaya.

2.6. Specifications and Analysis. Table 4 lists the specifications of commercial chloroformates. The lower boiling chloroformates are analyzed by gas–liquid chromatography. Higher molecular weight chloroformates are first hydrolyzed and then analyzed by titration, using the Volhard method.

2.7. Toxicity. Chloroformates, especially those of low molecular weight, are pungent lachrymators, vesicants, and produce effects similar to those of hydrogen chloride or carboxylic acid chlorides. They can also irritate the skin and mucous membranes, producing severe burns and possible irreversible tissue damage.

Inhalation of vapors of lower chloroformates result in coughing, choking, and respiratory distress, and, with some chloroformates like methyl chloroformate, inhalation can be fatal as a result of the onset of pulmonary edema, which may not appear for several hours after exposure (138). Table 5 gives the acute toxicities of some chloroformates (138–140).

Table 5. **Toxicity Information on Chloroformates: LD_{50} and LC_{50}**

Chloroformate	Oral, mg/kg[a]	Dermal, mg/kg[a]	Inhalation, mg/L[b,c]
methyl	220	>2,500	0.634
ethyl	411	>2,000	<1.62
n-propyl	650	>10,200	1.6
isopropyl	177.8	11,300	1.5
sec-butyl	1,030	>2,025	1.82
isobutyl	2,095	>2,500	1.8
2-ethylhexyl	3,038	>3,038	0.95[d]
allyl	178	1,470	0.3
phenyl	1,581	>3,200	>2.04
benzyl	<5,000	2,065	>2.1
4-*tert*-butyl cyclohexyl	>5,000	>2,000	0.72
ethylene bis	1,100	>2,000	43
diethylene glycol bis	8,13.2	3,400	>2.5

[a] LD_{50} values.
[b] LC_{50} values.
[c] For 1-h exposure (mg/L of air).
[d] For 4-h exposure (mg/L of air).

2.8. Uses. As illustrated in the chemical properties segment, chloroformates are reactive chemical species, and versatile synthetic intermediates. Derivatization of chloroformates with alcohols and amines is commonly practiced, and many industrial uses of the resultant carbamates and carbonates have been described. Chloroformates should be considered as intermediates for syntheses of pesticides, perfumes, drugs, foodstuffs, polymers, dyes, and other chemicals.

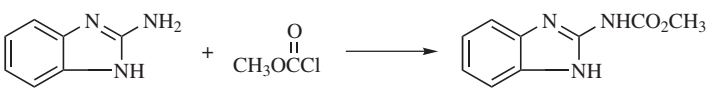
Some of these products, eg, carbonates, are used as solvents, plasticizers, or as intermediates for further synthesis. Diethylene glycol bis(chloroformate) [106-75-2] is the starting material for diethylene glycol bis(allyl carbonate) [142-22-3], CR-39, or Nouryset 200 monomer, used in the manufacture of break-resistant optical lenses, which is obtained by the reaction with allyl alcohol [107-18-6] (138). Alternatively, it can be obtained from allyl chloroformate [2937-50-0] and diethylene glycol (139) (see ALLYL MONOMERS AND POLYMERS). Other aliphatic or aromatic bis(chloroformates) are used to make high temperature resistant polycarbonate plastics, the most important example being Lexan or Makrolon (140) (see POLYCARBONATE).

A significant use of chloroformates is for conversion to peroxydicarbonates, which serve as free-radical initiators for the polymerization of vinyl chloride, ethylene, and other unsaturated monomers. The most widely used percarbonate initiators are diisopropyl peroxydicarbonate (IPP), di-2-ethylhexyl peroxydicarbonate (2-EHP), and di-*sec*-butyl peroxydicarbonate (SBP). The following list includes most of the commercially used percarbonates.

Percarbonate	CAS Registry number
diethyl percarbonate	[14666-78-5]
diisopropyl (IPP) percarbonate	[105-64-6]
di-*n*-butyl percarbonate	[16215-49-9]
di-*sec*-butyl (SBP) percarbonate	[19910-65-7]
dicyclohexyl percarbonate	[1561-49-5]
di-4-*tert*-butylcyclohexyl percarbonate	[26523-73-9]
di-*n*-hexadecyl percarbonate	[26322-14-5]
di-*n*-propyl (NPP) percarbonate	[16066-38-9]
di-2-ethylhexyl (2-EHP) percarbonate	[16111-62-9]

Carbamates derived from chloroformates are used to manufacture pharmaceuticals, including tranquilizers (144), antihypotensives, and local anesthetics, pesticides, and insecticides (see CARBAMIC ACID).

Methyl chloroforomate is the largest volume chloroformate used in the agricultural industry, primarily in the formation of carbamate functional groups. An important example is the synthesis of the mainstay fungicide Carbendazim (1*H*-benzimidazole-2-ylcarbamic acid methyl ester [10605-21-7]).



Carbendazim

Another important use of chloroformates is the protection of amino and hydroxyl groups in the synthesis of complex organic compounds such as peptide-based pharmaceuticals (73–77,145–147). The appropriate chloroformates are used in generating alkoxycarbonyl N-protecting groups of amino acids. Common examples of amino acid blocking agents derived from chloroformates include benzyloxycarbonyl (*Z* or Cbz), 9-fluorenyl-methoxycarbonyl (Fmoc), 4-nitrobenzyloxy carbonyl, and allyloxycarbonyl (Alloc). The industrial significance of chloroformate blocking agents is noted in the synthesis of artificial sweeteners such as aspartame, as well as the synthesis of the antiviral valacyclovir (148).

Carbamate likages of poly(vinyl ether) carbamates, used as detergents additives in gasoline, have been derived from the suitable chloroformate (149–151). Ethyl chloroformate is used in the manufacture of ore flotation agents by reaction with various xanthates (94).

Cholesteric liquid crystal materials, useful as nondestructive indicators, are often derived from cholesterol chloroformate (152–154). Decarboxylation of bis(chloroformates) to alkyl halides is used in the manufacture of the rubber component 1,6-dichlorohexane [2163-00-0] (155–157). Additionally, decarboxylation of alkoxyalkyl chloroformates provides alkyl chloride materials that are useful as surfactant intermediates (158). Bis(chloroformic esters) condense with diamines to give polyurethanes (142) (see URETHANE POLYMERS).

Blowing agents for producing foam rubber, polyethylene, and vinyl chloride are made from chloroformates, hydrazine, and a base. For example, diisopropyl azidoformate [2446-83-5] is made from isopropyl chloroformate (159).

The polymerization of derivatives of vinylic chloroformates has led to a series of interesting monomers (160). However, due to limited supply of the chloroformate raw material, applications are limited to small volume specialty products.

By virtue of their exceptional reactivity, chloroformates are also valued as general purpose derivatizing agents for gas and liquid chromatographic analysis of molecules containing active functionality such as amines and carboxylic acids (161,162).

3. Carbonates

Classically, chloroformates and alcohols or phenols give carbonic diesters. In addition, the higher diesters can be made from the lower ones by alcoholysis or ester interchange by heating the lower diester with a higher alcohol in the presence of acid such as HCl or H_2SO_4, or base such as sodium alcoholate. The driving force for these reactions is the formation of lower alcohols that can be distilled off. Mixed diesters can be prepared by treating a chloroformate with an alcohol or phenol having a different radical.

More recently, preparation of selected carbonic esters by nonphosgene routes, such as the metal catalyzed reaction of CO or NO_x with alcohols, or the catalytic reaction of CO_2 and oxiranes have been preferred. These oxidative carbonylation methods are more economic in many cases and naturally less hazardous than phosgene routes.Carbonates are indexed in *Chemical Abstracts* under carbonic acid, esters. Symmetrical diesters have the prefix di or bis. Unsymme-

Table 6. **Carbonates**

Carbonate	CAS Registry number	Formula
dimethyl	[616-38-6]	$CH_3OCOOCH_3$
diethyl	[105-58-8]	$C_2H_5OCOOC_2H_5$
divinyl	[7570-02-7]	$CH_2{=}CHOCOOCH{=}CH_2$
di-*n*-propyl	[623-96-1]	$CH_3CH_2CH_2OCOOCH_2CH_2CH_3$
diisopropyl	[6482-34-4]	$(CH_3)_2CHOCOOCH(CH_3)_2$
diallyl	[15022-08-9]	$CH_2{=}CHCH_2OCOOCH_2CH{=}CH_2$
methyl allyl	[35466-83-2]	$CH_3OCOOCH_2CH{=}CH_2$
diisobutyl	[539-92-4]	$(CH_3)_2CHCH_2OCOOCH_2CH(CH_3)_2$
isobutyl propyl	[40882-93-7]	$CH_3CH(CH_3)CH_2OCOOCH_2CH_2CH_3$
di-*tert*-butyl	[34619-03-9]	$(CH_3)_3COCOOC(CH_3)_3$
di-*sec*-butyl	[623-63-2]	$CH_3CH_2CHCH_3O$-$COOCH(CH_3)CH_2CH_3$
di-*n*-butyl	[542-52-9]	$CH_3CH_2CH_2CH_2O$-$COOCH_2CH_2CH_2CH_3$
methyl ethyl	[623-53-0]	$CH_3OCOOC_2H_5$
hexyl methyl	[39511-75-6]	$CH_3CH_2CH_2CH_2CH_2CH_2OCOOCH_3$
pentyl propyl	[40882-94-8]	$CH_3CH_2CH_2CH_2CH_2O$-$COOCH_2CH_2CH_3$
1-chloromethyl isopropyl	[79-22-1]	$ClCH_2OCOOCH(CH_3)_2$
1-chloroethyl ethyl	[50893-36-2]	$CH_3CHClOCOOC_2H_5$
1-chloroethyl cyclohexyl	[99464-83-2]	$CH_3CHClOCOOC_6H_{10}$
di-*n*-octyl	[1680-31-5]	$CH_3(CH_2)_6CH_2OCOOCH_2(CH_2)_6CH_3$
didodecyl	[6627-45-8]	$CH_3(CH_2)_{10}CH_2OCOOCH_2(CH_2)_{10}CH_3$
diphenyl	[102-09-0]	$C_6H_5OCOOC_6H_5$
phenyl allyl	[16308-68-2]	$C_6H_5OCOOCH_2CH{=}CH_2$
vinyl ethyl	[7670-06-1]	$CH_2{=}CHOCOOC_2H_5$
ethyl phenyl	[3878-46-4]	$C_2H_5OCOOC_6H_5$
ethylene	[96-49-1]	$\overset{OCOOCH_2CH_2}{\underbrace{\qquad\qquad}}$
allyl diglycol[a]	[142-22-3]	$O(CH_2CH_2OCOOCH_2CH{=}CH_2)_2$
ditolyl[b]	[41903-18-8]	$CH_3C_6H_4OCOOC_6H_4CH_3$
dibenzyl	[3459-92-5]	$C_6H_5CH_2OCOOCH_2C_6H_5$
di-2-ethylhexyl	[14858-73-2]	$CH_3(CH_2)_3CH(C_2H_5)CH_2O$-$COOCH_2CH(C_2H_5)(CH_2)_3CH_3$

[a] Diethylene glycol bis(allylcarbonate).
[b] Diethylene glycol bis(tolylcarbonate).

trical diesters are listed with the two radicals following each other. For example, ethyl phenyl carbonic diester is EtOCOOPh. Table 6 lists commonly used carbonates, their Chemical Abstracts Service Registry Number, and formulas.

3.1. Properties. The physical properties of selected carbonates are given in Table 7. The lower alkyl carbonates are neutral, colorless liquids with a mild sweet odor. Aryl carbonates are normally crystalline compounds with relatively low melting points. Carbonic esters are soluble in polar organic solvents such as alcohols, esters, and ketones, but not soluble in water. An exception is lower molecular weight cyclic carbonates such as ethylene carbonate and propylene carbonate which readily dissolve in water. Several lower aliphatic carbonates form azeotropic mixtures with organic solvents. For instance, dimethyl carbonate

Table 7. **Physical Properties of Selected Carbonates**

Carbonates	Mol wt	Sp gr, d_4^{20}	Refractive index n^t_D	Flash point °C	Viscosity[a] mPa · s (=cP)	Bp, °C[b]
dimethyl	90.08	1.073	1.3697[c]	21.7[d] 16.7[e]	0.664 (20)	90.2
diethyl	118.13	0.975	1.3846[c]	46.1[d] 32.8[e]	0.868 (15)	23.8 (1.33) 69.7 (13.33) 126.8
di-*n*-propyl	146.18	0.941	1.4022[c]	64[e]	[f]	165.5–166.6
diisopropyl	146.18					147.0
diallyl	142.15	0.994	1.4280[c]			97 (8.13) 105 (13.33)
di-*n*-butyl	174.14	0.9244	1.4099[g]			166 (97.31)
di-2-ethylhexyl	204.19	0.8974^{20}_{20}	1.4352[g]			207.7
diphenyl	214.08	0.8974^{87}_{4}				173 (1.33) 302
diethylene glycol bis(allyl)	274.3	1.143	1.4503	177[h]	9 (25)	160 (0.27)
tolyl diglycol	374.4	1.189	1.5229[g]			247–248 (0.27)
ethylene	88.06	1.3218^{39}_{4}	1.4158[i]			248

[a] At the temperature noted in parentheses (°C).
[b] At 101.3 kPa (=1 atm) unless otherwise noted in parentheses in kPa.
[c] Ref. 30.
[d] Tap open cup.
[e] Tag closed up.
[f] Brookfield no. 1 spindle; rpm (mPa · s) 10(5), 20(6.5), 50(8.0), 100(12.0).
[g] Ref. 38.
[h] Cleveland open cup.
[i] Ref. 42.

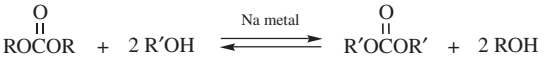
and ethylene carbonate form azeotropic mixtures with methanol and ethylene glycol, respectively (163).

3.2. Chemical Properties. The chemistry of carbonates is dominated by a reactivity similar to esters and a tendency to liberate CO_2. Carbonates undergo nucleophilic substitution reactions analogous to chloroformates except in this case, an ^-OR group (rather than chloride) is replaced by a more basic group. Normally these reactions are catalyzed by bases. Carbonates are sometimes preferred over chloroformates because formation of hydrogen chloride as a by-product is avoided, simplifying handling and in some cases eliminating impurities. However, the reactivity of carbonates toward nucleophiles is considerably less than chloroformates. Several recent reviews depict the synthetic utility of carbonates in organic chemistry (164–166).

Reaction with Water. The alkyl carbonate esters, especially the lower ones, hydrolyze very slowly in water when compared to the carbonochloridic esters (chloroformates). Under alkaline conditions, the rates of hydrolysis are similar to those of the corresponding acetic acid esters. The net result is the formation of hydroxy compounds and CO_2.

Reaction with Alcohols and Thiols. The likeness of carbonates to esters is evident in their tendency to undergo transesterification with alcohol and thiols. Transesterification of both cyclic and acyclic carbonates is commonly practiced in

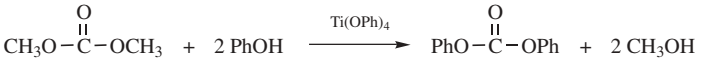
industry. The process requires that the equilibrium be shifted in the desired direction. In general, the replacement of one hydroxy with another is matter nucleophilicity, where the more nucleophilic alcohol or thiol replaces the less nucleophilic compound. In cases where the nucleophilicity is similar, the reaction is driven by the removal of the less volatile compound. In this way, the reaction of diaryl carbonate with a low mass alcohol generates dialkyl carbonates and the less nucleophilic phenol. In contrast, low molecular weight dialkyl carbonates can be driven to diaryl carbonates by reaction with phenols and removal of the lower boiling alcohol. The reactions are catalyzed by the usual transesterification catalysts such as sodium metal and Lewis acids (167–168).

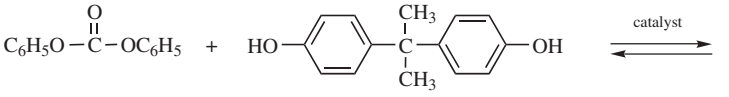


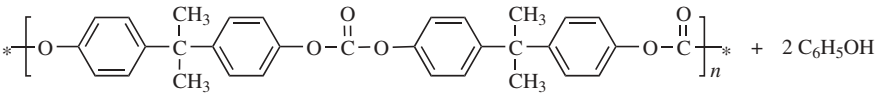
Transesterification has become a convenient method for synthesizing high alkyl, aryl, or alkyl aryl carbonates. Fiber- and film-forming polycarbonates are produced by carbonate exchange involving dialkyl, dicycloalkyl, or diaryl carbonates with alkyl, cycloalkyl, or aryl dihydroxy compounds (169–170).

Reaction with Phenols. Carbonates undergo carbonate interchange with aromatic hydroxy compounds. In cases involving aliphatic carbonates, the reaction is slow and thermodynamically unfavorable. The equilibrium heavily favors the aliphatic ester and high temperatures and very active catalysts are required to drive the reaction.

A model example of phenols reacting with carbonates is evident in the industrial sequence used in the phosgene-free manufacture of bisphenol A polycarbonates. In the initial stage, dimethyl carbonate is reacted with phenol at high temperatures in the presence of Lewis acids or metal complexes to yield diphenyl carbonate (171–174). The process involves complex reaction technology utilizing various reactor zones, azeotropic separation, and recycle loops (175–176). In the next stage of the sequence, purified diphenyl carbonate and bisphenol A [80-05-7] are combined with basic catalysts in a melt reactor. Phenol is liberated from the melt using staged heat and pressure techniques serving to drive the reaction to polymer (see POLYCARBONATE).







Reaction with Amines and Ammonia. Carbonates react with aromatic amines, aliphatic amines and ammonia to produce carbamates or ureas (177–178). For example, dimethyl carbonate reacts with ammonia in water to form methyl carbamate useful in coatings applications (179–180). Similar reactions have been used as a choice route to producing carbamate pesticides and bis(urethanes) for polymers (164,181).

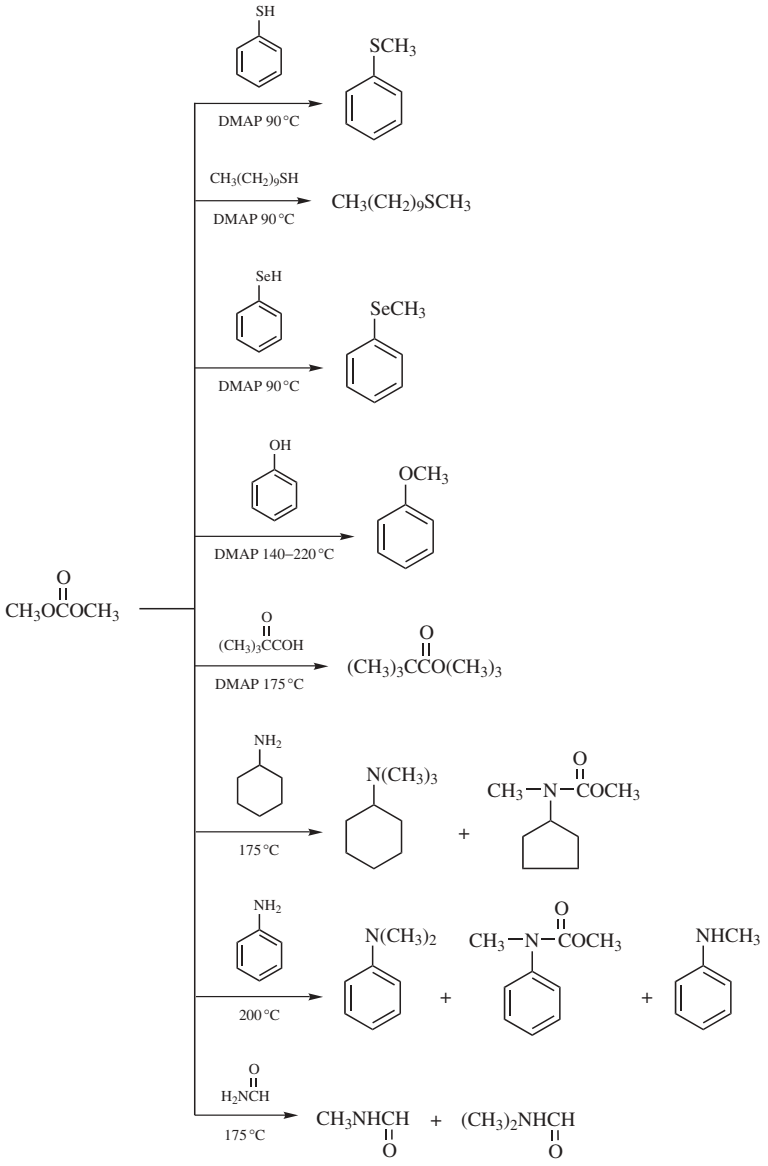
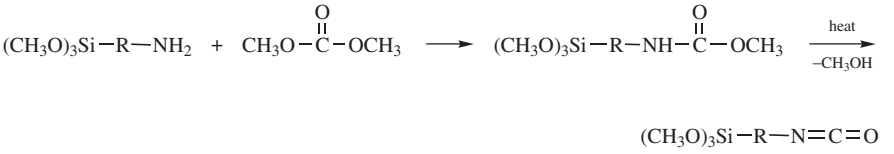


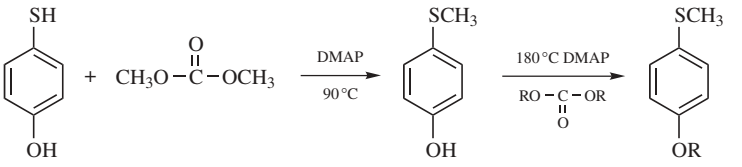
Fig. 1. Dimethyl carbonate as a methylating agent.

Carbamate esters derived from carbonates undergo thermal elimination of alcohol to yield isocyanates (175,182,183). The method, which primarily employs dimethyl or diphenyl carbonate, is recognized as a phosgene-free alternative to industrially important isocyantes such as methyl isocyante (184,185), TDI, and HMDI (186–189). Compared to current phosgene processes, the carbonate process is generally cost prohibitive, however advantages are found in cases where the isocyanate molecule includes acid sensitive functionality or the processes are set up for alcohol recycle. An example includes isocyantoorganosilanes which are useful in coatings applications (190).



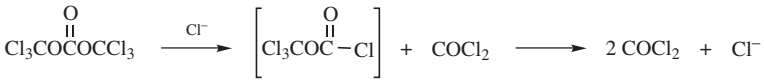
Alkylation. Dialkyl carbonates react with a variety of functional groups to produce the alkylated derivatives. Typical carbonates include dimethyl, diethyl, and dibenzyl carbonates, leading to the respective methylated, ethylated, and benzylated products. Alkylations have been noted on functionality ranging from thioorganics (191), phenols, anilines, amines, oximes (192), carboxylic acids, and silicon dioxide (193) to C alkylation of CH_2 acidic species such as arylacetonitriles and alkyl aryl acetates (164,177–178).

The reaction of dimethyl carbonate as a methylating agent has received a majority of the attention (177,178,194,206). The method offers safety advantages over typical methylating agents, such as hazardous dimethyl sulfate and methyl iodide. Methylation reactions with dimethyl carbonate can be achieved in the liquid phase, usually requiring high temperatures (120–220°C) and further requiring use of catalyst such as 4-dimethylaminopyridine [1122-58-3] (DMAP) or alkali base. Only the sulfur and selenium compounds do not require high temperatures for methylation. Methylations can also be performed by gas–liquid phase-transfer catalysis in the presence of PEG 6000 or in the gas-phase using zeolite catalysts (175,207–208). As seen in Figure 1, the organo sulfur compounds are methylated at the boiling point (90°C) of dimethyl carbonate, whereas methylation (or alkylation with other alkyl groups) of other functional groups requires higher temperatures. This has resulted in the selective methylation of sulfhydryl groups of compounds that contain other substituents that can be alkylated. The other substituents can then be alkylated at elevated temperatures (194). Thus,



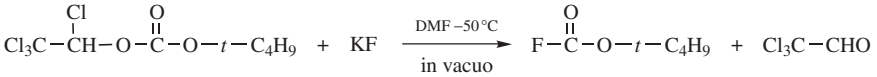
Miscellaneous Acylation Reactions. Chloroalkyl alkyl carbonates (described earlier) are more activated acylating agents than their alkyl counterparts.

An extreme example is bis trichloromethyl carbonate or triphosgene, which is often used as a solid source of phosgene (209–214). It is important to note that triphosgene readily decomposes to phosgene at high temperatures, and in the presence of trace metals and small quantities of nucleophilic sources such as chloride ion.



The less extreme acylating agent, 1-chloroalkyl alkyl carbonate, has been used as an entry to carbamates (213,214).

Additionally, the 1-chloroalkyl carbonyl group is used as an acid labile, base stable alcohol protecting group (90,215). The reactivity of the 1-chloroalkyl carbonates also offers entry to fluoroformates that cannot be prepared by halogen exchange of their analogous chloroformate, such as the *tert*-butyl chloroformate (216,217). Thus, *tert*-butyl fluoroformate, which exhibits higher thermal stability than its chloroformate analogue, is used industrially for BOC protection of amino acids and peptides (145,218).



3.3. Manufacture. The most important and versatile method for producing carbonates is the phosgenation of hydroxy compounds. Manufacture is essentially the same method as chloroformates except that more alcohol is required in addition to longer reaction times and higher temperatures. The products are neutralized, washed, and distilled. The more acidic alcohols are less reactive, and in many cases organic base is included as catalyst. Corrosion-resistant equipment similar to that described for the manufacture of chloroformates is required.

Diaryl carbonates are classically prepared from phosgene via an interfacial process comprising of caustic, triethylamine catalyst and methylene chloride (219,220). The process has reportedly been optimized by elimating solvent and including quaternary amines as phase transfer catalysts (221,222). Over the years, commercially important diphenyl carbonate (DPC) has undergone study to improve production techniques and product quality. A technique that strives for chloride free DPC involves the high temperature phosgenation of phenol with various homogeneous and heterogeneous catalysts. A sample of catalysts includes metal salts (223–226), pyridines (227–229), heterocyclic amines (230–232), phosphorous compounds (233–237), and alumosilicates (238). The phosgenation processes can be carried out continuously in both liquid and gas phases (239–241).

The continuous production of high purity methyl or ethyl carbonate from the alcohol and chloroformates has been patented (242). Chloroformate and alcohol are fed continuously into a Raschig ring-packed column in which a temperature gradient of 72–127°C is maintained between the base and head of the column; HCl is withdrawn at the head, and carbonate (99%) is withdrawn at the base.

Over the past 20 years, the trend is to manufacture carbonates without the use of phosgene. This method has the advantage of avoiding the use of highly toxic phosgene as well as considerably lower cost. The catalytic insertion of CO_2 with oxiranes directly provides the five-membered cyclic carbonate. Oxiranes such as ethylene oxide and propylene oxide undergo insertion at ~150–175°C under pressure with the aid of a quaternary ammonium salt catalyst to yield ethylene carbonate and propylene carbonate respectively (175,243–247). Transesterification with alcohols allows for entry to other acyclic carbonates as well as the production of ethylene or propylene glycol.

Another recent non-phosgene route to carbonates is the oxidative carbonylation of alcohols. The technology involves the catalytic reaction of methanol with carbon monoxide and oxygen to produce dimethyl carbonate. A variety of catalyst systems have been patented (204,247–251). EniChem practices the technology commercially using a copper chloride catalyst and a complex reactor design that involves recycle loops, azeotrope separation, and membrane separation (178,247,251,252). Aromatic carbonates have been made using a similar oxidative carbonylation process, however the technology has yet to be optimized (253–255). Entry to other aliphatic and cyclic carbonates has only been marginally sucessful and continues to be investigated.

$$2\,CH_3OH + 0.5\,O_2 + 2\,CuCl \longrightarrow 2\,Cu(OCH_3)Cl + H_2O \xrightarrow{CO}$$

$$2\,CuCl + CH_3O\overset{\overset{O}{\|}}{C}OCH_3$$

Dimethyl carbonate is also manufactured by carbonylation of methylnitrite through a catalytic redox process. The process is practiced commercially in the gas phase by Ube using a palladium supported catalyst system (175,247,256–257).

$$2\,CH_3OH + 0.5\,O_2 + 2\,NO \longrightarrow 2\,CH_3ONO + H_2O \xrightarrow{CO}$$

$$2\,NO + CH_3O\overset{\overset{O}{\|}}{C}OCH_3$$

The synthesis of dialkyl carbonates from urea and alcohol with organotin catalyst systems traditionally have been prone to thermal degradation products. However, a recent patent suggest that the problem can be overcome by employing novel organotins in a high boiling polar aprotic solvent such as a polyglycol ether, and distilling away the carbonate as it is formed (258). The operation

Table 8. **DOT Regulations for Carbonate Shipments**

Type	DOT hazard class	Tank truck	Drums
dimethyl carbonate	flammable liquid	yes	yes
diethyl carbonate	flammable liquid	yes	yes
diethylene glycol bis(allyl) carbonate	chemical NOS		yes

claims a continuous system that in theory has the possibility to allow for ammonia recycle back to urea. The net operation of the urea recycle system for dimethyl carbonate would utilize only methanol and carbon dioxide and thus has excellent economic potential.

3.4. Shipping and Storage. Dimethyl and diethyl carbonates are shipped in nonreturnable 208-L (55-gal) polyethylene drums with carbon steel overpack or high density polethylene drums. For bulk shipments, insulated stainless steel tank containers and trucks provide secure protection. Diethylene glycol bis(allyl) carbonate is shipped in drums as above. Diphenyl carbonate is delivered flaked in polyethylene sacks, or by tank car as a melt.

Carbonates are noncorrosive and should be plainly labeled and stored in cool, dry areas away from sources of ignition. The DOT Hazardous Materials Regulations control the shipment of carbonates as described in Table 8.

3.5. Economic Aspects. As in the case of the chloroformates, most of the carbonate production is used captively and production figures are not available. Both DMC and DPC are the largest volume carbonates, used primarily in the synthesis of bisphenol A polycarbonates. The DMC volumes would significantly increase if DMC were to gain interest as an octane enhancing additive in gasoline. Other heavy volume carbonates include DEC, ethylene carbonate, and propylene carbonate. Carbonate pricing in bulk range from $2–5/kg, with higher pricing for specialty esters (259). Major producers of aliphatic and aromatic carbonates include Enichem, Ube, Mitsubishi, Bayer, BASF, and PPG, as well as several sources in China. DPC is produced captively by GE using the Enichem DMC process in conjunction with their polycarbonate operation. Cyclic carbonates are available from Huntsman, Dow, BASF, Degussa, and Equistar.

3.6. Specifications and Analysis. Table 9 lists the specifications of the more important commercial carbonates. Assay is generally determined by gas or liquid chromatography. Water and traces HCl are detected using titration.

3.7. Health and Safety. Unlike chloroformates, diethyl and dimethyl carbonates are only mildly irritating to the eyes, skin, and mucous membranes. Diethylene glycol bis(allyl carbonate) may be irritating to the skin, but it is not classified as a toxic substance; however, it is extremely irritating to the eyes.

Protective clothing, rubber gloves, safety goggles, and adequate ventilation are recommended for all personnel handling high concentrations of carbonates. In case of fire, foam, carbon dioxide, or dry chemical extinguishing agents should be used. However, it is permissible to use a water spray to cool any drums in the vicinity, thus avoiding any spread of the fire.

3.8. Uses. The industrial utility of carbonates are widespread, ranging from pharmaceutical and cosmetic preparations to utility as specialty solvents

Table 9. **Specifications of Commercial Carbonates**

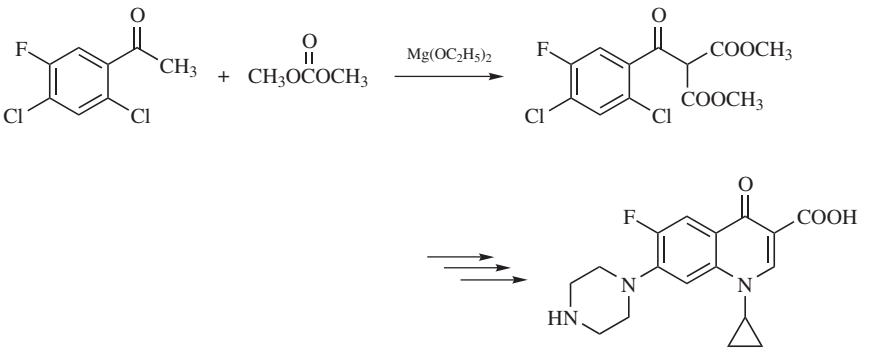
Assay	Dimethyl	Diethyl	Diethylene glycol bis(allyl)
min, %	98	98	94
acidity, max %	0.02	0.02	
water, max %	0.2	0.10	
sp gr, 20°C/4°C	1.070–1.075	0.973–0.977	1.14–1.16
nonvolatile matter, max %	0.01	0.005	1.0 at 150°C[a]
boiling point, °C	90	127	
viscosity, mPa · s (= cP)	0.664/20°C	0.868/28°C	25/25°C
surface tension at 20°C, mNm (=dyn/cm)		26.31	35
mol wt	90.1	118.1	274.3

[a] At 0.7 kPa (=5 mm Hg).

and application in polymers. The major volume carbonates include diphenyl, ethylene, and propylene carbonates as well as the simple aliphatics: diethyl, dimethyl, and dipropyl.

The diethyl ester is used in many organic syntheses, particularly of pharmaceuticals and pharmaceutical intermediates, dyes, and agricultural chemicals. It is also used as a solvent for many synthetic and natural resins, and in vacuum tube cathode-fixing lacquers.

Commercially, dimethyl carbonate (DMC) has emerged as the most important carbonate because of its lower cost from the nonphosgene route. The DMC can be used in the synthesis of important pharmaceuticals, such as the antimicrobial ciprofloxacin (Cipro) where it is used in place of diethyl malonate (260), and in the preparation of guaifenesin, a precursor for the muscle relaxant, methocarbamol (261).



Ciprofloxacin

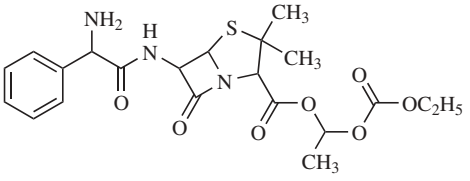
In many applications DMC is an effective carbonylating agent and is touted as a phosgene replacement (177,251). Huge quantities of bisphenol A polycarbonate are manufactured using a process that involves transesterification of DMC to diphenyl carbonate, followed by ester exchange with bisphenol A to give polycarbonate resin. Temperature resistant polycarbonate resins are used in plastics, the most important example being Lexan or Makrolon (143) (see POLYCARBONATE).

With its high oxygen content, low toxicity, and biodegradability, DMC has been considered as an oxygenate for gasoline. While it has yet to be used in commercial gasoline, hundreds of patents have claimed DMC's usefullness in fuels (247,261–263). Like many carbonates, DMC is an attractive solvent and is noted as a replacement for acetates and halogenated solvents in paint stipping and adhesive applications (175,264–265). Along with other carbonates (ie, methyl ethyl carbonate), DMC is also finding increasing application in the field of rechargable lithium batteries as a nonaqueous electrolyte component (266), as well as a blowing agent in polyurethane foam (267).

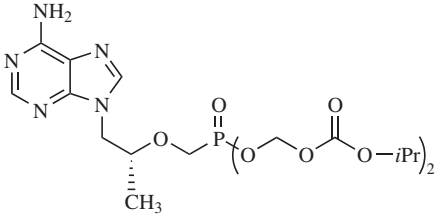
Dipropyl carbonate is also an organic intermediate, a specialty solvent, and is used in photoengraving as an assist agent for silicon circuiting. Low molecular weight carbonates are employed to generate −OH terminated aliphatic carbonated by transesterification with lower aliphatic diols (164). The resulting polyalkyl carbonates are useful in thermoplasic urethanes, paints, coatings, medical coatings and fibers, and thermoelastomers (175). Cyclic and aliphatic carbonates in combination with hydrogen peroxide are noted as alternatives to chlorinated solvents in paint and coating removal applications (268).

Diethylene glycol bis(allyl carbonate) polymerizes easily because of its two double bonds and is used for colorless, optically clear castings. Polymerization is catalyzed by the use of diisopropyl peroxydicarbonate [105-64-6] (269,270). Such polymers are used in the preparation of safety glasses, lightweight prescription lenses, glazing cast sheet, and optical cement (see ALLYL MONOMERS AND POLYMERS; POLYCARBONATES).

Specialty carbonates derived from 1-haloalkyl chloroformates are used for the manufacture of pro-drugs that have different properties than the parent drug, yet produce the same physological effect after *in vivo* hydrolysis. Important examples include Bacampicillin, the antibiotic pro-drug of Ampicillin (271), and the reverse transcriptase Viread, used in the treatment of acquired immuno deficiency syndrome (AIDS) (272,273).



Bacampacillin



Viread

Cyclic aliphatic carbonates are also excellent solvents for polymers and resins and are used as additives for hydraulic fluids, cure accelerators of phenol-formaldehyde resins used the plywood and chipboard industry, and cleaning solvents. Cyclic carbonates are also utilized as reactive dilutants for epoxy resins, accelerators in sand molding and polyurethane coatings, thermoset resins (274), metal extraction, and as a gellants in cosmetic applications (164).

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