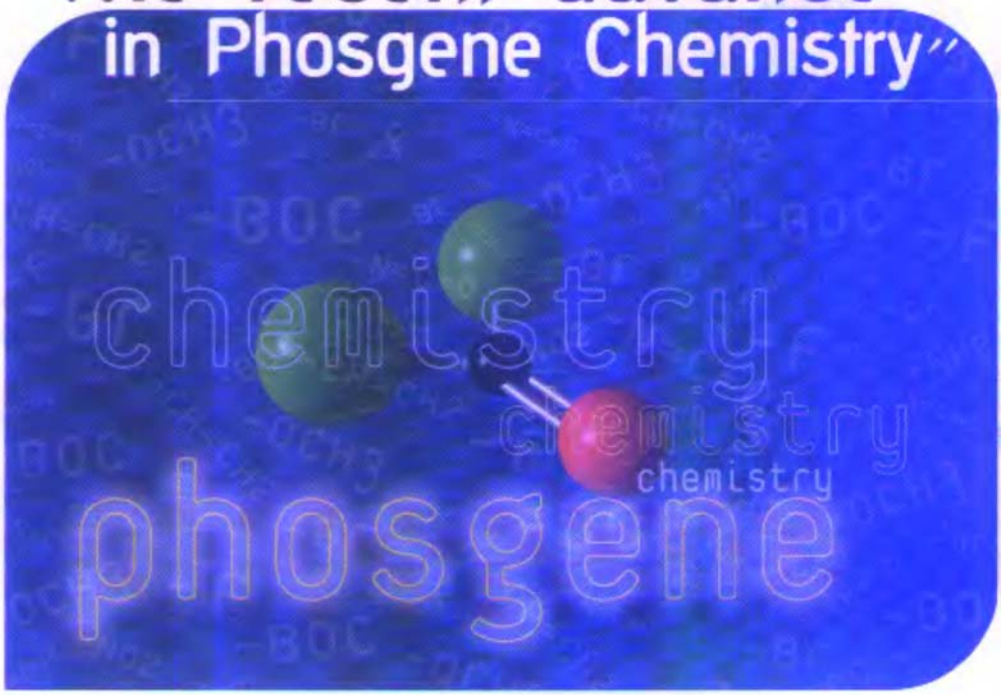
"The recent advance in Phosgene Chemistry"



Jean-Pierre SENET

L'acide chloroxicarbonique, qui peut tout aussi bien être considéré comme un chlorure d'oxide de carbone, offre une composition si simple et si remarquable que, s'il réalisait toutes les réactions que l'on a droit d'en espérer, on parviendrait à reproduire, à son aide, les combinaisons les plus curieuses de la chimie organique... (Read to the french « Académie des Sciences » on december 16 and 31, 1833).

Die Chlorkohlensäure (Phosgen), welche eben so gut als das Chlorür des Kohlenoxyds betrachtet werden kann, besitzt eine so einfache und merkwürdige Zusammensetzung, daß wenn es allen Reaktionen entspräche, die man die Recht davon erwarten könnte, man dahin gelangen würde, die merkwüdigsten Zusammensetzungen der organischen Chemie wieder hervorzubringen....(Translation published in « Annalen der Chemie »).

Chloroxycarbonic acid (phosgene) which can also be considered as a carbon oxide chloride, offers a composition which is simple and yet remarkable. If it produces all the reactions we expect of it, we will be able to reproduce some of the most fascinating combinations in organic chemistry.

Jean Baptiste Dumas

Jean Baptiste Dumas (b.1800 Alès, France - d.1884 Canne, France), French chemist and politician. Tutor at the Ecole Polytechnique (Paris 1821), one of the founders of the Ecole Polytechnique (Paris 1821), one of the founders of the Ecole Centrale des Arts et Manufactures (Paris 1829), Professor of Chemistry at the faculté des Sciences de Paris, at the faculté de Médecine, Lecturer at the Collège de france, Member of the Académie des Sciences (1832), elected at the Académie Française (1875).

Preface

At the early beginnings, organic chemistry was taken by the scientific community as the chemistry of living matter. After the discovery of the synthesis of urea by Wöhler in 1828, organic chemistry was defined as the chemistry of carbon-containing compounds.

Almost the entire amount of the carbon available on the earth surface exists in the form of carbonic acid (free or as calcium salts) and in fossil fuels obviously originated from living matter. It is well known that carbon dioxide is the necessary ingredient in the life cycle of animal and plants. Therefore, organic chemistry must be considered as strongly related to the chemistry of carbon dioxide and its derivatives.

Carbonic acid dichloride called « phosgene », discovered by John Davy in 1812, appears still nowadays the only efficient simple activated form of carbon dioxide, and despite intensive research done to replace it with less noxious starting material, phosgene remains a substitute for carbon dioxide. Moreover, because of the presence of acid chloride functions, phosgene exhibits a large range of other chemical reactions which make it a very useful multipurpose tool in organic chemistry.

The first chemical studies on phosgene chemistry have been associated with the development of organic chemistry during its classical era (1820 – 1940). In the period after world war two, phosgene chemistry has experienced a tremendous growth and wide interest. Vast numbers

of scientific papers and patents have been published by several thousands of organic chemists working in academic and industrial research laboratories.

By now, although phosgene chemistry is established as a fully-grown chemistry with well documented text books, monographs and reviews, it seems that truly important facets of new and unusual aspects are somewhat neglected. In this book, I have tried to provide an essentially complete survey of the work done for a quarter century at SNPE group in the chemistry of phosgene and related compounds, with special emphasis on unusual, unexpected and new reactions or applications.

Phosgene is widely used in organic chemistry as a building block providing the C = O such as in carbamates, carbonates, isocyanates, ureas, heterocycles etc., or as a reagent for chlorination, dehydration, alkylation, de-alkylation, protection and activation etc.

Consequently, I have chosen to divide this book in two volumes :

Volume 1 includes introduction, some considerations on physical properties and chemical reactivity, and four chapters devoted to phosgene and derivatives as building blocks.

Volume 2 presents applications of phosgene and derivatives as reagents and the general conclusion.

Of course, selection of topics to be included in these two volumes is undoubtedly influenced by the author's personal interest. So I would like to make here my apologies to any of my colleagues who may found their own work discussed inadequately.

Also, because nothing comes from nothing, in other terms because everything has predecessors, it is important to note that if John Davy discovered phosgene, Jean-Baptiste Dumas « invented » its chemistry and may be therefore considered as the true pioneer in the chemistry of phosgene. To take stock of this question, I have included in the first volume one section dedicated to the history of phosgene chemistry.

Furthermore, I wish to express my gratitude to all my colleagues from SNPE group and from the US and French Universities who have participated along these last 25 years in the development of news aspects of phosgene chemistry.

Finally, I would particularly like to acknowledge Professor Roy Olofson (The Pennsylvania State University) for his unfailing enthusiastic support during our more than ten years collaboration on the development of new synthetic reagents and preparative methods in phosgene and related compounds chemistry. I am deeply grateful to him for his patience, wisdom and kidness and for being a model as a scientist and a teacher.

Jean-Pierre G. SENET
Buthiers, Seine-et-Marne, France
August 1997

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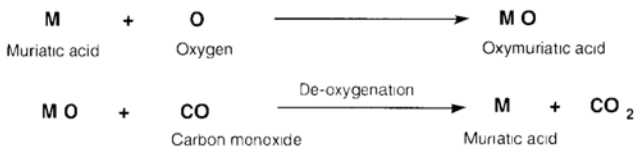
Introduction

I History of phosgene chemistry

The story of phosgene discovery (Ref. 1)

In the early beginning of the 19th century, chlorine gas was still uniformly considered as a combination of muriatic acid (hydrochloric acid) and oxygen called « oxymuriatic acid ».

However, in 1810, Dr. John Davy, Sir Humphry Davy's younger brother, expressed the opinion that oxymuriatic acid was, as a matter of fact, an elementary substance. This opinion was not at all accepted and several scientists, in order to refute the arguments of Dr. Davy, tried therefore to remove oxygen content of oxymuriatic acid by treatment with charcoal at a white heat or with carbon monoxide [Scheme 1].



Scheme 1 : Expected de- oxygenation of oxymuriatic acid (chlorine).

This was the opening of the so called « chlorine controversy » between Dr. John Davy and Dr. Murray, fervent supporter of the official theory. This debate took the form

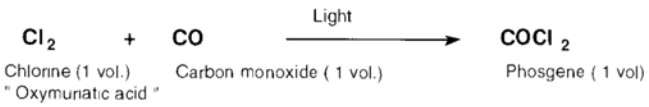
of letters contributed to « Nicholson's Journal », both authors arguing from their own experiments.

In an experiment of fundamental importance, after having exposed a mixture of one volume of carbonic oxide and one volume of oxymuriatic acid to bright sunshine, Dr. Davy noticed that the color of the chlorine has entirely disappeared, and that the remaining gas occupied the space of one volume. After addition of ammonia, he found no traces of carbonic oxide and observed an effervescence of the ammoniacal salt formed with nitric acid. He also noticed that the new gas resulting from the evident action of oxymuriatic acid and carbonic oxide did not fume when thrown into atmosphere and that it had a most intolerable suffocating odor and that water absorbed it very slowly.

These results were however again contested by Dr. Murray who, to support his opinion that oxymuriatic acid and carbon monoxide do not react, quoted unsuccessful trials from French chemists Gay-Lussac and Thenard :

« ... *mais à quelque dose qu'on ait mêlé le gaz acide muriatique oxigéné sec, et le gaz oxide de carbone préparé avec le fer et le carbonate de barite, quelque forte qu'ait été la lumière à laquelle on les a exposés, enfin quelque long qu'ait été le contact, il n'y a point eu d'action* ».

At last, in an important and well-argued letter read to the Royal Society on February 6, 1812, Dr. Davy refuted all the arguments of Dr. Murray and, on the basis of careful and indisputable experiments, proved the reality of the new gas [Scheme 2].



Scheme 2 : The discovery of phosgene.

To designate it, he suggested a simple name, that of **Phosgene** (or phosphene), from ancient Greek roots « light » and « to produce ».

The infancy of the phosgene chemistry

In spite of his neat discovery, Dr. Davy has not foreseen the prolific potentiality of phosgene as an outstanding building block and reagent in chemistry. However, while treating phosgene with ammonia, he was very close to another discovery of extreme importance, that of the elucidation of the nature of urea.

Dr. Davy noticed that phosgene dissolves in alcohol, but without mentioning any reaction.

In 1833, French chemist Jean-Baptiste Dumas while adding absolute ethyl alcohol in a flask containing phosgene, discovered its first synthetic derivative (Ref. 2). He noticed a strong and instant heating, and after work-up and analysis, he identified the resulting compound as a new chloroxicarbonic ether (ethyl chloroformate).

Dumas immediately had an inkling of the importance of phosgene chemistry with this prediction :

« *L'acide chloroxicarbonique, qui peut tout aussi bien être considéré comme un chlorure d'oxide de carbone, offre une composition si simple et si remarquable que, s'il réalisait toutes les réactions que l'on a droit d'en espérer, on parviendrait à reproduire, à son aide, les combinaisons les plus curieuses de la chimie organique* ».

Translation : « Phosgene exhibits such a simple and remarkable composition that, should it realize all the reactions one is entitled to hope for, one could reproduce, thanks to it, the strangest combinations in organic chemistry ».

All investigations since then have clearly fulfilled the expectation of Dumas who may be therefore considered as the pioneer in the chemistry of phosgene.

Jean-Baptiste DUMAS (1800-1884)
Pioneer in the Chemistry of Phosgene

1 2 Toxicity of phosgene

Phosgene is a highly toxic gas which was used as a chemical weapon during World War I.

At high concentration, it causes severe pulmonary irritation and can induce delayed pulmonary edema. It is the reason why all persons who have been exposed to phosgene, even in very low concentration, must see a physician immediately. Some relationships between phosgene concentrations in air and physiological effects on humans are summarized in table 1-1. The table 1-2 gives comparison between some toxic gases.

Perception of odor	>	0.4	ppm
Recognition of odor	>	1.5	ppm
Irritation in eyes, nose, throat, and bronchi	>	3	ppm
Beginning of lung damage	>	30	ppm-min
Clinical pulmonary edema	>	150	ppm-min
L(CT)0	~	300	ppm-min
L(CT)50	~	500	ppm-min
L(CT)100	~	1300	ppm-min

Table 1 1 Concentration-effect relationships of phosgene exposure in humans (Ref. 3).

Gas	Odor identification ppm	L(CT)0-30 min exp. ppm
Phosgene	1.5	10
Chlorine	1	873
Carbon monoxide	No	4 000
Ammonia	5	30 000

Table 1-2 : Comparison between some toxic gases.

Due to these high toxicity properties, the presence of large quantities of phosgene on a site must be strictly treated as major hazard. The regulatory requirements in transportation and safety know-how in the handling and storage of phosgene, have restricted its uses to specialized companies. Custom synthesis is a common practice in this field, because the transportation of raw materials to phosgene producers is preferred to the transportation of phosgene itself.

1-3 Breakdown of phosgene consumption the industry

Although information in this field is generally kept confidential, worldwide phosgene production is estimated to range from 6 to 8 millions tons/year.

The breakdown of phosgene consumption is the following :

- Di and polyisocyanates (TDI, TMDI) for polyurethanes 85%
- Aromatic polycarbonates 10%
- Manufacture of fine chemicals 5%

The consumption of phosgene for fine chemicals, about 300,000 T/year is roughly divided into :

- 50% for peresters and percarbonates used as polymerization initiators,
- 25 % for agrochemicals,
- 25 % for pharmaceuticals and dyestuffs.

1 4 Classification of phosgene reactions

Since the pioneering study by Dumas, phosgene chemistry, especially devoted to fine chemicals, has grown tremendously and still remains in an active field of investigation with 2500 papers and patents published each year. Almost all the chemical reactions of phosgene can be divided into two classes, depending on wether the structural unit remains in the final product or not.

First class : Reaction of phosgene as a building block to introduce the structural unit « carbonyl ». Some examples are given in table 1-3.

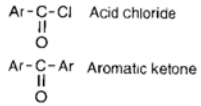
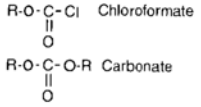
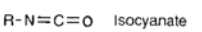
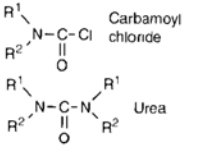
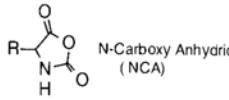
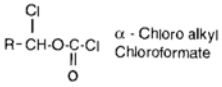
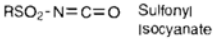
Substrate	Product
Aromatic : Ar-H	 Acid chloride; Aromatic ketone
Alcohol or phenol : R-OH	 Chloroformate; Carbonate
Primary amine : RNH2	 Isocyanate
Secondary or tertiary amine : $R^1R^2R^3N$ (R^3- = H or alkyl)	 Carbamoyl chloride; Urea
α-Amino acids H_2N-CHR-COOH	 N-Carboxy Anhydride (NCA)
Aldehydes : RCHO	 α - Chloro alkyl Chloroformate
Sulfonamide : RSO_2NH_2	 Sulfonyl Isocyanate

Table 1-3 : Examples of phosgene reactions to introduce the group >C=O.

Second class : Phosgene and derivatives as reagents

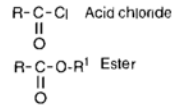
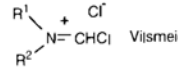
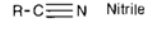
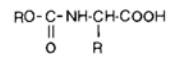
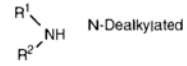
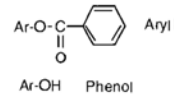
Substrate	Product
Carboxylic acid : R-COOH (+ R1OCOCl)	 Acid chloride; Ester
Alcohol : R-OH	 Alkyl chloride
N,N-Disubstituted : R^1R^2NCHO formamide	 Vilsmeier salt
Primary amide : $R\text{-}CONH_2$	 Nitrile
Alkyl formate : R-OCOH	 1,1- Dichloromethyl ether
Phenol : Ar-OH	 Aryl methyl ether
Amino acid : H_2N-CHR-COOH	 N- Protected amino acid
Tertiary amine : $R^1R^2R^3N$ (R^3 = alkyl)	 N-Dealkylated amine
Aryl methyl ether : Ar-O-Me (+ PhCOCl + catalyst)	 Aryl benzoate; Ar-OH Phenol

Table 1-4 : Examples of phosgene and derivatives as reagents.

2 Characteristics of phosgene

1 Physical properties

At ambient temperature and pressure, phosgene is a colorless gas which exhibits an irritating and suffocating odor. At low concentrations, it has a characteristic odor like moldy hay. However, the odor threshold of phosgene is higher than its toxic limit and one must remember that the sense of smell fails to detect small concentrations in air.

Some physical properties of phosgene are presented in table 2-1.

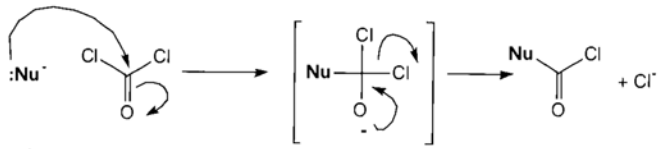
CAS number	75 - 44 - 5
Molecular weight	98.92
Structure	Planar molecule
	Inter atomic distances : C-O = 0.128 nm
	C-Cl = 0.168 nm
Melting point	- 130°C
Boiling point	+ 8.2°C
Vapor pressure	1.6 atm. (20°C) ; 3.99 atm. (50°C)
Vapor density	3.42
Liquid density	1.43 (0°C) ; 1.275 (50°C)
Conversion factor	1 ppm = 4.043 mg/m^3
Odor	Reminiscent of moldy hay

Table 2-1 : Principal physical properties of phosgene.

2-2 Chemical reactivity of phosgene

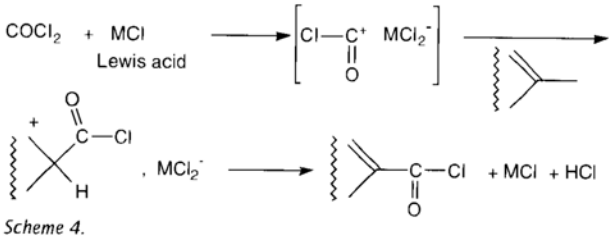
A large part of phosgene reactivity may be accounted for on the basis of two main mechanisms :

a) Nucleophilic attack on carbonyl function :



Scheme 3.

b) Electrophilic reactions, especially Friedel & Crafts related reactions :



Scheme 4.

Because some important aspects of the mechanism of the nucleophilic reactions with phosgene seemed somewhat neglected or unknown in the previous art, SNPE teams have focused their efforts in terms of basic and applied research on the catalysis of such reactions. The main goal of this active and long investigation was to improve industrial phosgenation processes and to extend the range of substrates able to react with phosgene.

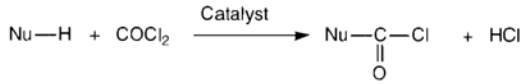
As a consequence, this investigation succeeded in development of many improved processes and the discovery of several previously unknown reactions which are discussed in this book.

The principal obstacle to progress in this field has been the difficulty of establishing the catalytic mechanism of phosgene reactions. Two catalytic paths are obviously possible :

— substrate activation by means of an increasing of its nucleophilicity ;

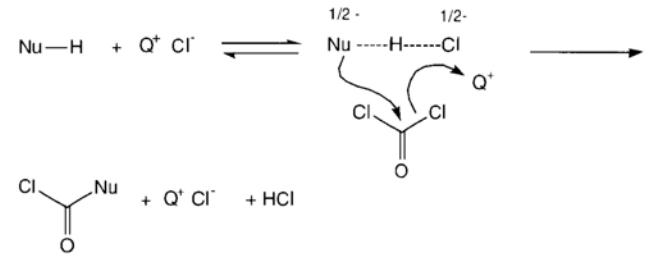
— phosgene activation by improvement of the « leaving character » of chloride anion.

Concerning phosgene reactions with active hydrogen substrates [Scheme 5] :



Scheme 5.

mechanistic studies performed with the help of Nantes University in France (Ref. 4) resulted in the revelation of substrate activation based on nucleophilicity of chloride anion in the case of Q+ Cl- type catalyst (quaternary ammonium chloride for example). The mechanism of nucleophilic assistance of these catalysts can be understood as an increase of the nucleophilicity of the substrate by proton abstraction followed by the condensation of the promoted anion on the electrophile (phosgene) [Scheme 6] :

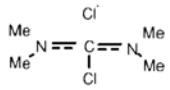


Scheme 6.

This mechanism has been confirmed by reacting a series of onium chloride salts with phenol using ^{35}Cl NMR determination as physical probe as shown in table 2-2.

Range of phosgenation efficiency (a)	Q + Cl -	Line width 1/2 (Hz) (c)
HIGH	TMCA (b)	240
	Tetra hexyl ammonium chloride	220.5
	Benzyl tributyl ammonium chloride	145.5
MEDIUM	Tetrabutyl ammonium chloride	141
LOW	Benzyl trimethyl ammonium chloride	58

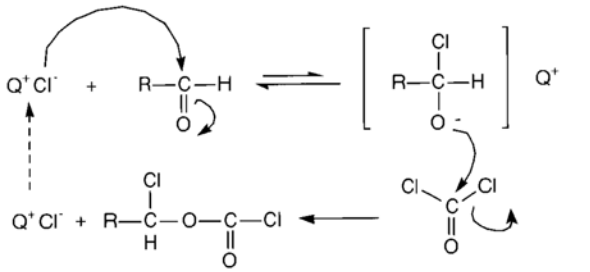
(a) Phosgenation of phenol into phenyl chloroformate or carboxylic acids into acid chlorides

(b) Tetramethyl chloroformamidinium chloride : 

(c) Line width of the chloride anion resonance in the system onium chloride salt/phenol (solvent : CH3CN)

Table 2-2 : General correlation between catalyst efficiency and nucleophilicity of chloride anion. Study by ^{35}Cl NMR.

We pointed out that the C-nucleophilicity of chloride anion is also acting. In the course of our research related to the reaction of phosgene with carbonyl compounds, we [illegible] roalkyl chloroformates when treated with phosgene in the presence of a Q+ Cl- catalyst (Ref. 5). The assumed mechanism involves the nucleophilic attack of the chloride anion on the aldehyde followed by the acylation of the intermediate chloroalkoxide anion by phosgene [Scheme 7] :



Scheme 7

The success of this new synthetic route to α-chorinated chloroformates which are very useful intermediates (see chapter 3, section 3-2) is strongly dependent on the nucleophilic power of the chloride anion as shown in table 2-3 :

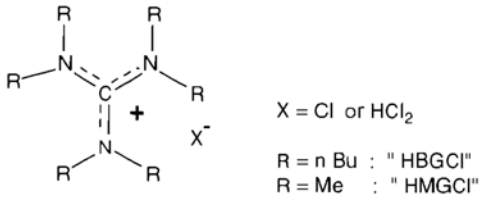
Catalyst (5 mol. %)	Nucleophilicity (Hz)	1-Chloro ethyl chloroformate Yield %
Benzyl tributyl ammonium chloride	145.5	95
Benzyl trimethyl ammonium chloride	58	0 (No reaction)

Table 2-3 : Correlation between nucleophilicity determined by ^{35}Cl NMR and results obtained in phosgenation of acetaldehyde.

The role of the nucleophilicity of the chloride anion is [illegible] by the high activity of complexed salts such as KCl/18 crown 6 as catalysts for the phosgenation of aldehydes.

Traces of HCl (moisture) inhibit the reaction because HCl_2^- anion exhibits much less nucleophilicity than Cl^-. Including hydrochloric acid scavenger such as little toluene diisocyanate in the mixture generally solves the problem.

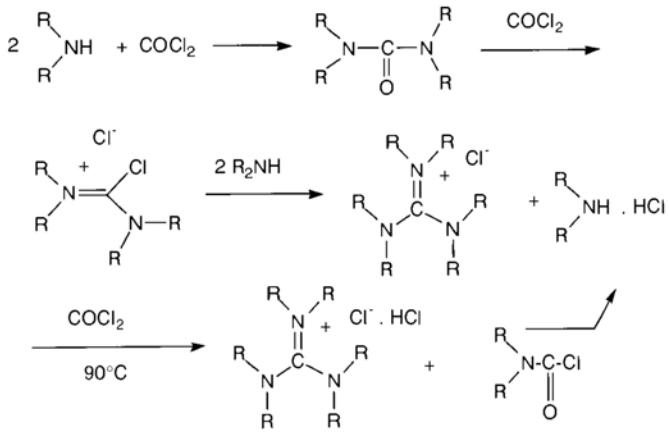
The nucleophilicity of the chloride anion is of course a function of the nature of the counterion Q^+. To increase the nucleophilicity, one can either or both increase the bulkiness and the dispersal of the positive charge of the counterion. We discovered that hexaalkyl guanidinium chlorides are very efficient and powerful phosgenation catalysts [Scheme 8] :



Scheme 8 : Hexaalkyl guanidinium chlorides.

We introduced these guanidinium salts in a 1985 patent (Ref. 6) on the conversion of carboxylic acids to acid chlorides with phosgene. In this process, only 0.02 mol. % of HBGCl was required, two orders of magnitude less than the quantities of other catalysts typically used. Many new other applications including phosgene reactions with phenols, thiols, aldehydes, epoxides or O-demethylation methods have been developed later and are discussed in this book.

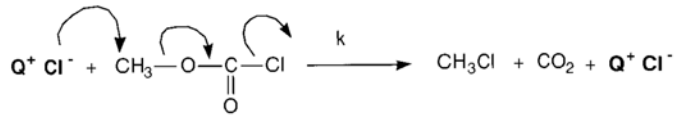
Moreover, these new catalysts may be considered themselves as phosgene derivatives because they are made from phosgene and secondary amines by the scheme depicted below [Scheme 9] :



Scheme 9 : Preparation of hexa alkyl guanidinium chlorides

This industrial process leads to hexabutylguanidinium chloride hydrochloride (HBGCl.HCl) which, as above mentioned, failed as a catalyst in the reaction requiring high C-nucleophilicity of chloride anion. Pure HBGCl may be obtained by shaking a solution of HBGCl.HCl with excess 10% NaOH. The dried ($MgSO_4$) organic layer is concentrated and then treated at 100°C under vacuum (0.2 torr) for 24 h. The off-white powder obtained is stored under nitrogen.

The decomposition of methyl chloroformate is a very convenient method to establish a nucleophilicity power scale of the chloride anion in onium chlorides, allowing thus to easily compare a priori the catalytic efficiency of different candidates. It is known that the decarboxylation of methyl chloroformate is catalyzed by $Q^+ Cl^-$ type compounds thus producing only methyl chloride and carbon dioxide according to a pure SN_2 reaction (Ref. 7) [Scheme 10] :



Scheme 10 : Decomposition of methyl chloroformate

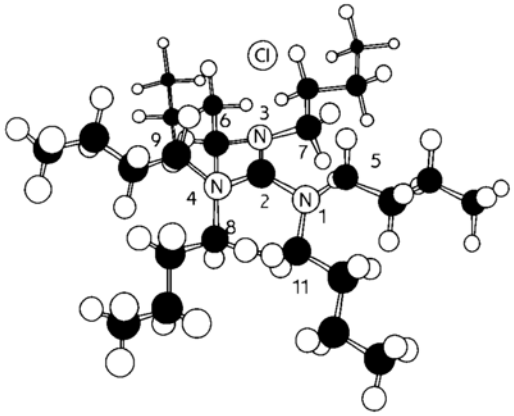
We used this specific reaction on IR analysis as kinet chemical probe (Ref. 8). Among the various oniu chlorides commonly encountered, hexabutyl guanidiniu chloride (HBGCl) exhibits the highest activity as shown i table 2-4 :

Catalyst	Relative rate constant
HBGCl	100
HMGCl	47
Tetrahexyl ammonium chloride	42
Benzyl tributyl ammonium chloride	27
Trioctyl methyl ammonium chloride	14

Table 2-4 : Relative rate constant values of SN_2 decomposition of methyl chlor formate at 70°C in the presence of onium chloride catalysts (1%). For HBGCl, the k value is 12.52 min.$^{-1}$ (Ref. 8).

As expected considering table 2-4, hexabutyl guanid nium chloride displays higher catalytic activity than it hexamethyl analogue. However, HMGCl offers som advantages because of its solubility in water which make easier elimination by aqueous washings and because precipitates in several phosgenation media after removal c phosgene excess.

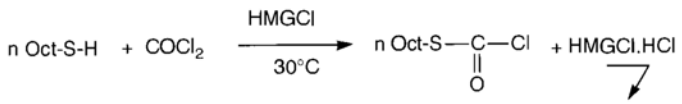
To sum up, hexabutyl guanidinium chloride exhibit some particularities due to its extraordinary bulkiness an the hydrophobicity of the the n-butyl substituents However, the dispersal of the positive charge is somewha counterbalanced by the out of plane distortion of the bulk substituents as suggested by molecular modeling calcula tions on HBGCl using the CSC Chem 3D program (Ref. 9 Due to this kind of geometry and for reasons of symmetry it is assumed that the chloride anion will be located alon the central axis and will interact weakly with the positiv center [Scheme 11] :



Scheme 11 : Molecular model of hexabutyl guanidinium chloride

Although hexamethyl guanidinium chloride (HMGCl) is less active than its hexabutyl congener, it is very useful in several industrial applications, because of its good water solubility, and also because its hydrochloride is often insoluble in organic mediums. These two properties allow easy removal of the catalyst after reaction.

For example, phosgenation of octane thiol proceeds rapidly in presence of HMGCl, even at 30°C to give octyl thiochloroformate [Scheme 12] :



Scheme 12 : Synthesis of n octyl thiochloroformate in presence of HMGCl.

After completion of the reaction and removal of phosgene excess, HMGCl.HCl which precipitates completely is filtrated thus giving very pure product (Ref. 10).

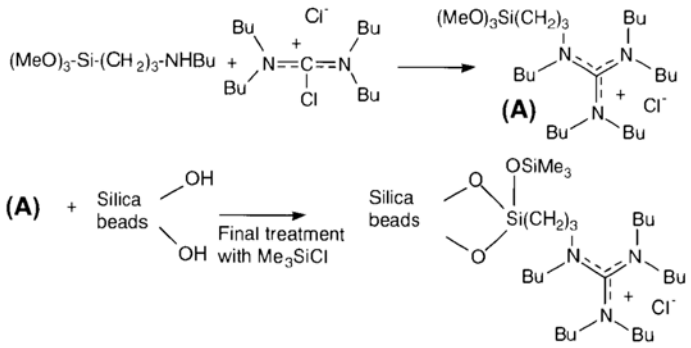
Another approach is to have a catalytic system strictly insoluble in all media and therefore easily removable by filtration and indefinitely reusable. Such heterogeneous catalyst offers many advantages, particularly in the case of products difficult to purify by distillation because of thermal instability or too high boiling point.

We have recently reported the preparation of silica-supported guanidinium salts, especially pentabutyl propyl-guanidinium chloride grafted on silica beads, and their uses as phosgenation heterogeneous catalysts (Ref. 11). For example, starting from macroporous silica glass beads having the following characteristics :

- diameter : 1 mm
- specific surface : 78 m^2/g
- porous volume : 0.9 cm^3/g
- OH content : 4.8 µ mol./m^2

we obtained at pilot scale a catalytic system bearing 0.085 meq./g of active sites.

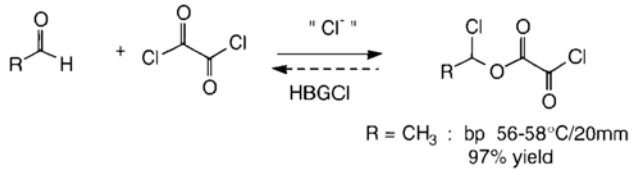
The synthesis route we developed is depicted on scheme 13 :



Scheme 13 : Synthesis route to silica-supported guanidinium chloride catalyst.

Since this supported catalyst is stable, insoluble and composed of mechanically strong particles of 1 mm diameter, it can be easily recovered by filtration and be reused. The high stability and activity of silica supported guanidinium salts, along with the ability to reuse the solid catalyst were demonstrated on repetitive batch phosgenations of carboxylic acids.

The utility of silica supported guanidinium salts was also well established in reactions sensitive to reversal while heating. Thus, we discovered that treatment of aldehydes with oxalyl chloride in the presence of a « naked » catalyst (*e.g.*, HBGCl) produces 1-chloroalkyl oxalyl chlorides in 60-97% yields (Ref. 12) [Scheme 14] :



Scheme 14 : Reaction of excess oxalyl chloride with aldehydes.

However, with aromatic aldehydes or with chloral, heating in the presence of the catalyst during distillation resulted in reversion to the aldehyde and attempts to entirely remove the fatty HBGCl catalyst, for example by pentane trituration failed due to the partial solubility of this salt in the non-polar medium.

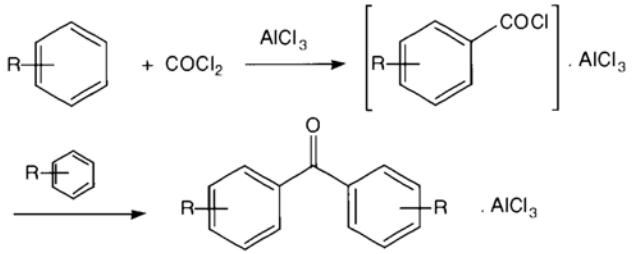
This problem was overcome by utilizing the supported catalyst above described. In a typical example, distilled 1,2,2,2-tetrachloroethyl oxalyl chloride was thus obtained from chloral in 95% yield after 4 h reaction.

3 Phosgene and derivatives as building blocks

Reactions at carbon center

In the course of several studies, we demonstrated that the Friedel-Crafts reaction of phosgene with aromatics depends critically on the purity of catalyst, the presence of water and on the ratio catalyst/substrate.

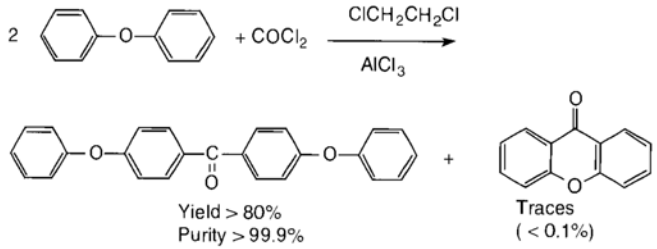
Generally, condensation of phosgene with aromatics in presence of Lewis acids affords benzophenones as the main products, unless a special mean is employed to remove the intermediate complex [Scheme 15] :



Scheme 15 : Friedel-Crafts reaction of phosgene with aromatics.

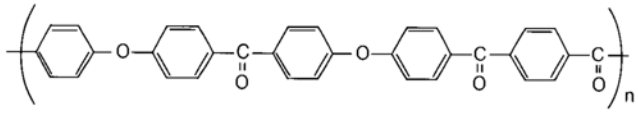
Note that the adduct ketone/$AlCl_3$ is much more stable than the adduct acid chloride/$AlCl_3$.

For example, condensation of diphenyl ether with phosgene under Friedel-Crafts conditions gives 4,4'-diphenoxy benzophenone as the major product (Ref. 13). We developed an improved process which leads to a very pure product with low content of xanthone [Scheme 16] :



Scheme 16 : Preparation of high purity 4,4'- diphenoxy benzophenone.

High purity 4,4'- diphenoxy benzophenone is a key starting material for the production of high molecular weight polymers. Thus, its polycondensation with terephtaloyl chloride in presence of Friedel-Crafts catalyst gives poly-ether-ether ketones (PEEK) with the structure depicted on scheme 17 :



Scheme 17 : Structural unit of thermoplastic poly ether ether ketones

Poly ether ether ketones are used as high performance engineering thermoplastics which offer an unique range of properties among them :

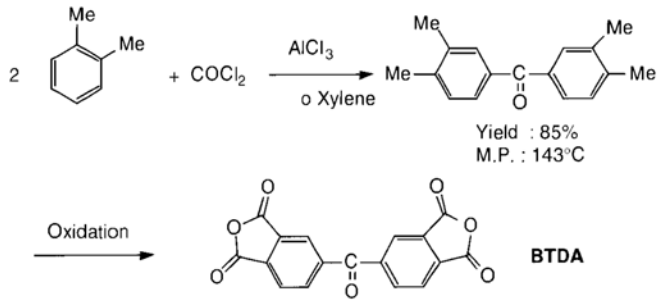
– continuous working temperature of 250°C ;

– high chemical resistance ;

– hydrolysis resistance on service of thousands of hours at temperature in excess of 250°C in steam under pressure ;

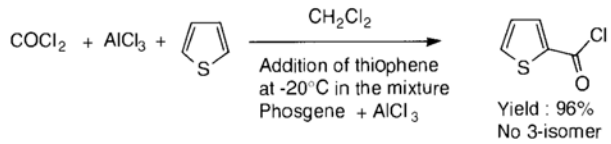
– easily processible.

Another example is the Friedel-Crafts phosgene reaction with o.xylene giving 3,3',4,4'-tetramethylbenzophenone in high yield and free of isomers (Ref. 14). This substituted benzophenone is easily oxidized into benzophenone tetracarboxylic acid dianhydride (BTDA) widely used for the manufacture of polyimides [Scheme 18] :



Scheme 18 : Synthesis of benzophenone tetracarboxylic dianhydride

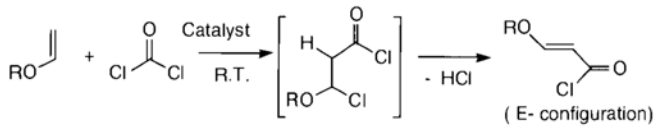
Friedel-Crafts reaction of phosgene with heterocyclic aromatic compounds is also difficult to stop at the acid chloride stage. However, under selected conditions, hetero-aromatics such as thiophene can be directly acylated to give thiophenecarbonyl chloride [Scheme 19] (Ref. 15) :



Scheme 19 : Preparation of 2-thiophenecarbonyl chloride

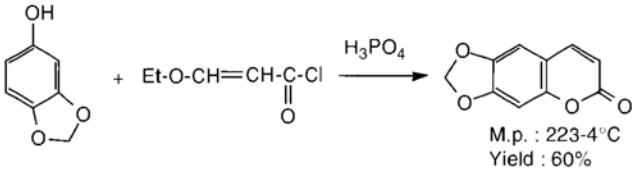
2-Thiophenecarbonyl chloride is used as intermediate in the synthesis of many pharmaceuticals. For example, its condensation with protected L-4-hydroxyproline followed by deprotection gives a product claimed as antiinflammatory and antidystrophic agent (Ref. 16).

Nucleophilic addition of vinyl ethers to phosgene is an efficient synthetic route to valuable 3-alkoxy and 3-phenoxy acryloyl chlorides. We studied an improved process based on literature data (Ref. 17) under special catalytic conditions [Scheme 20] :



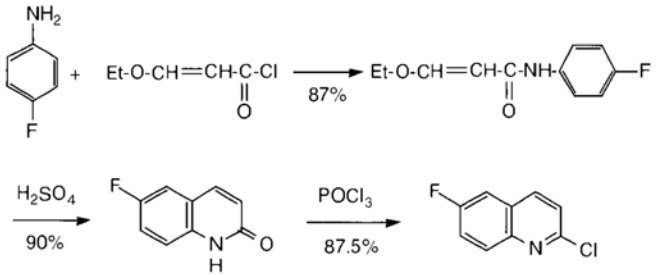
Scheme 20 : Phosgenation of vinyl ethers to give 3-alkoxyacryloyl chlorides

E-3-alkoxyacryloyl chlorides are high potential intermediates in organic synthesis, especially for the preparation of various heterocycles, such as coumarins [Scheme 21] :



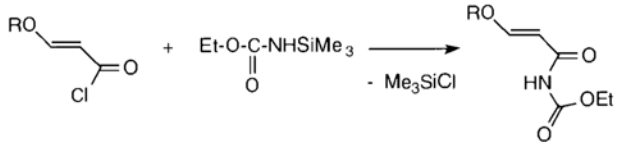
Scheme 21 : Preparation of Ayapin using 3-ethoxyacryloyl chloride (Ref. 18)

or quinolines [Scheme 22] :



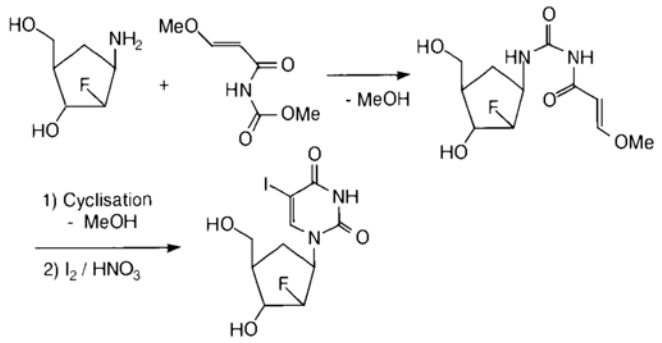
Scheme 22 : Synthesis of quinoline derivatives, valuable intermediates for the preparation of herbicides (Ref. 19)

Another valuable application of 3-alkoxyacryloyl chlorides is the preparation of N-alkoxyacryloyl carbamates according to an original process developed at SNPE Group [Scheme 23] :



Scheme 23 : Preparation of Ethyl N-alkoxyacryloyl carbamate

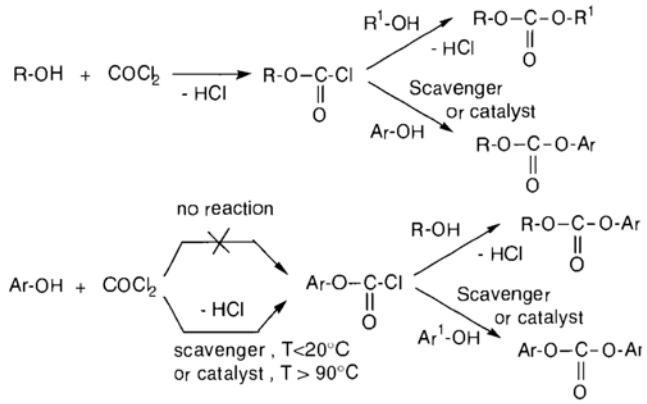
N-alkoxyacryloyl carbamates offer an interesting option to avoid the use of toxic and expensive alkoxyacryloyl isocyanates in the synthesis of uracil derivatives with antiviral activity [Scheme 24] :



Scheme 24 : Preparation of uracil derivatives as antivirals (Ref. 20)

Reactions an oxygen or sulfur center

Phosgene reacts easily with aliphatic mono or poly hydroxy compounds at room temperature or below to afford corresponding aliphatic chloroformates in good yields. In contrast, phenols are quite inert toward phosgene, even at temperatures as high as 150°C. Reaction of phosgene with phenols requires an acid scavenger such as tertiary amine or a mineral base (room temperature or below) or a catalyst (see section 2-2) such as HBGCl.HCl (temperature higher than 90°C) [Scheme 25].



Scheme 25 : Reactions of phosgene with alcohols and phenols

Aliphatic and aromatic chloroformates can reac further, easily with aliphatic hydroxy compounds to yiel carbonate diesters and only in presence of bases o catalysts with phenols.

The chemistry of chloroformates has been alread reviewed in depth (Ref. 21) and this section 3-2 is limite to unusual or unexpected products or reactions, mostl developed in SNPE Group. Table 3-1 gives some example of non conventional chloroformates.

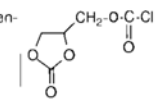
Name ... chloroformate	Structure	R.N.	B.P. °C/mm	Applications
Chloromethyl	$Cl\text{-}CH_2O\text{-}C(=O)\text{-}Cl$	22128-62-7	106/760	Pharmaceuticals Agrochemicals Photo resists
Trichloromethyl	$Cl_3C\text{-}O\text{-}C(=O)\text{-}Cl$	503-38-8	125/748	Phosgene substitute (also called « diphosgene »)
1-Chloroethyl	$CH_3\text{-}CH(Cl)\text{-}O\text{-}C(=O)\text{-}Cl$	50893-53-3 (±) 95597-56-1	117/760	Antibiotics (pro drugs) N-dealkylation of t. amines Pharmaceuticals
1,2,2,2-Tetrachloro ethyl	$Cl_3C\text{-}CH(Cl)\text{-}O\text{-}C(=O)\text{-}Cl$	98015-53-3	80/14	Peptide chemistry, pharmaceuticals
Vinyl	$CH_2{=}CH\text{-}O\text{-}C(=O)\text{-}Cl$	5130-24-5	89-90/ 760	Polymers Contact lenses Pharmaceuticals N-dealkylation
Isopropenyl	$CH_2{=}C(CH_3)\text{-}O\text{-}C(=O)\text{-}Cl$	57933-83-2	94.5/ 747	Pharmaceuticals Peptide chemistry
2,2-Dichloro vinyl	$Cl_2C{=}CH\text{-}O\text{-}C(=O)\text{-}Cl$	113421-96-8	82-85/ 120	Polymers (optical fibers) Agrochemicals
2,2,2-Fluorodinitro ethyl	$F\text{-}C(NO_2)_2\text{-}CH_2\text{-}O\text{-}C(=O)\text{-}Cl$	31841-79-9	58/2	Explosives Propellants
t-Butyl	$(CH_3)_3C\text{-}O\text{-}C(=O)\text{-}Cl$	24608-52-4	3-4/0.9-1.7 Dec.	Peptide chemistry (this chloroformate is very unstable)
2-Oxo-1,3-dioxolan-4-yl methyl		23385-72-0	Dec.	UV curable acrylic resins Hydro gels Blowing agents for plastic foams Foods additives

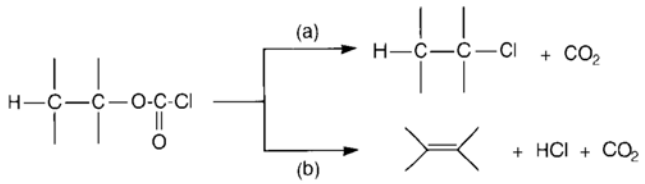
Table 3-1 : Some unusual aliphatic chloroformates.

3-2-1 Highlights of some particular chloroformates and carbonates starting from alcohols or phenols

In the course of previous studies devoted to new substituted chloroformates, we were interested in the synthesis of nitro and aminoalkyl chloroformates.

Thus, for application in explosives and propellants, a safe process for the preparation of 2,2,2-fluorodinitroethyl chloroformate was developed starting from fluorodinitroethanol (Ref. 22). See table 3-1.

The case of aminoalkyl chloroformates is more complicated because of the instability of chloroformates in presence of amines. It is well known (Ref. 21) that aliphatic chloroformates decompose by two paths depicted in scheme 26 :



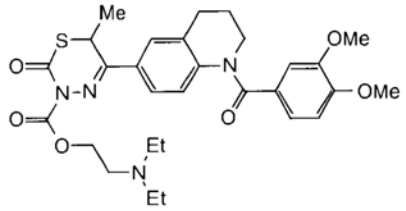
Scheme 26 : Decomposition paths of aliphatic chloroformates

Temperature of decomposition varies widely depending :
- on the structure of the aliphatic radical ;
- on the presence and nature of other compounds, especially amines or quaternary ammonium salts (SNi or SN2 mechanisms).

Therefore, the preparation of aminoalkyl chloroformates requires carefully selected conditions (Ref. 23) :
- Low temperatures (below + 10°C) ;
- Addition of amino alcohols into phosgene solutions ;
- Solvents selected in order to have a complete precipitation of the hydrochlorides ;
- Filtration carried out away from any trace of moisture.

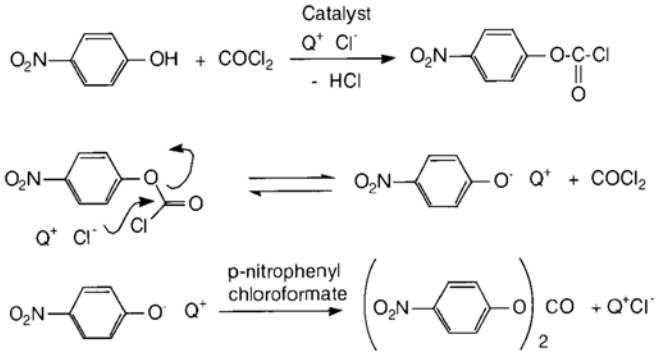
Amino chloroformates are generally isolated as their hydrochlorides and stored under dry nitrogen at low temperature (< +5°C). They are interesting potent intermediates for pharmaceuticals. Thus, 2-(N,N-diethylamino) ethyl chloroformate is used in the preparation of new

cardiovascular agents for the acylation of quinolylthiadiazinone (Ref. 24) [Scheme 27] :



Scheme 27 : New cardiovascular agent.

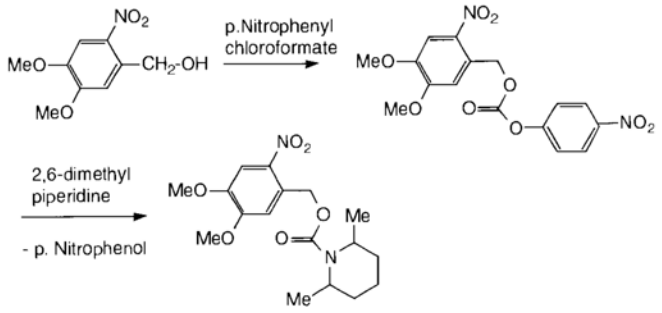
The manufacture of aromatic chloroformates bearing electrons withdrawing groups is posing a problem. For example, the phosgenation of p-nitrophenol in presence of a catalyst to afford p-nitrophenyl chloroformate is equilibrated. The balance is easily tipped towards starting materials by elimination of phosgene excess. As a consequence, attempts of purification by distillation give rise to the formation of 4,4'-dinitrodiphenyl carbonate and, more hazardous, phosgene according to the mechanism depicted on scheme 28 :



Scheme 28 : The problem of p-nitrophenyl chloroformate synthesis.

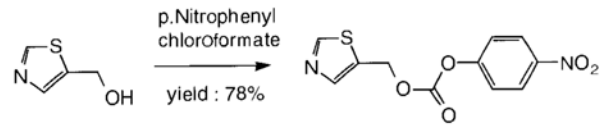
Again, this difficulty was overcome by complete elimination of the catalyst from the mixture before distillation thus giving a pure and stable chloroformate.

p-Nitrophenyl chloroformate is widely used in industrial chemistry, especially as a protecting agent or as a phosgene substitute in the synthesis of urethanes. For example, a new amine photogenerator was prepared from p-nitrophenyl chloroformate (Ref. 25) according to the scheme 29.



Scheme 29 : Preparation of a new amine photogenerator.

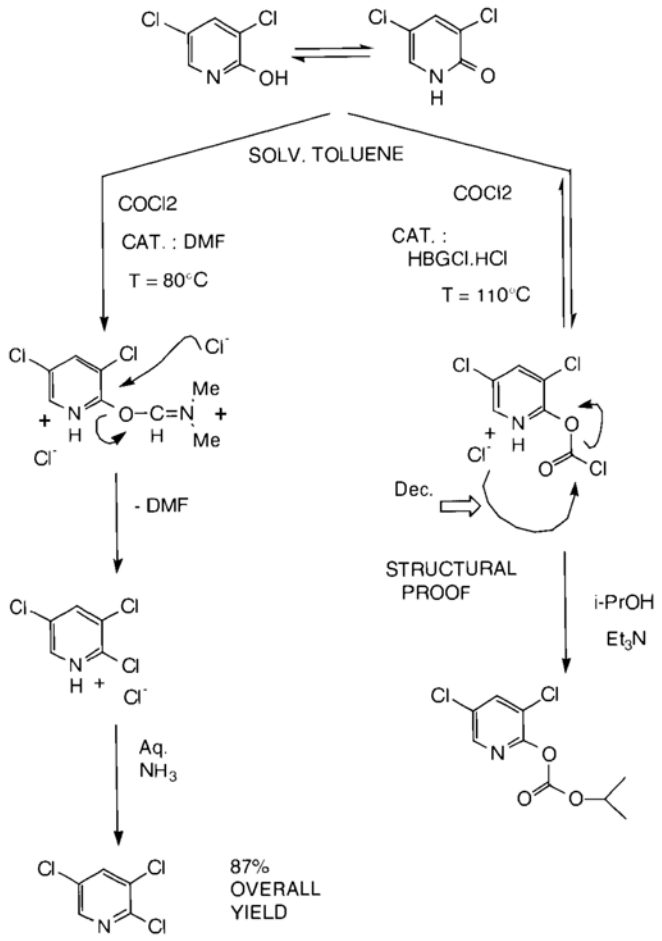
In another example, p-nitrophenyl chloroformate was required to introduce a sophisticated carbamate function in a multi-steps synthesis of retroviral protease inhibiting compounds (Ref. 26). The structure of the intermediate carbonate is given in scheme 30.



Scheme 30 : Preparation of a key intermediate for the synthesis of retroviral protease inhibitors.

The final result of the reaction of phosgene with certain hydroxy compounds may depend drastically on the catalyst used. For example, the phosgenation of 3,5-dichloro-2-hydroxy pyridine in toluene, in presence of DMF, gives 2,3,5-trichloropyridine in good yields. This compound is a valuable intermediate for producing herbicides (Ref. 27). Surprisingly, we found that the phosgenation in presence

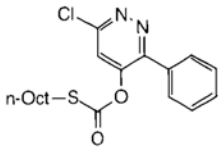
of hexabutylguanidinium chloride hydrochloride (HBGCl. HCl) leads quantitatively to 3,5-dichloro-2-pyridinyl chloroformate (Ref. 28). On further heating, in presence of HBGCl.HCl, this new chloroformate decomposes slowly to afford starting material and phosgene almost quantitatively (reverse reaction, see scheme 31).



Scheme 31 : Unusual reaction of phosgene with 3,5-dichloro-2-pyridone.

Phosgene in excess reacts with thiols in presence of a catalyst to afford thiochloroformates. However, in industrial processes, it is often difficult to avoid formation of side products, especially disulfides and thiocarbonates.

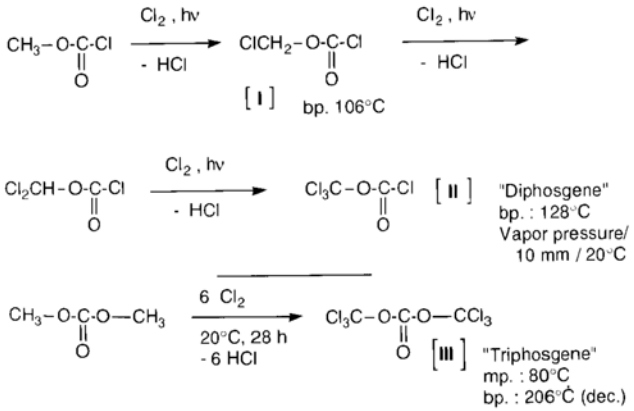
As already discussed in section 2-2, use of HMGCl.HCl catalyst, soluble during the reaction, insoluble after completion and removed by simple filtration, gives high quality products. For example, n-octyl thiochloroformate, useful intermediate for the manufacture of herbicides [See scheme 32] is obtained in quantitative yield, without any traces of side products. Moreover, the filtered catalyst is indefinitely reusable.



Foliar active herbicide
introduced by Chemie-Linz AG
Trade mark " **Lentagran** "

Scheme 32 . PYRIDATE from n-Octyl thiochloroformate.

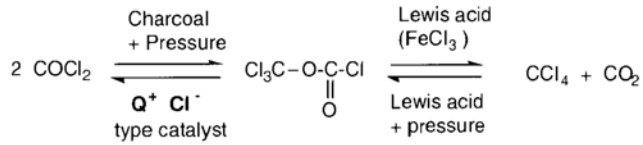
Chlorination of methyl chloroformate and dimethyl carbonate affords useful phosgene substitutes : chloromethyl chloroformate [I], trichloromethyl chloroformate [II] also called « Diphosgene » and bis(trichloromethyl) carbonate [III] known as « Triphosgene » [see scheme 33] :



Scheme 33: Chlorination products from methyl chloroformate and dimethyl carbonate.

The properties of chloromethyl chloroformate which has been made also by phosgenation of monomeric formaldehyde (Ref. 29), are discussed further in section 3-2-2.

Some interesting relationships between « Diphosgene », phosgene (Ref. 30) and the dismutation of phosgene into carbon tetrachloride and carbon dioxide (Ref. 31) are depicted in scheme 34 :



Scheme 34 : Reverse dismutation of phosgene.

The reversibility of the decomposition of « Diphosgene » into carbon tetrachloride and carbon dioxide is still a controversial topic. However, the production of phosgene by reaction of carbon tetrachloride and carbon dioxide over catalysts such as Lewis acids was recently claimed in Russian patents (Ref. 32). The reaction is assumed to proceed through the formation of trichloromethyl chloroformate or bis(trichloromethyl) carbonate.

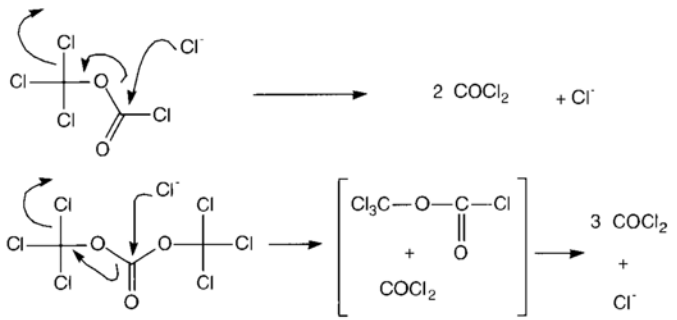
At the present time, one crucial question still remains : what is the industrial value of « Diphosgene » and « Triphosgene » as liquid and solid substitutes for phosgene ? Are the two reagents really safer than phosgene ?

Both reagents have proved to be useful substitutes for phosgene in all its main applications. Indeed, they are sold commercially as the efficient equivalents of 2 and 3 phosgene molecules respectively in processes yielding chloroformates, carbonates, carbamates, ureas and isocyanates, as well as in chlorinations, carboxylations and dehydrations (For a recent review of « Triphosgene » use in organic synthesis, see Ref. 33).

Accurate amounts can be easily weighed, limiting problems due to excess reagent. It is possible also to increase reagent concentrations compared with phosgene itself.

However, there is little prospect that either reagent will be utilized in significant industrial processes.

Both reagents decompose to phosgene on heating, slowly when pure, very rapidly and quantitatively in presence of a nucleophile such as a « naked » chloride anion [Scheme 35] :

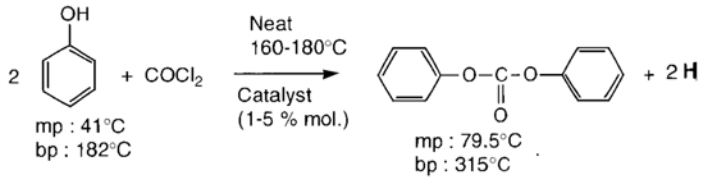


Scheme 35 : Decomposition of « Diphosgene » and « Triphosgene ».

As noted by S. Damle (Ref.34), *the toxicity of both diphosgene and triphosgene is exactly the same of phosgene since both decompose on heating and upon reaction with any nucleophile. Even a trace of moisture leads to formation of phosgene.*

Thus, in any transportation or handling accident, both compounds are phosgene.

The manufacture of symmetrical or mixed carbonates by reaction of chloroformates with alcohols or phenols is well documented. In the course of different studies devoted to the manufacture of aromatic carbonates, we have designed a one-step procedure that affords diphenyl carbonate in excellent yield and purity using simple equipment and no solvent [Scheme 36] :



Scheme 36 : Improved diphenyl carbonate synthesis.

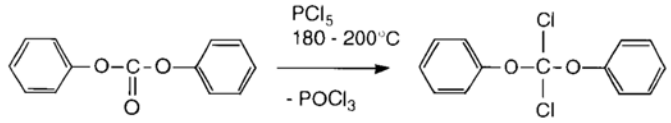
Table 3-2 gives a comparison between some catalysts :

Catalyst	Temperature	Time for 100% conversion
HBGCl.HCl	160 - 175 °C	7.75 H
HMGCl.HCl	165 - 170 °C	5.25 H
IMIDAZOLE	160 - 170 °C	2.50 H

HBGCl.HCl = Hexa n-butyl guanidinium chloride hydrochloride.
HMGCl.HCl = Hexamethyl guanidinium chloride hydrochloride.

Table 3-2 : Comparison of the efficiency of some catalysts in the synthesis of diphenyl carbonate in bulk (3% Mol. Catalyst/phenol)

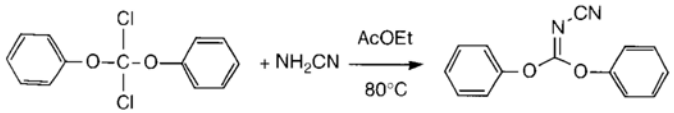
Among the numerous applications of diphenyl carbonate, the preparation and chemistry of dichlorodiphenoxy methane appears somewhat neglected. This phosgene derivative can be prepared in good yield by treatment of diphenyl carbonate with phosphorus pentachloride at high temperature (Ref. 35) according to scheme 37 :



bp : 183-187 °C / 12 mm
mp : 42-44 °C
80 % yield

Scheme 37 : Preparation of dichlorodiphenoxy methane.

Besides being a key starting material for the preparation of polyorthocarbonates, dichlorodiphenoxy methane is a versatile synthon for the construction of heterocyclic systems of medicinal interest (Ref. 36). Its condensation with cyanamide affords diphenyl cyanocarbonimidate in high yield (Ref. 35) as shown in scheme 38 :

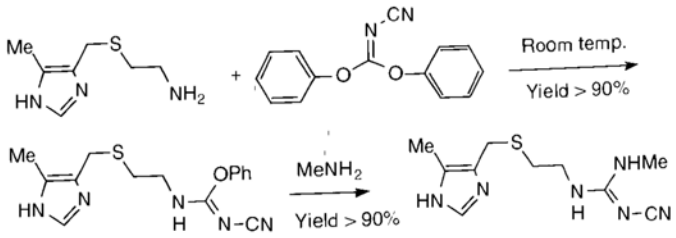


91 % yield
mp : 156-8°C

Scheme 38 : Preparation of diphenyl cyanocarbonimidate from dichloro diphenoxy methane.

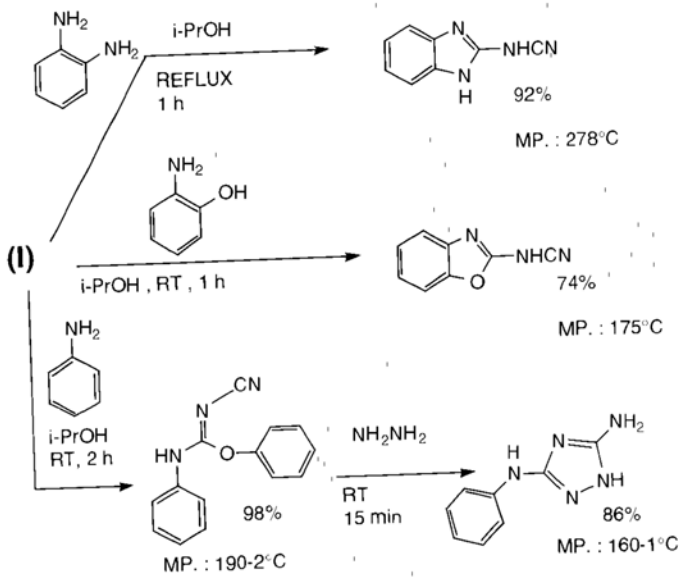
The availability of diphenyl cyanocarbonimidate provides a simple, low cost, high yield access to N-cyanoguanidines which are active as histamine H2 antagonists.

For example, researchers from Smith Kline & French Laboratories has described (Ref. 36) a new facile synthesis of the anti-ulcer drug Cimetidine (« Tagamet ») depicted on scheme 39 :



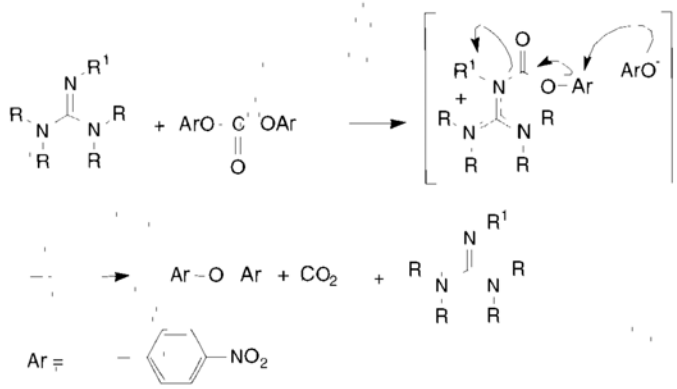
Scheme 39 : Preparation of Cimetidine from diphenyl cyanocarbonimidate

Scheme 40 shows some other examples of applications in heterocyclic chemistry (Ref. 35).



Scheme 40 : Examples of diphenyl cyanocarbonimidate (I) applications.

The decarboxylation of aromatic carbonates substituted by electron withdrawing groups is an efficient method to get substituted diphenyl ethers. We found that pentaalkyl guanidines are superior catalysts for the synthesis of 4,4'-dinitrodiphenyl ether from 4,4'-dinitro diphenyl carbonate (Ref. 37). The generally accepted mechanism involves nucleophilic attack by the substituted guanidine at the carbonyl of the carbonate to form an acylated guanidinium phenoxide salt. In a second step, the p.nitro phenoxide anion attacks the aromatic ring of the acylated guanidinium cation (SN_{Ar} reaction) to lead to the expected ether after loss of CO_2 [Scheme 41].



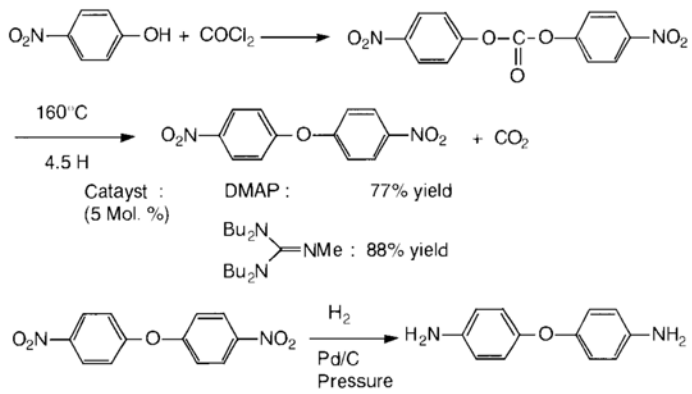
Scheme 41 : Mechanism of the decarboxylation of 4,4'-dinitrodiphenyl carbonate catalyzed by pentaalkyl guanidines

Nucleophilicity of the guanidine must be carefully controlled to avoid arylation of the catalyst itself. This could be easily accomplished through a proper choice of the substituents. Note also that delocalization of charge over the three nitrogens in the assumed intermediate guanidinium cation enhances the nucleophilicity of its counter anion, e.g. the p.nitro phenoxide anion.

With 2-methyl-1,1,3,3-tetrabutyl guanidine as catalyst, the decarboxylation proceeds at temperature lower than those described with conventional base catalysts. The result is even better compared with using 4-N,N-dimethylamino pyridine (DMAP) as shown in scheme 42.

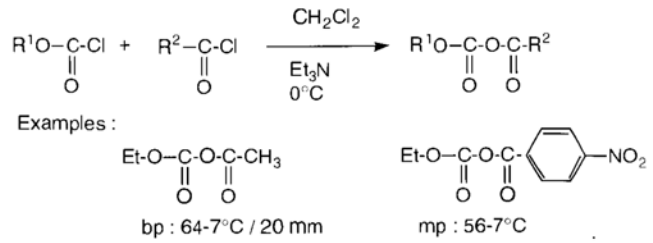
4,4'-Dinitro diphenyl ether can be easily hydrogenated to 4,4'-diamino diphenyl ether especially suitable for the manufacture of polymers such as polyimides.

The required pentaalkyl guanidines were easily prepared through phosgenation of the appropriate urea to give the corresponding chloroformamidinium salt which reacts with an excess of amine to yield the expected guanidine (Ref. 37).



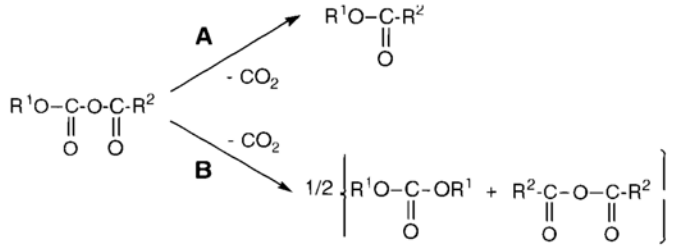
Scheme 42 : Improved synthesis of 4,4'-dinitro diphenyl ether and 4-4'-diamino diphenyl ether

One of the most convenient esterification methods developed earlier was based on the decarboxylation of unstable mixed carboxylic-carbonic anhydrides prepared by reaction of chloroformates with carboxylic acids (Ref. 38) according to scheme 43.



Scheme 43 : Preparation of mixed carboxylic-carbonic anhydrides.

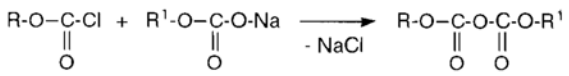
The course of the decomposition of the mixed anhydrides [Scheme 44] which leads to the formation of expected esters (path **A**) or to a mixture of symmetrical carbonates and anhydrides (path **B**) strongly depends on the structures of the chloroformate and the carboxylic acid but also on the choice of the catalyst.. Because selective production of esters if of great interest, we have studied the thermal instability of the mixed anhydrides and developed a new efficient and selective esterification reaction with chloroformates using a silica supported guanidinium catalyst (Ref. 39). This method will be discussed in vol. 2 section 4-4.



Scheme 44 : Decomposition paths of mixed carboxylic-carbonic anhydrides.

The use of the mixed carboxylic-carbonic anhydrides is also a powerful method of carboxylic acids activation for the formation of amide bounds in peptide chemistry (see vol. 2, section 4-4).

Reaction of chloroformates with sodium alkyl carbonates, easily available through reaction of carbon dioxide with sodium alkoxides, affords dicarbonates also called pyrocarbonates as shown in scheme 45.



Scheme 45 : Preparation of dicarbonates from chloroformates.

Pyrocarbonates find useful applications in several fields, such as :

- Preservatives for wines, soft drinks, fruit juices, especially in the case of diethyl pyrocarbonate : R = R^1 = Ethyl.
- Blowing agents for plastics, polyurethane foams as Freon® substitutes. For example, t.butyl methyl pyrocarbonate (R = methyl, R^1 = t. butyl) was claimed as a foaming agent added during processing of polymers to achieve a cellular structure by liberation of carbon dioxide (Ref. 40).
- Protection of amino groups. Di-t.butyl dicarbonate called $(Boc)_2O$ (which is not made from the very unstable t.butyl chloroformate) is well known as the most popular reagent for the preparation of t.Boc protected amines, especially t.Boc-amino acids in peptide chemistry.

We reported the synthesis (data on table 3-3) and some applications of dibenzyl dicarbonate (Ref. 41) and diallyl dicarbonate (Ref. 42).

Dicarbonate	Yield	mp or bp
Dibenzyl dicarbonate	79 %	mp. 28 °C
Diallyl dicarbonate	82 % (60 % distilled)	bp. 65 °C/0.05 Torr

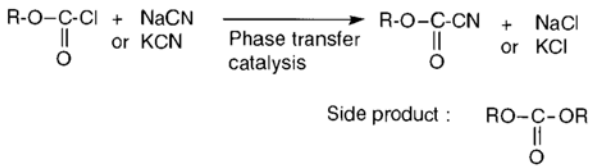
Table 3-3 : Synthesis of new useful dicarbonates.

Dibenzyl dicarbonate offers some advantages in the preparation of N-benzyloxycarbonyl amino-acids, compared to the widely used benzyl chloroformate. For example, preparation of dipeptide-free N-benzyloxycarbonyl glycine is easily achieved under standard pH-stat conditions if the pH is carefully regulated.

Diallyl dicarbonate was used for the allyloxycarbonyl protection of amino compounds including amino acids, amino sugars and nucleosides. Except for the reaction with amino acids, the reagent does not require an additional base, and the only by-products, allyl alcohol and carbon dioxide are both volatile. For example, N-allyloxycarbonyl glucosamine was obtained analytically pure by simple evaporation of the reaction mixture.

These two reagents, Z_2O and $(Alloc)_2O$, conveniently supplement the known chloroformates for the protection of amines.

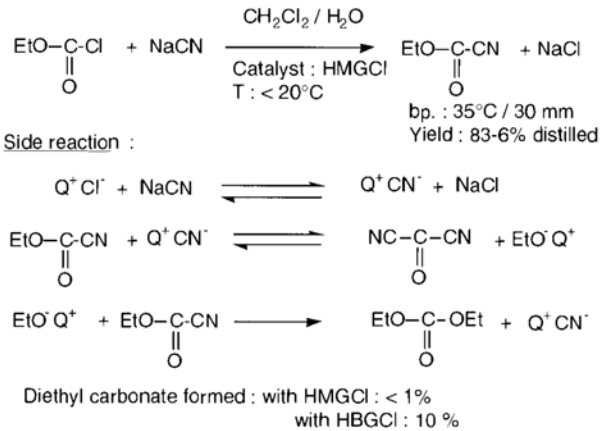
Cyanoformate esters may be prepared through reaction of alkyl chloroformates with cyanides salts by procedures using phase-transfer catalysis with 18-crown-6 (Ref. 43) or quaternary ammonium salts (Ref. 44) according to scheme 46.



Scheme 46 : Preparation of cyanoformate esters from chloroformates.

Although convenient for the preparation of small quantities of cyanoformate esters such as ethyl cyanoformate, we found the method to be unsatisfactory for the production on a larger scale because of the formation of carbonate esters reducing the yield.

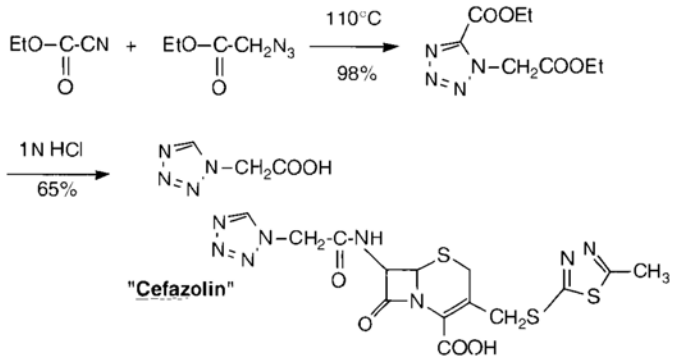
In the course of our studies devoted to the scaling up of ethyl cyanoformate preparation, we noticed that the side reaction is strongly related to the nucleophilicity of the cyanide anion which depends on the structure of the counter cation of the catalyst. Quite good results can be achieved by a proper choice of the catalyst as depicted in scheme 47.



Scheme 47 : Improved preparation of ethyl cyanoformate.

Ethyl cyanoformate is an effective dipolarophile undergoing 1,3-dipolar addition to azides, for example with ethyl azidoacetate to afford tetrazoleacetic acid derivatives (Ref. 45). Tetrazoleacetic acid is a key starting material for the preparation of pharmaceuticals such as the antibiotic « Cefazolin » [Scheme 48].

The chemistry of cyanoformate esters has been the subject of a recent review (Ref. 46).



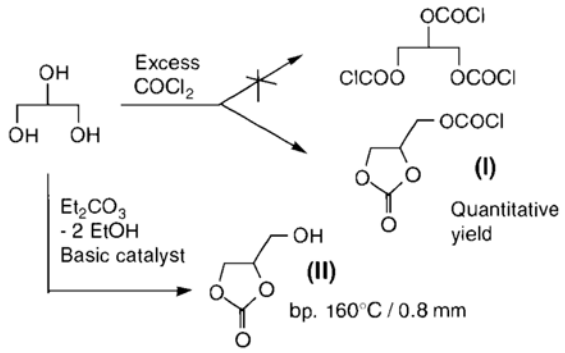
Scheme 48 : Preparation and use of tetrazoleacetic acid starting from ethyl cyanoformate.

3-2-2 Reaction of phosgene at oxygen center of unconventional substrates

3-2-2-1 Reaction of phosgene with glycerol

The reaction of large excess phosgene with glycerol does not afford the corresponding trischloroformate but a monochloroformate bearing a five membered cyclic carbonate function (2-oxo-1,3-dioxolan-4-yl methyl chloroformate (I) as shown on scheme 49. The corresponding alcohol (II)

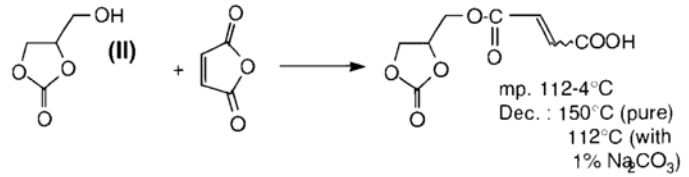
can be easily obtained through transesterification between glycerol and diethyl carbonate under basic conditions.



Scheme 49 : Preparation of chloroformate-carbonate through phosgenation of glycerol.

The chloroformate (I) and the corresponding alcohol (II) are very interesting intermediates for numerous applications :

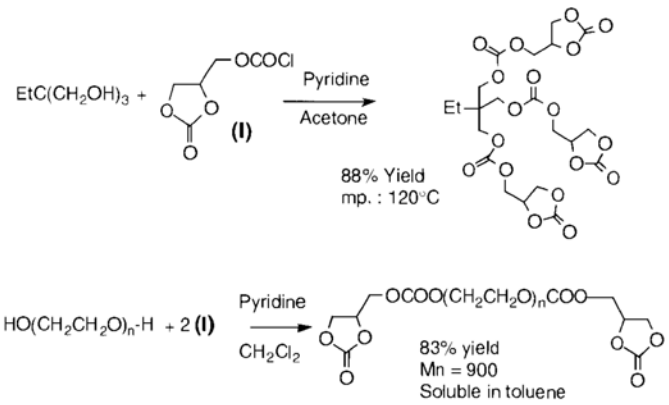
– Blowing agents adapted to the production of cellulated or expanded polymers (Ref. 47), for example by reaction of (II) with maleic anhydride [Scheme 50].



Scheme 50 : Preparation of a foaming agent for expanded polymers.

– Leavening systems for preparing baked goods to supply carbon dioxide required (Ref. 48).
– Extractants for metals.

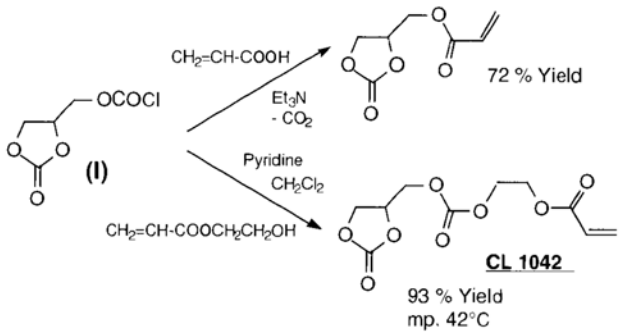
For example, compounds obtained through reaction of chloroformate (I) with trimethylol propane and with polyethylene glycol are highly effective chelating agents suitable in hydro-metallurgy to recover valuable metals ions from aqueous solutions (Ref. 49) [Scheme 51].



Scheme 51 : Cyclic carbonates suitable for the extraction of metals from aqueous solutions.

- Paint powders for automotive, for example the reaction product of methacryloyl chloride and the alcohol (II) (Ref. 50).
- Ultraviolet-curable acrylic resins.

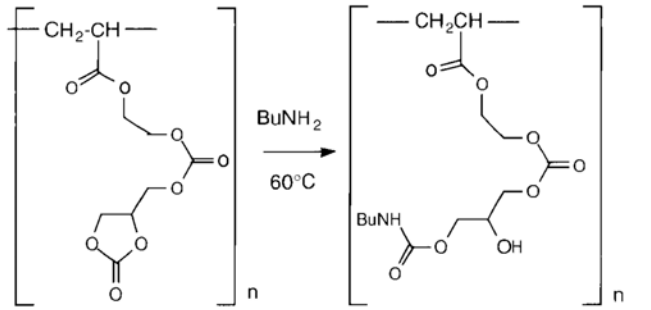
The reaction of chloroformate (I) with acrylic acid followed by the decarboxylation of the unstable mixed carboxylic-carbonic anhydride formed, gives the 2-oxo-1,3-dioxolan-4-yl methyl acrylate in good yield (Ref. 51). The reaction of (I) with 2-hydroxyethyl acrylate in the presence of a base affords a new acrylic monomer, SNPE code number CL 1042, in excellent yield (Ref. 51) [Scheme 52].



Scheme 52 : Preparation of UV-curable monomers from glycerol chloroformate-carbonate.

The study of light-induced polymerization of the new compounds, especially CL 1042, demonstrated the outstanding reactivity of acrylic monomers containing five membered cyclic carbonate function (Ref. 52). Photopolymerization even occurs without any added photoinitiator.

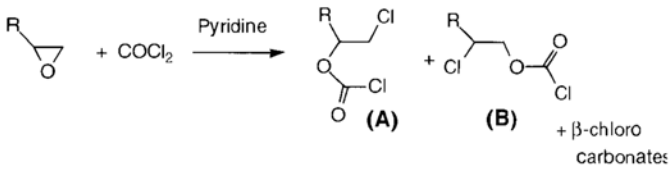
These new monomers combine high reactivity and intensive cure to give hard but still flexible materials. CL 1042 was used in 50% amount as reactive diluent in formulation with polyurethane oligomers bearing pendant acrylate groups (Ref. 53). CL 1042 was also employed to synthesize copolymers with pendant cyclic carbonate groups. Their chemical modification by ring opening reaction provided a convenient method for preparing functional polymers (Ref. 54), as shown on scheme 53 :



Scheme 53 : Chemical modification of copolymers containing pendant cyclic carbonate functions.

3-2 2 2 Reaction of phosgene with epoxides

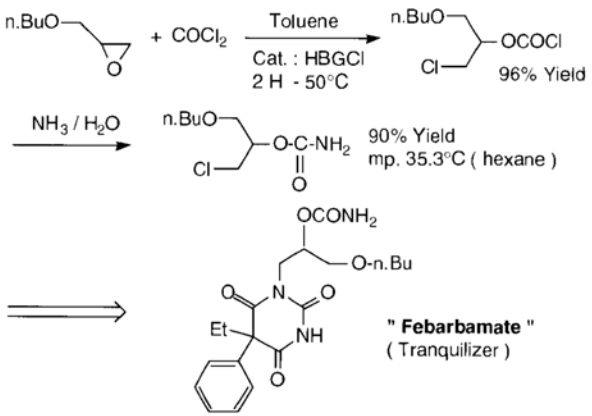
The reaction of phosgene with an epoxide catalyzed by pyridine to afford β-chloro chloroformates is well known (Ref. 55). Unfortunately, this reaction often leads to non regio-specific ring opening of the epoxides and produces bis-β-chlorocarbonates as side products in yield up to 20 - 30% [Scheme 54].



Scheme 54 : General reaction of epoxides with phosgene.

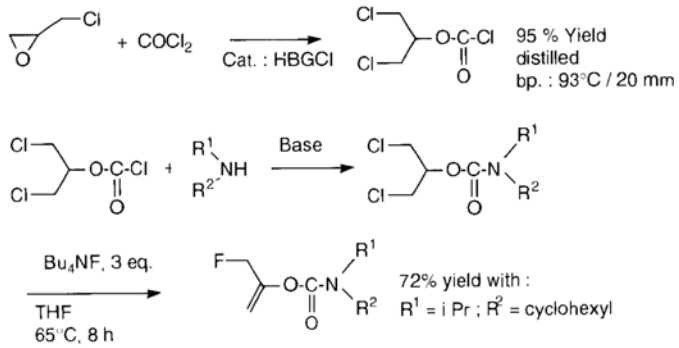
When the reactions of monoalkyl epoxides with phosgene were conducted, within 2-6 h, using HBGCl or silica-supported guanidinium chloride as catalyst, neat or in toluene solution, the results are strikingly different. The ring opening reaction gave single products with C-Cl bond formation at the carbon that lacks the substituent. Moreover, the reaction did not produce any of the symmetrical carbonate. The β-chloro chloroformate (**A**) (see scheme 54) are thus isolated in nearly quantitative yields (Ref. 56).

For example, the phosgenation of n-butylglycidyl ether in toluene, in presence of 0.5 mol.% HBGCl, at 30°C within 2 h, gave the corresponding 1-chloromethyl-2-n.butoxy ethyl chloroformate in 96% yield. This chloroformate is the key starting material for the preparation of an intermediate carbamate used in the « Febarbamate » manufacture as shown in scheme 55.



Scheme 55 : Preparation of intermediate carbamate for a pharmaceutical manufacture.

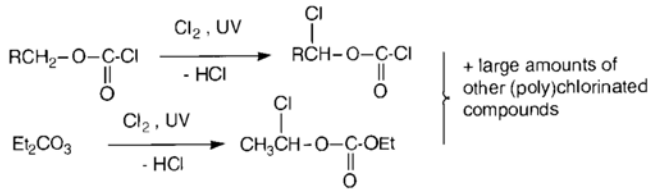
In another example, 1-chloromethyl-2-chloroethyl chloroformate was easily prepared by catalyzed addition of phosgene to epichlorhydrin using the same procedure. This chloroformate is an useful intermediate for a simple preparative route to new fluoroisopropenyl carbamates (Ref. 57) depicted in scheme 56 :



Scheme 56 : New isopropenyl carbamates from phosgene and epichlorhydrine.

3.2.2.3 Reaction of phosgene with aldehydes and ketones : novel α-chlorinated chloroformates and related reagents

Photochlorination of alkyl chloroformates, generally limited to the case of methyl chloroformate and ethyl chloroformate, was the only method for the preparation of 1-chloroalkyl chloroformates before the work done at SNPE [Scheme 57].

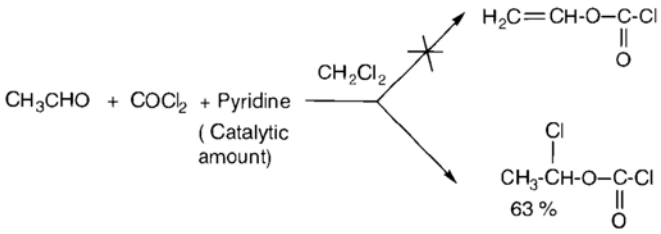


Scheme 57 : Photochlorination of alkyl chloroformates and diethyl carbonate.

This method useful for chloromethyl chloroformate synthesis gives poor yields and bad quality in the case of

1-chloroethyl chloroformate, and completely fails with higher chloroformates, because of the lack of selectivity of the radical chlorination.

Eighteen years ago, in the course of unsuccessful attempts to prepare vinyl chloroformate by phosgenation of aldehydes in presence of tertiary amines, especially pyridine, we discovered a new route to α-chloroalkyl chloroformate (Ref. 58) as presented in scheme 58 :



Scheme 58 : The origin of the discovery of the new α-chlorinated chloroformates route.

The value of this new route immediately was recognized because 1-chloroethyl ethyl carbonate which could be obtained from 1-chloroethyl chloroformate and ethanol already was on the market as an alkylating agent to prepare the orally active antibiotic « Bacampicillin ».

Not long after, together with Olofson and coworkers at Penn State University, we found that aldehydes are readily converted to 1-chloroalkyl chloroformates when treated with phosgene in the presence of a « naked Cl^- » catalyst (Ref. 5). The reaction has been found to proceed cleanly in good to excellent yields and to be quite general with almost all aldehydes, but not with most ketones (Ref. 59).

On a laboratory scale, one of the favored catalyst is the benzyl tri-n-butyl ammonium chloride (BTBAC). The most important reagent, α-chloroethyl chloroformate (« ACE-Cl »), typically is isolated in 96% yield by stirring acetaldehyde with phosgene (1.1 eq.) neat for an hour in the presence of 3 mol. % BTBAC. Even chloromethyl chloroformate can be prepared using this process, but it is essential to introduce the monomeric gaseous formaldehyde into the

reactor already containing the catalyst and phosgene, so that formaldehyde reacts immediately, thus avoiding its repolymerisation (Ref. 60). However, in this last case, we found the procedure difficult to scale up, because of technical problems of formaldehyde polymerization. Note that the reaction does not work with the polymeric forms of formaldehyde, either trioxane or paraformaldehyde.

Some results are gathered in table 3-4 (Ref. 5, 58, 60).

R	Catalyst (mol. %/aldehyde)	Yield %	Boiling point °C/mm
H	BTBAC (1.8)	42 (a)	106/760
Me	BTBAC (3.0)	96	77/180
Me	18-Crown-6 (5.7) KCl (35.2)	78	117/760
Et	BTBAC (9.0)	89	62-3/52
Cl3C	BTBAC (10.7)	65	75-9/19
i-Pr	BTBAC (12.5)	87	58-9/28
CH2 = CH	Pyridine (10)	54	38/10
Cyclohexyl	Pyridine (10)	87	90-3/10
	BTAC (10.3)	87	81-3/1
Phenyl	Pyridine (10)	68	70/0.4

(a) With respect to the phosgene used

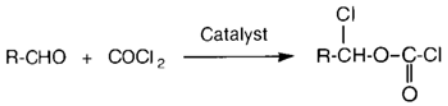
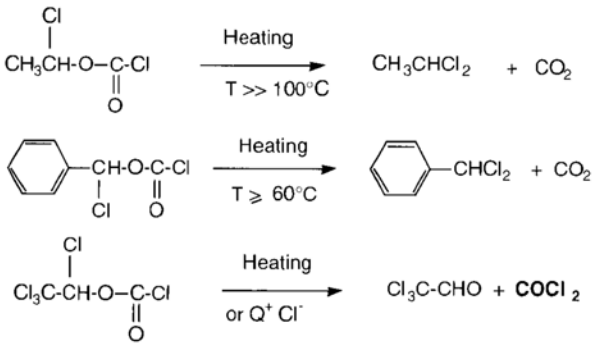


Table 3-4 : Preparation of some 1-chloroalkyl chloroformates.

The yields and recoveries presented in this table are those for isolated materials (purity > 99%).

Phosgene can be replaced with either diphosgene or triphosgene in the same conditions to give the corresponding 1-alkyl chloroformates in very good yields (Ref. 61).

For safety reasons, because a possible reversibility of the reaction between phosgene and aldehydes was suspected, we thoroughly studied the thermal stability of 1-chloroalkyl chloroformates. This stability greatly depends on the structure of the R radical. Simple alkyl compounds are much more stable than the aralkyl compounds which begin to decompose at 60° C or below. It is important to note that the only products of thermal decomposition are the derived 1,1-dichlorides and carbon dioxide [Scheme 59]. In contrast, the chloroformate from chloral reverts easily to the aldehyde and phosgene when heated. This decomposition is catalyzed by « naked Cl^- » and **particular precaution must be taken in the handling of tetrahaloethyl chloroformates**, and more generally in the case of 1-chloroalkyl chloroformates containing strong electron withdrawing groups (with regard to the mechanism of the decomposition, see farther on in this section).



Schema 59 : Thermal stability of 1-chloroalkyl chloroformates.

1-Chloroalkyl chloroformates like conventional chloroformates react easily with alcohols, either in the presence of base or simply by heating to give the expected 1- chloralkyl carbonates. 1-Chloroalkylchloroformates react also with phenols, but only in presence of a base to afford 1-chloroalkyl aryl carbonates.

1-Chloroethyl ethyl carbonate itself was first prepared by Müller by heating ethanol with 1-chloroethyl chloroformate previously prepared through chlorination of ethyl chloroformate in direct sunlight (Ref. 62).

The addition of 1-chloroalkyl chloroformates to alcohols or phenols is a quite general method and gives good to excellent yields. Some examples are given in table 3-5.

R	R1	Method	Yield (%)	bp. °C/mm mp. °C	Ref.
H	Et	Pyridine	76	bp. 53/14	63
Me	Et	Pyridine	97	bp. 67/22	64
Me	Et	Heating (70°C)	80	bp. 160/760	5
Me	i-Pr	Pyridine	62	bp. 57-9/10	65
Me	t-Bu	Pyridine	90	bp. 88/20	64
Me	Cyclohexyl	Heating	77	bp. 77/1	SNPE
Me	Benzyl	Pyridine	94	bp. 100/0.5	64
Me		Pyridine	88	bp. 95/0.2	64
Me	Phenyl	Pyridine	94	bp. 117/0.5	64
Me		Pyridine	98	mp. 98-100	64
Cl3C	t-Bu	Pyridine	87	mp. 68-70	66
Cl3C		Triethylamine	83	mp. 108°C	67

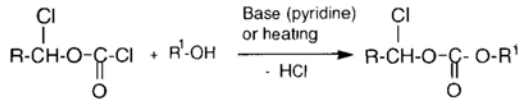
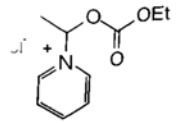


Table 3-5 : Preparation of 1-chloroalkyl carbonates.

The use of a trialkyl amine, for example triethyl amine, as a scavenger is not recommended because 1-chloroalkyl chloroformates react very easily with tertiary alkyl amines to afford N,N-disubsituted carbamates (Ref. 68) as discussed in section 3-3.

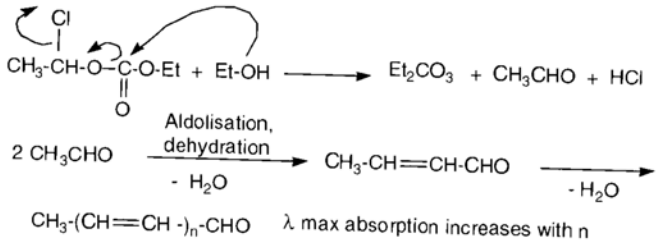
Although pyridine appears as one of the best scavengers in the process using a base, any excess must be avoided

because of the formation of a quaternary ammonium salt as depicted on scheme 60 :



Scheme 60 : Quaternary ammonium salt from pyridine and 1-choroethyl ethyl carbonate.

In the course of our work devoted to the development of an industrial process to manufacture ton lots of 1-chloroethyl ethyl carbonate, we studied the main side reaction which is the transesterification of the desired product with ethanol [Scheme 61].



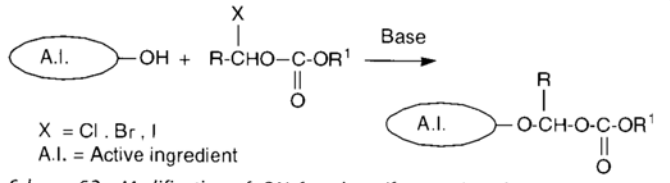
Scheme 61 : Main side reactions in the preparation of 1-chloroethyl ethyl carbonate.

Experimentally, the rate of formation of diethyl carbonate was found to be proportional to the concentration of both 1-chloroethyl ethyl carbonate and ethanol, so that the reaction rate may be expressed in term of following equation with an assumed first order with respect to both reactants :

$$d[EtOH]/dt = k [EtOH] [MeCHClOCOOEt]$$

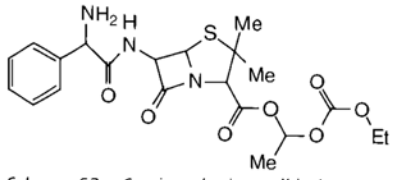
At 75°C, the k value was determined at 7.2×10^{-5} mol.$^{-1}$.l.min^{-1}. The heat of activation was calculated at 25 kcal. mol.$^{-1}$.

In the past 25 years, there have been numerous publications and patents claiming applications of 1-haloalkyl carbonates to mask acid or hydroxy functions of certain types of active compounds such as parmaceuticals or pesticides according to the scheme 62.



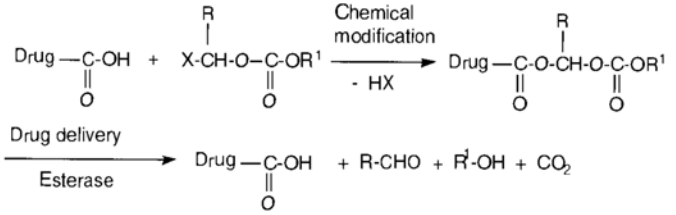
Scheme 62 : Modification of -OH functions (from carboxylic acids or phenols) using α-chloroalkyl carbonates.

This kind of application was initially developed to produce Bacampicillin, a prodrug from Ampicillin [Scheme 63].



Scheme 63 : Semi-synthetic antibiotic « Bacampicillin » from Ampicillin and 1-iodoethyl ethyl carbonate.

Current penicillins or cephalosporins clinically used for injection are not suitable for oral administration because of their low absorption from the gastro-intestinal tract. The prodrug approach by chemical modification into bio-labile derivatives with improved physicochemical properties (i.e. lipophilicity) that enables better transport through biological barriers, is a powerful mean for improving drug delivery. The success of such approach requires a latentiating group stable in both gastric acidic and basic intestinal conditions, and easily removable by enzymatic hydrolysis. The modification of carboxylic acid function or phenolic function by the alkyloxycarbonyloxyalkyl ester group is especially suitable as shown in scheme 64.



Scheme 64 : The prodrug concept applied to drug with a carboxylic function.

To meet all requirements needed, it is possible to select the radicals R and R^1, for example :

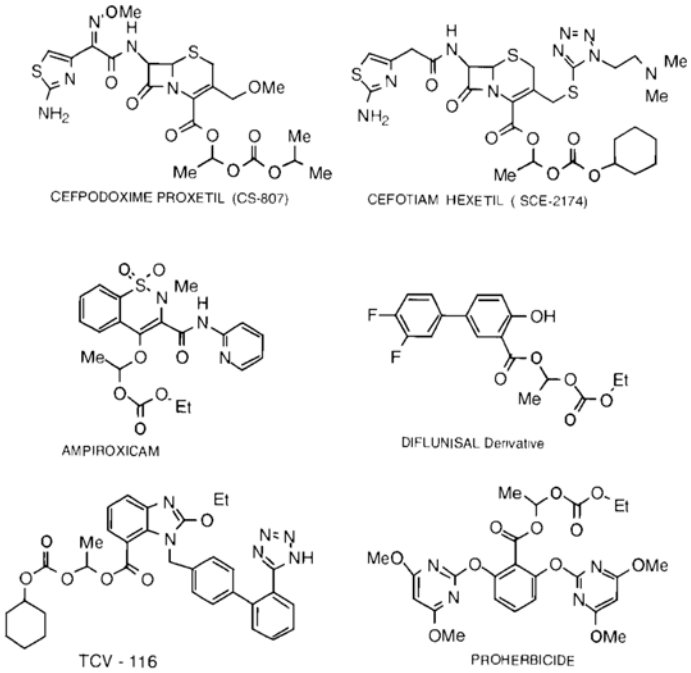
R = H or methyl

R^1 = Et, isopropyl, cyclohexyl, even sugar derivatives (see farther on in this section).

Besides Ampicillin, 1-chloroalkyl alkyl carbonates and particularly 1-chloroethyl ethyl carbonate (CEEC), 1-chloroethyl isopropyl carbonate (CEIC), 1-chloroethyl cyclohexyl carbonate (CECC) and chloromethyl ethyl carbonate (CEMC), have been proposed to modify numerous compounds. Among the many types of prodrugs patented which require this method, there are examples of :

- Antibiotics such as Cefpodoxime Proxetil from Sankyo Co., Ltd.(Ref. 69), Cefotiam Hexetil from Takeda Chem. Indust., Ltd (Ref. 70, 71)
- Antiflammatories and analgesics such as Ampiroxicam from Pfizer and Toyama Chem. Co. (Ref. 65, 72) or a derivative of Diflunisal (Ref. 73)
- Antihypertensives, for example TCV 116 from Takeda Chem. Indust., Ltd (Ref. 74)
- Herbicides (Ref. 75).

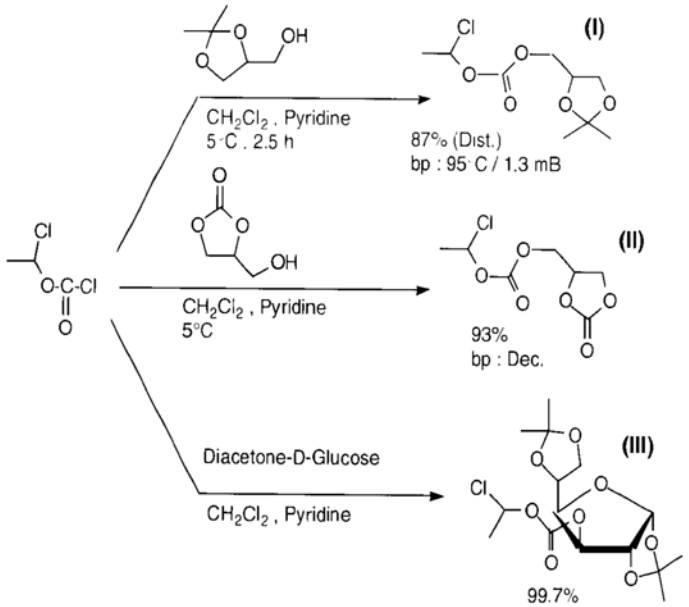
Some structures of these pro-active ingredients are given in scheme 65.



Scheme 65 : Examples of Prodrugs from 1-chloroalkyl alkyl carbonates.

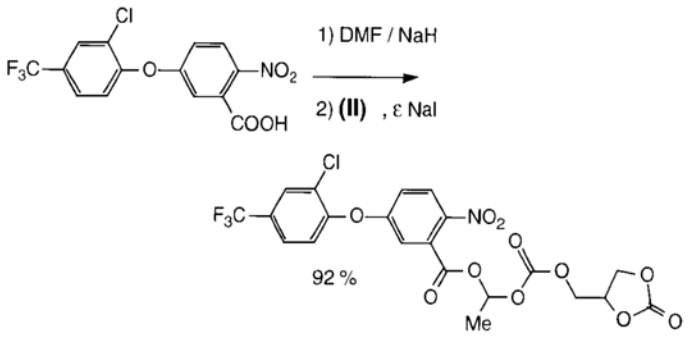
Chemical modification of agrochemicals, to improve their pesticidal properties and to reduce toxicity toward nontarget organisms, has been the object of intensive research in both academia and industry, especially in the field of insecticides (Ref. 76). For example, « Carbosulfan » is a very active systemic herbicide derived from « Carbofuran » and much less toxic for mammalians than its parent compound.

In order to improve transport through biological barriers of the plants, we thought that the chemical modification of known pesticides with 1-chloroalkyl alkyl carbonates containing sugar or glycerol moiety should be of some interest. For this purpose, we synthesized at laboratory scale several new α-chlorinated carbonates (Ref. 77). The products prepared and results obtained are depicted on scheme 66.



Scheme 66 : Some new 1-chloroalkyl alkyl carbonates, useful starting materials for the preparation of prodrugs and propesticides.

The 1-Chloroalkyl carbonate (II), obtained through the reaction of 1-chloroalkyl chloroformate with glycerol carbonate was used for the preparation of a proherbicide derived from « Acifluorfen » (Ref. 77) [See scheme 67].



Scheme 67 : Proherbicide from Acifluorfen.

Since in terms of leaving group ability in SN_2 reactions I > Br > Cl, α-iodoalkyl alkyl carbonates are the reagents of choice for the chemical modification of either carboxylic acid or phenolic functions. However, these α-iodo carbonates exhibit severe instability (Ref. 78) and are generally prepared in-situ or just before use (Ref. 79,80, 81).

Thus, research efforts in different industrial laboratories have been directed toward the preparation of 1-bromoalkyl alkyl carbonates assumed to be more stable than the 1-iodo derivatives, and more reactive than the parent chloro compounds. For example, 1-bromoethyl ethyl carbonate was made by the halide exchange of 1-chloroethyl ethyl carbonate with LiBr or NaBr, or by a radical type bromination of diethyl carbonate (Ref. 82). However, in the case of halide exchange, the conversion is low and a mixture results. Even with a large excess of bromide salt, this problem remains. Radical bromination was found to give unsatisfactory results for the same reasons than the chlorination, and failed in the case of unsymmetrical dialkyl carbonates because of its non-regioselectivity.

We reported a new method consisting of using a volatile bromine containing reagent (E- Br), especially HBr, and a catalyst to accomplish the exchange (Ref. 83, 84). The equilibrium is driven to the desired product by removal of the more volatile E-Cl formed as shown in table 3-6. This table gathers some results thus obtained.

1-Bromoethyl phenyl carbonate (bp. 72-7 °C/0.4 mm) was prepared in 91 % yield from TMS-Br and 1-chloroethyl phenyl carbonate using this technic.

It should be noted that 1-bromoalkyl carbonates can be also easily obtained through HBr addition to the double bond of vinyl alkyl or vinyl aryl carbonates (Ref. 85) This process will be described in section 3-2-2-4 devoted to vinylic chloroformates and derivatives.

R	R1	Catalyst Eq.	Temp. °C	Time Hours	Yield %	bp. °C/mm
Me	Et	none	80	1	–	
Me	Et	MgBr2 0.038	65	24	80	62-6/18
Me	i-Pr	TBAB(a) 0.014	85	6	82	B0-3/18
n-Bu	Me	BTBAC(b) 0.019	85	7	69	60-2/2

HBr was added continuously by bubbling the anhydrous gas into the medium
(a) TBAB : tetra n-butyl ammonium bromide
(b) BTBAC : benzyl tri-n-butyl ammonium chloride

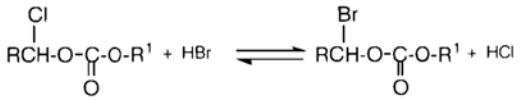
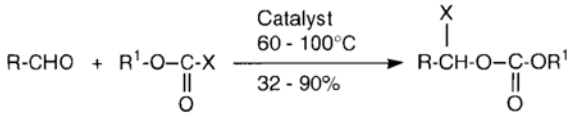


Table 3-6 : Preparation of some 1-bromoalkyl alkyl carbonates.

In order to complement the usual 1-chloroalkyl carbonates synthesis, we decided to find a new route to a broader class of these compounds. More particularly, we tried to open access to carbonates in which the alcohol (R^1-OH) doesn't exist and to the previously unknown 1-fluoro-alkyl carbonates.

Our efforts succeeded in the discovery of a different method of preparation based on the reaction of an aldehyde with a halogenoformate in presence of a catalyst (Ref. 86, 87), as depicted in scheme 68.



X = F, Cl, Br, I

Scheme 68 : New route to 1-haloalkyl carbonates.

Besides the synthesis of 1-chloroalkyl carbonates, this method is general enough to be used for the preparation of 1-fluoroalkyl, 1-bromoalkyl or 1-iodoalkylcarbonates as shown in table 3-7. However, the method gives poor results or even failed when the haloformate is too unstable in presence of the catalyst (see section 3-2-1). For example, attempts to prepare 1-chloroethyl ethyl carbonate (CEEC) itself in 1,2 dichloroethane at 60°C with 0.05 equ. pyridine, gave almost total decomposition of ethyl chloroformate.

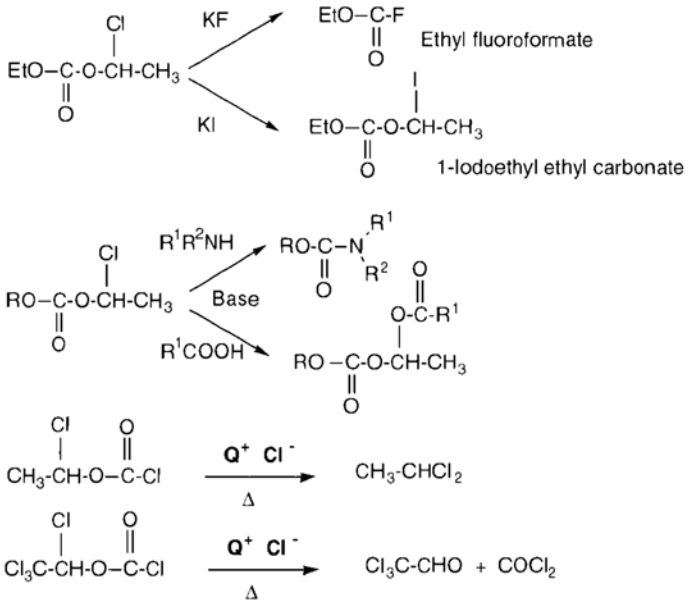
R	R1	X	Catalyst	Temp. °C	Time Hours	Yield %	bp °C/Torr mp [°C]
CH3	Ph	Cl	Pyridine	80	5	71	67-8/0.15
CH3	CHCl-CH3	Cl	Pyridine	60	4	49	67-72/9
CH3	CH=CCl2	Cl	Pyridine	80	1.5	83	44-5/0.1
CH3	Ph	Br	Pyridine	83	1	82	74-9/0.03
CH3	Ph	I	Pyridine	70	1.5	80	93-7/0.45 [59-61]
CCl3	CH2Cl	Cl	Pyridine	80	5	76	60-1/11
CCl3	CHCl-CCl3	Cl	Pyridine	80	4	88	90-5/0.05 [63-4]
CCl3	Ph	F	DMAP	82	24	32	82-6/0.03
H	(CH2)7CH3	F	KF/ 18-C-6	65	2	76	82-5/2.5
CCl3	Et	F	KF/ 18-C-6	65	20	72	77-8/5
Ph	C(CH3)=CH2	Cl	Pyridine	83	20	67	92-6/0.2

Table 3-7 : Preparation of 1-haloalkyl carbonates.

None of the catalysts tested : quaternary ammonium salts, N,N-dimethylamino pyridine (DMAP), 1-methyl imidazole, tertiary amines, Michler's ketone, quinoline etc. performed as well as pyridine. For the preparation of 1-fluoroalkyl carbonate, the best catalytic system found was the KF/18-crown-6 complex. To avoid side reactions, only aldehydes without hydrogen at C-2 should be used in this case.

Fluoroformates (Ref. 88) and phenyl iodoformate (Ref. 89) used here were prepared according to literature procedure (see also farther on in this section). The preparation of isopropenyl chloroformate, as well as 2,2-dichlorovinyl chloroformate will be presented in section 3-2-2-4.

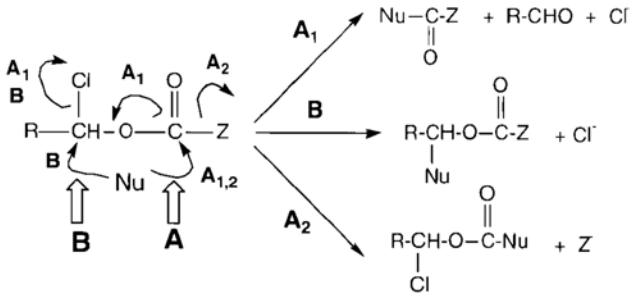
At the beginning of our work devoted to new potential applications of 1-chloroalkyl chloroformates and 1-chloroalkyl carbonates, available literature data as well as our preliminary experiments indicated strong variations in the products distribution resulting from nucleophilic attacks. Scheme 69 gives some examples demonstrating that the types of obtained products strongly depend on the nature of reactant.



Scheme 69 : Examples of variations of nucleophilic attacks pathways to 1-chloroalkyl chloroformates and carbonates.

In fact, 1-chloroalkyl chloroformates and derivatives pose a very interesting mechanistic problem, since they present two reactive electrophilic centers which may be

attacked by nucleophiles following three different pathways as shown in scheme 70 :



Scheme 70 : Possible types of nucleophilic attacks to 1-chloroalkyl-oxycarbonyl derivatives.

Research in our laboratories over the last fifteen years has been directed to understanding the mechanisms which are operative in nucleophilic attacks of 1-chloroalkyloxycarbonyl compounds, in order to be able to further predict new potential reactions as well as to improve existing methods.

The reactions factors assumed to affect the products distribution and the kinetics of the reactions are the following :

- Strength of nucleophilicity of the nucleophile.
- Strength of electrophilicity of center **A** and **B**.
- Nucleofugacities of 1-chloroalkoxide anions and Z anions.
- Solvent and temperature effects.
- Steric effects.

Our approach was outlined in the framework of the Hard-Soft Acid-Base theory (HSAB, Ref. 90). In a short definition, the HSAB theory states that hard nucleophiles prefer to react with hard electrophiles and soft nucleophiles prefer to react with soft electrophiles.

There are two electrophilic centers in the 1-chloroalkyloxycarbonyl derivatives (designated **A** and **B** in scheme 70). Center **B** is a carbon sp^3 hybridized and is softer than the carbonyl group, center **A**.

The factors that influence the degree of hardness work

for both centers **A** and **B** in the same way. That is electron withdrawing groups (in R or Z) increase the hardness of both centers :

- In term of the R group

The following order of hardness is proposed for centers **A** and **B** :

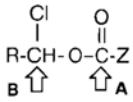
R = CCl3 > Aryl > Alkyl > H

Note that is also the same order for nucleofugacity (leaving group capability) in a **A1,2** type reaction

- In term of the Z group

Electron withdrawing groups in the R radical will make centers **A** and **B** both harder. The order chosen in our work was based on the Infra-Red carbonyl stretch. Assuming that electron withdrawing Z groups will give a higher C=O stretch, we established the order of decreasing hardness presented in table 3-8.

Z	F	Cl	OAr		OR^1	SAr		
C=O stretch (cm^{-1})	1840	1780	1780	1775	1765	1745	1740	1729



R = Alkyl

*Table 3-8 : Decreasing hardness order of centers **A** and **B** as a function of Z group.*

The nucleophiles we studied can be placed in one of three categories :

- « Hard » nucleophiles : F^-, R-COOH, ROH, R^1R^2NH, ^-OCN.
- « Borderline » nucleophiles : ArO^-, $ArNH_2$, Imidazole, Br^-, Cl^-.
- « Soft » nucleophiles : I^-, ^-SCN, RS^-, ArS^-, $(R^1O)R^2P(=X)S^-$, $(RO)_3P$, CN^-.

The reactions of 1-chloroalkyl chloroformates with amines, as well as further reactions of the resulting products are not dicussed here in this section and are reserved for section 3-3.

One of the first representative reaction with hard nucleophiles we developed was the reaction of 1-chloroalkyl carbonates with fluorides anion. This reaction proceeds through **A1** attack mechanism, which is in accord to the HSAB theory, thus converting 1-chloroalkyl carbonates to fluoroformates in good yields (Ref. 91).

In the preferred literature, most fluoroformates are prepared from their analogous chloroformates through halogen exchange using excess KF activated by a little 18-Crown-6. However, this method proved to be impractical for tertiary alkyl fluoroformates and/or benzyl fluoroformates, either because the corresponding chloroformates are not stable or because of the lack of selectivity of the fluoride attack. Acylation of the respective alcohols with COF_2 or COFCl requires complex equipment not accessible to standard laboratories and/or multipurpose plants.

When the easily available 1-chloroethyl carbonates ($RCHCl\text{-}OCO_2R^1$; $R = CH_3$) are heated, neat or in solution (benzonitrile or diglyme) with KF in the presence of 18-Crown-6, they fragment to aldehydes and fluoroformates in good to excellent yields (Ref. 92) as shown in table 3-9.

R1	Catalyst (18-C-6) mole/%	Solvent	Temp/press °C/mm	Time h	Yield %	bp °C/mm [mp. °C]
t- Butyl	6	None	70/37	30	84	40-2/175
t. Amyl	5	None	70/14	34	83	35-6/36
1-Adamantyl	4	None	120/1.2	36	76	[30-2]
Benzyl	5	None	55/1.2	4	60	44-6/1
Cholesteryl	9	Ph-CN	40/3	31	82	[114-7]
Phenyl	5	None	75/20	1.5	70	60-3/20

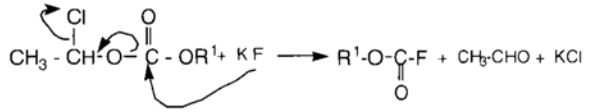
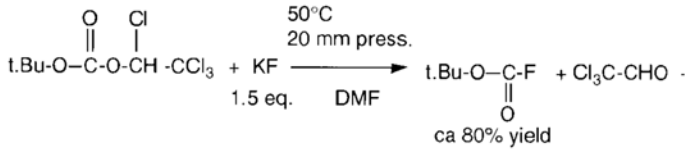


Table 3-9 : Fluoroformates prepared from 1-chloroethyl carbonates.

It should be noted that this new methodology exemplifies an unusual conversion of an ester to an acid halide.

Because the radical R = CCl_3 inductively increases the hardness of the electropholic center **A** and makes 1,2,2,2-tetrachloroethoxide anion a better leaving group than 1-chloroethoxide, 1,2,2,2-tetrachloroethyl tert-butyl carbonate is a more reactive acylating agent than the analogous carbonate from acetaldehyde (R = CH_3) and doesn't require a catalyst. Thus, heating 1,2,2,2- tetrachloroethyl tert-butyl carbonate at 50°C for 8 h with KF in the polar solvent DMF under vacuum of 20 mm, with a simultaneous treatment of the distillate with ethylene glycol, pure t.butyl fluoroformate (BOC-F) was isolated in 75-79% yield [Scheme 71].



Scheme 71 : Economics for commercial synthesis of BOC - F : NO CATALYST.

These results are of particular interest since t. butyl fluoroformate (BOC - F) has been highly recommended by Schnabel (Ref. 93) and Carpino (94) as a substitute for the expensive di-tert.butyl dicarbonate called $(BOC)_2O$. Indeed, BOC - F is an extremely clean and efficient reagent for the amino protection of amino-acids into BOC-AA.

However, the reagent is not stable enough to be shipped safely because it decomposes more or less rapidly into isobutene, carbon dioxide and HF, thus developing autogenous pressure in containers. This has led SNPE and its subsidiary ISOCHEM to manufacture and react BOC-F on site, thus offering low cost protected amino compounds.

Furthermore, we succeeded in the preparation of FMOC-F (9-fluorenylmethyl fluoroformate) as a crystalline solid (mp. 41°C). This reagent exhibits the same stability as FMOC-ONSu and can be easily shipped. Compared with FMOC-ONSu, FMOC-F gives similar to superior results in the protection of amines in peptides synthesis.

Fluoroformates offer also some decisive advantages as carboalkoxylating reagents for polar reactants. While chloroformates react explosively with DMSO (Pummerer reaction) and exothermically with DMF (Vilsmeier-Haack reaction), Olofson and coworkers (Ref. 95) have found that fluoroformates are stable in this solvents below 100 °C. Several important classes of hydroxyl and amino-containing compounds only soluble in polar solvents such as DMSO and DMF can be easily and efficiently carboalkoxylated with fluoroformates. For example, percarboethoxylation of glucose was readily achieved in good yield with ethyl fluoroformate in DMSO as shown in scheme 72.

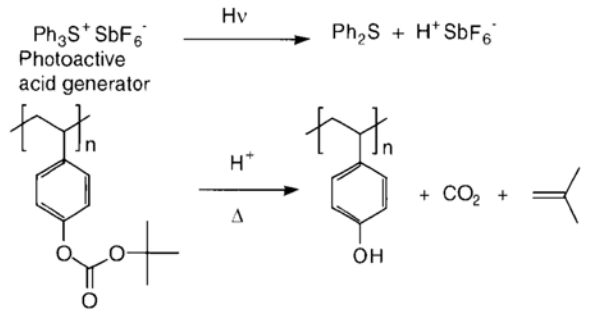
Scheme 72 : Efficient synthesis of penta-O-(ethoxycarbonyl)-D-glucose.

Under selected conditions, fluoroformates included BOC-F react easily with products containing phenolic functions to afford aromatic carbonates in high yields. This result proved to be suitable for the production of valuable monomers used in resist materials for microelectronic.

Recent progress has been made in microelectronic device fabrication, particularly in microlithography used to manufacture the high-resolution circuit elements of integrated circuit (Ref. 96). Deep-UV photolithography based on chemically amplified resist is likely to be the first technology that met the severe performance criteria required. The best known chemically amplified resist is based on poly (4-t-butoxycarbonyloxy styrene) or copolymers (Ref. 97).

As shown in scheme 73, irradiation of the resist results in the decomposition of an added photoactive acid generator (Crivello's salt) thus liberating a Brönsted's acid, which upon heating leads to cleavage of the t-BOC protecting group. The irradiated regions are soluble in basic water

and insoluble in organic solvents. Image development can be achieved either with aqueous base affording a positive-tone image or with an organic solvent to give negative-tone image.

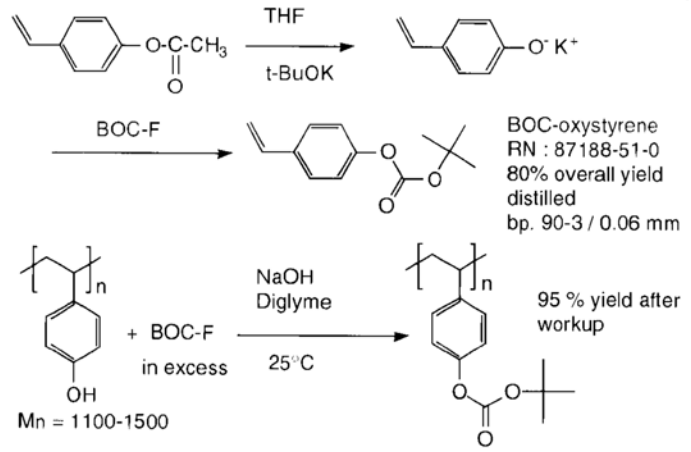


Scheme 73 : Photocatalyzed removal of the BOC protecting group of poly (BOC-oxystyrene).

The required monomer, 4-t-butoxycarbonyloxystyrene, is widely described in the literature. Because 4-hydroxy styrene is difficult to isolate due to its rapid polymerization, BOC-oxystyrene is generally prepared by treatment of 4-acetoxystyrene with strong base thus giving the corresponding phenoxide, immediately followed by addition of $(BOC)_2O$ in THF solution (Ref. 98).

At SNPE Group, we developed processes suitable for the manufacture of either BOC-oxystyrene from 4-acetoxystyrene and BOC-F or directly poly (BOC-oxystyrene) through reaction of BOC-F with poly (4-vinyl phenol), MARUKA Lyncur M from MARUZEN Petro-chemical Co. Ltd. As shown in scheme 74, these processes are quite simple and afford good yields (Ref. 99).

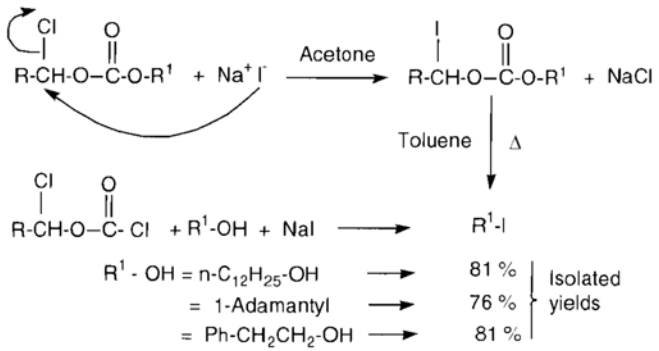
Researchers from Nippon Telegraph and Telephone Corp. disclosed positive-working resists developable with alkali aqueous solutions, consisting of a novolak resin, an acid-generating agent and 2,2-[p-(t-butoxycarbonyloxy) phenyl] propane (Ref. 100). In our laboratories, the latter was readily prepared in good yield through reaction of bisphenol A with BOC-F, using usual procedure.



Scheme 74 : Preparation of 4-t-butoxycarbonyloxy styrene and its polymer using BOC-F.

Similar to the case of fluoride attack, the reaction of the soft nucleophile iodide anion with 1-chloroalkyl carbonates is in good accordance with the HSAB theory. The reaction proceeds selectively through **B** mechanism to give 1-iodoalkyl carbonates [Scheme 75].

The poor stability of such compounds has been already mentioned in this section. Caubère and coworkers (Ref. 78) reported that when 1-iodoethyl alkyl carbonates were heated in toluene at 75-105 °C, they decompose rapidely to form the corresponding alkyl iodides.



Scheme 75 : New preparation of alkyl iodides.

Because during the reaction the authors observed the transient back formation of the corresponding free alcohol R^1-OH, they demonstrated that the reaction can be performed one-pot from 1-chloroethyl chloroformate, alcohol and NaI, thus discovering a new preparation of alkyl iodides as shown in scheme 75.

Another example of soft nucleophile attack according to the HSAB theory was given by the reaction of thiocyanate salts with 1-chloroethyl carbonates affording the corresponding 1-thiocyano and/or 1-isothiocyano ethyl carbonates in good yields (Ref. 101).

Because of the interest of compounds containing both carbonate and isothiocyano groups in phytosanitary chemistry, the mechanism of the reaction was thoroughly studied in order to understand the origin of the N-bounded compounds (Ref. 102). Some examples of the reaction are given in table 3-10.

R	M	Solvent	Time h.	(I)+(II) %	(I)/ (I) + (II)	(II)/ (I) + (II)
Et	K	MeOH	23	58	1	0
Et	NH4	MeOH	76	78	1	0
Et	K	HCONH2	4	76	0.83	0.17
Et	NH4	HCONH2	4.75	86	0.85	0.15
t-Bu	NH4	HCONH2	17	89	0.79	0.21
n-C8H17	K	MeOH	73	70	0.93	0.07
Ph	NH4	HCONH2	72	51	1	0

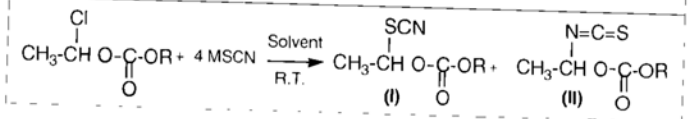


Table 3-10 : Reaction of 1- chloroethyl carbonates with MSCN in protic solvent at 20°C.

From this study, the authors concluded that most isothiocyanates (**II**) must be due to a N-condensation of the thiocyanate anion rather than an isomerization. Because $^-N{=}C{=}S$ is harder nucleophile than ^-SCN, attack of the isothiocyanate anion to the carbonyl will explain the observed decomposition.

However, the authors discovered that in acetone, in the presence of Bu_4PBr but in the absence of alkali thiocyanate, thiocyanates (**I**) were readily isomerized under mild conditions to the corresponding isothiocyanates (**II**) as shown in table 3-11.

R	Time hours	Yield, isolated (**II**) %
Et	72	81
t-Bu	13	81
n-C8H17	26	56
Ph-CH2	48	82

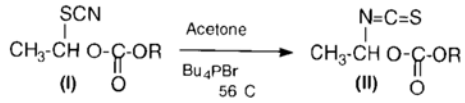
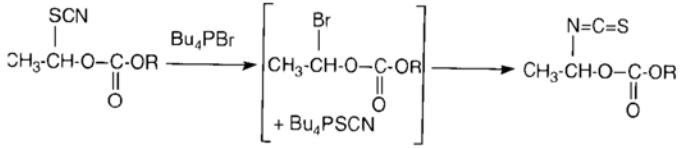


Table 3-11 : Isomerization of 1-thiocyanoethyl carbonates to 1-isothiocyanoethyl carbonates.

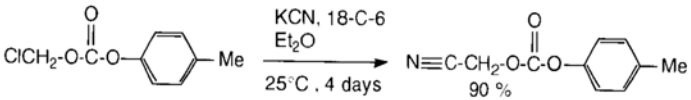
The authors proposed the mechanism given in scheme 76 (Ref. 101).



Scheme 76 : Proposed mechanism of 1-thiocyanoethyl carbonate isomerization.

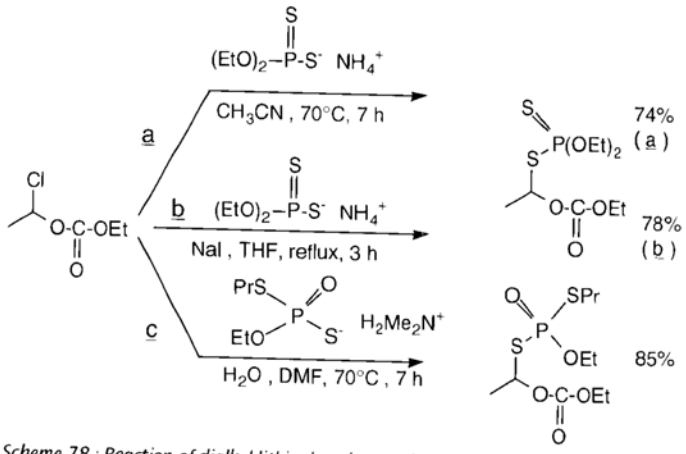
It could be suggested that the bromine atom would give a more marked cationic like transition state. Therefore according to the HSAB theory, the substrate would be attacked by the harder side of thiocyanate anion.

As predicted, the soft nucleophile cyanide anion reacts with 1-chloroalkyl carbonates to afford 1-cyanoalkyl carbonates in good yields as shown with the example depicted in scheme 77.



Scheme 77 : Example of 1-cyanoalkyl carbonate preparation.

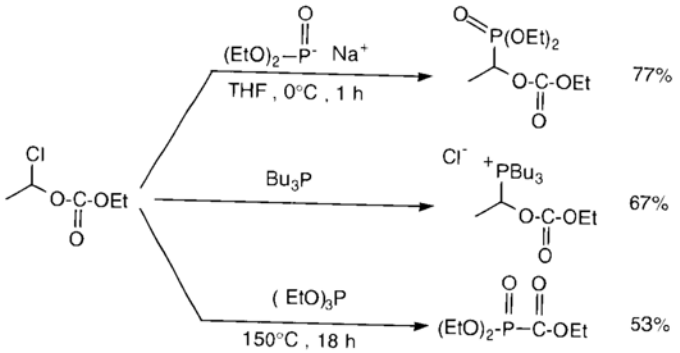
Scheme 78 gives two examples [reaction a and c] of the preparation of insecticidal phosphoric acid esters from dialkyldithiophosphate anions and 1-chloroethyl ethyl carbonate claimed in a patent (Ref. 103).



Scheme 78 : Reaction of dialkyldithiophosphate anions with 1-chloroethyl carbonate.

Reaction b in scheme 78 was performed in our laboratories. In reaction c, the thiophosphate anion is an ambident nucleophile and can attack with either the oxygen or the sulfur. As found, attack with sulfur is in accord with the HSAB theory.

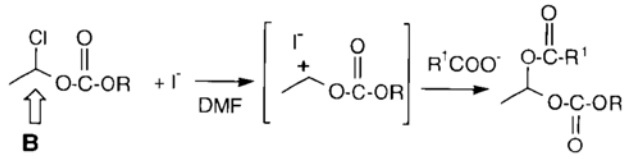
Some other examples of attack of 1- chloroethyl ethyl carbonate with soft nucleophile phosphorous compounds are gathered in scheme 79 (Ref. 104).



Scheme 79 : Examples of reactions of 1-chloroethyl ethyl carbonate with phosphorous compounds.

The last reaction with triethyl phosphite appears to be a violation of the HSAB theory.

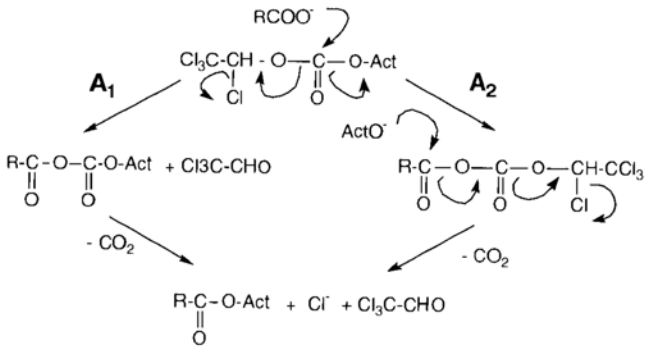
As already developed in the start of this section, the reaction of carboxylate anions with 1-chloroethyl carbonates is widely used for the preparation of commercial prodrugs. The hard nucleophile R^1COO^- attacks selectively the soft center **B**, that is apparently contrary to the HSAB theory. However, the required use of added NaI may favour a cation-like transition state, the cationic intermediate having therefore two hard electrophilic centers and **B** attack would not be in violation of the rule [Scheme 80].



Scheme 80 : Assumed mechanism of the reaction of carboxylate anion with 1-chloroethyl carbonates.

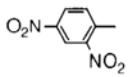
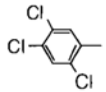
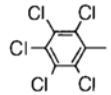
N-protected amino acids have been converted to active esters for subsequent peptide coupling by treatment with the tetrachloroethyl carbonate of N-hydroxysuccinimide, 2,4,5-trichloro penol, pentafluoro phenol, etc. (Ref. 67).

The reaction proceeds by initial attack of the carboxylate on the carbonyl and release of either chloral and chloride anion (A_1 mechanism) or N-oxysuccinimide (or phenoxide) anion (A_2 mechanism) as depicted on scheme 81.



Scheme 81 : Assumed mechanism of active esters synthesis using 1,2,2,2-tetrachloroethyl carbonates.

Mixed aryl and oximido tetrachloroethyl carbonates are crystalline and stable compounds easily obtained by reaction of tetrachloroethyl chloroformate with substituted phenols or N-hydroxy imides as shown in table 3-12.

Act-	Yield %	mp (°C) bp (°C/mm)	Crystn solv.
	83	108	Pet. ether
	66	121-122	Pet. ether
	92	150-5/0.02	
	91	80/0.05	
	98	120	Ethyl acetate
	85	145-147	Dichloromethane

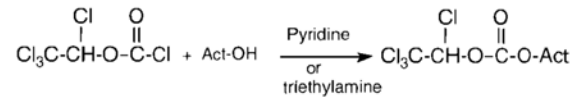
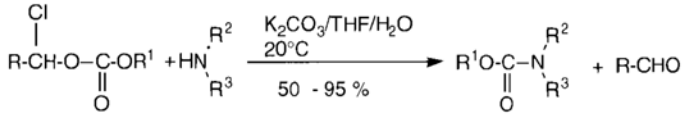


Table 3-12 : Preparation of some aryl and oximido tetrachloroethyl carbonates.

The new method provides an easy preparation of N-protected amino acid active ester derivatives using cheap reagents, in a reaction where the by product is water soluble and easily eliminated from the reaction mixture. The process is illustrated by the isolation of the N-succinimidyl ester of BOC-Alanine in 94 % yield from activation of BOC-Ala with 1,2,2-2-tetrachloro-ethyl N-succinimidyl

carbonate. The method will be developed in volume 2, section 4-4.

Again, according to the HSAB theory, secondary and primary amines react with 1-chloroalkyl carbonates as hard nucleophiles through A_1 attack mechanism to afford carbamates in high yields. This reaction has been shown to be very general under different reaction conditions utilizing differents types of amines including amino acids (Ref. 64, 66, 105, 106, 107). Scheme 82 below displays the general picture of the reaction.

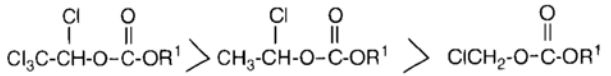


R = H , CH_3 , CCl_3

R^1 = alkyl, aryl

Scheme 82 : 1-Chloroalkyl carbonates as reagents for the synthesis of carbamates.

In terms of the rate of the reaction and the yield, the following trends are observed :

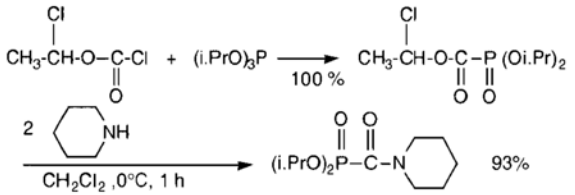


The release of an aldehyde can be a severe limitation in the use of this reaction since the aldehyde formed can react with the starting amine to lead to a considerable decrease of the yield of the expected carbamate. However, this difficulty can be simply overcome depending on the choice of the respective structure of the carbonate and the amine, and on the reaction conditions (Ref. 64).

Therefore, 1-chloroalkyl carbonates have been proposed as new acylating agents and thus are valuable precursors to carbamates, thiocarbamates and unsymmetrical ureas as outlined in section 3-3, this volume.

1,2,2,2-Tetrachloroethyl-t.butyl carbonate (BOC-OTCE) was especially developped as a crystalline, nontoxic reagent for the N-BOC protection of amino acids (Ref. 66) [see section 3-3].

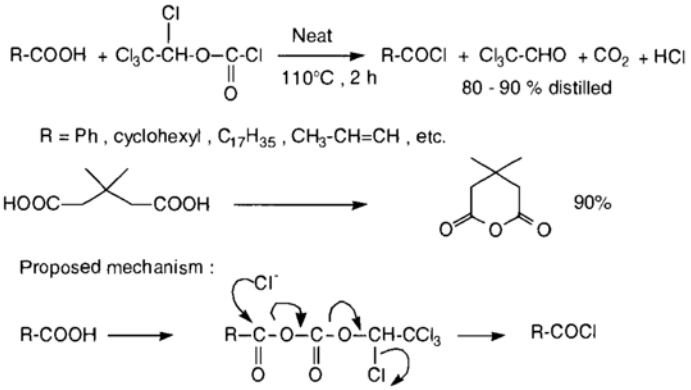
In related chemistry, the Arbusov reaction products of 1-chloroethyl chloroformate and trialkyl phosphites were easily converted into amino alkyl phosphonates as depicted in scheme 83 (Ref. 108).



Scheme 83 : Acylation of phosphonate compound.

Some interesting miscellaneous reactions have been also explored. For example, 1,2,2,2-tetrachloroethyl chloroformate reacts with carboxylic acids at 110°C without solvent to afford acid chlorides or cyclic anhydrides in high yields (Ref. 109).

Since the reaction doesn't require any catalyst, such result cannot be explained by the decomposition of the chloroformate to phosgene and chloral. The assumed mechanism is given in scheme 84.



Scheme 84 : Preparation of acid chlorides or anhydrides through reaction of 1,2,2,2-tetrachloroethyl chloroformate with carboxylic acids.

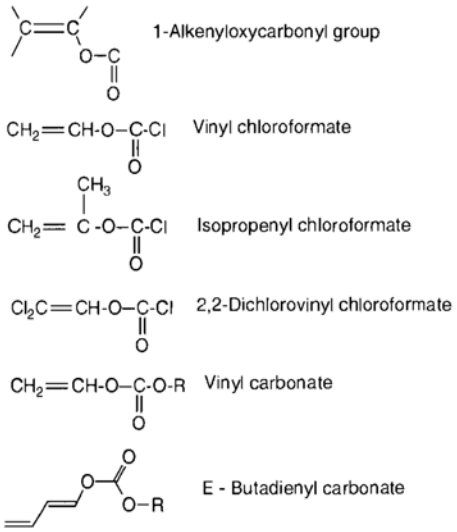
In another case, we have observed and studied the rearrangement of 1-chloroallyl chloroformate to E,Z-3-chloro-1-propenyl chloroformate (Ref. 110) [Scheme 85].

Scheme 85 : Rearrangement of 1-chloroallyl chloroformate.

While studying the mechanism, we demonstrated the reversibility of the rearrangement in presence of $TiCl_4$.

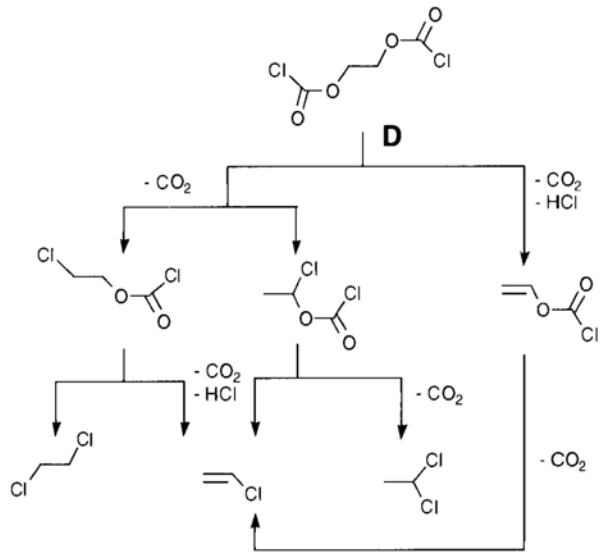
3-2-2-4 Vinylic chloroformates, carbonates and carbamates

The synthesis and chemistry of 1-alkenyloxycarbonyl species [Scheme 86] have been areas of major research interest in academic laboratories as well in the industry, especially at the early beginnings for polymers applications.



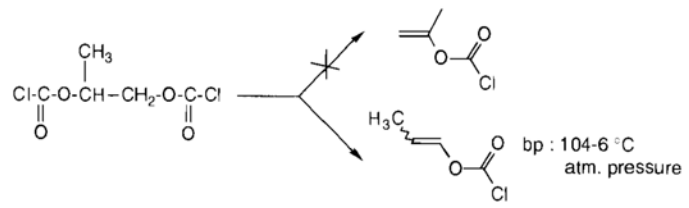
Scheme 86 : Examples of vinylic oxycarbonyl species.

Much of the early work described in the literature was centered around vinyl chloroformate classically made by the gas phase pyrolysis of ethylene glycol bis-chloroformate at 460-480°C (Ref. 111, 112, 113). However, this route proved to be industrially and economically impracticable because of low yields (11-44%) and formation of large amount of chlorinated side products and tars. Scheme 87 presents the decomposition pathways of ethylene glycol bis-chloroformate.



Scheme 87 : Pyrolysis of the bis-chloroformate of ethylene glycol at 460-480°C

Besides the severe difficulties encountered in the scaling up, this process was stymied by the impossibility of generalization to other 1-alkenyl chloroformates. For example in the same conditions, pyrolysis of the bischloroformate of propylene glycol affords selectively the 1-propenyl chloroformate instead of the desired isopropenyl chloroformate as shown in scheme 88 (Ref. 111).



Scheme 88 : Pyrolysis of the bis-chloroformate of propylene glycol.

In an obscure short paper published in 1934 (Ref. 114), Matuszak reported the first preparation of the previously unknown isopropenyl chloroformate. While working as a physical chemist at the US Bureau of Mines, he isolated this compound by microfractionation from a reaction mixture of 70 ml of acetone and 7 ml of liquid phosgene after half an hour at room temperature.

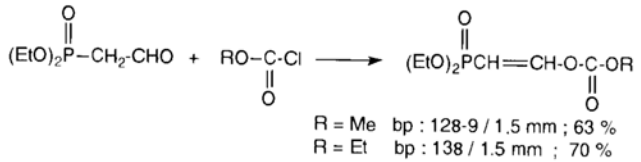
Several chemists teams in the world, as well as researchers in our laboratories attempted to reproduce this exciting simple and cheap process. Unfortunately, whatever the conditions and catalysts used, all the carried out trials failed and the only products isolated were mesityl oxide and various chlorinated compounds. The conclusion of most investigators was that Matuszak did not isolate isopropenyl chloroformate but a mixture of chlorinated products. However, as shown in table 3-13, the properties given by Matuszak closely correspond to those of the isopropenyl chloroformate made by the mercury process (see farther on in this section).

Isopropenyl chloroformate	Boiling point °C/mm	Density 20 °C/20 °C	Refractive index 20°C
Phosgenation of acetone	93/746	1.103	
Phosgenation of chloro-mercuri acetone	94.5/747	1.121	1.4138

Table 3-13 : Comparison of properties of the product obtained by Matuszak and properties of the isopropenyl chlororoformate made by the mercury process.

In spite of numerous failures to prepare vinyl chloroformate and isopropenyl chloroformate by direct phosgenation of either acetaldehyde or acetone, we accepted the challenge to find economical routes to vinylic chloroformates and their derivatives, vinylic carbonates and carbamates.

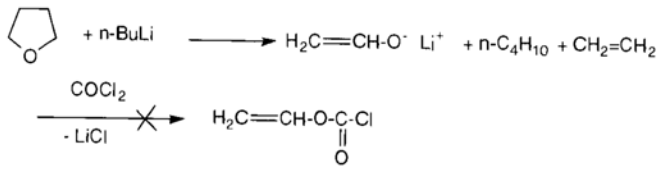
We have shown in 1975 investigations that easily enolizable aldehydes could react with chloroformates to afford vinyl carbonates in good yields as illustrated in scheme 89.



Scheme 89 : Reaction of alkyl chloroformates with diethyl (2-oxo ethyl phosphonate).

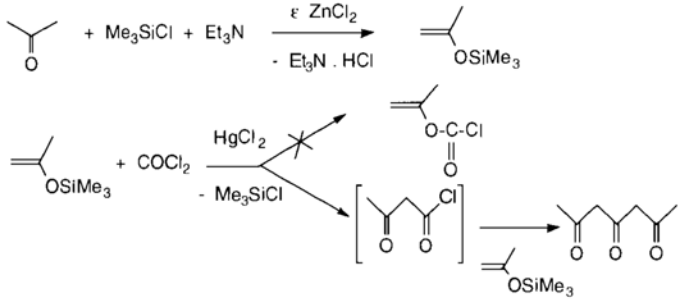
Olofson and coworkers (Ref. 115) found that reaction of ketones with LiTMP produced enolates which were specifically O-acylated with chloroformates when hexamethyl phosphoro triamide (HMPT) was added in the reaction mixture thus giving alkenyl carbonates in 49-90 % yield.

Therefore, our first idea was to O-acylate simple enolates with phosgene. In a first course of attempts, we investigated the reaction of phosgene with alkaline metals enolates. For example we prepared lithium enolate of acetaldehyde through cleavage of tetrahydrofuran by n- butyllithium (Ref. 116) and reacted with phosgene under various conditions. Unfortunately, no trace of vinyl chloroformate was found in all experiments performed [Scheme 90].



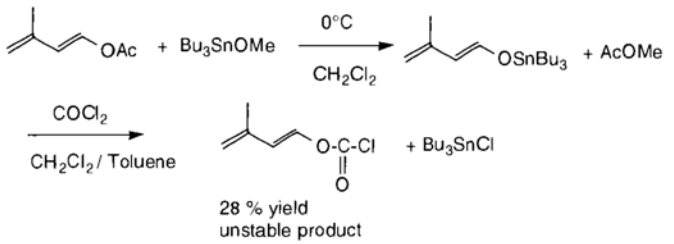
Scheme 90 : Reaction of phosgene with the lithium enolate of acetaldehyde.

The phosgenation of enol silanes was studied in a second stage of our investigations. Several silyl enol ethers from acetaldehyde, acetone, cyclohexanone were prepared according to general procedures given in the literature. However, again, all the attempts failed, the only products isolated resulted from C-acylation of the enols. For example, phosgenation of the enol silane of acetone in presence of catalytic amount of mercury (II) chloride afforded 2,4,6-heptanetrione as the major product as depicted in scheme 91.



Scheme 91 : Phosgenation of the enol silane from acetone.

The phosgenation of the tributyltin enolate of acetone led to the same results although some trials performed at low temperature (below - 20°C) showed the possibility to obtain small amounts of isopropenyl chloroformate. It is noteworthy that, in a recent work devoted to a new synthesis of retinal (Vitamin A aldehyde), Bienaymé from Rhône-Poulenc (Ref. 117), obtained isopropen-1-yl chloroformate in low yield through phosgenation of the reaction product of tributyltin methoxide with 1-acetoxy isoprene as depicted in scheme 92.



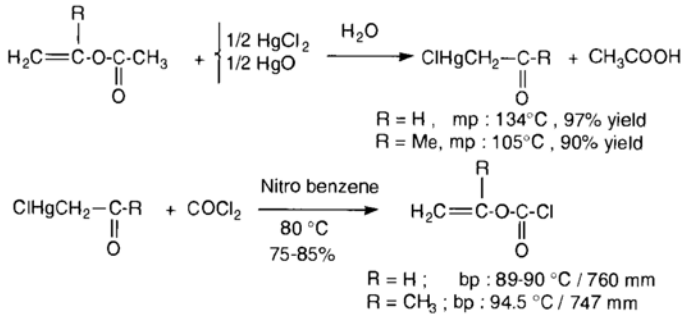
Scheme 92 : Preparation of isopren-1-yl chloroformate.

At this point of our investigations, we thought that the good way to synthesize enol chloroformates may be the reaction of phosgene with α-C-metallated aldehydes and ketones. With this new course of action, we were able for the first time to obtain the desired compounds by treating chloromercury acetaldehyde or chloromercury acetone with phosgene in polar solvent.

At about the same time, Olofson and coworkers turned a similar concept into a practicable laboratory route to enol chloroformates (Ref. 118). When we became acquainted with this work, contacts were initiated which were later to provide the basis for a long collaboration in new areas of chloroformate chemistry between SNPE and Penn State University.

In the first step of the SNPE process, chloromercury acetaldehyde and chloromercury acetone are easily prepared by reaction in water of vinyl acetate and isopropenyl acetate respectively with a 1:1 mixture of mercury (II) oxide and mercury (II) chloride (Ref. 119).

In the second step, the dried chloromercurials compounds are treated with phosgene at 80°C in nitrobenzene as the key solvent (Ref. 120). Vinyl chloroformate and isopropenyl chloroformate are isolated by simple distillation in 75-85 % yield [see scheme 93].

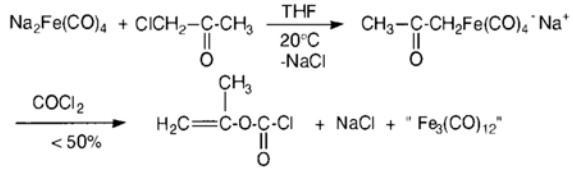


Scheme 93 : Preparation of vinyl and isopropenyl chloroformates by the mercury process.

The system was designed to recycle the $HgCl_2$ in nitro benzene without removal from the reactor. However, the process was severely handicapped by the bad reputation of mercury compounds whatever the strictly controlled

safety precautions and efficient cleaning up methods used.

To circumvent the difficulty, we attempted to start from other α-C-metallated keto compounds. Thus, we prepared acetonyltetracarbonylferrate by the reaction of disodium tetracarbonylferrate (Caution : pyrophoric !) with chloroacetone in THF according to literature data (Ref. 121). Phosgenation in situ afforded isopropenyl chloroformate but in very variable and non-reproducible yields not exceeding 50 % as depicted in scheme 94 (Ref. 122).



Scheme 94 : Isopropenyl chloroformate through phosgenation of acetonyltetracarbonylferrate.

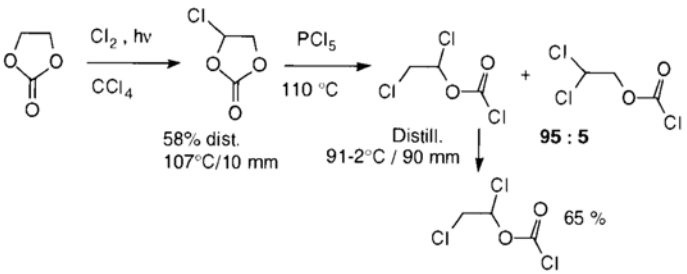
The studies in this area were not further pursued. However, it seems that several high-potential possibilities still remain untapped. To give just one example, the phosgenation of the reaction product of zirconium tetrachloride with acetone : $Cl_3ZrCH_2COCH_3$ described by Joseph and Blumenthal (Ref. 123), should yield, under selected conditions, isopropenyl chloroformate.

In the course of other studies related to dehalogenation methods through electrosynthesis with sacrificial anode, we thought that the dehalogenation of 1,2-dihaloalkyl chloroformates should provide with an interesting route to vinylic chloroformates.In order to check the feasibility of such process, we carried out a set of exploratory experiments under aprotic conditions using 1,2-dibromoethyl chloroformate and 1,2-dibromoisopropyl chloroformate as starting materials (Ref. 124), these materials having been made by bromination of vinyl and isopropenyl chloroformates. The electroreduction was performed in an undivided cell equipped with a stainless steel cathode and a consumable zinc anode using acetonitrile as the solvent and $Bu_4N^+BF4^-$ as the electolytic salt. The promising results obtained are given in scheme 95.

Scheme 95 : Preparation of vinylic chloroformates by electroreduction of 1,2-dibromoalkyl chloroformates.

These pretty good results prompted us to find a practical route to 1,2-dihaloalkyl chloroformates.

1,2-Dichloroethyl chloroformate is a known product made by classical chlorination of vinyl chloroformate with Cl_2. We have developed a new, easily practicable route by treatment of 4-chloroethylene carbonate with PCl_5 at 110°C which gives a mixture of the desired chloroformate and the dichloro isomer in a 95 : 5 ratio as depicted in scheme 96. Careful fractional distillation afforded the 1,2-dichloroethyl chloroformate in 65 % pure yield (Ref. 125).



Scheme 96 : Novel preparation of 1,2-dichloroethyl chloroformate.

The starting material, the 4-chloroethylene carbonate was prepared by standard photo-chlorination of the cheap ethylene carbonate as described in the literature.

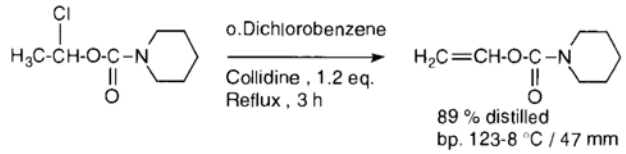
Unfortunately, the dechlorination of 1,2-dichloroethyl chloroformate by the electroreduction method afforded only very bad yields of vinyl chloroformate, whatever the conditions selected. Moreover, all the attempts to prepare the 1,2-dibromoethyl chloroformate failed.

At this point of our investigations, and on account of the

high commercial interest of vinylic chloroformates derivatives (see farther on in this section), we decided to focus our efforts on the synthesis of alkenyl carbamates and carbonates by methods which do not require vinylic chloroformates.

1-Chloroalkyl carbonates and carbamates are easily made from reaction of 1-chloroalkyl chloroformates with alcohols and amines through standard processes (see section 3-2-2-3, this volume) or original methods developed by SNPE research teams (section 3-3). If a simple method for the β-elimination could be devised, the ready availability of 1-chloroalkyl carbamates and carbonates would seem to make these compounds attractive precursors to vinylic carbamates and carbonates.

Olofson and coworkers discovered a relatively simple process of thermal elimination of hydrochloric acid from 1-chloroethyl carbamates to produce vinyl carbamates in high yields (Ref. 126). In a typical example, N-(vinyloxycarbonyl) piperidine was obtained in 89 % yield just by refluxing N-(1-chloroethyloxycarbonyl) piperidine for 3 h in o.dichlorobenzene containing 1.2 eq. recyclable 2,4,6-collidine as an acid scavenger [see scheme 97].



Scheme 97 : Preparation of VOC-piperidine from ACE-piperidine.

Without collidine, the reaction has been proved to work but is much slower. When the methyl of the 1-chloroethyloxycarbonyl group is substituted by alkyls, the elimination is easier, probably due to inductive stabilization of the carbocation intermediate.

The effects of various conditions such as added mineral or organic salts (to catalyse the E_1 elimination), temperature and solvents were carefully studied by Wooden (Ref. 127).

Some representative examples of the method are gathered in table 3-14.

R1	R2	-NR3R4	Base	Solvent	Yield (%)	bp. (°C/mm)
H	H		Collidine	o.DCB	82	134-6/49
H	Me		Collidine	Tetrachloro ethylene	84	86-90/0.5
H	H		Collidine	Bromo benzene	78	81-5/0.2
R'	H		Collidine	Bromo benzene	86	125-7/0.6
Me	Me		None	1,2-Dichloro ethane	97	Light red gum

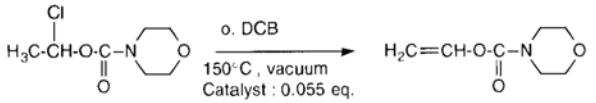
Table 3-14 : Preparation of 1-alkenyl carbamates from 1-chloroalkyl carbamates.

As illustrated in table 3-14, many extra functionnalities are tolerated. Some moieties even catalyze the elimination by increasing salt concentration (see last example in the table).

The value of hexabutylguanidinium chloride (HBGCl or HBGCl.HCl) as an acylation catalyst has been already outlined in section 2-2 of this volume. In a later study devoted to the evaluation of potential facilitation of E_1 elimination in sensitive systems by including HBGCl, Kreutzberger (Ref. 128) proposed a modification of the Wooden method based of the use of a « salt promoter ».

In refluxing tetrachloroethylene (121°C), with collidine as the acid scavenger, the guanidinium salts are superior to tetrabutyl ammonium bromide (TBAB). Moreover, the comparisons of experiments without collidine in o.dichlorobenzene under vacuum demonstrated a decisive advantage of HBGCl.HCl over TBAB as shown in scheme 98.

The efficiency of HBGCl which allows to avoid the use of collidine combined with its thermal stability at temperatures exceeding 200°C made this salt a prime candidate as « salt promoter » in this process.

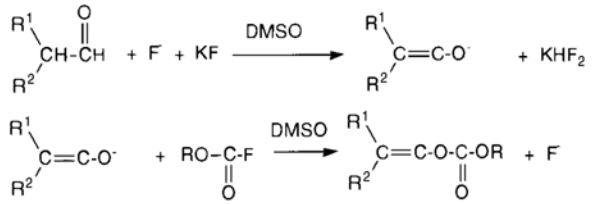


Catalyst : - TBAB , 9 h. 100% completion
non isolated, 80 % by NMR
20 % decomposition.
- CHBG.HCl , 7 h, 100% completion
100% yield NMR, 85 % isolated.

Scheme 98 : Comparison of two E_1 promoters in the synthesis of N-(vinyloxy-carbonyl) morpholine.

In contrast to the carbamate chemistry, thermal elimination of hydrochloric acid from 1-chloroalkyl carbonates requires much higher temperature and is accompanied by major yield destructive side reactions. The key to an economical route to vinylic carbonates was discovered by Olofson and coworkers (Ref. 129). This discovery was the consequence of a beautiful observation made by Dang, Olofson's student, on the formation of neopentyl fluoroformate and, unexpectably of vinyl neopentyl carbonate while heating 1-chloroethyl neopentyl carbonate with KF in benzonitrile (Ref. 130).

Treatment of enolizable aldehydes with fluoroformates and KF in DMSO (55-100°C for 15-24 h) afforded 1-alkenyl carbonates in 72-92 % yield. According to Olofson's studies, the activated fluoride anion acting as a base deprotonates the aldehyde to yield an enolate which reacts rapidly with the fluoroformate to give the desired vinylic carbonate as shown in scheme 99 (Ref. 131). Excess KF neutralises the HF which is liberated in the reaction as KHF_2.



Scheme 99 : Mechanism of the reaction of fluoroformates with aldehydes in presence of KF in DMSO.

Note that the reaction also can be carried out in acetonitrile if 18-crown-6 is used as a catalyst. In this latter

case, chloroformates may be substituted for fluoroformates if two equivalents of KF are included in the medium.

Some results obtained using the fluoroformates method are presented in table 3-15.

n	R	R1	R2	Temp., °C Time, h	Yield %	bp. °C/mm Hg
1	Et	H	H	55/20	73	43-5/45
1	C6H5-CH2-	H	H	70/15	87	112-5/4
1	i-Pr	H	H	80/5	86	44-6/33
2	- CH2CH2CH2-	H	H	80/24	92	130-2/0.5
2	CH2CH2-O-CH2CH2	H	H	90/8	80	123-30/0.7
1	Et	Me	Me	90/24	74	45-7/16
1	CF3-CH2-	H	H	80/20	81	43-4/25

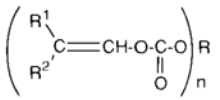


Table 3-15 . Preparation of 1-alkenyl carbonates from aldehydes, fluoroformates and KF in DMSO.

The good yield obtained in the last experiment of table 3-15 is notable, because the 2,2,2-trifluoroethyl vinyl carbonate has been proposed as useful monomer in optical fibers applications (Ref. 132).

1-Alkenyl chloroformates, especially vinyl and isopropenyl chloroformates, as well as vinylic carbonates and carbamates have found number of valuable applications in various fields.

In order to illustrate the considerable potential of these vinylic compounds in organic syntheses, selected types of applications are presented in the following pages.

The use of vinyl chloroformate and its derivatives as monomers in the manufacture of thermoplastic or crosslinked polymers is the oldest application developed.

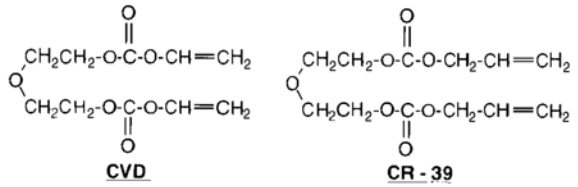
Polymerization and copolymerization of vinyl chloroformate (Ref. 133, 134, 135), vinyl carbonates and carbamates (135, 136) using standard radical initiators (e.g. peroxydicarbonates) to yield high molecular weight polymers and random copolymers is well documented. More recently,

in a work carried out to assess the kinetics of radical polymerization of some vinyl alkyl carbonates, Ebdon and coworkers showed that contrary to the conclusions of the previous studies, the compounds can be polymerized readily to give polymers of high molecular weight with conventional radical initiators such as benzoyl peroxide (Ref. 137).

The chemical modification of poly (vinyl chloroformate) and its copolymers has been also studied. Treatment of such polymers with amines, alcohols and phenols affords the corresponding poly (vinyl urethanes) and poly (vinyl carbonates) (Ref. 138, 139). Poly (mixed anhydrides) have been also prepared by chemical modification of poly (vinyl chloroformate) by carboxylic acids under various conditions (Ref. 140, 141, 142).

The materials obtained from polymerization of vinyl carbonates and carbamates are hard (but not brittle) clear thermoplastics with high decomposition temperatures, excellent chemical resistance and varying glass transition temperatures.

It is noteworthy that the heretofore not accessible at acceptable cost diethyleneglycol bis-vinyl carbonate called « CVD » [see scheme 100] is made in 80% yield using the fluoroformate process as depicted in table 3-15.



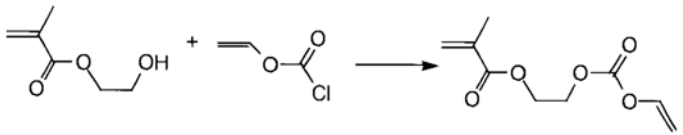
CVD **CR - 39**

Scheme 100 : Compared structures of two monomers for the fabrication of optical plastic lenses.

CVD is known to polymerize an order of magnitude more easily (Ref. 143) than the analogous bis-allyl carbonate marketed under the designation CR-39 which is the leading material for casting prescription eyewear since decades. The crosslinked homopolymer of CVD exhibits similar properties but with the advantages of much better scratch resistance and higher hardness and modulus.

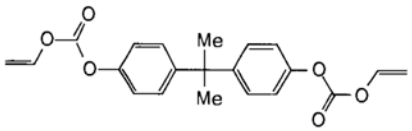
Methacryloxyethyl vinyl carbonate prepared from hydro-

xyethyl methacrylate and vinyl chloroformate [Scheme 101] was claimed as an UV curable crosslinking agent useful in the formulation of hydrogels for contact lenses manufacture (Ref. 144).



Scheme 101 : Synthesis of methacryloyloxyethyl vinyl carbonate used in the preparation of biomedical articles.

Aromatic bis-vinylcarbonates, for example the reaction product of vinyl chloroformate with bisphenol-A [Scheme 102], are recommended for the preparation of highly sensitive, high-contrast positive working resists (Ref. 145).



Scheme 102 : Aromatic bis-vinyl carbonate for the manufacture of high performance photoresists.

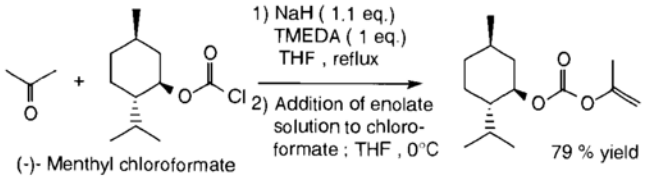
New N-vinyloxycarbonyl leucine alkyl esters have been synthesized from vinyl chloroformate and polymerized to yield polymers and copolymers optically and physiologically active with liquid crystals properties (Ref. 146).

Vinyl carbonates and carbamates containing chromophore groups have been prepared and claimed as useful polymerisable photoinitiators for photoreticulable polymers (Ref. 147).

Polymers and copolymers of vinylic carbonates and carbamates may find interesting applications as aroma and flavours releasing agents. For example, isopropenyl menthyl carbonate has been patented (Ref. 148) as an useful monomer for the manufacture of a smoking composition comprising an admixture of tobacco and a menthol-release agent. Recently, Harwood et. al (Ref. 149) have published a new preparation of enol carbonates including especially isopropenyl menthyl carbonate by selective O-acylation of ketones sodium

enolates generated in the presence of N,N,N',N'-tetramethylethylene diamine (TMEDA) as depicted in scheme 103.

In our continuing trials to extent the scope of the vinylic carbonates synthesis through the fluoroformate process, vinyl menthyl carbonate was obtained in excellent yield (80%) from menthyl fluoroformate. The polymer of vinyl menthyl carbonate was also proposed as menthol-release agent. It is noteworthy that this polymer can be easily prepared by reaction of menthyl fluoroformate with poly(vinyl alcohol) in DMSO.



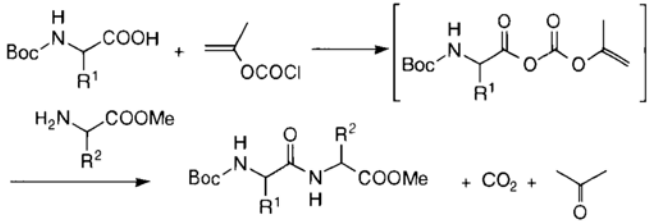
Scheme 103 : Efficient synthesis of isopropenyl menthyl carbonate for the manufacture of polymeric menthol-release agents.

Vinylic chloroformates, as well as their derivatives are not limited to roles as monomers.

Initial Olofson's publications (Ref. 150, 151) outlined the use of vinyl chloroformate (VOC-Cl) as a reagent for amine protection, especially in peptide synthesis, via the electrophile-labile carbamate. Amino acids are converted to their N-vinyloxycarbonyl derivatives by standard acylation with VOC-Cl, for example by Schnabel's pH-stat procedure. The most significant advantage of the VOC-group is associated with its removal which is facilited by the high reactivity of the C=C bound toward electrophiles. Acid-induced hydrolysis with HCl or HBr in Ac-OH or with HCl gas through an inert solvent containing the peptide followed by warming the hydrohalide adduct in ethanol affords the deblocked peptide salt in excellent yield. The value of the methodology was underscored in an efficient process for the construction of the heptapeptide sequence, H-Ser-Phe-Leu-Pro-Val-Asn-Leu-OH (all L) (Ref. 151).

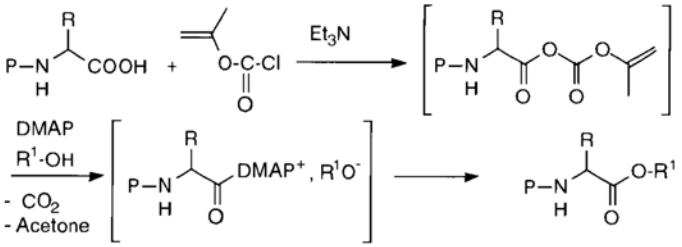
Isopropenyl chloroformate (IPCF) has no value in amine protection but appears to be the most versatile chloroformate for acid activation. Thus, IPCF was proved

to be an excellent reagent for the amino acid activation in peptide amide bound formation via the mixed anhydride intermediate as depicted in scheme 104 (Ref. 152).



Scheme 104 : Amino acid activation for peptide amide bound formation by isopropenyl chloroformate.

Reaction of N-protected amino acids activated by isopropenyl chloroformate with primary, secondary and tertiary alcohols in presence of 4-dimethylamino pyridine as catalyst affords the corresponding esters in good yield as shown in scheme 105 (Ref. 153).



Scheme 105 : IPCF activation for one-pot esterification of N-protected amino acids.

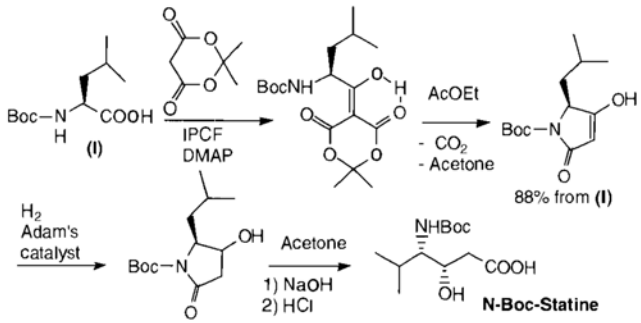
Some examples are given in table 3-16.

α-Amino esters	Yields (%)	mp (°C)	[α]D, C1, MeOH
Z-Ala-OCH2-pNO2C6H4	78	99-100	- 16.3
Boc-Phe-OBzl	92	64-5	- 6.3
Boc-Val-OCH2-o,p Cl2C6H3	85	110-1	- 10.5
Fmoc-Trp-O-[2,3-O-(isopropylidene glyceryl]	65	61-2	- 12
Boc-Val-O(+) Bornyl	60	54-7	- 75
Z-Phe-O-t.Bu	88	B1-2	- 9.9
Z-Pro-O-t.Bu	90	—	- 51
Z-Trp-O-t.Bu	60	70-1	- 5.2

Table 3 - 16 : α-Amino esters by IPCF activation of N-protected α-amino acids.

It is noteworthy that Takeda and coworkers (Ref. 154) recently proposed allyl isopropenyl dicarbonate made from isopropenyl chloroformate and sodium allyl carbonate as a convenient reagent for the preparation of allyl esters of carboxylic acids. Allyl isopropenyl dicarbonate reacts with carboxylic acids in the presence of DMAP under mild neutral conditions to give allyl esters in high yields. Allyl esters which could be deprotected by palladium catalysts are especially useful in the case of unstable compounds under acid or basic conditions, for example O-glycopeptides, penicillin derivatives, etc.

The condensation of a chiral N-protected amino acid with Meldrum's acid in the presence of isopropenyl chloroformate and DMAP is the key for a stereospecific synthesis of N-protected Statine (Ref. 155). The novel route to Statine is depicted in scheme 106.



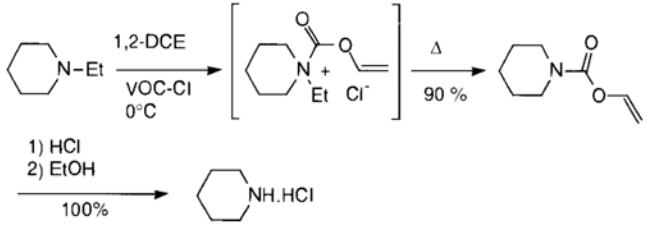
Scheme 106 : Stereospecific synthesis of Statine from IPCF.

More recently, a similar synthetic strategy was utilized to prepare the Dolastatin 15 via acylation of Meldrum's ester (156). In this work, isopropenyl chloroformate was found to give the best results of several mixed carbonic anhydrides derived from the required starting carboxylic acid when used in the presence of 5 molar equivalents of DMAP. Dolastatin proved to exhibit promising remarkable anticancer properties.

Olofson and coworkers also introduced vinyl chloroformate as a reagent for the N-dealkylation of tertiary amines (Ref. 157, 158, 159). Compared with commonly utilized reagents in N-dealkylation procedures, the use of VOC-Cl leads to significantly improved yields under milder conditions combined with greater discrimination between alkyl groups in unsymmetrical amines. The procedure is illustrated by the selective N-deethylation of N-ethyl piperidine to afford piperidine.HCl in 90% yield (Ref. 159) as depicted in scheme 107.

The N-dealkylation selectivities follow the order : benzyl; allyl; t.butyl >> s.alkyl ≥ n.alkyl >> piperidine scission.

The methodology was subsequently applied to the preparation of the potent analgesic Nalbuphine and the potent narcotic antagonists Naloxone and Naltrexone (Ref. 160).

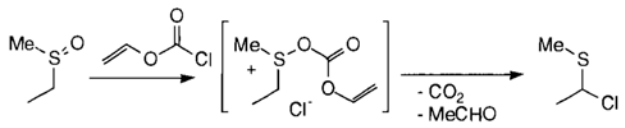


Scheme 107 : N-Deethylation of N-ethyl piperidine with vinyl chloroformate.

However, vinyl chloroformate largely has been replaced for N-dealkylation by 1-chloroethyl chloroformate which shows similar dealkylation selectivities and equally easy replacement of N-alkyl by the carbamate group (see section 3-3).

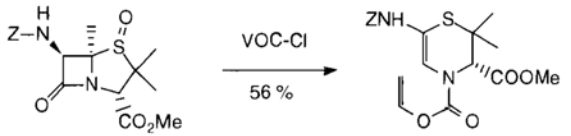
Vinyl chloroformate might find interesting applications in Pummerer related rearrangements. Thus, VOC-Cl reacts with sulfoxides to yield α-chlorosulfides as shown in scheme 108 (Ref. 161). In this type of reaction, VOC-Cl is more

reactive than the commonly used reagents.



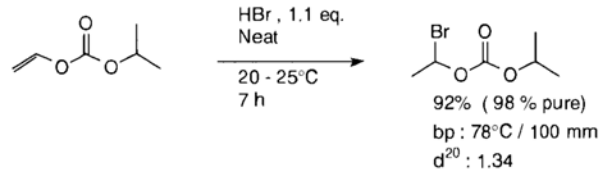
Scheme 108 : Pummerer rearrangement with vinyl chloroformate.

With penicillin β-sulfoxide, VOC-Cl induces a novel rearrangement involving cleavage of the C-S-C bound as depicted in scheme 109,



Scheme 109 : Novel rearrangement from penicillin β-sulfoxide and vinyl chloroformate.

Alkenyl carbonates readily add HBr to give 1-bromoalkyl carbonates which are better alkylating agents for the modification of carboxylic acid functions than 1-chloroalkyl carbonates as already mentioned in section 3-2-2-3 (Ref. 85). For example, 1-bromoethyl tisopropyl carbo nate (BEIC) was prepared at pilot scale in 92 % distilled yield by bubbling HBr through vinyl isopropyl carbonate, neat, at 20-25°C as depicted in scheme 110.

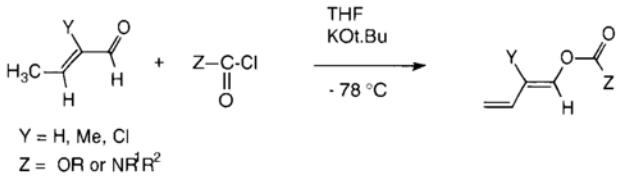


Scheme 110 : Preparation of 1-bromoethyl isopropyl carbonate (BEIC).

Besides the synthesis of vinylic carbonates and carbamates, Olofson and coworkers reported a simple synthesis of 1-(1,3- butadienyl)carbonates and carbamates (Ref. 162).

Crotonaldehyde and its congeners are easily and often stereospecifically converted to trans-butadienyl carbonates and carbamates by treatment with potassium tert.butoxide

followed with addition of a chloroformate or carbamoyl chloride as depicted in scheme 111. Some examples are given in table 3-17.



Y = H, Me, Cl
Z = OR or NR^1R^2

Scheme 111 : Alkyl dienyl carbonates and carbamates from reaction of crotonaldehydes with KOt.Bu and acyl chlorides.

Y	Z	Yield (%)	bp (°C/mm)
H	O-Et	83	42/3
H	O-Allyl	58	55/0.8
H	O-CH2CCl3	68	99/0.7
Me	O-Et	78	48-51/0.6
Cl	O-Et	32	58-61/1.5
H	N(Et)2	75	74-84/1

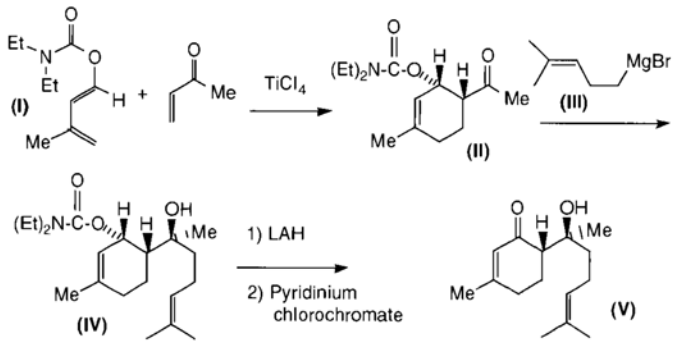
Table 3-17 : Preparation of trans-1-(1,3-butadienyl) carbamates and carbonates.

The alkyldienyl carbamates were utilized both at Pennstate University and at SNPE in parallel studies to develop a stereospecific synthesis of (±) - Hernandulcin and congeners (Ref. 163).

The intensely sweet sesquiterpene, Hernandulcin, was isolated from a plant known to the Aztecs as *Tzonpelic Xihuilt* or « sweet herb » (Lippia dulcis). Hernandulcin which could be considered the prototype of a new class of dietary sucrose substitutes is said over 1000 times sweeter than sucrose. However to a human panel at SNPE, while tasting synthetic Hernandulcin made by the new methodology, some aftertaste and a slight bitterness was perceived by 50 % of the persons.

In our method, the N,N-diethyl butadienyl carbamates (I) reacts both regio and stereospecifically to methyl vinyl ketone to give the cyclohexene (II) in 89% yield, which in turn adds the Grignard's reagent (III), again regio and ste-

reospecifically to form (IV) which, after LAH reduction and oxidation affords (±) - Hernandulcin (V) as depicted in scheme 112,

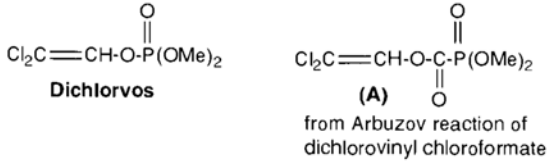


Scheme 112 : Novel preparation of the sweet sesquiterpene Hernandulcin.

In the course of several investigations devoted to the synthesis of new halogen substituted carbamates and phosphonato esters for agricultural screening, we were interested in the compounds containing the 2,2-dichlorovinyloxycarbonyl unit.

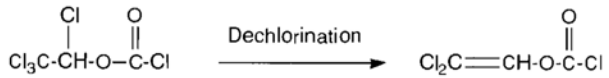
Various insecticides used extensively in the world continue to take advantage of the toxicity to insects of particular patterns of halogens in the molecule. To be more acceptable than many other agricultural agents in today's ecologically sensitive society, they must contain functionalities guaranteeing ready degradation by environmental agents.

A report published thirty years ago (Ref. 164) outlined the potential insecticidal activity of 2,2-dichlorovinyl carbamates and carbonates. However, progress in this area has been stifled because 2,2-dihalovinyl chloroformates were unknown. For the preparation of the phosphonato ester (A) assumed to exhibit interesting insecticidal properties as compared to the well known insecticide Dichlorvos, we needed the heretofore unknown 2,2-dichlorovinyl chloroformate [see scheme 113].



Scheme 113 : Compared structures of the insecticide Dichlorvos and a parent compound containing the 2,2-dichlorovinyloxycarbonyl unit.

The facile preparation of 1,2,2,2-tetrachloroethyl chloroformate by treatment of chloral with phosgene in the presence of a reusable « naked Cl- » catalyst has been already described in section 3-2-2-3. We thought that if this chloroformate could be induced to undergo a Boord elimination of chlorine, the desired 2,2-dichlorovinyl chloroformate would be easily available as shown in scheme 114.



Scheme 114 : Expected route to 2,2-dichlorovinyl chloroformate.

However, several precedents in the literature would seem to negate a favourable outcome for such a scheme. For example, the treatment of 2,2,2-trichloroethyl acetate with zinc leads to 1,1-dichloroethylene in a dramatically exothermic process. Since chloroformate anion is a better leaving group than acetate, it should compete with chloride for that role. Chloroformate ion also should be lost in an anticipated subsequent zinc-mediated elimination to yield the explosive chloroacetylene. Moreover, the well-known decomposition of chloroformate in presence of zinc salts provides another problem.

Despite these strong omens of failure, the reaction was successfully performed (Ref. 165, 166). When zinc dust was added in small portions to a solution of 1,2,2,2-tetrachloroethyl chloroformate in THF at room temperature, dichlorovinyl chloroformate was isolated in 75% distilled yield. Initiation of the reaction after addition of the first portion of zinc is variable in time and no more zinc should be added until the first portion has been consumed to

avoid any uncontrollable exotherm. No induction period was found in the same reaction from 1-chloro-2,2,2-tribromoethyl chloroformate but the yield of 2,2-dibromovinyl chloroformate was only 33 % [Scheme 115].

Yield	75 %	33 %
bp.	82-5 °C / 120 mm	68-3 °C / 12 mm

Scheme 115 : 2,2-dihalovinyl chloroformates.

Both chloroformates are stable for at least several months at room temperature if all traces of the byproducts zinc salts are carefully removed by distillation.

Even more surprising, we discovered that 2,2-dichlorovinyl chloroformate is isolated in 50% distilled yield when chloral is treated with phosgene and zinc dust in methyl acetate (Ref. 167). Efforts were made to generalize this process by extending the reaction to other α-chloro and α-bromo aldehydes and ketones as shown in table 3-18 (Ref. 167).

When Z is hydrogen, alkyl or aryl, the chloroformate is obtained only when A and B are halogen or alkyl but not hydrogen.

A	B	Z	Yield (%)	bp. (°C/mm)
Cl	Cl	Ph	66	86-8/0.4
Me	Me	Ph	54	57-74/0.5
Me	Me	CN	67	80-3/10
Me	Me	P(O)(OMe)2	83	–
Cl	Me	H	56	68-71/52
-(CH2)5-		H	59	48-50/0.7
Me	-(CH2)4-		68	80-2/8

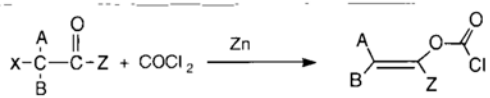
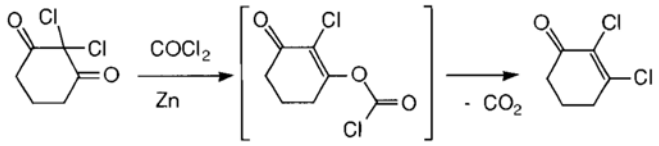


Table 3-18 : Preparation of substituted vinylic chloroformates from α-halo carbonyl cpds.

It is noteworthy that the reaction applied to 2,2-dichloro-1,3-cyclohexane dione leads to the previously unknown dichlorocyclohexenone through a clean decomposition of the intermediate enol chloroformate as depicted in scheme 116.



Scheme 116 : Preparation of 2,3-dichloro-2-cyclohexen-1-one.

The value of being able to include cyano and phosphonato groups among allowed Z substituents is of particular interest. Several model experiments were carried out to guarantee the efficiency of these enol chloroformates as acylating agents. Thus, many carbonates, carbamates, phosphonato esters have been obtained in good to excellent yields from reaction of the new chloroformates with alcohols or phenols, amines, trialkyl phosphites (Ref. 168).

Significantly, 1,2-dichlorovinyl carbonates and carbamates may have an interesting future as specialty monomers, for example as core materials in all-plastic optical fibers.

It is known that the optical absorption which is the major drawback of the classical plastic materials such as PMMA, is dominated by the higher harmonics of the carbon-hydrogen stretching vibrations. The value of polymers from 2,2-dichlorovinyl chloroformates derivatives has to do with their lower optical absorption as compared to standard plastics in the visible and near-infrared regions of the spectrum (0.6 to 1.5 μm). Some new 1,2-dichlorovinyl carbonates prepared by standard procedures in 90-95 % yield for that purpose are gathered in table 3-19 (Ref. 169).

Entry	Monomer	bp. (°C/mm)	N_D^{20}	$Density^{20}$
1	Cl2C=CH-OC(O)OC6F5	115/15	1.4663	1.658
2	Cl2C=CH-OC(O)OCD3	56/15	1.4590	1.420
3	Cl2C=CH-OC(O)OCH2CCl3	142/760	1.5005	1.604

Table 3-19 : New vinylic carbonates as monomers for optical fibers applications.

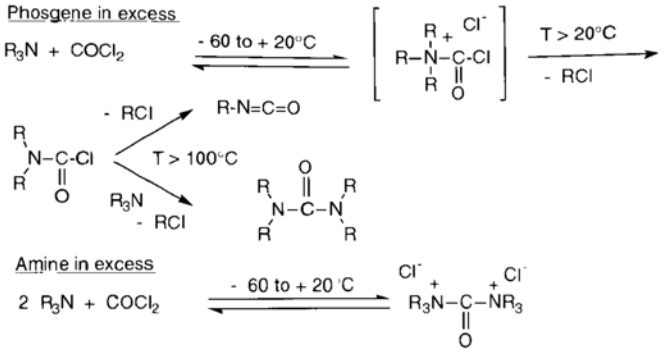
Their polymerization and copolymerization with vinyl acetate or vinyl methyl carbonate was also studied. Whatever the radical initiator used (AIBN, benzoyl peroxide, dicyclohexyl percarbonate) the monomers are too hindered to self-polymerize.

Monomer (1) and (2) polymerize with vinyl acetate to give alternating 1:1 copolymers with an unusual head to tail structure and T_g 95°C and 75-90°C respectively.

3-3 Reactions at a nitrogen center

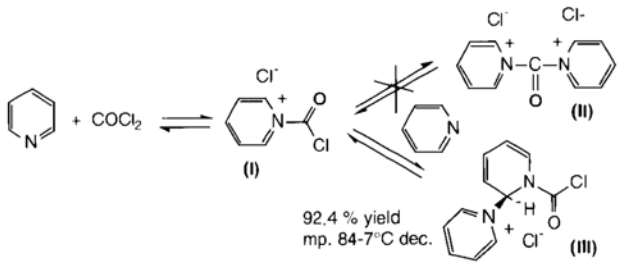
3-3-1 Highlights of some reactions of phosgene with amines, imines, oxazolines

Phosgene reacts with tertiary amines at low temperatures to afford unstable crystalline 1:1 or 1:2 phosgene-amine adducts. In the case of tertiary alkylamines, these complexes decompose with elimination of alkyl chlorides to give carbamoyl chlorides and then isocyanates as depicted in scheme 117.



Scheme 117 : Reaction of phosgene with tertiary alkyl amines.

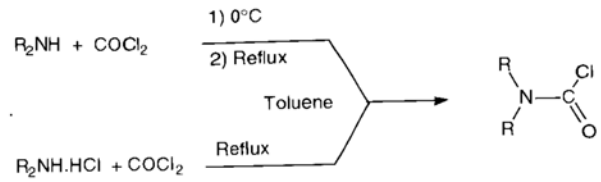
The originally proposed 1:2 structure (**II**) for the phosgene-pyridine adduct was deduced by analogy to the commonly observed 1:1 pyridinium salt (I) as shown in scheme 118. However, as a conclusion of a study of low temperature ^{13}C NMR and solid-state ^{13}C CP/MAS spectra, King Jr. and coworkers (Ref. 170) assigned a dihydropyridine-pyridinium (2-DHPP) structure (**III**) to the 1:2 salt.



Scheme 118 : Structure of the 1:2 phosgene-pyridine adduct.

Note that the adduct (**III**) which can be stored at least one year at room temperature and which reverts easily to its components in solution was proposed as a convenient (safe ?) storage system for phosgene under the term « phosgene - in - a - can » (Ref. 170).

The reaction of phosgene with secondary amines or their hydrochlorides is a well known useful route to carbamoyl chlorides as shown in scheme 119 (Ref. 171).

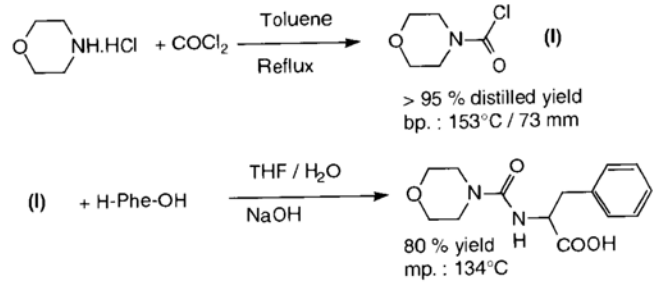


Scheme 119 : Preparation of carbamoyl chlorides from secondary amines.

Caution ! several carbamoyl chlorides are mutagenic and carcinogenic suspected agents. Low molecular weight products exhibit high toxicity levels. For example, dimethylcarbamoyl chloride is a powerful lachrymator and a confirmed carcinogen and mutagen. Extreme care should be taken to avoid inhalation or skin contact.

In order to develop various new applications of carbamoyl chlorides, we were interested in the synthesis of compounds containing functional groups such as ether oxides of tertiary amines. Thus, we studied and scaled up an improved process for the production of N-chlorocarbonyl morpholine based on a modification of literature data (Ref. 172) [Scheme 120].

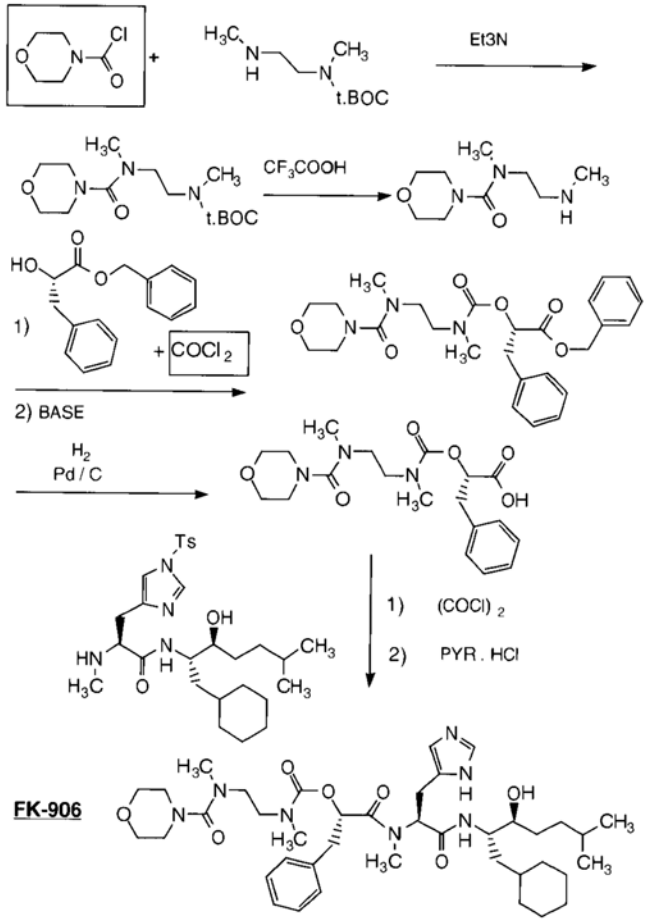
N-chlorocarbonyl morpholine has found some valuable applications to convert amino acids to N-morpholinocarbonyl amino acids, for example N-morpholinocarbonyl-(L)-phenylalanine [Scheme 120] for the preparation of renin-inhibiting peptides.



Scheme 120 : Preparation of N-chlorocarbonyl morpholine and condensation with L-phenylalanine.

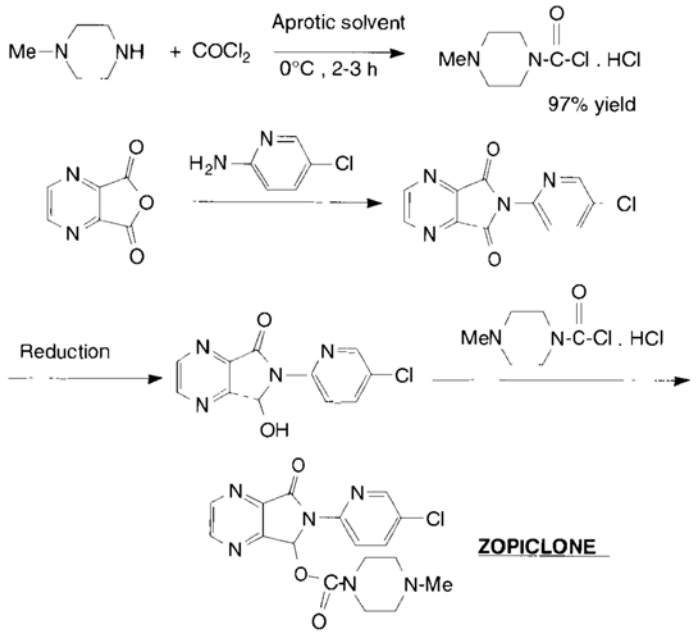
Such modified peptides were proposed for the treatment of hypertension, originally in a patent from Squibb (Ref. 173) and then in numerous patents from other companies.

In another example, N-chlorocarbonylmorpholine is used (besides several other phosgene derivatives) in a multi-step synthesis of FK-906, an antihypertensive renin inhibitor from Fujisawa in phase II in Japan, as depicted in scheme 121 (Ref. 174).



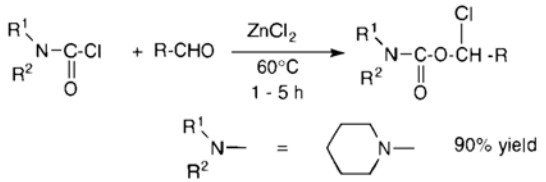
Scheme 121 : N-Chlorocarbonyl morpholine in the preparation of the hypertensive renin inhibitor FK-906.

Some work in our laboratories was also devoted to improve the preparation process of carbamoyl chlorides containing tertiary alkylamine functions,such as N-chlorocarbonyl, N'-methyl piperazine hydrochloride. This carbamoyl chloride is for example used in the synthesis of the sedative and hypnotic pharmaceutical Zopiclone as shown in scheme 122 (Ref. 175).



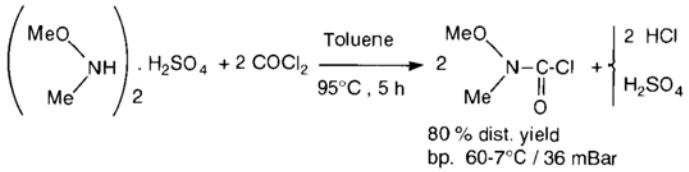
Scheme 122 : Synthesis of carbamoyl chloride derived from N-methyl piperazine and its use in the preparation of Zopiclone.

While studying the reactivity of carbamoyl chlorides, we found that they react easily with aldehydes in the presence of a Lewis acid as the catalyst to afford 1-chloroalkyl carbamates in good yield as shown in scheme 123 (Ref. 176). The chemical properties of 1-chloroalkyl carbamates which can be obtained by other routes are discussed in section 3-3-2.



Scheme 123 : Reaction of carbamoyl chlorides with aldehydes.

N-Methyl-N-methoxycarbamoyl chloride made by phosgenation of methoxy methyl amine hydrochloride is a very useful intermediate for the synthesis of N-methoxy ureas herbicides. However, we found the method to be unsatisfactory for the production on a large scale, because of rather low yields and also of technical difficulties. To overcome these problems, we developed a new procedure based on the reaction of phosgene with methoxy methyl amine sulfate as depicted in scheme 124. Sulfuric acid formed is easily removed by decantation (Ref. 177).



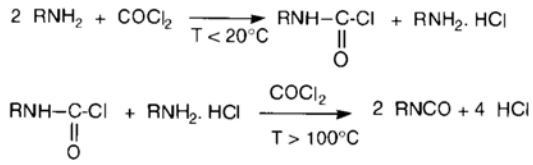
Scheme 124 : Preparation of methyl methoxy carbamoyl chloride from the sulfuric acid salt of methoxy methyl amine.

Among the more than 30 methods available for the preparation of isocyanates, phosgenation of primary amines or their hydrochlorides still remains the most popular. The method is employed on a large scale for the industrial production of mono and polyisocyantes.

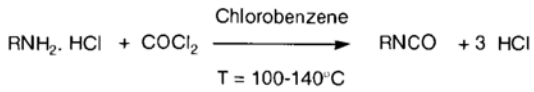
Four phosgenation procedures are used. The procedures without any acid scavenger are the methods commonly employed for the production of almost all commercial isocyanates.

A - Without acid scavenger

A_1 Two steps process



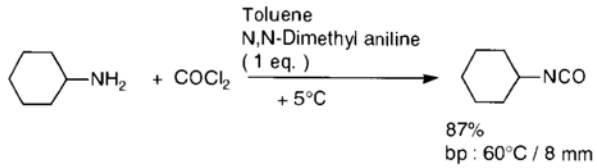
A_2 One step process



B - With acid scavenger

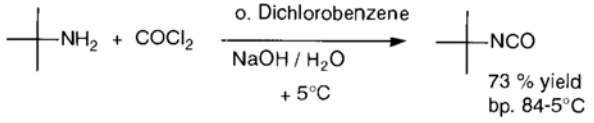
B_1 Anhydrous medium

Example :

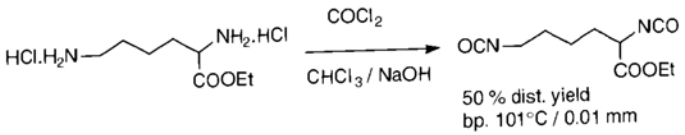


B_2 Biphasic process

Example :



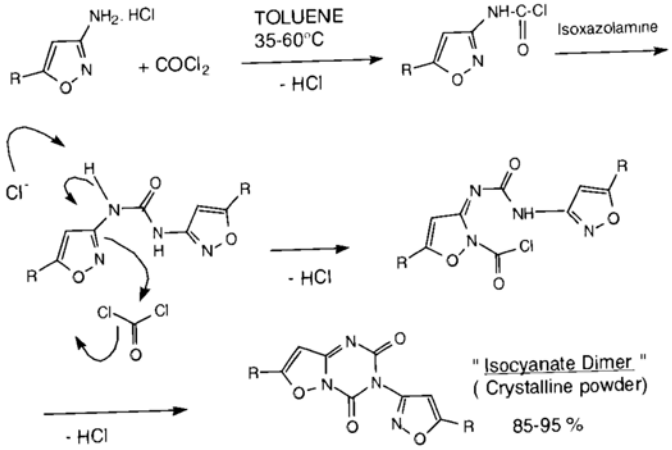
In the course of several studies devoted to the syntheses of unusual isocyanates, we developed an improved process for the preparation of the already known ethyl-2,6-diisocyanato hexanoate by phogenation of L-Lysine ethyl ester as depicted in scheme 125 (Ref. 178).



Scheme 125 : Phosgenation of L-Lysine ethyl ester to the corresponding isocyanate.

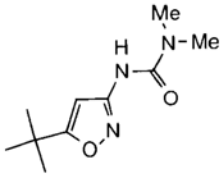
This diisocyanate is especially useful in the preparation of biocompatible polyurethanes or polyureas.

In another example, surprisingly, we found that the phosgenation of a substituted isoxazolamine hydrochloride doesn't afford the expected free isocyanate but a peculiar dimer according to the mechanism depicted on scheme 126 (Ref. 179).



Scheme 126 : A peculiar isocyanate dimer from phosgenation of substituted isoxazolamines.

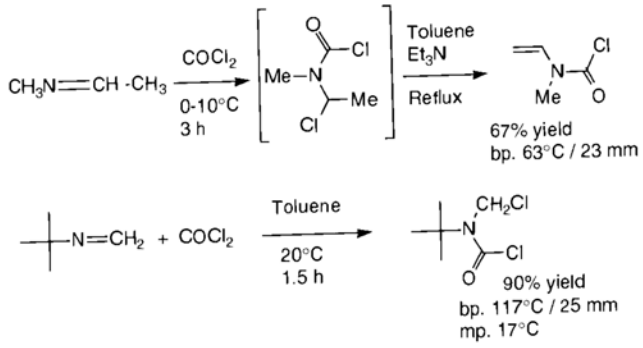
This dimer reacts as two molecules of free 5- alkylisoxazolyl-3-isocyanate with secondary amines or with alcohols to give the corresponding ureas or carbamates useful as agrochemicals or fine chemicals intermediates. For example, 3-amino-5-tert-butyl isoxazole is a key intermediate for 3-(5-tert-butylisoxazolyl)-1,1-dimethyl urea (common name : Isouron) which is useful as a herbicide for sugar cane and other crops (Ref. 180) [Scheme 127].



Scheme 127 : Isouron.

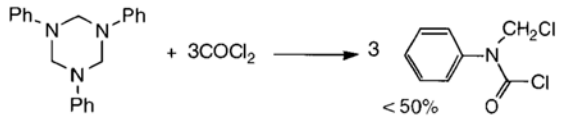
The reaction of phosgene with CH-acid imines followed by dehydrochloridation in the presence of triethylamine affords N-substituted vinyl carbamoyl chlorides in good yields. For example, N-methyl-N-vinyl carbamoyl chloride was prepared in 67% distilled yield through phosgenation of ethylidene methyl amine as depicted in scheme 128 (Ref. 181).

If there is no hydrogen atom available on the β-carbon, for example in the case of the Schiff's base of tert-butyl amine and formaldehyde, N-(1-chloralkyl) carbamoyl chloride are obtained in excellent yields [Scheme 128].



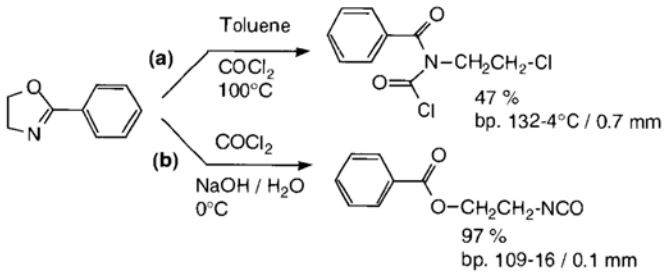
Scheme 128 : Reaction of phosgene with Schiff's bases.

It is noteworhy that N-(1-chloroalkyl) carbamoylchlorides are valuable starting materials for the synthesis of pesticides. We have carried out some trials based on literature data (Ref. 182) in order to synthesize N-phenyl-N-chloromethyl carbamoyl chloride by phosgenation of 1,3,5-triphenylhexahydro-s-triazine as shown in scheme 129. However, all the efforts to appreciably improve the described yield (24 %) failed, the best yield obtained being around 50%.



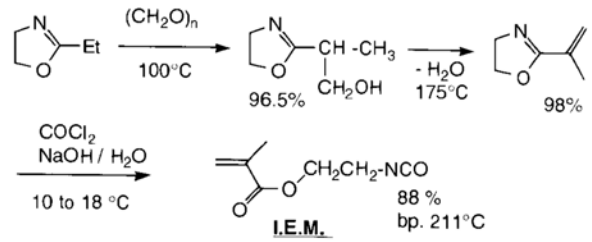
Scheme 129 : Attempt to prepare N-pheny-N-chloromethyl carbamoyl chloride in good yield.

Phosgene reacts also readily with substituted oxazolines, for example 2-phenyloxazoline, to afford depending on the conditions either N-(2-chloroethyl–N-chlorocarbonyl amides or isocyanato ethyl esters as depicted on scheme 130 (Ref. 183, 184).



Scheme 130 : The two pathways for the phosgenation of phenyl oxazoline.

Process (b) in scheme 130 was applied to the industrial preparation of isocyanatoethyl methacrylate (I.E.M.) as depicted in scheme 131 (Ref. 185).



Scheme 131 : Industrial process for the preparation of I.E.M.

I.E.M. is an interesting monomer which combines to well-known functionalities in on molecule. Unfortunately, I.E.M. exhibits a very high level of toxicity. It is recommended that the average eight-hour working environment not exceed 0.025 ppm.

3-3-2 Reactions of 1-chloroethyl chloroformates with amines : synthesis and useful applications of 1-chloroalkyl carbamates

1-Chloroalkyl chloroformates react easily with primary and secondary amines under the same standard conditions used with classical chloroformates (Ref. 21).

The process is illustrated in the conversion of piperidine to N(1-chloroethyloxycarbonyl) piperidine. Piperidine (2.3 eq.) in ether was added to a cooled solution of 1-chloroethyl chloroformate in ether. The piperidine hydrochloride was filtered off and the expected carbamate was isolated from the filtrate in 77% yield (Ref. 127).

Some examples of representative carbamates obtained by this method are gathered in table 3-20.

R	R^1	R^2	Yield (%)	bp. (°C/mm)	Ref.
H	H	Me	68	83/3	186
H	OH	3-ClC6H4	76	mp. 55-7	187
Me	(CH2)5		77	70-2/0.4	127
Et	CH2CH2-O-CH2CH2		84	95-7/0.9	127
i-Pr	Me	Cyclohexyl	92	111-13/0.6	127
Me			73	80/0.5	188

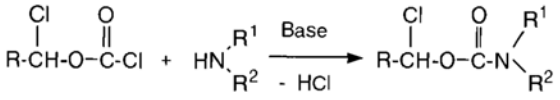
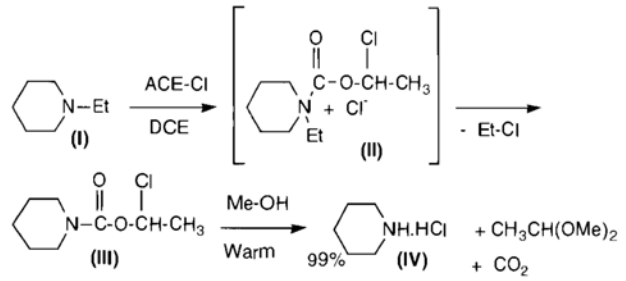


Table 3-20 : Preparation of 1-chloroalkyl carbamates by reaction of 1-chloroalkyl chloroformates with primary and secondary amines.

We discovered that 1-chloroethyl chloroformate is undoubtedly the best reagent for the selective N-dealkylation of tertiary amines (Ref. 189).

Thus, in the initial test system (N-deethylation of N-ethylpiperidine), the use of α-chloroethyl chloroformate (acronym : ACE-Cl) surpassed the yield obtained with vinyl chloroformate : (**I**) -> (**IV**), 99% vs 90% as shown in scheme 132 (Ref. 189).

Besides its interest for the synthesis of 1-chloroethyl carbamates from tertiary amines and the N-dealkylation of tertiary amines, this result is also quite unexpected. With most chloroformates other than vinyl chloroformate (VOC-Cl), for example : EtOCOCl, Cl_3CH_2OCOCl, $Ph-CH_2OCOCl$, the cationic intermediate analogous to (**II**) fragments to alkyl chloride, carbon dioxide and (**I**).



Scheme 132 : N-Deethylation of N-ethyl piperidine via N-(1-chloroethyl-car

Thus, only trace yields of alkylcarbamates are obtained and the tertiary amine primarily catalyzes the decarboxylation of the chloroformate. Phenyl chloroformate itself previously recommended for N-dealkylation (Ref. 190) afforded PhOC(=O)-piperidine in only 34% yield.

The high-yield dealkylation with ACE-Cl is therefore very surprising. Presumably, the $-CHCl-CH_3$ unit is too hindered to undergo competitive SN_2 attack by Cl^- and the 1-chloroethyl cation generated by an alternative SN_1 (E_1) cleavage must be too unstable. Because the substituent is electron withdrawing, ACE-Cl is more reactive toward tertiary amines than simple alkyl chloroformates.

Olofson and Martz have thoroughly studied the scope of the new N-dealkylation process with ACE-Cl (Ref. 68-191) and shown that the selectivities follow the same order as those of VOC-Cl : benzyl; allyl; t.butyl >> s.alkyl ≥ n. alkyl >> piperidine ring scission. In its reactivity, ACE-Cl parallels VOC-Cl with the advantage that the conditions required for ACE removal are much milder thus expanding the functionalities allowed in the amine to be dealkylated.

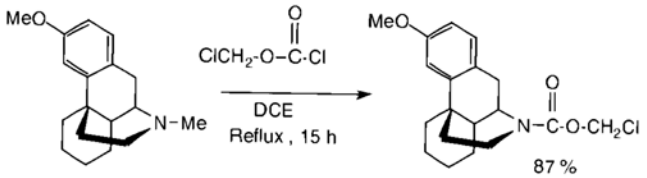
Even N-dealkylation of aromatic amines occurs cleanly with ACE-Cl as it is illustrated in a strigent test by the conversion of N,N-diethyl aniline to 1-chloroethyl N-methyl-N-phenyl carbamate in 87 % yield (Ref. 68). Caubère and Bachelet used this methodology while operating without a solvent for the demethylations as well as for the deethylations of dialkylamino benzofurans in good yields (Ref. 192).

Olofson and Martz have developed numerous applications of ACE-Cl to the N-dealkylation of significant tertiary amines, especially in the field of analgesics and narcotic antagonists alkaloids, for example in a brilliant synthesis of Nalbuphine from Oxycodone in 69 % overall yield (Ref. 191). The scope and limitations of ACE-Cl as a new reagent for the selective, high-yield N-dealkylation of tertiary amines will be examined in section 4-5 of vol. 2.

Chloromethyl chloroformate reacts also selectively with tertiary alkyl amines to afford O-chloromethyl N,N-dialkyl carbamates in yields ranging from 83 to 99 % (Ref. 193).

For example, N-methylpiperidine was refluxed with 1.5 eq. of chloromethyl chloroformate in 1,2-dichloromethane (DCE) for 30 min.. After vacuum evaporation of the volatiles, the distilled O-chloromethyl carbamate was isolated in 97 % yield.

To test the scope of the reaction, the over-the-counter antitussive Dextromethorphan was N-demethylated to the morphinan in 87 % yield as depicted in scheme 133.



Scheme 133 : N-Demethylation of Dextromethorphan by chloromethyl chloroformate.

Some examples of 1-chloroalkyl carbamates obtained through N-dealkylation of tertiary amines are gathered in table 3-21 (Ref. 127, 193).

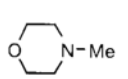
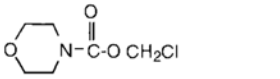
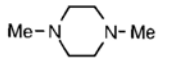
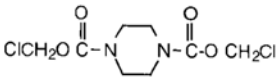
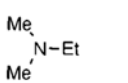
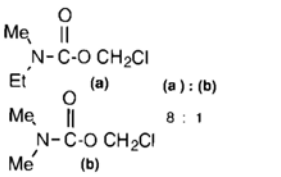
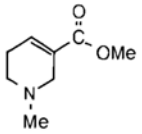
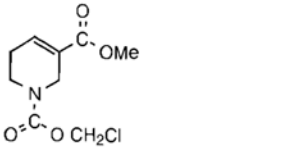
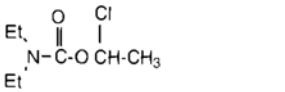
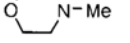
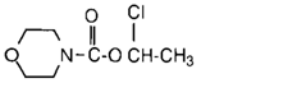
R	Tertiary amine	Carbamate	yield (%)
H			96
H			99
H		 (a) : (b) = 8 : 1	96
H			83
Me	Et_3N		96
Me			84

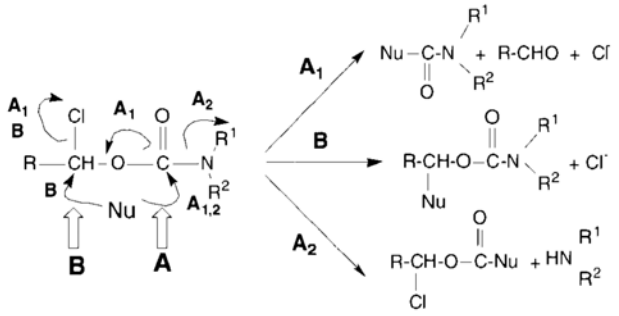
Table 3-21 : Preparation of 1-chloroalkyl carbamates by reaction of R-CHCl-OC(=O)Cl with tertiary amines.

The value of 1-chloroethylcarbamates as starting materials for the synthesis of vinyl carbamates has been already pointed out in section 3-2-2-4 of this volume.

As already discussed in section 3-2-2-3, 1-chloroalkyl carbamates present two electrophilic centers which may be attacked by nucleophiles following differents pathways as shown in scheme 134.

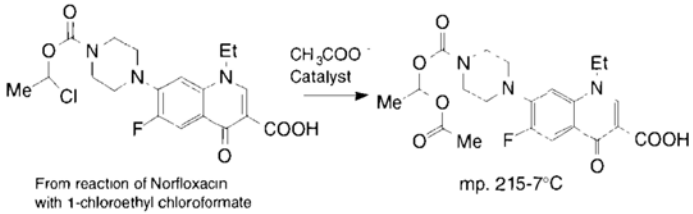
Similar to he case of reaction with 1-chloroalkyl carbonates studied in section 3-2-2-3, carboxylates anions react with 1-chloroalkyl carbamates to give alkylation derivatives

through a **B** attack mechanism. This reaction was widely used in numerous patents on prodrugs.



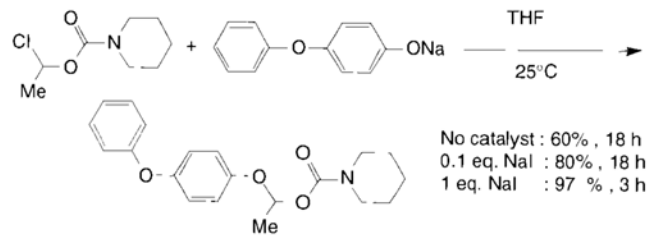
Scheme 134 : Possible types of nucleophilic attacks to 1-chloroalkyl carbamates.

For example this concept was applied to the synthesis of novel (acyloxyalkoxy) carbonyl bioreversible moieties for primary as well as secondary amines functions in drugs as illustrated with the case of a prodrug from the antibacterial Norfloxacin in scheme 135 (Ref. 194).



Scheme 135 : Preparation of a prodrug derived from Norfloxacin.

Since the -NR^1R^2 group makes center **A** and **B** both much less harder than does the OR group, we expect some differences between the reactivities of 1-chloroalkyl carbamates and 1-chloroalkyl carbonates. For example the reaction of the hard-soft borderline nucleophiles phenoxide type anions with 1-chloroalkyl-N,N-dilakyl carbamates proceeds selectively through **B** mechanism to give exclusively alkylation instead of acylation as shown in scheme 136.



Scheme 136 : Reaction of N (1-chloroethyloxycarbonyl) piperidine with sodium 4-phenoxyphenoxide.

Some results obtained in our laboratories for pesticides screening purposes are gathered in table 3-22.

R	-NR^1R^2	Ar-O	Time (h)	Yield (%)
Me	-NMe2	Ph-O-Ph-O	4	90
Me	-NMe2	p.CF3-Ph-O-Ph-O	4	76
Me	Morpholino	Ph-O-Ph-O	4	90
Me	Morpholino	p.CF3-Ph-O-Ph-O	3	83
CH2=CH-	-NEt2	Ph-OPh-O	1	82

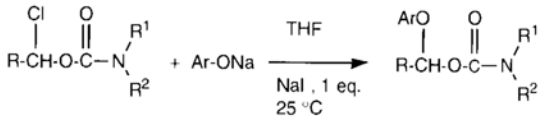
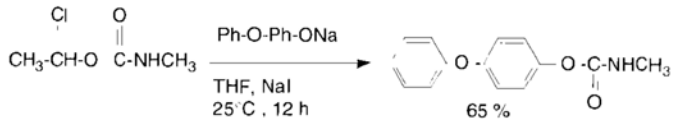


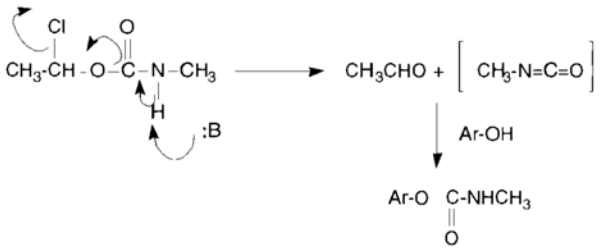
Table 3-22 : Reaction of 1-chloroalkyl carbamates with sodium phenoxides.

In opposition to the preceding case, the reaction of phenoxides anions with 1-chloroalkyl-N-monoalkyl carbamates leads to acylation instead of alkylation as shown in scheme 137.



Scheme 137 : Reaction of sodium phenoxy phenoxide with 1-chloroethyl-N-methyl carbamate.

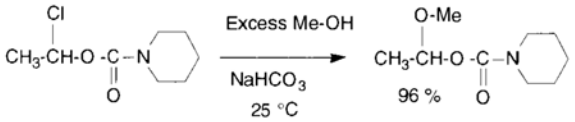
However, it is not certain whether the isocyanate or the carbamate is the acylating agent in such reaction. In fact, as depicted in scheme 138, it is possible that this reaction could proceed through a mechanism involving the transient formation of methyl isocyanate rather than through the normal addition (A_1) directly to the carbonyl group followed by loss of acetaldehyde.



Scheme 138 : Possible mechanism of the reaction of 1-chloroethyl-N-methyl carbamate with phenols.

The study of the reaction of 1-chloroethyl-N-methyl carbamate with phenols was undertaken in the hope that it might replace the noxious methyl isocyanate (M.I.C) in the preparation of insecticidal N-methyl carbamates.

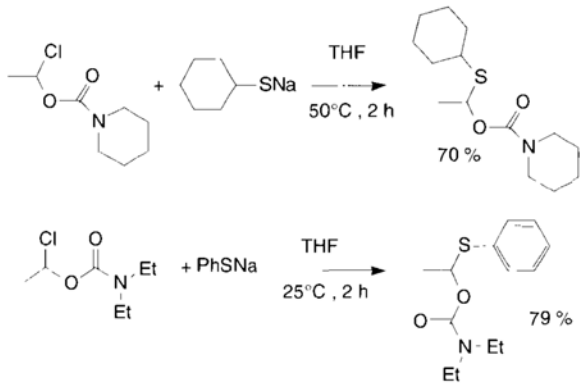
Surprisingly, we found that the reaction of an alcohol with 1-chloroethyl-N,N-dialkylcarbamates can proceed through **B** mechanism to give alkylation rather than acylation (Ref. 195). This result appears to be a violation of the HSAB theory. In a typical example, N-(1-chloroethyloxycarbonyl) piperidine was added to a stirred mixture of sodium hydrocarbonate and methanol at 25°C. The reaction was instantaneous. Solids were removed by filtration, excess alcohol was then distilled off and the resulting product was isolated by flash chromatography in 96% yield [Scheme 139].



Scheme 139 : Synthesis of N-(1-methoxyethyloxycarbonyl) piperidine.

More than twenty 1-alkoxyethyl-N,N-dialkyl carbamates has been prepared by this methodology which should have some interest in the design of new prodrugs.

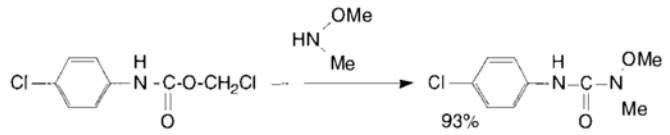
The same kind of reactions occurs with thiols and thiophenols as shown in scheme 140.



Scheme 140 : Reaction of thiols with 1-chloroethyl-N,N-dialkyl carbamates.

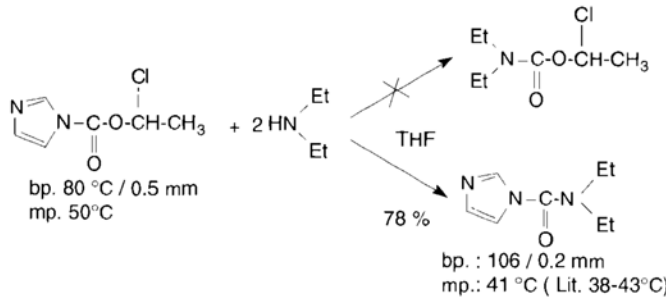
According to the HSAB theory, secondary and primary amines react as hard nucleophiles through A_1 attack mechanism with 1-chloroalkyl carbamates to affords ureas. However, the reaction is slower and less easy than the reaction of amines with 1-chloroalkyl carbonates and strong nucleophilic amines are generally required to reach good yields.

Thus, the reaction has some value for the synthesis of known ureas derived from methoxymethyl amine such as the herbicide Linuron [see scheme 141] (Ref. 196).



Scheme 141 : Preparation of the herbicide Linuron from chloromethyl-N(4-chlorophenyl) carbamate.

The reaction of secondary amines with 1-(1-chloroethyloxycarbonyl) imidazole demonstrates the powerful nucleofugacity (leaving group efficiency) of the chloroethoxide anion as shown in scheme 142 (Ref. 197).



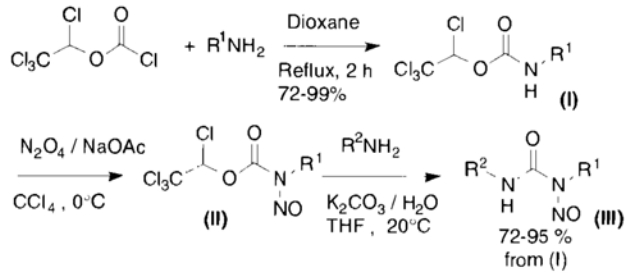
Scheme 142 : Reaction of 1(1-chloroethyloxycarbonyl) imidazole with diethylamine.

In the course of our studies dedicated to the reactivity of 1-chloroalkyl carbamates toward primary and secondary amines, we discovered that the easy to prepare 1,2,2,2-tetrachloroethyl carbamates are valuable versatile intermediates for the synthesis of N-nitrosoureas (Ref. 198).

N-(2-Chloroethyl)-N-nitroso ureas are an active class of antitumor agents, which are usually obtained by nitrosation of the previously prepared urea. Because of difficulties in achieving regioselective nitrosation, several authors have suggested alternatives processes. Unfortunately, the starting materials proposed are either unstable such as carbamoyl azides (Ref. 199) or extremely toxic such as the 2-chloroethyl isocyanate (Ref. 200).

Although we have noticed that 1,2,2,2-tetrachloroethyl carbamates (I) do react with amines to give ureas in modest yield, we thought that when the carbamates (I) are nitrosated to (II), the reactivity of the carbonyl should be greatly enhanced and good yiels of N-nitrosoureas (III) would be obtained. As depicted in scheme 143, the results are quite good, the only drawback being that some minor impurities may arise from the reaction of the amino compounds with the release chloral (Ref. 201).

The carbamates (I) are easily prepared from the required amine and 1,2,2,2-tetrachloroethyl chloroformate just by refluxing in THF or dioxane without any acid scavenger.The reaction mixture is easily freed from hydrochloric acid by heating and evaporation of the solvent generally gives (I) as pure crystals. Table 3-23 gives some examples of carbamates obtained by this method.



Scheme 143 : Novel preparation of N-nitrosoureas.

Entry	R^1	Yield (%)	mp. (°C) or bp (°C/mbar)
1	Cl-CH2CH2-	96	81-2
2	F-CH2CH2-	72	115-20/7
3	(L)-HO2C-CH2CH(COOH)-	99	131-3

Table 3-23 : 1,2,2,2-tetrachloroethyl carbamates (I) prepared.

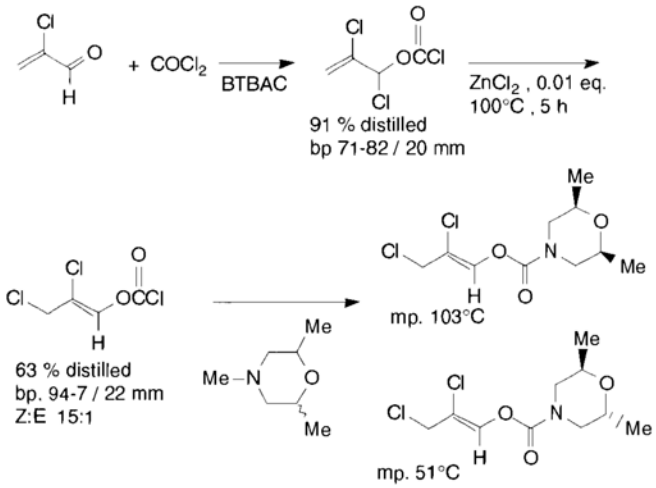
The 1,2,2,2-tetrachloroethyl carbamates (I) are then nitrosated with nitrogen tetroxide by a known procedure. The intermediates nitrosocarbamates (II) are obtained as oils and used as are in the next step to afford the expected N-nitrosoureas (III). For example, the antitumor drug Lomustine was prepared in 87 % yield from the carbamate [(I), entry 1of table 3-23]. Some results obtained by this method are gathered in table 3-24.

Entry	R^1	R^2	Yield from (I) (%)	mp. (°C)
1	Cl-CH2CH2-	c-C6H11-	87	87-8
2	F-CH2CH2-	c-C6H11-	72	44-5
3	Cl-CH2CH2-	C6H5-	75	78-80
4	Cl-CH2CH2-	HOCH2CH2-	95	oil
5	ClCH2CH2-	Et-OOC-CH2-	88	oil

*Table 3-24 : N-Nitrosoureas (**III**) prepared (see scheme 143).*

Some other interesting miscellaneous chemistry of chloroalkyl carbamates has been also explored. Thus, as already mentioned, acrolein and its congeners H_2C=CR-CHO are easily converted to the chloroformates H_2C=CRCH(Cl)OC(=O)Cl which rearrange in the presence of $ZnCl_2$ to the allylic isomer $ClCH_2$-CR=CHOC(=O)Cl. We prepared some carbamates derived from these chloroformates for testing as agrochemicals.

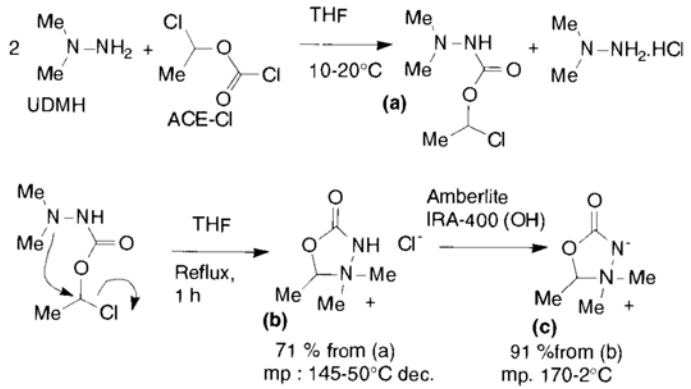
One example using 2-chloroacrolein as starting material is given in scheme 144 (Ref. 202). Industrially, 2-chloroacrolein is easily made in up to 97% yield by adding chlorine to aqueous acrolein followed by steam distillation of the resulting mixture.



Scheme 144 : Example of 3-chloroalkenyl carbamate synthesis for testing.

In continuation of our studies on the synthesis and reactivity of 1-chloroalkyl carbamates, and because our group was involved in the chemistry of 1,1-dimethyl hydrazine (UDMH), we have examined the reactions of 1-chloroalkyl chloroformates with unsymmetrical dialkyl hydrazines. During this work, we discovered unexpectedly a new efficient generator of the heretofore difficult to prepare N,N-dimethylamino isocyanate (Ref. 203). Thus, five membered ring carbalkoxy aminimides were prepared from UDMH and 1-chloroalkyl chloroformates in three steps [Scheme 145]. Upon heating, these aminimides give high yields of Me_2N-N=C=O. This unusual isocyanate dimerizes or can be trapped in the presence of a nucleophile.

In a preferred example, when UDMH in anhydrous THF was added to a solution of 1-chloroethyl chloroformate in THF at 10-20°C, the intermediate carbazate (**a**) was formed. After filtration to remove the UDMH hydrochloride, we accomplished a cyclisation to (**b**) just by refluxing the THF solution for 1 h.. The resulting hygroscopic salt (**b**) precipited immediately in 71 % overall yield. In solid form, (**b**) is stable undefinitely at room temperature. The cyclic aminimide (**c**) was then easily prepared from (**b**) by treatment with a resin supported base in high yield. The three steps of the synthesis are depicted in scheme 145.

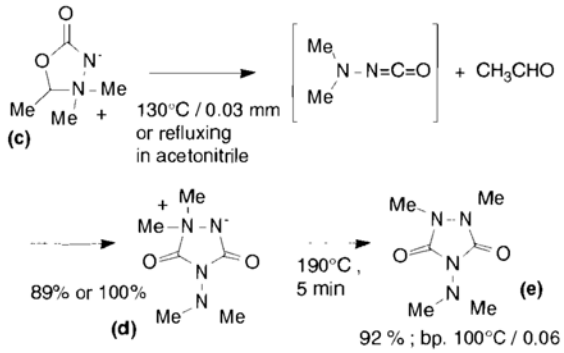


Scheme 145 : New cyclic aminimide from UDMH and ACE-Cl.

Carbalkoxy aminimides have received little attention in the literature and to our knowledge, cyclic carbalkoxy aminimides have never before been synthesized.

Dialkylamino isocyanates are known transient intermediates and, in the absence of other reagents, have been shown to dimerize. When the cyclic aminimide (**c**) was heated at 130°C under vacuum (0.3 mm) for 3 h, (**d**) was obtained in 89% yield. At higher temperature (**d**) was formed but rearranged to (**e**) as depicted in scheme 146.

The chemistry of aminimides has been reviewed elsewhere (Ref. 204, 205) and the chemistry of dimethyl amino isocyanate, prepared in the form of dimer (**d**) through a phosphoramide synthesis, studied (206).



Scheme 146 : Thermal decomposition of the cyclic carbalkoxy aminide (c) to give N,N-dimethyl amino isocyanate.

Our method represents a simple, rapid and high yield preparation of N,N-dimethylamino isocyanate. This interesting intermediate has been the subject of several publications and is useful for the synthesis of a wide variety of heterocycles, carbazates, and other molecules containing a hydrazine group.

We have prepared several carbazates and semicarbazides just by heating the cyclic carbalkoxyaminimide (**c**) and the nucleophile (:NuH) for 1 h in refluxing 1,2-dichloroethane. Some examples are given in table 3-25.

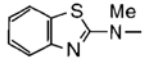
Entry	:Nu-	Nu-CO-NH-NMe_2 Yield (%)
1	Et-O-	87
2	Ph-CH2-N(Me)-	89
3	Me_2N-C(=O)-C(S-Me)=N-O-	95
4		74
5	EtO2C-CH2-NH-	76

Table 3-25 : Preparation of UDMH derivatives through reaction of cyclic carbalkoxy aminimide (c) with a nucleophile :Nu-H.

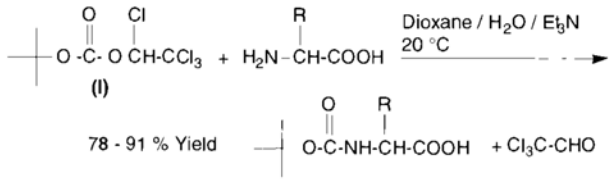
3-3-3 1-Chloroalkyl carbonates as acylating agents for the synthesis of carbamates and nocarbamates

The reaction of secondary and primary amines with 1-chloroalkyl carbonates to afford carbamates in high yield has been already tackled in term of mechanism in section 3-2-2-3 (Ref. 64, 66, 105, 106, 107).

At the beginning, while studying the synthetic potential of 1-chloroethyl ethyl carbonate, we found that it readily reacts with amines at the carbonyl function to give the corresponding ethyl carbamates in good to excellent yields. We thought therefore that 1,2,2,2-tetrachloroethyl tert-butyl carbonate (**I**) (code number CN 916) should be a valuable reagent for the Boc-protection of amino acids [Scheme 147] (Ref. 66, 207).

(**I**) was easily prepared in good yield from 1,2,2,2-tetrachloroethyl chloroformate and tert-butanol by a simple procedure. In a typical example, pyridine (1 eq.) was slowly added to a cooled (0°C) solution of t.butyl alcohol and 1,2,2,2-tetrachloroethyl chloroformate (1 eq. of each). After stirring for 4 h at 20°C, washing with water and evaporation of the solvent and recrystallization from hexane, (**I**) was obtained in 87% yield (mp. 70°C).

We discovered that (I) satisfactorily reacts with various amino acids in standard conditions. The reaction mixture is freed from excess reagent and byproducts by extraction with ether and the Boc-amino acids are readily obtained by conventional extraction and crystallisation procedures according to scheme 147.



Scheme 147 : tert-Butoxycarbonylation of amino acids by 1,2,2,2-tetrachloroethyl - tert-butyl carbonate (1).

Reagent (I) proved to be especially useful in the case of unprotected hydroxy amino acids as examplified by the synthesis of Boc-L-Serine and Boc-L-Tyrosine [See table 3-26].

The 1-chloroethyl congener of (I), the 1-chloroethyl-tert-butyl carbonate (II) which is a medium boiling liquid (bp. 88°C/20 mm), was found to give unsatisfactory results, because it is much less reactive than (I), and also because of the formation of acetaldehyde and its consequent reaction with the starting amino compound.

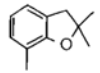
Some examples of preparation of N-Boc-amino acids with (I) are shown in table 3-26.

Amino acid	Yield of N-Boc-AA (%)	Melting point (°C)	$[\alpha]^{20}D$
Gly	86	85-8	
L-Ala	90	80-1	-24, c 2.1 AcOH
L-Phe	79	85-87	+28, c 1.5 EtOH
L-Pro	91	132-3	-60, c 2.0 AcOH
L-Tyr	82	206 (DCHA salt)	+32, c 1.8 MeOH
L-Asp	60	117-9	-5, c 1.0 MeOH
L-Ser	78	139-40	+8, c 2.8 MeOH

Table 3-26 : Preparation of N-Boc-amino acids using 1,2,2,2-tetrachloroethyl-tert-butyl carbonate (I).

The crystalline 1,2,2,2-tetrachloroethyl fluorenyl methyl carbonate obtained in 98% yield (mp. 98-100°C) from 1,2,2,2-tetraethyl chloroformate and fluorene methanol proved to be suitable for the preparation of Fmoc-amino acids in good to excellent yields (Ref. 64).

The reaction was also performed with various types of amines using different kinds of 1-chloroalkyl carbonates (Ref. 64) and was proved to be quite general except with weakly nucleophilic amines. Some examples of carbamates obtained by the reaction of 1-chloroethyl carbonates with primary and secondary amines are given in table 3-27.

Entry	R^1	R^2	R^3	Yield (%)	mp (°C) bp. (°C/mm)
1	Et	-(CH2)5-		88	bp 95/18
2	Ph-CH2-	H	Ph-CH2-	84	bp 175/0.1
3	Ph-CH2-	H	HO-CH2CH2-	74	bp 170/0.5 mp. 62-3
4		H	Me	79	mp. 148
5	Ph-CH2	-(CH2)2-O-(CH2)2-		84	bp. 140/1 mp. 49.5

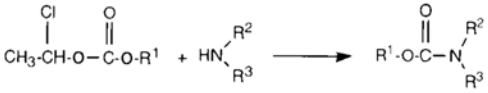
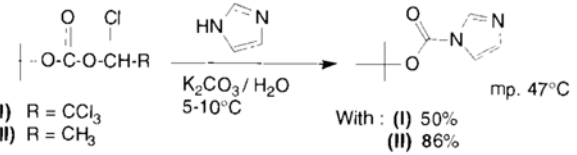


Table 3-27 : Carbamates prepared from 1-chloroethyl carbonates.

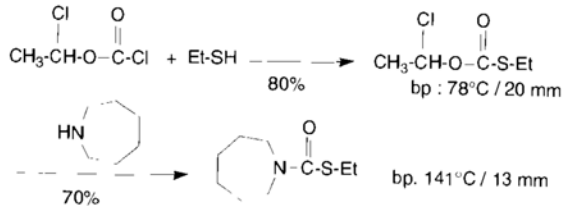
Imidazole also reacts with 1,2,2,2-tetrachloroethyl-tert-butyl carbonate (I) or with 1-chloroethyl-tert-butyl carbonate (II) to give its tert-butyloxycarbonyl derivative in 50 and 86 % yield respectively as shown in scheme 148.



Scheme 148 : Preparation of Boc-imidazole.

The application of the above method to the syntheses of insecticides carbamates Carbofuran (entry 4, table 3-27) and Aldicarbe was briefly studied. Thus, Carbofuran was readily obtained in 79% yield from 1-chloroethyl benzofuranyl carbonate which was itself obtained in 89% yield from the corresponding hydroxy benzofuran.

The method was also successfully applied to the reaction of 1-chloroethyl-S-ethyl thiocarbonate to give thiocarbamates, for example the herbicide Molinate as depicted in scheme 149.

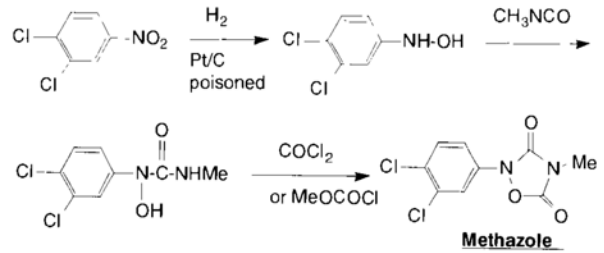


Scheme 149 : New preparation of the herbicide Molinate.

3-3-4 Reaction of phosgene and its derivatives with carbamates, ureas and amides

As part of our program concerning the study of safe alternatives to the handle of the extremely hazardous methyl isocyanate (MIC), we were interested in the development of new routes to 3,5-dioxo-1,2,3-oxadiazolidine derivatives which are valuable as pharmaceuticals and agrochemicals.

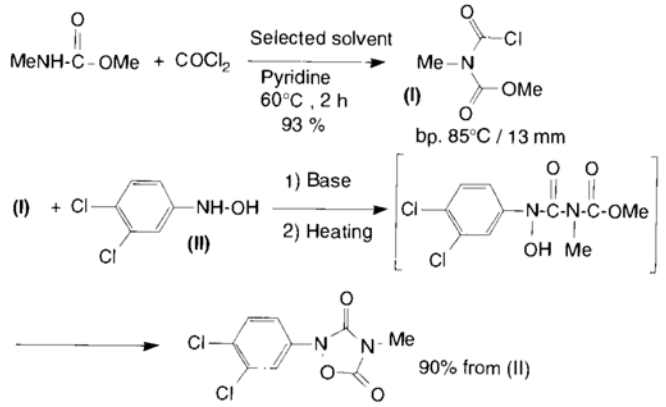
In a typical example, we developed a new synthetic strategy that does not use MIC for the preparation of the herbicide Methazole. Methazole was classically made through the reaction of MIC with 3,4-dichlorophenyl hydroxylamine followed by treatment with methyl chloroformate and cyclisation as shown in scheme 150.



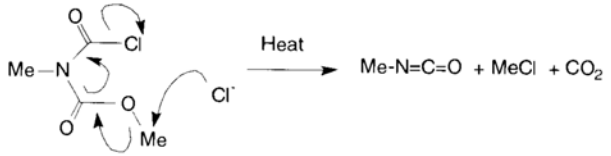
Scheme 150 : Classical synthesis of the herbicide Methazole.

In our laboratories, the reaction of phosgene with methyl N-methyl carbamate by an improvement of the procedure described in the literature (Ref. 208) afforded methyl N-chlorocarbonyl-N-methyl carbamate (I) in high yield. The one-pot condensation of the intermediate (I) led to Methazole in excellent yield as depicted in scheme 151.

For safety reasons, we thoroughly studied the thermal stability of the intermediate (I). We found that it decomposes to methyl isocyanate on heating, very slowly when pure, more rapidly and quantitatively in presence of a nucleophile, according to the mechanism depicted in scheme 152.

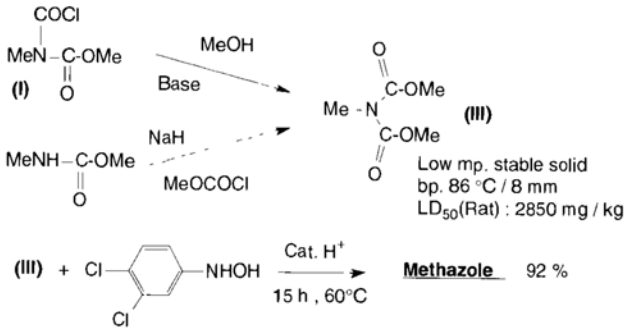


Scheme 151 : Preparation of Methazole without methyl isocyanate.



Scheme 152 : Thermal instability of methyl-N-chlorocarbonyl-N-methyl carbamate (I).

Moreover, (**I**) exhibits a high level of toxicity. In order to overcome these problems, we investigated other routes and discovered a novel and safer route to Methazole, starting from the interesting intermediate (**III**) as shown in scheme 153.

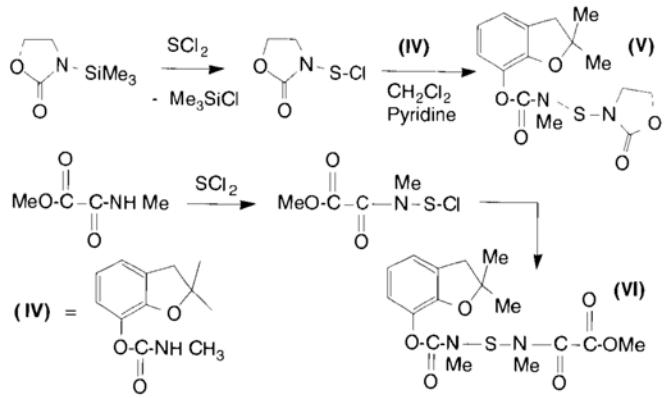


Scheme 153 : Novel and safe preparation of Methazole.

Also, carbamates can be modified by other acylating agents than phosgene and chloroformates.

In the course of our attempts dedicated to the search of new pesticides, we were interested in the design of proinsecticides, especially procarbamates which are less toxic to mammalians than the parent carbamates. N-Acyl-N-methyl or N-sulfenyl-N-methyl carbamates derived from Carbofuran or Aldicarbe are quite effective insecticides and are often equal to superior to their parent compound against insects.

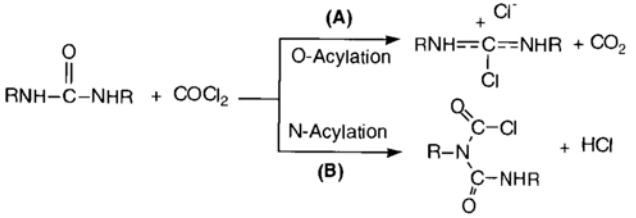
In collaboration with SIPCAM (Italia) we studied the synthesis and activity as insecticides of two new types of Carbofuran derivatives (**V**) et (**VI**) depicted in scheme 154 (Ref. 209, 210).



Scheme 154 : Syntheses of new sulfenyl Carbofurans.

The reaction of phosgene with substituted ureas is well known. Phosgene reacts with tetrasubstituted ureas as a chlorinating agent to afford chloroformamidinium chlorides in high yields. This topic will be discussed in volume 2.

In the case of N,N'-dialkyl ureas, phosgene is attacked by both oxygen and nitrogen atoms to give a mixture of chloroformamidinium chlorides (**A**) (O-acylation of the ureas) and allophanoyl chlorides (**B**) (N-acylation) as shown in scheme 155 (Ref. 211).

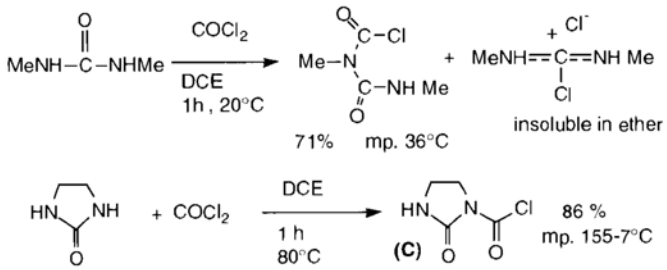


Scheme 155 : Phosgenation pathways of N,N'-dialkyl ureas.

The distribution of O-acylation and N-acylation can be slightly controlled by the reaction conditions, but structural features of the N,N'-dialkyl ureas seem to be the dominant factors.

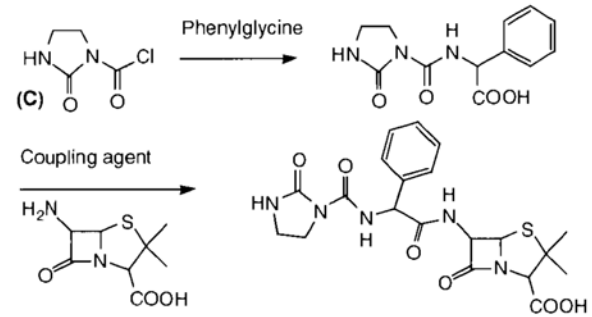
Acylation reaction which affords chloroformamidinium chloride is of great interest for the commercial synthesis of carbodiimides, especially dicyclohexylcarbodiimide (see volume 2).

In the case of low molecular weight subtituents, the separation of products (**A**) and (**B**) is very easy because of the insolubility of the salt (**A**) in organic solvents. Scheme 156 presents two examples of phosgenation of N,N'-disubstituted ureas.



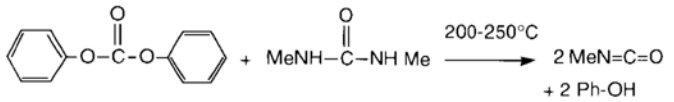
Scheme 156 : Examples of phosgenation of N,N'-disubstituted ureas.

N-Chlorocarbonyl-2-imidazolidone (**C**) is for instance used in the preparation of pharmaceuticals such as the antibiotic Azlocillin [Scheme 157].



Scheme 157 : Preparation of the antibiotic Azlocillin.

In order to produce methyl isocyanate in good safety's conditions, Bayer A.-G. has developed an industrial process based on the reaction of diphenyl carbonate with N,N'-dimethyl urea at high temperature according to scheme 158 (Ref. 212).

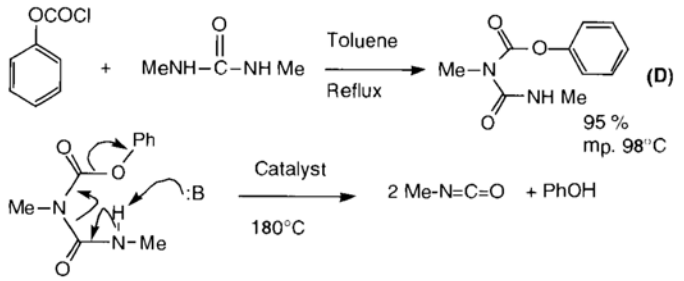


Scheme 158 : Preparation of MIC through reaction of diphenyl carbonate with dimethyl urea.

It is noteworthy that in this process, one mole of phenol is released for one mole of MIC produced.

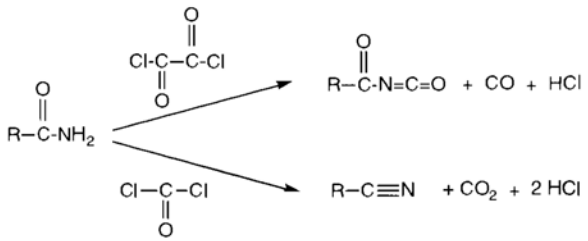
We studied at a laboratory scale a similar route of synthesis starting from phenyl chloroformate instead of diphenyl carbonate (Ref. 213). The new process presents the advantage that only half a mole of phenol is formed per mole of MIC.

Thus, phenyl chloroformate was reacted with dimethyl urea in toluene at reflux to give methyl N-phenoxycarbonyl-N-methyl urea (**D**) in 95 % yield. No added base was required. The intermediate (**D**) decomposed on heating at 180°C in presence of a selected basic catalyst to afford MIC in quantitative yield [Scheme 159].



Scheme 159 : Novel preparation of MIC from phenyl chloroformate.

It is well known that oxalyl chloride reacts with non-substituted amides to afford acyl isocyanates in high yields (Ref. 214). In contrast, phosgene acts as a dehydrating agent to give nitriles as shown in scheme 160. This interesting reaction, its mechanism and applications will be discussed in volume 2.



Scheme 160 : Reactions of oxalyl chloride and phosgene with primary amides.

Acyl isocyanates, especially trichloro acetyl isocyanate (**TAI**), 2,6-difluoro benzoyl isocyanate (**DFBI**) and methacryloyl isocyanate (**MAI**) are very valuable intermediates for pharmaceuticals, agrochemicals, plastics, adhesives and coatings. The structures, physical data and types of applications of these three major acyl isocyanates are given in table 3-28.

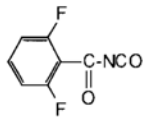
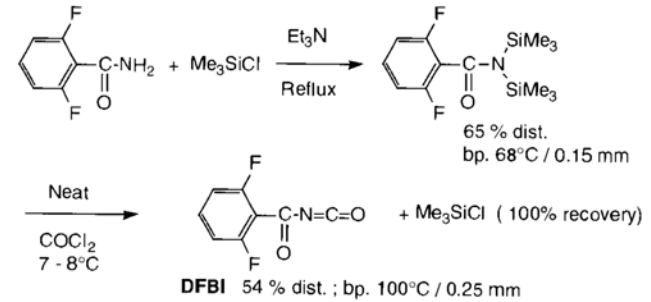
Name	Structure	Data	Applications
TAI	$Cl_3C-C(=O)-NCO$	bp : 80°C/27 mm LD_{50} > 2000mg	Pharmaceuticals : prep. of antibiotics such as sodium Cefuroxime
MAI	$H_2C=C(CH_3)-C(=O)-NCO$	bp. 122 °C (Atm. press.)	Vinyl functionalized resins for adhesives, coatings, fibers, electronic, medical materials etc.
DFBI		bp. 80°C/0.3 mm	Synthesis of difluoro -benzoylureas as insecticides (numerous patents)

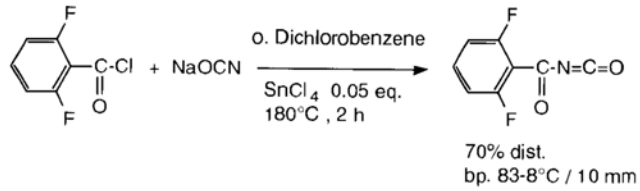
Table 3-28 : Valuable industrial acyl isocyanates.

The demonstrated utility of these high-reactive isocyanates prompted us to search for a phosgenation process more economical than the oxalyl chloride route. Our attempts succeeded in the development at a laboratory scale of a method based on the reaction of phosgene with N,N-disilyl amides as depicted in scheme 161 (Ref. 215).



Scheme 161 : Novel preparation of DFBI by phosgenation of N,N-bis(trimethylsilyl)-2,6-difluoro benzamide.

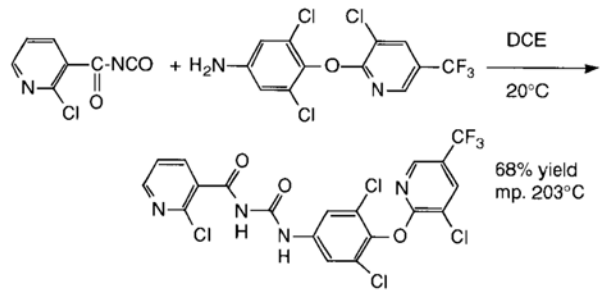
It is noteworthy that, in the course of our studies on the preparation of acylisocyanates, we put some improvements to the known procedure by condensation of aroyl chlorides with sodium cyanates. We found that special catalysts and solvants must be used for receiving satisfactory yields as depicted in scheme 162 (Ref. 216, 217).



Scheme 162 : Preparation of DFBI from 2,6-difluoro benzoyl chloride.

The scope and limitations of this process will be presented in volume 2 in the chapter dedicated to the chemistry of acid chlorides.

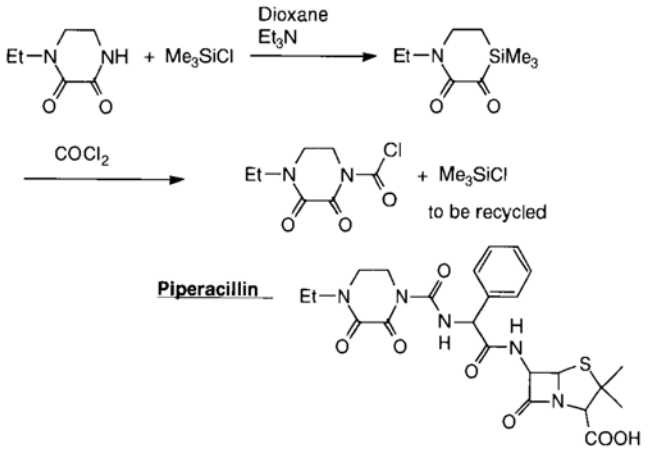
During our continuous collaboration with Ishihara Sangyo Kaisha Ltd, we prepared 2-chloro nicotinoyl isocyanate and patented the synthesis of interesting new insecticides effective against larvae, especially from lepidoptera (Ref. 218). The synthesis is depicted in scheme 163.



Scheme 163 : Preparation of a new N-pyridylcarbonyl-N'-phenyl urea as insecticide.

In the reactions with N-substituded amides, phosgene generally acts as a chlorinating agent yo give Vilsmeier salts (see volume 2). As in the case of primary amides, the use of N-silyl amides is often required to observe N-acylation in reasonable yields.

The preparation of 4-ethyl-2,3-dioxo-1-piperazinecarbonyl chloride provides with a good illustration of a commercial process through a silylation (Ref. 219). We studied thoroughly the process depicted in scheme 164, and brought some improvements. This carbamoyl chloride is used for the preparation of antibiotics such as Piperacillin or Cefoperazone.



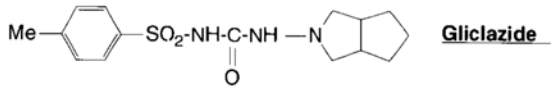
Scheme 164 : Phosgenation of dioxo piperazine and structure of the derived antibiotic Piperacillin.

3-3-5 Reaction of phosgene with sulfonamides : preparation of sulfonyl isocyanates

p. Toluene sulfonyl isocyanate (PTSI) is an interesting highly-reactive isocyanate which has found several valuable applications such as :

– dehydrating agent for mastic and filler resins, especially for building trade ;

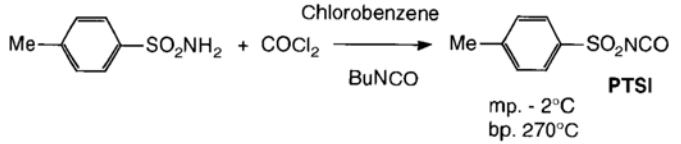
– chemical intermediate for the synthesis of hypoglycemic pharmaceuticals, for example Tolbutamide or Gliclazide :



Gliclazide

– key starting material for the preparation of resins for nail lacquers, to replace conventional arylsulfonamido formaldehyde resins which release carcinogenic formol (Ref. 220).

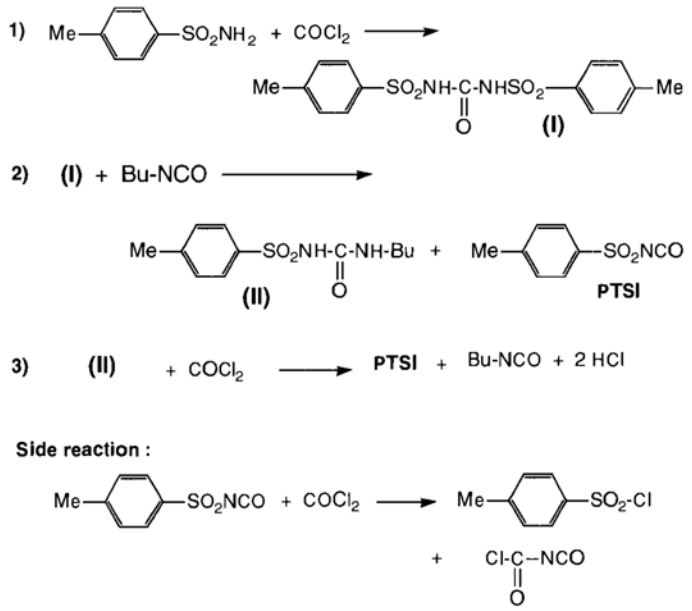
The synthesis of p. toluene sulfonyl isocyanate by phosgenation of p.toluene sulfonamide in presence of an alkyl isocyanate as the catalyst, generally n-butyl isocyanate, is well described in several patents and publications [Scheme 165].



Scheme 165 : Preparation of p.toluene sulfonyl isocyanate (PTSI).

In order to economically improve the industrial process and to avoid side reaction such as the formation of tosyl chloride, we thoroughly studied the mechanism of the phosgenation. We demonstrated that contrary to the impressions given in the literature, the sulfonyl urea (**II**) is not the only true intermediate in the reaction [Scheme 166]. Our trials showed that the phosgenation proceeds in a first stage through the readily and quantitative formation of the insoluble symmetrical sulfonyl urea (**I**) which reacts with butyl isocyanate to afford sulfonyl urea (**II**) and PTSI. The intermediate (**II**) reacts then, more slowly, with phosgene to give PTSI and regenerates butyl isocyanate. The assumed mechanism is depicted in scheme 166 (Ref. 221).

The formation of tosyl chloride was shown to proceed through phosgenation of PTSI itself, thus affording chlorocarbonyl isocyanate which polymerizes.



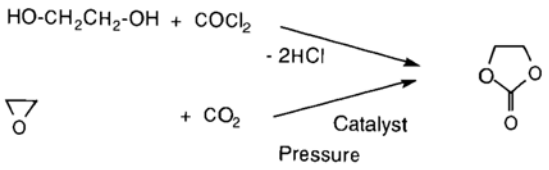
Scheme 166 : Mechanism fo the catalysed synthesis of PTSI.

3-4 Ring formation reactions

This chapter uses an organization based on the nature of the two hetero atoms involved in the closing of the ring by the carbonyl group : O<->O ; O<->N ; N<->N ; N<->S.

3-4-1 Cyclisation between two oxygen atoms

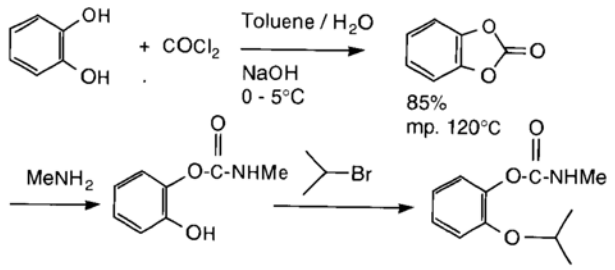
Although ethylene carbonate can be easily made by phosgenation of ethylene glycol, the only industrial process is the carbonatation of ethylene oxide [Scheme 167].



Scheme 167 : Preparation of ethylene carbonate.

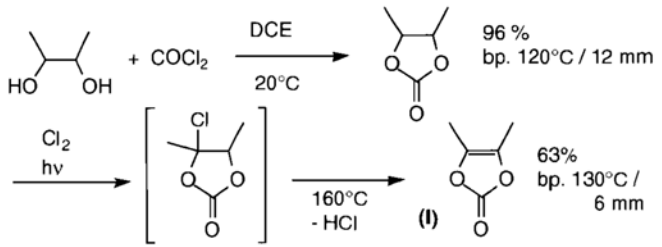
However, the phosgenation process has much more value in less simple products. We previously have treated in section 3-2-2-1 the reaction of excess phosgene with glycerol which affords a monochloroformate containing a five membered cyclic carbonate function.

The phosgenation of catechol is of high interest, because the resulting o-phenylene carbonate is the key starting material for the preparation of the insecticide Propoxur as shown in scheme 168.



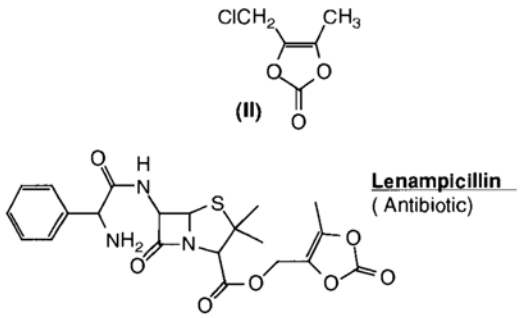
Scheme 168 : Preparation of the insecticide Propoxur.

Phosgenation of 2,3-butane diol presents a high potential value in the pharmaceutical field. The cyclic carbonate thus obtained can be photochemically chlorinated to give a vinylene carbonate (I) as depicted in scheme 169 (Ref. 222).



Scheme 169 : Preparation of vinylene carbonate derived from 2,3-butane diol.

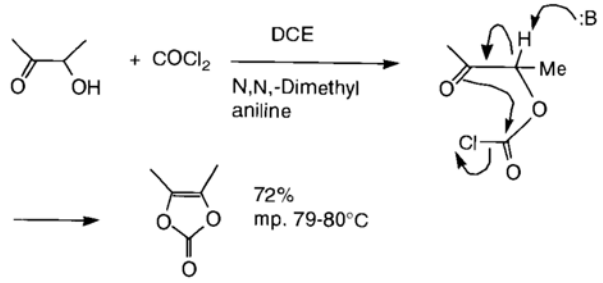
The substituted vinylene carbonate (I) can be used for the preparation through chlorination and dehydrochlorination of the intermediate (II) which is the key reagent for the production of Lenampicillin [Scheme 170].



Scheme 170 : Substituted vinylene carbonate for the modification of antibiotics.

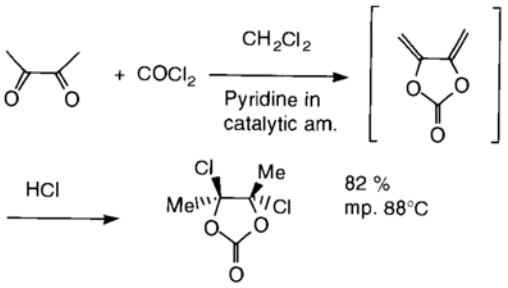
(II) is also used in the synthesis of Cefcanel, a new cephalosporin from Kyoto Yakuhin and Astra (Ref. 223).

It is noteworthy that the vinylene carbonate (I) in scheme 169 can be obtained by phosgenation of acetoin as depicted in scheme 171 (Ref. 224).



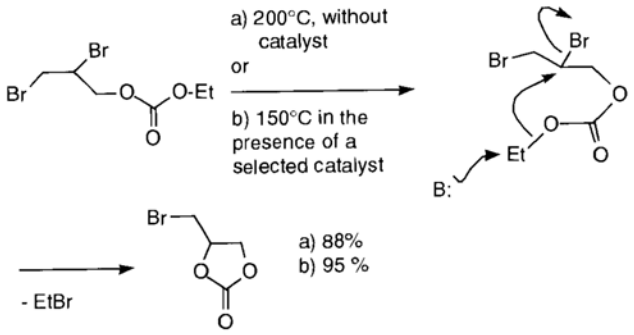
Scheme 171 : Phosgenation of acetoin.

King Jr reported a facile synthesis of chlorinated dioxolanones by a simple, one-pot, direct addition of phosgene to 1,2-diones (Ref. 225). Thus, the reaction of 2,3-butane dione with phosgene in the presence of pyridine affords trans-4,5-dichloro-4,5-dimethyl-1,3-dioxolane-2-one in 82% yield as shown in scheme 172.



Scheme 172 : Phosgenation of 2,3-butane dione.

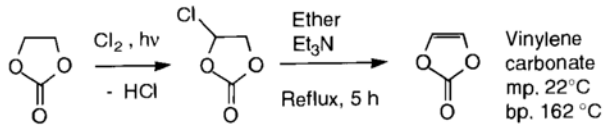
In an obscure paper, Pews reported the formation of bromomethyl ethylene carbonate through an unusual thermal rearrangement of 2,3-dibromopropyl ethyl carbonate (Ref. 226). We studied the scope and limitations of this reaction and defined the best conditions of the process as shown in scheme 173.



Scheme 173 : Unusual access route to substituted ethylene carbonate.

Chlorinated derivatives of ethylene carbonate itself are very interesting and valuable compounds.

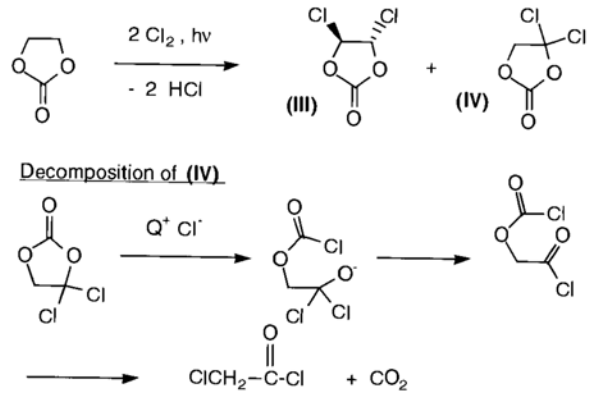
When ethylene carbonate is monochlorinated, the chloroethylene carbonate thus obtained is the starting material for the synthesis of vinylene carbonate which is used in radical polymerization to yield high-molecular weight polymers and copolymers or in Diels-Alder cycloadditions [Scheme 174] (Ref. 227).



Scheme 174 : Preparation of vinylene carbonate.

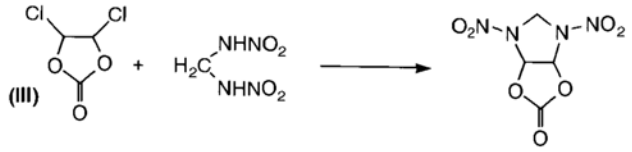
When ethylene carbonate is partly chlorinated, the two dichlorinated products (**III**) and (**IV**) formed cannot be separated by distillation and an 85:15 mixture of (**III**) : (**IV**) only is available commercially.

We discovered that (**IV**) cleanly decomposes to chloracetyl chloride in presence of « naked chloride anion ». This method which destroys preferentially (**IV**) allows to recover (**III**) in 92 % yield by subsequent fractional distillation [Scheme 175].



Scheme 175 : Preparation of pure dichloro ethylene carbonate (III).

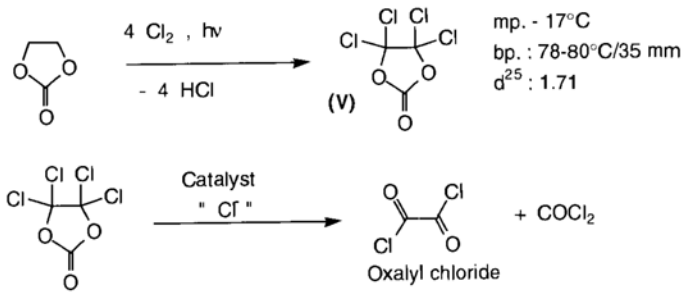
(**III**) was claimed as the key for the synthesis of novel explosives as shown in scheme 176 (Ref. 228).



Scheme 176 : Novel explosive from dichloro ethylene carbonate.

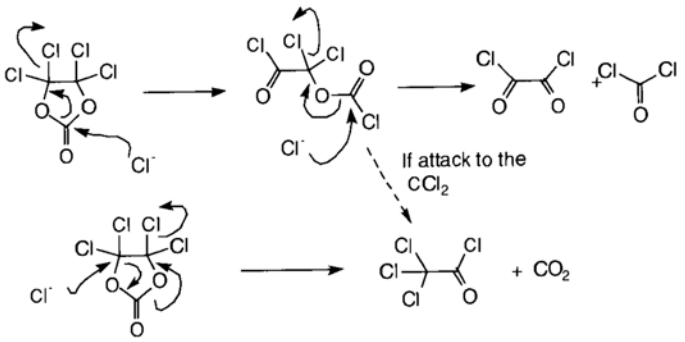
Photochemical perchlorination of ethylene carbonate affords tetrachloroethylene carbonate (**V**) in high yield (Ref. 229). When (**V**) is treated with a trace of a nucleophile, it cleaves quantitatively to oxalyl chloride and phosgene [Scheme 177] (Ref. 230).

This decomposition is today's standard process for the manufacture of oxalyl chloride.



Scheme 177 : Preparation of tetrachloroethylene carbonate and its decomposition to oxalyl chloride and phosgene.

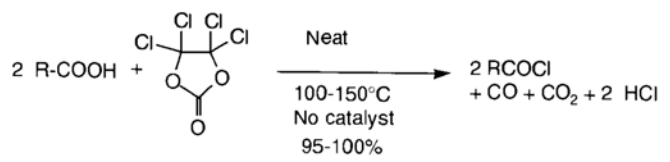
While studying the catalyzed decomposition of tetrachloroethylene carbonate (**V**) by onium salts, we observed the formation of a little trichloroacetyl chloride. Since (**V**) present three reactive electrophilic centers : the carbonyl group and the two carbon both linked with two chlorine atoms, it can be attacked following two different pathways as diagrammed in scheme 178.



Scheme 178 : Possible types of nucleophilic attacks to tetrachloroethylene carbonate by Cl-.

We thought that if a catalyst for directing cleanly the reaction either to the formation of oxalyl chloride or to trichloroacetyl chloride could be devised, the ready availability of (**V**) would seem to make this compound a very attactive intermediate. This work is currently under investigation.

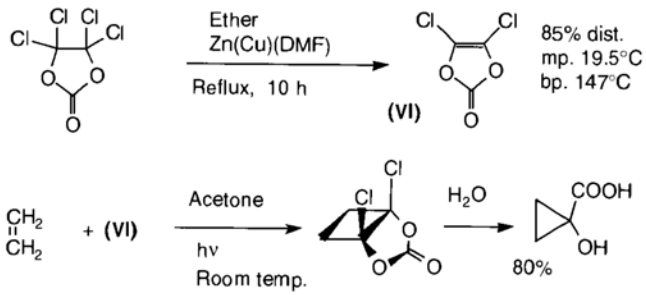
Also, we discovered that tetrachloroethylene carbonate can be used as a highly effective chlorinating agent for acid chlorides preparation as depicted in scheme 179 (Ref. 231).



Scheme 179 : Preparation of acid chlorides using tetrachloroethylene carbonate.

The main issue under discussion is how this reaction can work without any catalyst. In contrast to oxalyl chloride, phosgene requires a catalyst to convert carboxylic acid to acid chloride. Thus, the above reaction would give acid chloride in no more than 50% yield.

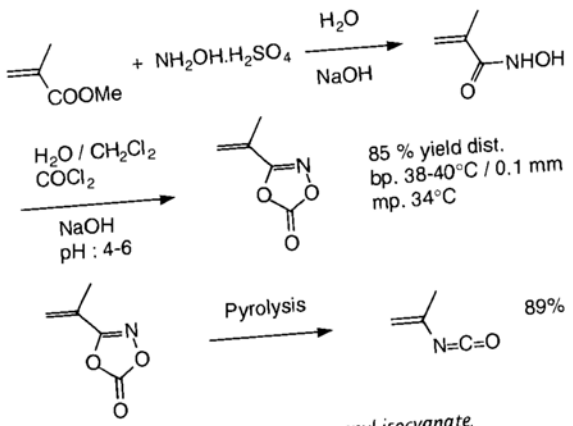
Furthermore, we studied the described dechlorination of tetrachloroethylene carbonate (**V**) to dichlorovinylene carbonate (**VI**) with zinc (Ref. 229). (**VI**) is an interesting intermediate which as a cyclophile permits simultaneous introduction of masked α-hydroxy keto and α-diketo functions respectively into the cycloadducts (Ref. 232). One example is given in scheme 180.



Scheme 180 : Synthesis and example of use of dichlorovinylene carbonate.

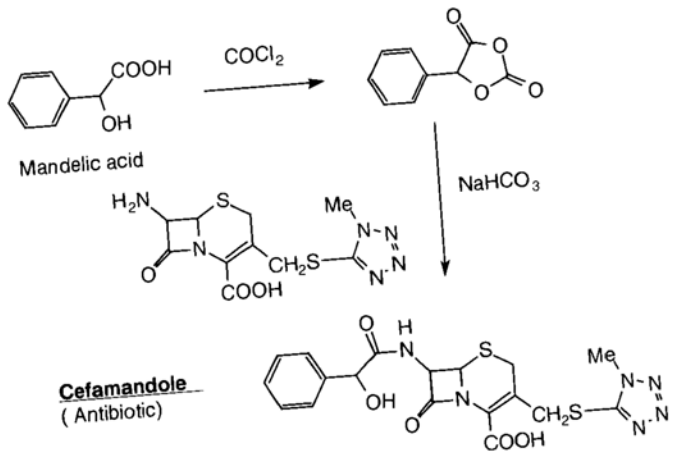
Phosgenation of hydroxamic acids affords nitrile carbonates which has been suugested as isocyanates precursors (Ref. 233).

One demonstrative example applied to the synthesis of isopropenyl isocyanate is given in scheme 181 (Ref. 234). Note that the use of a catalyst such as ferric salts permits to lower the required decomposition temperature.



Scheme 181 : Preparation of isopropenyl isocyanate.

Phosgenation of α-hydroxy acids affords cyclic mixed carboxylic-carbonic anhydrides which can be used as activated form of acid function in reaction with amines to afford amides as illustrated by the example given in scheme 182 (Ref. 235).

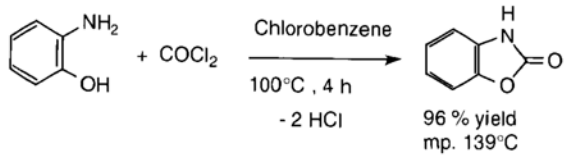


Scheme 182 : Preparation of Cefamandole.

3-4-2 Cyclisation between oxygen and nitrogen atoms

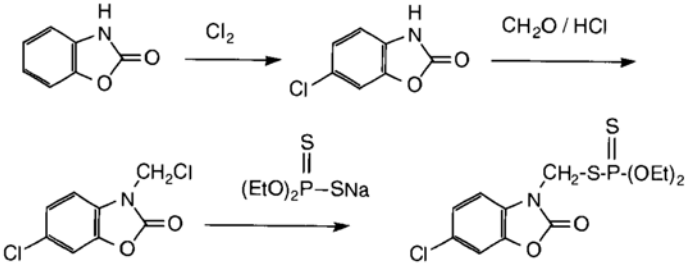
Phosgene reacts easily with amines containing a hydroxyl function in 2 or -3 position to afford oxazolidones (cyclic five membered carbamates) or oxazinones (cyclic six membered carbamates) respectively.

The preparation of 3-H-benzoxazol-2-one from o-aminophenol and urea is well known but the reaction is accompanied by the formation of tars and other side reactions. In contrast, phosgene reacts cleanly with o-aminophenol. We have devised a simple process without any acid scavenger which affords pure benzoxazolone in excellent yield as depicted in scheme 183 (Ref. 236).



Scheme 183 : Improved phosgenation process to benzoxazolone.

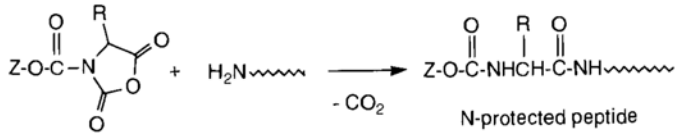
Benzoxazolone is a valuable compound for several applications, for example as a key starting material for the manufacture of Phosalone, an insecticide used mainly on cotton [Scheme 184].



Scheme 184 : Synthesis of Phosalone.

Some other interesting substituted benzoxazolones are also used as pharmaceuticals, for example the muscle relaxant Chlorzoxazone [Scheme 185] (Ref. 237).

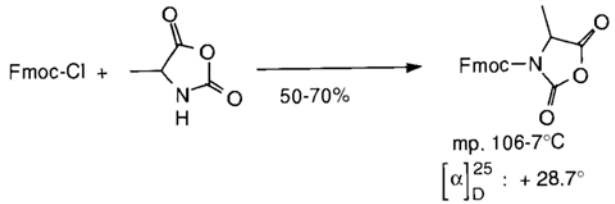
This brief presentation outlines the utility of the NCA's. But this is only part of the picture. Added to this are urethane N-carboxy anhydrides called **UNCA's** we developed under license of Bioresearch Inc. (Ref. 249). UNCA's which are both protected and activated form of amino acids are highly effective coupling agents for the synthesis of peptides as illustrated in scheme 198.



Scheme 198 : Principle of use of UNCA's as coupling agents in peptides synthesis.

UNCA's are crystalline solids which are stable in the absence of water and nucleophiles. They react readily and cleanly with amino functions without racemization. Carbon dioxide is the only by-product which allows facile purification and isolation.

One example of synthesis of UNCA's is given in scheme 199.

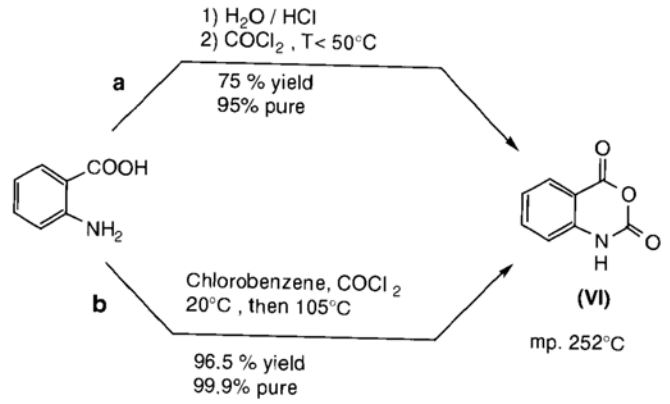


Scheme 199 : Example of preparation of UNCA's.

Let us now consider to what extent the previous reaction of phosgene with α-amino acid can be applied to β-amino acids to yield six membered cyclic O-acyl carbamates.

2H-3,1-Benzoxazine-2,4(1H)-dione known as isatoic anhydride (**VI**) is the most popular six membered cyclic O-acyl carbamate. The synthesis of isatoic anhydride by ring closure of anthranilic acid with phosgene is well described (Ref. 250). However, we have developed an

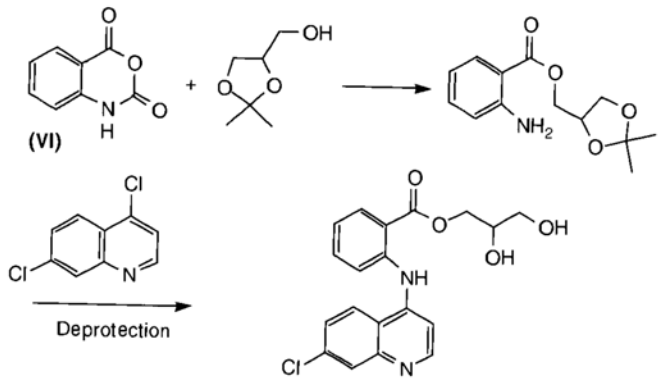
improved phosgenation process which leads to higher yield and purity as demonstrated in scheme 200 (Ref. 251).



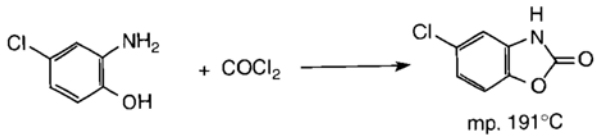
Scheme 200 : Comparison between described (a) and SNPE (b) routes to isatoic anhydride.

Isatoic anhydride (**VI**) is an extremely versatile compound because of the ease of its reactions with nucleophiles or electrophiles as outlined in a rewiew (Ref. 252).

For example it is claimed as a starting material in the synthesis of the analgesic Glafenine as shown in scheme 201 (Ref. 253).

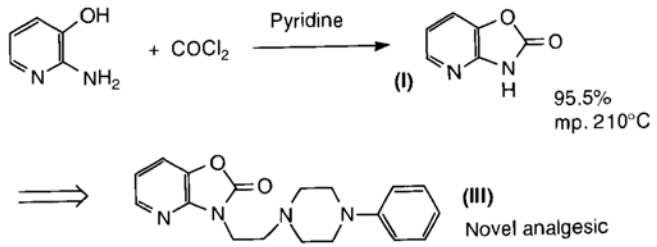


Scheme 201 : Preparation of Glafenine.



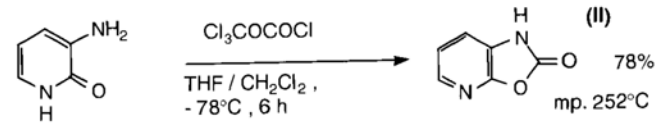
Scheme 185 : Preparation of Chlorzoxazone (muscle relaxant).

Oxazolopyridines, such as the novel analgesic (**III**) now being in clinical trials, constitute a medicinal class of heterocyclic compounds. Phosgenation of 2-amino-3-hydroxy pyridine in the presence of pyridine as scavenger and solvent leads to the oxazolopyridine (**I**) in excellent yield as shown in scheme 186 (Ref. 238).



Scheme 186 : Preparation and use of an oxazolopyridine.

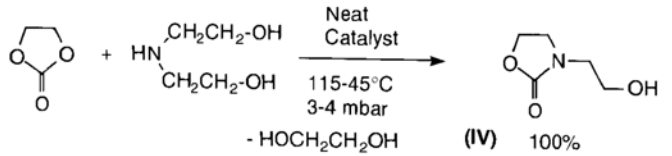
The regioisomeric system (**II**) derived from the readily available 3-amino-2-pyridone is less easy to prepare. Guillaumet and coworkers reported the synthesis of (**II**) via a one-step process using diphosgene (Ref. 239). The reaction was carried out in CH_2Cl_2/THF mixture in presence of triethyl amine at -78°C, and the product isolated and purified by flash chromatography [Scheme 187].



Scheme 187 : Preparation of oxazolo[5,4-b] pyridin-2 (1H)-one.

In aliphatic serie, we have developed the synthesis of N-(2-hydroxyethyl) oxazolidone (**IV**) at an industrial scale,

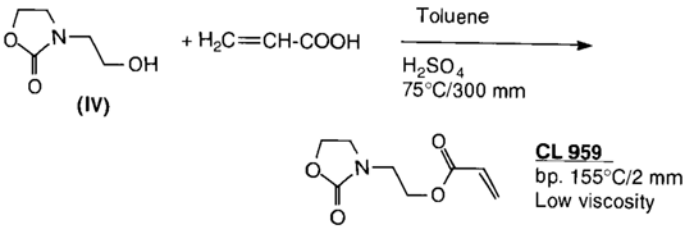
according to the process depicted in scheme 188 (Ref. 240).



Scheme 188 : Preparation of N-(2-hydroxyethyl) oxazolidone.

The substituted oxazolidone (**IV**) is especially useful as building block for acrylic monomers syntheses or for pharmaceuticals.

Thus, the esterification of (**IV**) by acrylic acid affords a new acrylic monomer, SNPE code number CL 959, in good yield as shown in scheme 189.



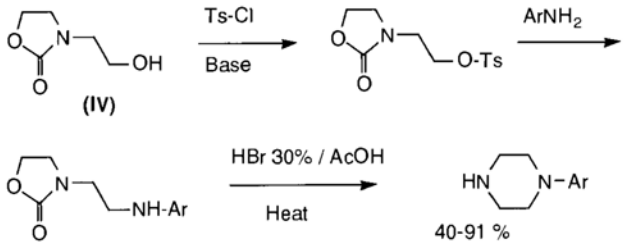
Scheme 189 : Preparation of new UV-curable monomer from N-(2-hydroxy-ethyl) oxazolidone.

Acticryl CL 959 has widespread applications, mainly as reactive diluent in fast drying coatings (Ref. 241). It is useful in various industrial sectors for :

- classical coatings for wood, paper, plastics, metals ;
- adhesives, pressure sensitive adhesives ;
- optical fibers ;
- electronics, photo-resists.

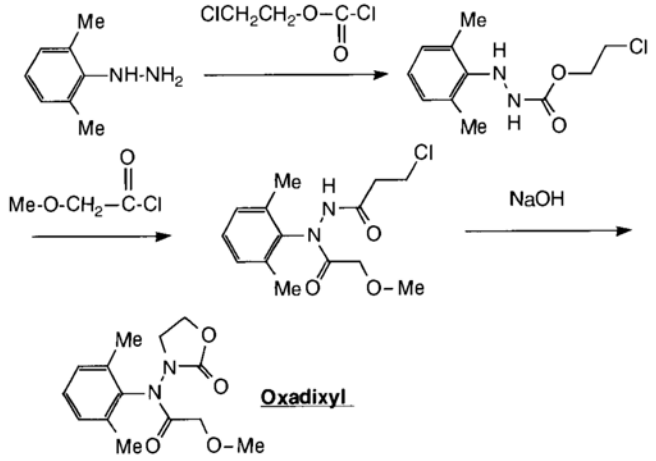
N-(2-Hydroxyethyl) oxazolidone (**IV**) should be also a valuable intermediate for the synthesis of N-arylpiperazines which are widely used in the preparation of pharmaceuticals such as the neuroleptic Fluanisone.

Squibb reported an interesting example at the 207 th ACS National Meeting depicted in scheme 190 (Ref. 242).



Scheme 190 : Novel preparation of N-arylpiperazines.

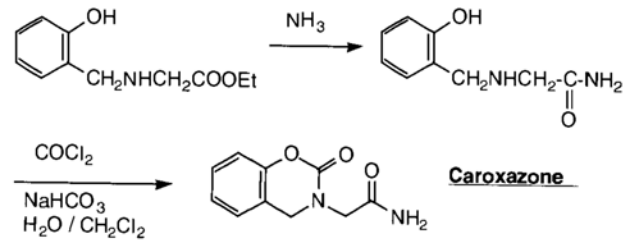
Oxazolidones can be also prepared from the reaction of primary amines with 2-haloalkyl chloroformates. This method has found widespread applications in various sectors of the chemical industry. The industrial preparation process of the systemic fungicide Oxadixyl is a good first illustration [Scheme 191] (Ref. 243).



Scheme 191 : Industrial scale preparation of the fungicide Oxadixyl.

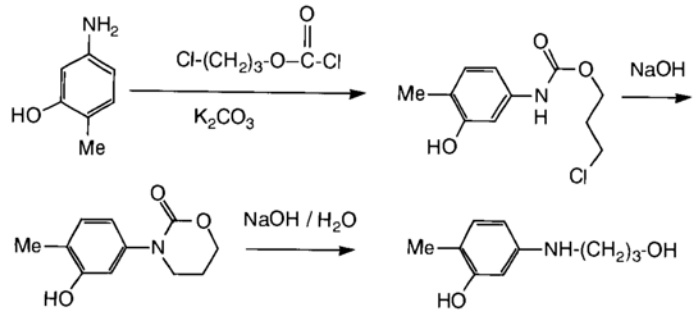
The reaction of phosgene with amines containing an -OH function in 3-position readily affords oxazinones as already mentioned.

The preparation of the antidepressant Caroxazone depicted in scheme 192 illustrates the value of the method (Ref. 244).



Scheme 192 : Preparation of the antidepressant Caroxazone.

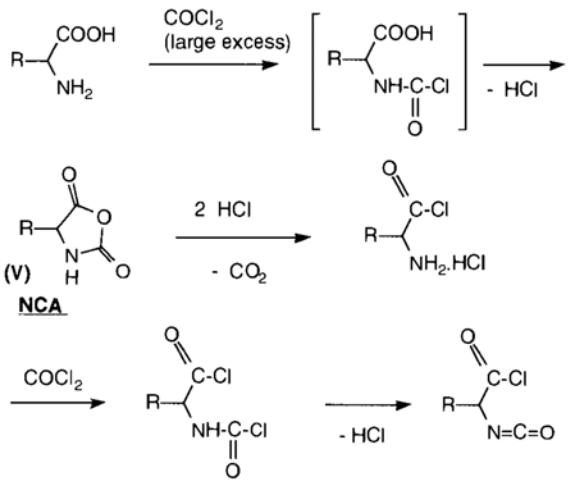
The intermediary synthesis of oxazinones derivatives is the key for the N-hydroxypropylation of substituted anilines used as components in hair dyes (Ref. 245, 246). One example is given in scheme 193.



Scheme 193 : Hydroxypropylation of substituted anilines for the preparation of hair dyes.

Phosgene reacts with α and β-amino acids to yield five and six membered O-acylcarbamates respectively.

Thus, phosgene has proven to be very effective in the preparation of N-carboxy anhydrides (NCA) from α-amino acids. These compounds : 2,5-dioxo-1,3-oxazolidines (**V**), also called Leuch's anhydrides have widespread applications especially but not only in peptides synthesis [Scheme 194].

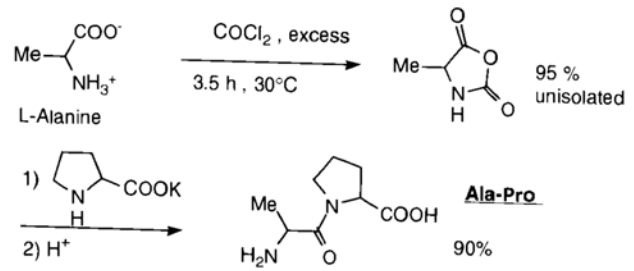


Scheme 194 : General picture of N-carboxy anhydrides preparation and further reactions.

Although sensitive to traces of moisture and more generally to nucleophilic attacks, NCA are now produced and sold in large quantities. The scope and limitations of their chemistry, as well as their applications are not discussed in details here in this section and are reserved for section 4-4 in vol. 2 dedicated to the protection and activation of functional groups.

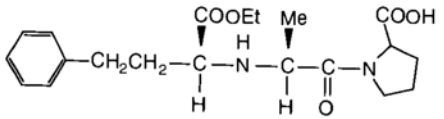
However, some representative examples of applications are given in the present section.

The NCA coupling method is conceptually simple and elegant. This method is now used in efficient large scale production of peptides, for example for the preparation of semi-synthetic dipeptides Enalapril and Lisinopril (Ref. 247). The synthesis of Ala-Pro which is the key building block to synthesize Enalapril is diagrammed in scheme 195.



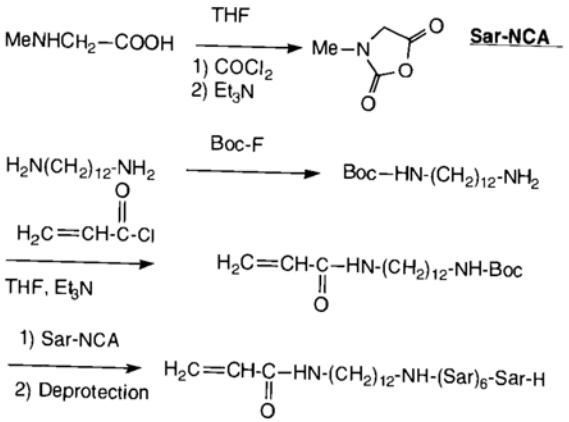
Scheme 195 : Preparation of Ala-Pro through Ala-NCA.

Enalapril (structure in scheme 196) is an angiotensin-converting enzyme (ACE) inhibitor for the control of hypertension.



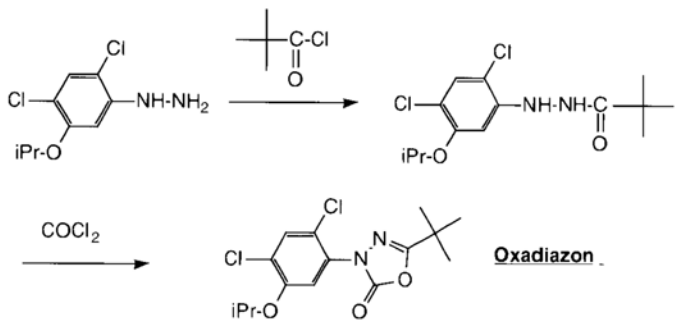
Scheme 196 : Enalapril.

In another example, Sarcocine-NCA prepared by phosgenation of sarcosine, followed by cyclisation in the presence of triethyl amine is used for the preparation of lipopeptide-based branched polymers forming thermotropic and lyotropic liquid crystals as shown in scheme 197 (Ref. 248).



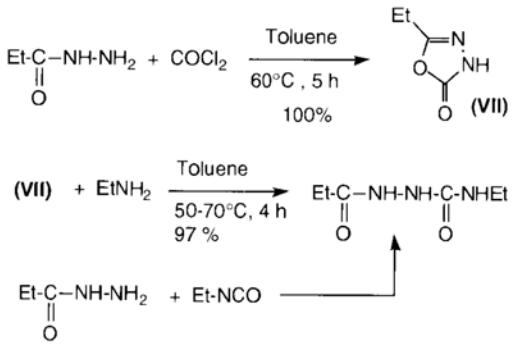
Scheme 197 : Preparation of Sarcosine-NCA and use in the preparation of oligomers for lipopeptides.

Phosgene reacts with hydrazides to afford 1,3,4-oxadiazolinones. One well known example is the synthesis of the selective herbicide Oxadiazon from Rhône-Poulenc [Scheme 202] (Ref. 254).



Scheme 202 : Preparation of the herbicide Oxadiazon.

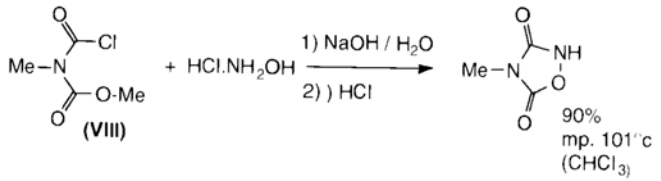
We have studied the preparation of 5-ethyl-1,3,4-oxadiazolinone (**VII**) by phosgenation of propionyl hydrazide as depicted in scheme 203 (Ref. 255).



Scheme 203 : Preparation and use of 5-ethyl-1,3,4-oxadiazolinone.

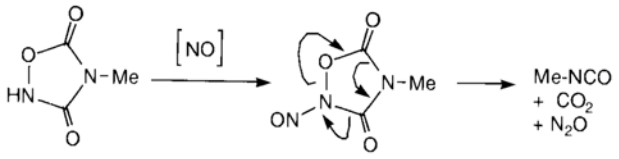
Compound (**VII**) can be further transformed to triazolones, useful building blocks for pharmaceuticals such as Etoperidone or Nefazodone (see cyclisation between two nitrogen atoms, next section). In the case of Etoperidone, this transfomation avoids the use of toxic ethyl isocyanate to get the required intermediate as shown in scheme 203.

3,5-Dioxo-1,2,4-Oxadiazolidines have been found as a moiety of the natural excitatory amino acid Quisqualic acid and their synthesis by numerous methods has been extensively studied by Zinner and co-workers (Ref. 256). Reaction of methyl-N-chlorocarbonyl-N-methyl carbamate, (**VIII**), (preparation given in section 3-3-4, this volume) with hydroxylamine affords 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine (Acronym : MODD) in good yield as shown in scheme 204 (Ref. 257).



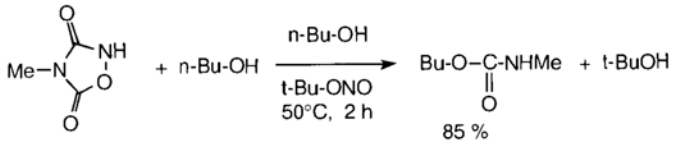
Scheme 204 : Improved preparation of MODD.

While exploring new alternatives to the handle of lower alkyl isocyanates, we thought that the nitrosated MODD could be a good candidate for a new synthesis of methyl isocyanate through a two-components safe process according to the mechanism depicted in scheme 205 (Ref. 258).



Scheme 205 : Expected generation of methyl isocyanate by a two-components safe process.

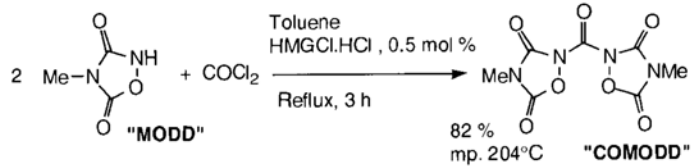
Some trials applied to a model reaction by trapping the methyl isocyanate as butyl N-methyl carbamate were very promising as demonstrated in scheme 206.



Scheme 206 : Use of MODD/t-butyl nitrite as methyl isocyanate precursor.

Furthermore, while studying the potential applications of MODD as a building block for the synthesis of 2-acyl-3,5-dioxo-1,2,4-oxadiazolidines, we discovered that it is a very good leaving group. This led us to the design of the previously unknown symmetrical 2,2'-carbonyl-bis(3,5-dioxo-4-methyl-1,2,4-dioxazolidine), (acronym : COMODD), as a new coupling reagent for the preparation of carbamates from hydroxy compounds and primary or secondary amines (Ref. 259).

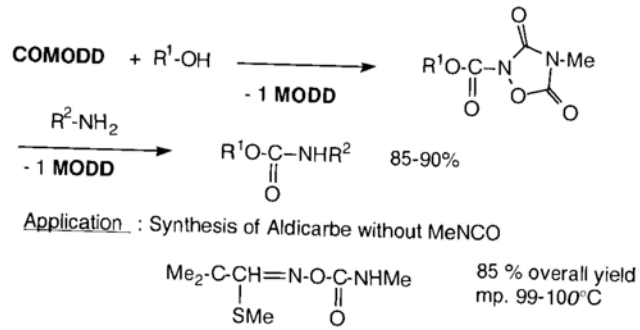
COMMOD was readily obtained in good yield by simple phosgenation of MODD in refluxing toluene in presence of hexamethylguanidinium chloride hydrochloride (HMGCl.HCl) as the catalyst [Scheme 207].



Scheme 207 : Preparation of COMODD.

Compared with 1,1'-carbonyldiimidazole, COMODD is a crystalline, stable and non-hygroscopic compound. MODD released after use of COMODD as coupling reagent is water soluble and therefore can be easily recycled. Moreover, in contrast to imidazole, MODD is acidic (pKa measured at 20°C : 3.6). This characteristic can be very useful in the case of substrates sensitive to basic conditions.

MODD readily reacts with hydroxy compounds to afford 2-alkoxycarbonyl-MODD. These intermediates do not need to be isolated and are reacted with an excess of amine to give the corresponding carbamate in good yield as depicted in scheme 208 (Ref. 260). For example, the insecticide Aldicarbe was obtained in 85% yield without use of the noxious methyl isocyanate.

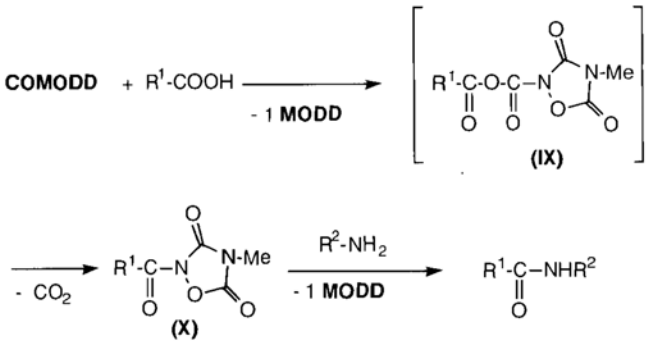


Scheme 208 : COMODD as an useful tool for carbamates synthesis.

It is possible to prepare BOC- or Z-amino acids from the isolated 2-BOC- or 2-Z- MODD but the method was found of little synthetic interest mainly because of the sensitivity of 2-alkoxycarbonyl-MODD toward hydrolysis. However, Z-amino acids were obtained in medium yields and were found to be free of dipeptides impurities.

We discovered also that COMODD reacts with carboxylic acids to give the unstable mixed anhydrides (**IX**) which are rapidly decarboxylated to the 2-acyl-MODD (**X**). As above mentioned, (**X**) are not isolated but are reacted in situ with an amine to afford the corresponding amides as shown in scheme 209 (Ref. 260).

This reaction has been successfully applied to the coupling of amino acids. Yields are generally good and the dipeptides are easily freed of by-products by simple washes. The MODD released or its sodium salt are readily soluble in water and thus are easily separated from the fully protected dipeptide.



Scheme 209 : COMODD as an useful tool for amides synthesis.

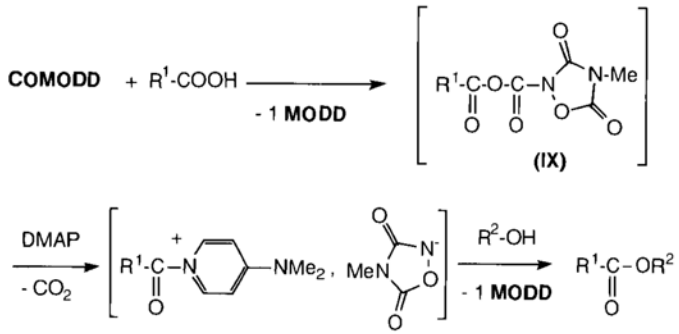
In a typical procedure, one equivalent of COMODD is added to a solution of the protected amino acid and N-methylmorpholine (2 eq.) in acetonitrile or dichloromethane and stirred at room temperature for 1 h. The amino acid ester or its hydrochloride is then added and the reaction mixture is stirred for an additionnal hour. After conventional washes of the organic phase, the dipeptide is crystallized from a suitable solvent. As shown in table 3-29, several dipeptides were prepared and no deviations were found in their optical rotations.

Dipeptide	Yield (%)	mp. (°C)	[α]D°
BOC-Phe-Gly-OEt	86	86-8	-4 (c 1 EtOH)
Z-Val-Gly-OEt	66	165-166	- 27 (c 1 EtOH)
Z-Leu-Phe-OMe	74	80-81	- 20 (c 2 MeOH)
Z-Ala-Phe-OMe	88	96-98	- 10 (c 1 EtOH)
Z-Phe-Ala-OMe	83	127-129	-22 (c 1.25 EtOH)
Bz-Leu-Gly-OEt	78	137-139	- 4 (c 3.1 EtOH)
BOC-Tyr(OBzl)-Gly-OEt	79	117-119	+ 2 (c 0.5 EtOH)

Table 3-29 : Preparation of dipeptides using COMODD as a coupling agent.

In a second publication, we reported the use of COMODD for the one-pot esterification of carboxylic acids, especially amino acids, under mild conditions (Ref. 261).

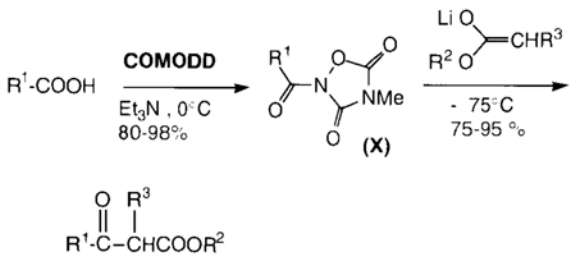
The reaction was efficient with both primary and secondary alcohols. Providing that an excess of the alcohol is added, tertiary alcohols are esterified in medium but still satisfactory yields. The reaction is catalyzed with DMAP, but no base was necessary if the alcohol already contained a pyridine function. We assume that the reaction proceeds through the mixed anhydride (**IX**) as depicted in scheme 210.



Scheme 210 : COMODD as a reagent for the direct esterification of carboxylic acids.

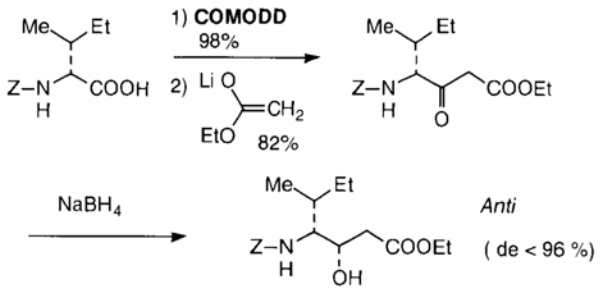
In a typical procedure, COMODD (1 eq.) and the appropriate alcohol (1.1 eq.) are added within 5 min. to a solution of the acid (1 eq.), triethylamine (1,1 eq.) and DMAP (0.1 eq.) in dichloromethane and the reaction mixture is stirred at room temperature for 2 h. Conventional acidic and basic washes afford the corresponding ester in good yield. For example esterification of Z-Ala-OH with p-nitrobenzylic alcohol using this method gave the expected ester in 89% yield (mp. 95-96°C). No sign of racemization was detected in the syntheses of amino esters examined.

Acyl-MODD (**X**) provided by activation of N-protected-α-amino acids and O-protected-α-hydroxy acids with COMODD have been proved to be suitable for the synthesis of β-keto ester as depicted in scheme 211 (Ref. 262).



Scheme 211 : Use of COMODD in the synthesis of β-keto esters.

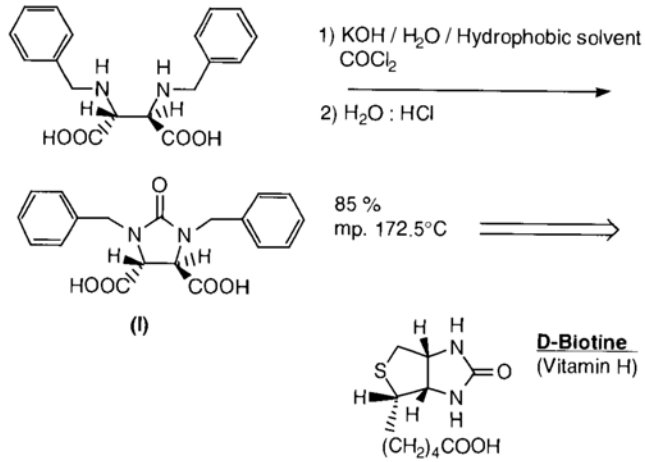
This activation was successfully used in the preparation of unusual γ-amino-β-hydroxy esters such as the protected derivative of (3S4R5S)- Isostatine from D-allo-isoleucine as shown in scheme 212 (Ref. 262).



Scheme 212 : Preparation of (3S4R5S) Isostatine with COMODD.

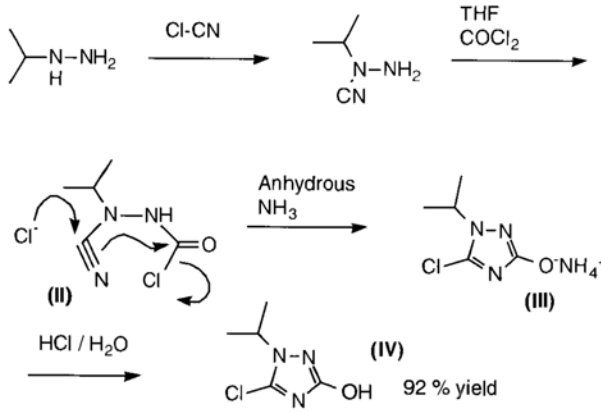
3-4-3 Cyclisation between two nitrogen atoms

Phosgenation of ethylene diamine type compounds is a well established method for the preparation of 2-imidazolidones (cyclic five membered ureas). The utility of this method is illustrated by the synthesis of a valuable intermediate (**I**) for D-biotine manufacture. We have developed an improved interfacial process which affords (**I**) in good yield and high purity as shown in scheme 213.



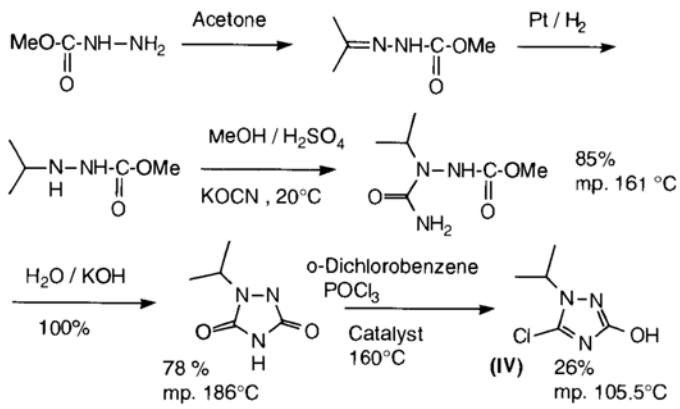
Scheme 213 : Preparation of the key intermediate for the synthesis of Biotine.

Phosgene reacts with cyanohydrazines to yield 3-hydroxy-5-chloro-1,2,4-triazoles. The utility of the process is demonstrated by the preparation of the key intermediate for the production of the soil-applied nematocide Isazofos (Ref. 263). Thus, phosgenation of 1-cyano-1-isopropyl hydrazine in THF gives a transient N-chlorocarbonyl compound (**II**) which is cyclized to (**III**). This salt, insoluble in THF is recovered by filtration and the desired product (**IV**) is isolated in good yield by simple acidification as depicted in scheme 214.



Scheme 214 : Described process for the preparation of a intermediate used for the manufacture of Isazofos.

While exploring the synthesis and chemistry of urazoles, we studied an alternative process starting from carbazate which avoids the handling of the extremely noxious cyanogen chloride. The new synthesis of (**IV**) is diagrammed in scheme 215 (Ref. 264).



Scheme 215 : Synthesis and use of 1-isopropyl urazole.

Note also that reaction of methyl-N-chlorocarbonyl-N-methyl carbamate (preparation through phogenation given in section 3-3-4, this volume) is very suitable for the preparation of numerous urazoles. Some examples are presented in table 3-30 (Ref. 265).

R	Yield (%)	mp. (°C)
H	56	238-9
Me	81.4	122-3
Ph	89.5	222-3

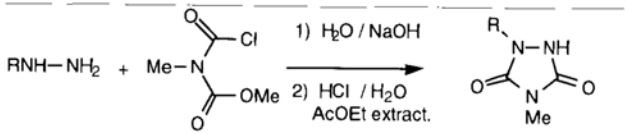
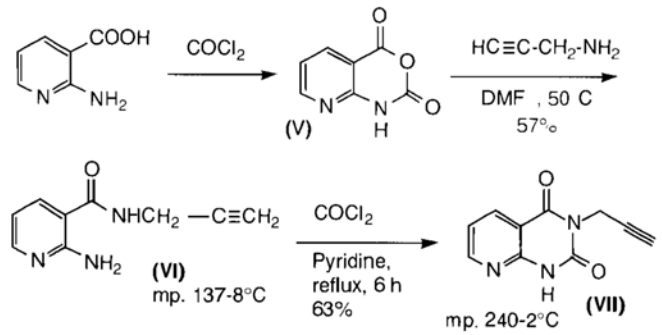


Table 3-30 : Use of methyl-N-chlorocarbonyl-N-methyl carbamate for the preparation of urazoles.

The biological activities of condensed pyrimidine systems as diuretics, antitumor agents or as antagonists of constituents of nucleic acid and of folic-folinic acid family of vitamins prompted differents authors to study the synthesis of cyclic six membered acylureas such as pyrido[2,3-d] pyrimidinones (Ref. 266).

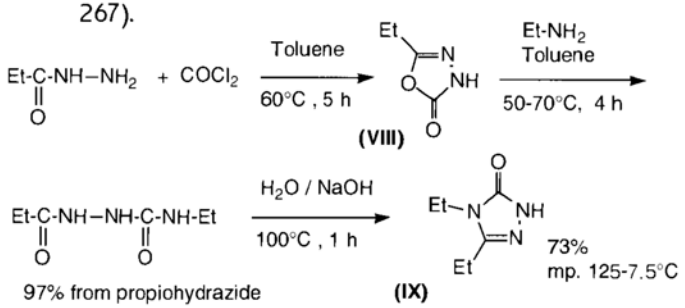
Reaction of phosgene with 1-amino nicotinic acid afforded the 3-azaisatoic anhydride (**V**). Treatment of (**V**) in DMF with propargylamine yielded the 1-aminonicotinamide (**VI**). Phosgenation of (**VI**) in pyridine under reflux gave the expected product (**VII**) as depicted in scheme 216.



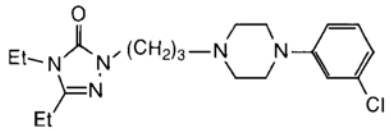
Scheme 216 : Example of preparation of cyclic six membered acylureas through a « double phosgenation » process.

5-Ethyl-1,3,4-oxadiazolinone (**VIII**), prepared by phosgenation of propionyl hydrazide as already described in section 3-4-2, is a key building block for the synthesis for the synthesis of 1,2,4-triazol-3-ones type antidepressants (Ref 255).

Thus, we obtained the triazolone (**IX**) in 73 % overall yield according to scheme 217 without the need of the highly toxic ethyl isocyanate. (**IX**) is suitable for the manufacture of Etoperidone [Stucture given in scheme 218] (Ref. 267).



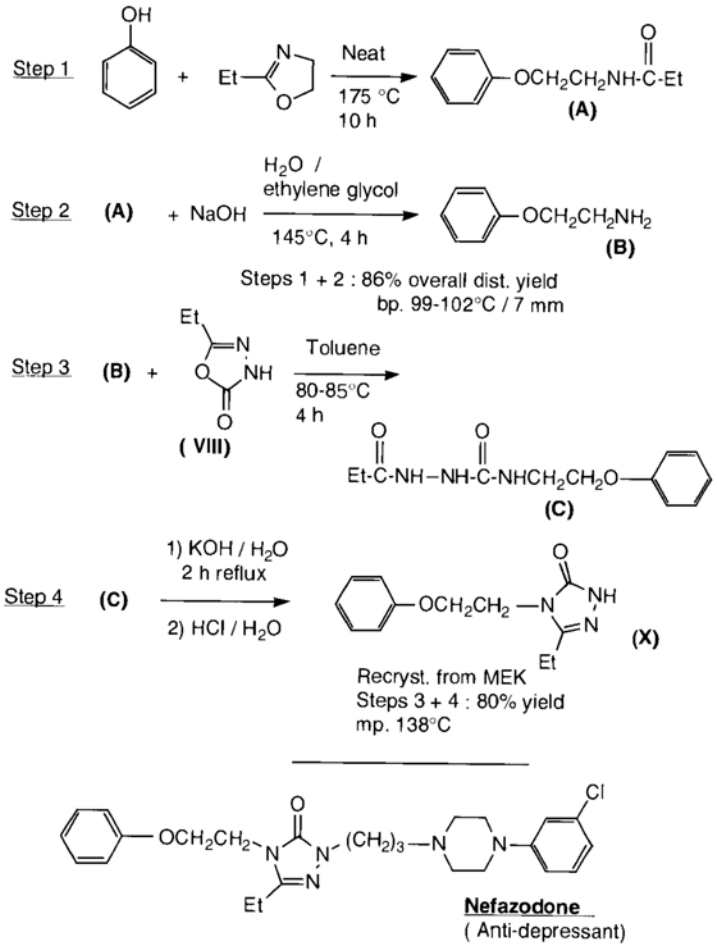
Scheme 217 : Preparation of the key intermediate for the manufacture of Etoperidone.



Scheme 218 : Etoperidone (anti-depressant).

In another study, we devised a new route to the triazolone intermediate (**X**) useful for the synthesis of Nefazodone as depicted in scheme 219 (Ref. 255, 268).

Nefazodone.HCl was launched in 1994 in the US and in Canada by Bristol-Meyers Squibb as Serzone® for the treatment of depression (Ref. 269).

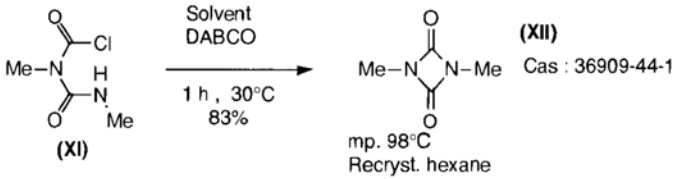


Scheme 219 : New synthesis of an useful intermediate (X) for Nefazodone.

N-Methyl carbamates are valuable products, especially as pesticides, for example the insecticide Carbofuran, as well as numerous pharmaceuticals. Industrially, the reaction of methyl isocyanate with hydroxy compounds is by far one of the most widely utilized procedures for the production of numerous N-methyl carbamates.

The Bhopal incident (India, 1984) has dramatically outlined the high toxicity level of methyl isocyanate and moreover its very exothermic self-polymerization which requires extreme care during its production and storage (Ref. 270).

In this volume, we have already examined some alternatives to the synthesis in situ and/or to the use of methyl isocyanate. We thought that 1,3-dimethyl diazetidine dione (**XII**) (methyl isocyanate dimer) should be a suitable methyl isocyanate precursor which can release methyl isocyanate in safe conditions. This dimer was prepared from N-chlorocarbonyl-N-methyl N'-methyl urea (**XI**) obtained by phosgenation of N,N'-dimethyl urea as previously described in scheme 156, section 3-3-4. Cyclization of (**XI**) in a suitable solvent and in presence of a base such as DABCO afforded the expected dimer (**XII**) as depicted in scheme 220.



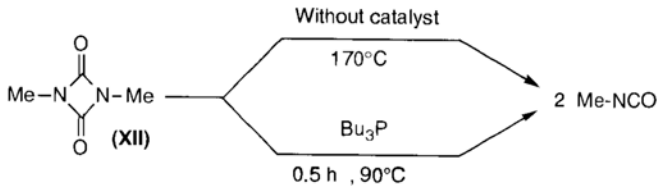
Scheme 220 : Preparation of methyl isocyanate dimer.

The NMR and IR analytical data of (**XII**) are the following :

^{1}H NMR (CDCl3) δ 2.87 ppm

IR 1780 cm^{-1}.

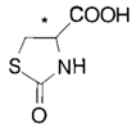
This dimer was thermically (170°C) or catalytically decomposed to 100% methyl isocyante as shown in scheme 221.



Scheme 221 : Use of (XII) as methyl isocyanate generator.

3-4-4 Cyclisation between a nitrogen atom and a sulfur atom

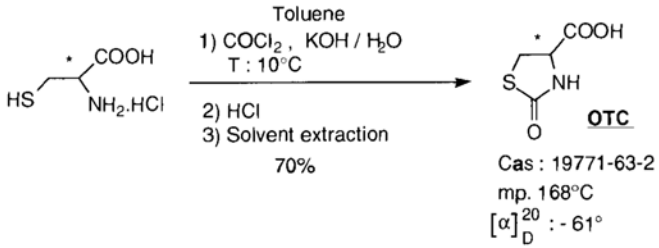
L-2-Oxothiazolidine-4-carboxylate (OTC) :



is a non-toxic precursor of cysteine proposed as a prodrug capable of penetrating into living cells. Therefore, its orally or parenterally administering to humans provides a method of restoring the glutathione level of numerous tissues where 5-oxoprolinase is present, especially in the liver (Ref. 271). In HIV-seropositive patients, it was proved to increase the levels of gluthatione, the lack of which is suspected to be a factor of their immunodeficiency (Ref. 272).

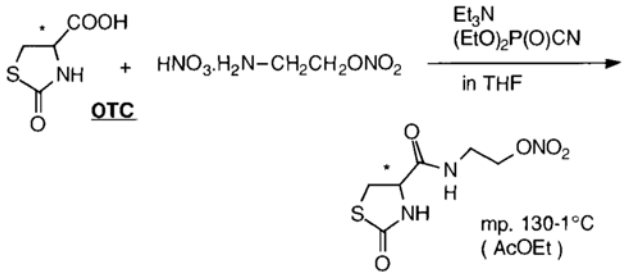
OTC is available by several methods, among them the reactions of phosgene (Ref. 273) or more recently triphosgene (Ref. 274), with L-Cysteine or L-Cysteine methyl ester appear the more convenient.

We developed at a laboratory scale a biphasic phosgenation process from L-Cysteine hydrochloride at controlled pH as depicted in scheme 222 (Ref. 275).



Scheme 222 : Preparation of OTC by phosgenation.

It is noteworthy that OTC can have other types of pharmaceutical applications than the delivery of cystein into the human body. For example, nitrated derivatives of OTC were recently patented as valuable coronary vasodilators which replace nitroglycerin without having its disadvantages (Ref. 276). An example of synthesis of these new interesting pharmaceuticals is given in scheme 223.



Scheme 223 : Preparation of a nitrated derivative of OTC as a vasodilator.

This is the end of volume 1 mainly dedicated to the use of phosgene and its direct derivatives as building blocks providing the carbonyl group in organic molecules.

Obviously, several major topics related to this type of applications are inadequately discussed or even purely and simply forgotten. Please forgive me for these inadequacies which are not at all intentional.

Also, the reader wiil understand that some sensitive subjects have been deliberately omitted for confidentiality reasons.

It is obvious that substantial work remains to be done and it is the author's secret hope that this first volume will serve as a catalyst to open the way to new research on the chemistry of phosgene.

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