

New α -chlorinated carbonates, process for the production thereof and application thereof to the protection of amine groups of amino acids

5 The invention relates to new α -chlorinated carbonates, to the process for the production thereof and to the application thereof to the protection of amine groups of amino acids.

10 Carbonates are very valued compounds which are employed in very different fields such as, for example, solvents, plasticizers, lubricants, transesterification agents or intermediates in peptide production.

15 In order to perform certain syntheses in which amino acids are involved, the amine group of these acids needs to be protected temporarily. This amine group is very often blocked by converting into a carbamate group which enables the racemization phenomenon to be avoided during coupling and it is easily cleaved, for example by acidolysis, hydrogenolysis or any other known method (E. Schröder and K. Lübke, "The Peptides", tome 1, page 20 39, Academic Press, New York - London 1965).

The groups which are most commonly employed for this purpose are:

25 benzyloxycarbonyl (Z),
tert-butyloxycarbonyl (BOC),
fluorenylmethyloxycarbonyl (Fmoc),
trichloroethyloxycarbonyl (TROC),
vinylloxycarbonyl (VOC).

The tert-butyloxycarbonyl (BOC) group is particularly valued.

30 The introduction of these protective groups is generally carried out by the action of the corresponding chloroformate on the amine group.

35 However, chloroformates cannot always be employed. Some are not very stable or are difficult to handle. This is so, for example in the case of para-methoxybenzyl, furfuryl or tert-butyl chloroformate. For example, the latter, even when it is prepared in situ, is not satisfactory because of the formation of ureas in the presence of an excess of phosgene.

Other carbamate-forming agents such as the following have been proposed:

azides of different protective groups. Their synthesis is performed in several stages and is difficult. They may decompose in an explosive manner, as in the case of the azide of BOC;

BOC fluoride, para-methoxybenzylfluoride or furfuryl fluoride; however, their preparation is difficult because it requires the use of starting materials such as ClCOF or BrCOF, which are not available on the market, which must be handled with care;

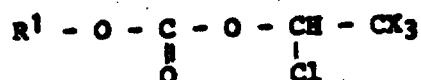
some tests have been carried out with very specific carbonates such as mixed carbonates of protective and para-nitrophenyl groups; however, they do not react with all amino acids. An alcohol or a phenol is formed, which is very often difficult to remove and the reaction is reversible;

dicarbonates of protective groups. Their synthesis is difficult and expensive. Additionally, a protective residue is lost;

carbonates of oxime, hydroxysuccinimide, enol or S-dimethylpyrimidyl, which are also difficult to prepare and require expensive starting materials.

Consequently, for many years, there has been an unsatisfied need for new compounds which are easy to produce with good yields, which are stable, which could be employed to attach without difficulty the most advantageous protective groups to the amine group of amino acids and which do not have the disadvantages of the abovementioned compounds.

According to the invention, the new alpha-chlorinated carbonates are of general formula:



in which X represents a fluorine, chlorine or bromine atom and R^1 is other than the group $\underset{\underset{Cl}{|}}{CH} - CCl_3$ and represents:

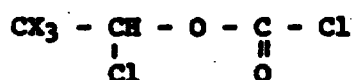
a substituted or unsubstituted, saturated or unsaturated

C₁ to C₂₀ aliphatic radical or C₇ to C₂₀ araliphatic radical (which aliphatic or araliphatic radicals may be primary, secondary or tertiary), or C₇ to C₂₀ alicyclic radical, the substituents of R₁ being chosen from
 5 amongst halogen atoms, groups containing silicon, and heterocyclic or non-heterocyclic groups containing nitrogen, oxygen or sulphur atoms.

X preferably represents chlorine.

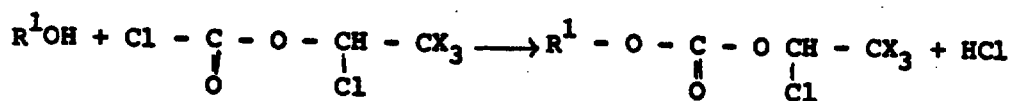
R¹ is especially chosen from amongst groups which
 10 are commonly employed for protecting, in the form of carbamates, the amine group of amino acids, such as tert-butyl, para-nitrobenzyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl or trimethylsilylethyl groups.

According to the invention, the new alpha-
 15 chlorinated carbonates are prepared by reacting a hydroxyl compound of formula R¹OH with an alpha-chlorinated chloroformate of formula:



X and R¹ having the above meanings, in a solvent medium
 20 at a temperature from -20° to +50°C in the presence of a hydrochloric acid-accepting agent which is added following the two reagents.

The following reaction takes place:



25 The solvent medium consists of one or more solvents which are inert towards the reagents. Chlorinated aliphatic solvents, for example dichloromethane or dichloroethane, cyclic or non-cyclic ethers, ketones such as acetone or 2-butanone, nitriles, esters or aliphatic
 30 or aromatic hydrocarbons are preferably chosen.

The acid-accepting agent is generally an organic or inorganic base. Pyridine or triethylamine is preferably employed.

The base is added following the two reactive components and preferably gradually.
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The temperature is preferably between -5° and $+5^{\circ}$. At the end of the reaction, the mixture may be brought to ambient temperature for a few minutes to a few hours.

5 The α -chlorinated chloroformates themselves may be prepared by the chlorination of chloroformates or preferably by the phosgenation of the corresponding aldehydes as described in European Application No. 40,153.

10 The starting compounds and the base are generally introduced in stoichiometric quantities. An excess of alcohol may be employed. The carbonate obtained is readily isolated by customary methods.

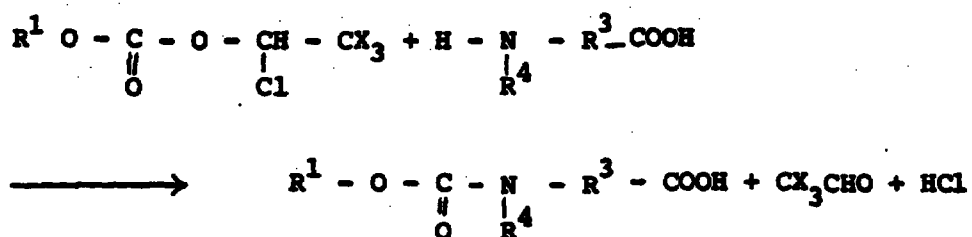
The carbonates of the invention have never been described in the literature until now. The presence of
15 a $\text{CX}_3\text{-CH-}$ group in their structure makes them highly
 $\begin{array}{c} | \\ \text{Cl} \end{array}$
 original and gives them very specific properties which make them very useful as synthesis intermediates.

The invention especially relates to an application of the new α -chlorinated carbonates.

20 In this application, the new α -chlorinated carbonates described above are employed to protect the amine group of amino acids.

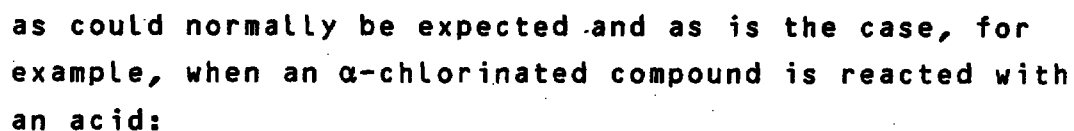
More precisely, they are reacted, in a solvent medium in the presence of a hydrochloric acid-binding agent and at a temperature of between -5° and 100°C , with
25 an amino- and/or iminocarboxylic acid containing at least one hydrogen atom on the amino or imino group, of formula $\text{NH-R}^3\text{-COOH}$ in which R^3 and R^4 , independently or linked
 $\begin{array}{c} | \\ \text{R}^4 \end{array}$
 represent the usual radicals of amino acids.

30 The reaction may be written as follows:



This reaction is surprising; there is an HCl

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The invention is most frequently applied to alpha-amino acids; however, beta-, gamma- and delta-amino acids may also be employed.

The carboxylic group may also be replaced by a sulphonic or phosphoric group.

As examples of amino acids, there may be mentioned L-phenylalanine, L-proline, glycine, L-tyrosine, L-serine, L-aspartic acid, ethyl glycinate, phenylglycine and L-alanine.

As α -chlorinated carbonates, those in which X is chlorine and the radical R^1 is one of the protective groups most commonly employed to acylate the amine group, for example 1,2,2,2-tetrachloroethyl 2',2',2'-trichloroethyl, 9-fluorenylmethyl, para-nitrobenzyl or 2-trimethylsilyl-ethyl carbonates, are preferably employed. These carbonates are especially highly valued in the case of unprotected hydroxyamino acids such as L-serine or L-tyrosine. 1,2,2,2-Tetrachloroethyl tert-butyl carbonate is particularly advantageous.

The presence of an acid-binding agent is essential for the removal of the hydrochloric acid formed during the reaction. This may be an organic or inorganic base.

Among preferred bases, there may be mentioned sodium or potassium hydroxide, sodium or potassium carbonate or bicarbonate, or magnesium oxide, which are generally employed in the form of an aqueous solution, or tertiary amines, for example pyridine or triethylamine.

The basic substance is most frequently introduced in an excess, preferably of the order to 1.1 to 3 equivalents per amine group to be protected.

It may be advantageous to maintain the pH constant throughout the period of reaction using conventional apparatuses.

The solvent medium may consist of one or more solvents which are inert towards the reagents. As organic solvent, chlorinated aliphatic solvents such as dichloromethane or 1,2-dichloroethane, cyclic or non-cyclic ethers, for example tetrahydrofuran or dioxane, acetone, pyridine, acetonitrile or dimethylformamide, or alcohols such as ethanol or tert-butanol are preferably chosen. Water may also be employed, alone or mixed with the solvents mentioned above. A 1:1 dioxane:water mixture is

particularly valued.

The reaction temperature depends on the nature of the solvent, on the reactivity of the starting compounds as well as on other reaction conditions. It is preferably
5 between 0° and 30°C.

Atmospheric pressure is the most commonly employed pressure. The reaction time is variable. It is generally between 0.5 and 36 hours and most frequently between 2 and 6 hours.

10 The starting compounds may be added in stoichiometric quantities. The use of an excess of one of the reagents is most frequently preferred.

The sequence of introduction of the reagents is not a fundamental characteristic of the invention. In
15 general, the α -chlorinated carbonate is added following the addition of the amino acid.

The blocked amino acids can readily be recovered and isolated in the crystalline form, converting them, if required, into ammonium salts, for example into di-
20 cyclohexylammonium salt.

Using the new α -chlorinated carbonates of the invention, obtained with starting materials which are available and by a simple process, it is possible to block in the form of carbamates, the amine group of
25 the wide variety of amino acids by known protective groups. Until now, this has either been impossible or very difficult to achieve. The yields are very high. The reaction conditions are mild and no racemization takes place.

30 All operations of desired coupling of the acid group, which are conventional in peptide synthesis (cf. for example, E. Gross & J. Meienhofer Eds, "The peptides. Analysis, synthesis, biology" Academic Press, New-York & London - Vol. 3 - 1980) may be carried out on the amino
35 acids thus protected.

These amino acid derivatives are widely employed as intermediates for the production of food products and pharmaceutical products. The synthesis of ASPARTAM (cf.

Tetrahedron, Vol. 39, No. 24, p. 4121 to 4126 - 1983.

B. YDE & AL) may, for example, be mentioned.

(21)

The invention is illustrated by the following examples.

5 Example 1

Synthesis of 1,2,2,2-tetrachloroethyl tert-butyl carbonate

9.9 g (0.04 mol) of 1,2,2,2-tetrachloroethyl chloroformate are added, in a single addition, to a solution of tert-butanol (3 g; 0.04 mol) in dichloromethane (50 ml). The mixture is cooled to 0°C and 3.2 g (0.04 mol) of pyridine are added dropwise. The mixture is stirred for 4 hours at ambient temperature. 20 ml of ice-cold water are then added and the organic phase is separated and washed with 20 ml of ice-cold water. It is dried over magnesium sulphate and the solvent is evaporated off. 11.3 g of a white solid (yield: 99%) are obtained, which are recrystallized in petroleum ether (yield 87%; m.p.: 70°C), and 9.9 g of purified carbonate are obtained.

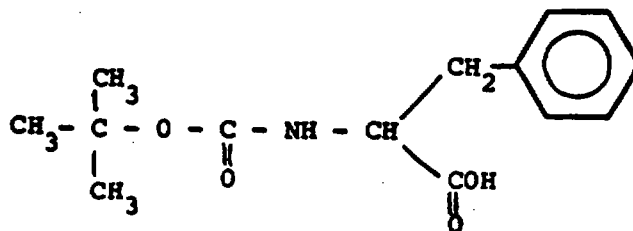
b.p.: 96°C/866 Pa (6.5 mm Hg)

20 IR: $\nu_{\text{CO}} = 1,770 \text{ cm}^{-1}$

$^1\text{H NMR}$ (CDCl_3 , TMS): 1.5 (s, CH_3) 6.7 (s, CH)

Example 2

Preparation of tert-butyloxycarbonyl-L-phenylalanine



4.2 ml (30 mmol) of triethylamine are added to a solution of L-phenylalanine (1.65 g; 10 mmol) in aqueous dioxane (1:1; 30 ml) and the mixture is stirred until the contents are dissolved (approximately 10 min). 2.85 g (10 mmol) of 1,2,2,2-tetrachloroethyl tert-butyl carbonate are then added and the mixture is stirred for 6 hours at 20°C. 50 ml of water are then added and extraction is carried out with 2 x 20 ml of ethyl acetate. The aqueous phase is acidified (pH 2-3) with 1 N HCl and then extracted with 3 x 30 ml of ethyl acetate. The extract is washed with saturated NaCl solution, dried over MgSO_4 and

evaporated. The product obtained is crystallized in ethyl acetate and petroleum ether. 2.1 g of the expected carbamate are obtained (yield: 79%); m.p.: 85-87°C; m.p.-lit. + 86-88°C; specific rotation = +28 (c = 1.5; EtOH);

lit. = 24.7 (c = 1.5; EtOH).

b) Preparation of N-tert-butyloxycarbonyl-L-alanine

The procedure is as in Example 2a).

Starting with 1.78 g (20 mmol) of alanine, 3.4 g (yield: 90%) of BOC-L-alanine are obtained.

m.p.: 80 - 81°C; m.p.-lit. = 83-84°C

$[\alpha]^{20}_D = -24.9$ (c = 2.1; AcOH); $[\alpha]^{20}_D = -22.4$ (c = 2.1; AcOH)

D

D

Example 3

Preparation of tert-butyloxycarbonyl-L-proline

The reaction is carried out as in Example 2.

Starting with 1.15 g (10 mmol) of L-proline, 1.95 g (yield: 91%) of the expected carbamate are obtained.

m.p.: 130-131°C; m.p.-lit.: 132-133°C.

$[\alpha]^{20}_D = -60$ (c = 2.0; AcOH); $[\alpha]^{20}_{D\text{lit.}} = -60.2$ (c = 2.0; AcOH)

D

D_{lit.}

20 Example 4

Preparation of tert-butyloxycarbonylglycine (BOC-Gly)

The reaction is carried as in Example 2.

Starting with 0.75 g (10 mmol) of glycine, 1.5 g (yield: 86%) of the expected carbamate are obtained.

25 m.p.: 80-85°C; m.p.-lit.: 86-88°C

Example 5

a) Preparation of BOC-Gly at controlled pH

5.6 g (0.075 mol) of glycine are dissolved in 150 ml of aqueous dioxane (50%) and the pH adjusted with 4 N sodium hydroxide. 23.6 g (0.083 mol) of 1,2,2,2-tetrachloroethyl tert-butyl carbonate are added in a single addition and the pH is maintained constant by adding 4 N sodium hydroxide. When the reaction is complete, approximately 200 ml of water are added and the aqueous phase is washed with 2 x 100 ml of ethyl ether. The aqueous phase is then acidified to pH 3 with 6 N HCl and extraction is carried out with 3 x 200 ml of ethyl acetate

(AcOEt). After drying and evaporating the solvent, crystallization is carried out in AcOEt:petroleum ether (40-70°C). BOC glycine is obtained, which melts at 85-87°C.

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PH	Time	Sodium hydroxide consumed	Yield isolated
10	5 h	2 eq	45%
9	20 h	2 eq	71.4%
8	30 h	1 eq	31%

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15 b) The reaction is carried out as in a) using various amino acids.

The results are collated in the following table:

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	Amino acid	pH	Yld %	m.p. °C	$[\alpha]_D^{20}$	c/solvent
5	Pro	8.6	80	135-136	- 60	2/AcOH
	Trp	8.3	74	135-140	- 21.2	1/AcOH
	Asp (OBzl)	*	42	98-100	- 19	2/DMF
	His (Tos)	10	50	154	+ 25.4	1/MeOH
	Ala	10.1	70	84	- 25.5	2/AcOH
10	Val	9.5	80	78	- 6.0	1/AcOH
	Ile	9.5	71	66	+ 3.3	1/AcOH
	Leu	9.75	95	75	- 27	1/AcOH
	Met	9.7	75	oil	-	-
	Glu (OBzl)	9	42	132 (DCHA salt)	+ 13.6	1,1/MeOH
15	His (Tos)	*	50	154	+ 25.4	1/MeOH
	Tyr (Bzl)	9.8	43	98-100	+ 27.4	2/EtOH
	Ser (Bzl)	9.5	74	61	+ 21	2/EtOH 80%
	Thr (Bzl)	9.0	76	114	+ 16.3	1/MeOH
	Arg (NO ₂)	9.5	25	100-114	- 23.0	1,9/pyridine
20	Cys (Acm)	9.5	46	-	-	-
	Lys (z)	10.2	84	oil	-	-

* base employed: triethylamine

Example 6Preparation of tert-butyloxycarbonyl-L-tyrosine

1.81 g (10 mmol) of tyrosine are dissolved in 20 ml of aqueous dioxane (1:1) by adding 1.4 ml (10 mmol) of triethylamine and 15 mmol of sodium hydroxide. 2.85 g (10 mmol) of 1,2,2,2-tetrachloroethyl tert-butyl carbonate are then added and the mixture is stirred for 6 hours at 20°C.

The rest of the procedure is as in Example 2.

The product obtained is crystallized in the form of the dicyclohexylammonium salt. 3.8 g (yield: 82%) are obtained.

m.p.: 206°C; m.p.-lit.: 212°C.

Example 7Preparation of tert-butyloxycarbonyl-L-serine

The reaction is carried out as in Example 2, the reaction time being 24 hours instead of 6 hours. Starting with 1.05 g (10 mmol) of L-serine, 3.1 g (yield: 78%) of the desired carbamate are obtained in the form of the dicyclohexylammonium salt.

m.p.: 139-140°C; m.p.-lit.: 140-142°C

$[\alpha]^{20}_D = +8$ (c 2.8; MeOH); $[\alpha]^{20}_{lit.} = +13$ (c = 3.0; MeOH)

Example 8Preparation of tert-butyloxycarbonyl-L-aspartic acid

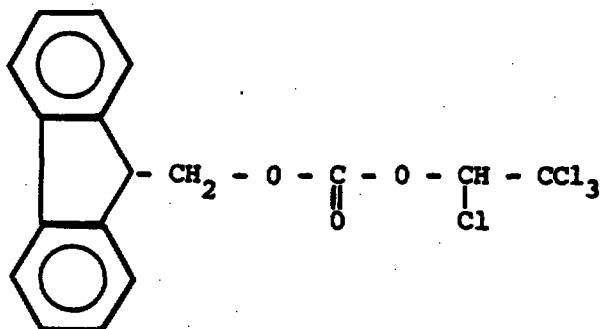
The reaction is carried out as in the previous example.

Starting with 1.33 g (10 mmol) of L-aspartic acid, 1.4 g (yield: 60%) of the expected acid are obtained.

m.p.: 116-118°C; m.p.-lit.: 114-116°C

$[\alpha]^{20}_D = -5$ (c = 1.0; MeOH); $[\alpha]^{20}_{lit.} = -6.2$ (c = 1.0; MeOH)

Example 9Preparation of 1,2,2,2-tetrachloroethyl 9-fluorenylmethyl carbonate



6.7 g (0.027 mol) of 1,2,2,2-tetrachloroethyl
chloroformate are added, in a single addition, to a solu-
tion of 9-fluorenylmethanol (4.9 g; 0.025 mol) in 50 ml
5 of dichloromethane.

The mixture is cooled to 0°C and 2.2 ml of pyri-
dine are added dropwise. The mixture is stirred for
4 hours at 0°C. 50 ml of dichloromethane are then added
and the organic phase is washed with 2 x 50 ml of ice-cold
10 water. Drying is carried out over magnesium sulphate and
the solvent is evaporated off. The residue is crystal-
lized in hexane and 9.3 g of the expected carbonate
(yield: 98%) are obtained.

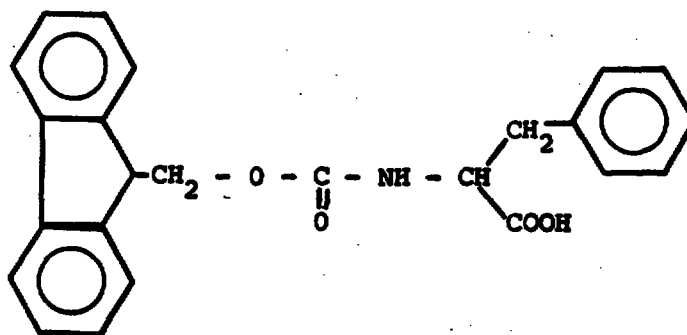
m.p.: 98-100°C

15 IR: $\nu_{C=O}$: 1,750 cm^{-1}

^1H NMR: (CDCl_3 , TMS): 4.5 ppm $\text{CH}_2\text{-O}$; 6.75 ppm CH-Cl
0

Example 10

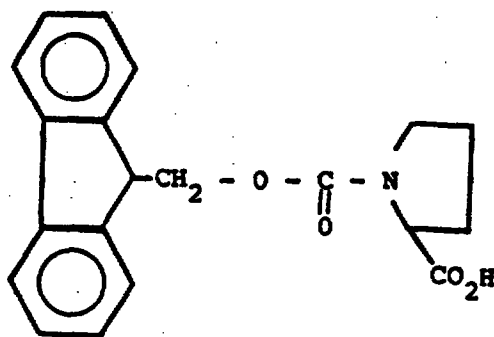
Preparation of 9-fluorenylmethoxycarbonyl-L-phenyl- 20 alanine



0.83 g of L-phenylalanine (5 mmol) is dissolved in aqueous dioxane (1:2; 12 ml) containing 1.4 ml of triethylamine (10 mmol). The mixture is cooled to 0°C and 2.05 g (5 mmol) of the above carbonate dissolved in 4 ml of dioxane are added in a single addition. After 2 hours at 0°C, 20 ml of water are added and extraction is carried out with 2 x 20 ml of ether. The aqueous phase is then acidified (pH 2-3) with 6 N HCl and extraction is carried out with 3 x 50 ml of ethyl acetate. Drying over MgSO₄ and evaporation are carried out. The product obtained crystallizes in ethyl acetate and petroleum ether; 1.44 g of the expected derivative (yield: 75%) are obtained.
m.p.: 178-179°C
m.p. (lit.): 178-179°C (lit.: L-Lapatsanis et al. Synthesis (1983) 671).

Example 11

Preparation of 9-fluorenylmethyloxycarbonyl-L-proline (FMOC-Pro)

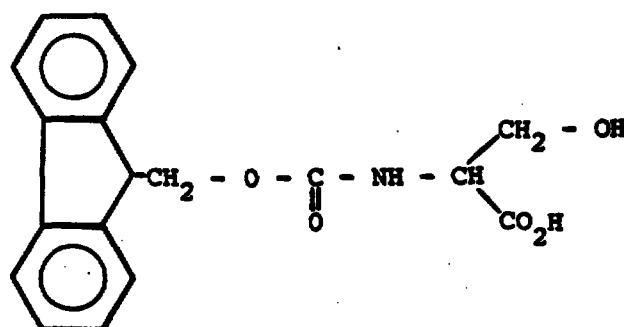


The procedure is as in Example 10. Starting with 0.58 g (5 mmol) of L-proline, 1.4 g (yield: 83%) of FMOC-L-proline are obtained.
m.p.: 112-113°C (m.p. (lit.): 116-117°C)

Example 12

Preparation of 9-fluorenylmethyloxycarbonyl-L-serine

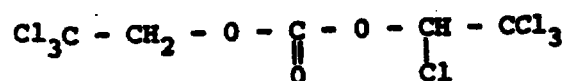
(28)



5 The procedure is as in Example 10, but the reaction is continued for 24 hours at 20°C. Starting with 0.53 g (5 mmol) of L-serine, 1.32 g (yield: 81%) of FMOC-(L)-serine are obtained. M.p.: 73-75°C. m.p. after recrystallization = 83-86°C (m.p. lit.: 86-88°C)

Example 13

Preparation of 2,2,2-trichloroethyl 1',2',2',2'-tetrachloroethyl carbonate



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The procedure is as in Example 1. Starting with 14.9 g of trichloroethanol (0.1 mol), 24.1 g (yield: 67%) of the expected carbonate are obtained.

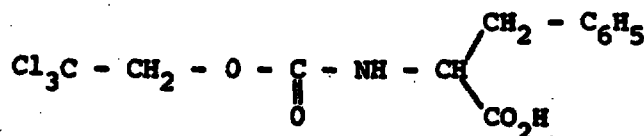
b.p.: 108°C/6.6 Pa; m.p.: 36°C

15 IR: $\nu_{\text{CO}} = 1,770 \text{ cm}^{-1}$

^1H NMR (CDCl_3 , TMS): 4.85 (s, CH_2) 6.7 (s, CH)

Example 14

Preparation of trichloroethoxycarbonyl-L-phenylalanine (TROC-L-Phe)



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The procedure is as in Example 10. Starting with 0.83 g (5 mmol) of L-phenylalanine and 1.98 g (5.5 mmol) of 2,2,2-trichloroethyl 1',2',2',2'-tetrachloroethyl carbonate, 1.43 g (yield: 84%) of TROC-L-phenylalanine are obtained.

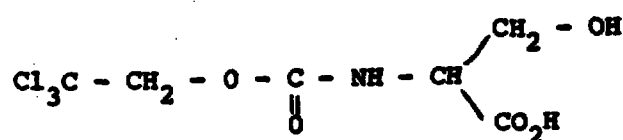
25

m.p.: 128-129°C (m.p. lit.: 129-130°C)

(59)

Example 15

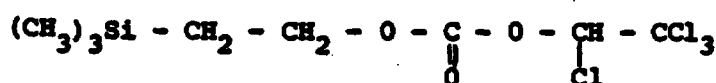
Preparation of trichloroethoxycarbonyl-(L)-serine



5 The procedure is as in Example 12. Starting with 0.53 g (5 mmol) of L-serine and 1.98 g (5.5 mmol) of the carbonate as in Example 13, 1.15 g (yield: 82%) of TROC-L-serine are obtained. m.p.: 111-113°C; m.p.-lit.: 114-115°C.

Example 16

10 Preparation of 1,2,2,2-tetrachloroethyl 2-trimethylsilyl-ethyl carbonate

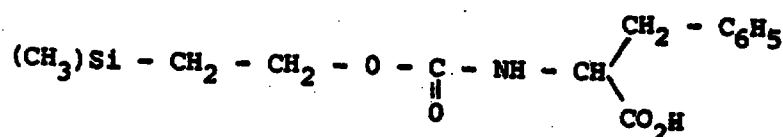


15 The procedure is as in Example 1. Starting with 5.91 g of trimethylsilylethanol and 12.35 g of tetrachloroethyl chloroformate, 13.6 g (yield: 83%) of the expected product are obtained. b.p.: 92-94°C/6.6 Pa
IR: $\nu_{\text{CO}} = 1,750 \text{ cm}^{-1}$

^1H NMR (CDCl_3 , TMS external): 0.1 (s, $\text{CH}_3\text{-Si}$) 1.1 (t, CH_2Si)
4.35 (t, $\text{CH}_2\text{-O}$) 6.7 (s, CH-Cl)

20 Example 17

Preparation of trimethylsilylethyloxycarbonyl-(L)-phenylalanine



25 The procedure is as in Example 12. Starting with 0.83 g (5 mmol) of phenylalanine and 1.8 g (5.5 mmol) of the above carbonate, 1.4 g (yield: 100%) of trimethylsilylethyloxycarbonyl-L-phenylalanine are obtained in the form of an oil.

^1H NMR (CDCl_3 , TMS) 0 (s, $\text{CH}_3\text{-Si}$) 0.9 (t, $\text{CH}_2\text{-Si}$) 3.0

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(CH₂Ph)

4.0 (t, O-CH₂-C-Si) 4.5 (m, CH-N) 5.2 (s, NH)
CO₂

7.2 (s, Ph-H) 8.7 (C-OH)
O

5

2 ml of dicyclohexylamine are added to this oil dissolved in 5 ml of ether and after crystallization, 1.93 g (yield: 78%) of the dicyclohexylammonium salt are collected. m.p.: 111-112°C.

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Example 18

Synthesis of para-nitrobenzyl 1,2,2,2-tetrachloroethyl carbonate

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3.83 g (25 mmol) of para-nitrobenzyl alcohol and 6.17 g (25 mmol) of 1,2,2,2-tetrachloroethyl chloroformate are dissolved in 50 ml of dichloromethane. The mixture is cooled to 0°C and 2.02 ml of pyridine are added dropwise. The mixture is stirred for 4 hours at 10°C and then, 50 ml of ice-cold water are added, the organic phase is separated and further washing is carried out with 2 x 50 ml of water. The organic phase is dried over magnesium sulphate, the solvent is evaporated off and 8.7 g of the desired product (yield: 96%) are obtained.

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b.p.: 190-195°C/0.05 mm Hg.

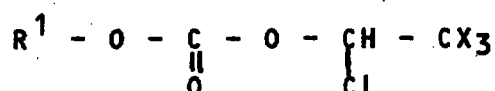
m.p.: 53-55°C (crystallization solvent: aqueous ethanol; crystallization yield: 54%).



(21)

Claims

1. New alpha-chlorinated carbonates characterized in that they have the formula:



5 in which X represents a fluorine, chlorine or bromine atom and R^1 is other than the group $\underset{\text{Cl}}{\underset{|}{CH}} - CCl_3$ and

represents:

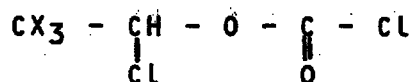
a substituted or unsubstituted, saturated or unsaturated C_1 to C_{20} aliphatic radical or C_7 to C_{20} araliphatic
10 radical (which aliphatic or araliphatic radicals may be primary, secondary or tertiary), or C_7 to C_{20} alicyclic radical, the substituents of R^1 being chosen from amongst halogen atoms, groups containing silicon, and heterocyclic or non-heterocyclic groups containing nitrogen, oxygen or
15 sulphur.

2. Alpha-chlorinated carbonates according to Claim 1, characterized in that X is chlorine.

3. Alpha-chlorinated carbonates according to any one of the preceding claims, characterized in that R^1 is the
20 tert-butyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl, trimethylsilylethyl or para-nitrobenzyl group.

4. Alpha-chlorinated carbonate according to any one of the preceding claims, characterized in that it is 1,2,2,2-tetrachloroethyl tert-butyl carbonate.

25 5. Process for the preparation of alpha-chlorinated carbonates according to any one of the preceding claims, characterized in that a compound of formula R^1OH is reacted with an alpha-chlorinated chloroformate of formula:



X and R¹ having the above meanings, in a solvent medium at a temperature from -20° to +50°C in the presence of an acid-accepting agent which is added following the two starting compounds.

6. Process according to Claim 5, characterized in that the acid-accepting agent is an organic or inorganic base.
- 10 7. Process according to Claim 6, characterized in that the base is added gradually.
8. Process according to Claim 6 or 7, characterized in that the base is pyridine or triethylamine.
9. Process according to any one of Claims 5 to 8,
- 15 characterized in that the solvent medium consists of one or more solvents which are inert towards the reagents, chosen from amongst chlorinated aliphatic solvents, cyclic or non-cyclic ethers, ketones, nitriles, esters and aliphatic or aromatic hydrocarbons.
- 20 10. Use of the alpha-chlorinated carbonates according to any one of Claims 1 to 4, characterized in that the alpha-chlorinated carbonate is reacted, in a solvent medium in the presence of an acid-binding agent and at a temperature of between -5° and 100°C, with an amino- and/or imino-
- 25 carboxylic acid containing at least one hydrogen atom bound to the amino or imino group, of formula $\text{NH} - \text{R}^3 - \text{COOH}$
 $\quad \quad \quad |$
 $\quad \quad \quad \text{R}^4$
- in which R³ and R⁴, independently or linked together, represent the usual radicals of natural or synthetic amino acids.
- 30 11. Use according to Claim 10, characterized in that the amino acid is a natural or synthetic compound which may or may not be optically active or may be racemic.
12. Use according to Claim 10 or 11, characterized in
- 35 that R⁴ represents a hydrogen atom, R³ a C₁ to C₂₀ aliphatic or C₇ to C₂₀ araliphatic radical which may be substituted or unsubstituted, saturated or unsaturated; or R³ and R⁴ are linked together and form, with the nitrogen atom, a



33

saturated or unsaturated, substituted or unsubstituted
4- to 6-membered heterocycle.

13. Use according to any one of Claims 10 to 12,
characterized in that R^3 and/or R^4 are substituted with
5 functional groups which may be blocked or otherwise.

14. Use according to any one of Claims 10 to 13,
characterized in that the carboxyl group of the amino acid
is replaced by a sulphonic or phosphoric group.

15. Use according to any one of Claims 10 to 14,
10 characterized in that the amino acid is in the form of an
acid derivative.

16. Use according to any one of Claims 10 to 15,
characterized in that the amino acid is L-phenylalanine,
L-proline, L-glycine, L-tyrosine, L-serine, L-aspartic
15 acid, ethyl glycinate, phenylglycine, L-alanine, L-trypto-
phan, benzyl ester of aspartic acid, histidine, histidine
tosylate, alanine, valine, isoleucine, leucine, methionine,
benzyl ester of glutamic acid, benzyl ether of tyrosine,
of serine and of threonine, nitroarginine, benzyloxycar-
20 bonyllysine or acetamidomethylcysteine.

17. Use according to any one of Claims 10 to 16,
characterized in that the solvent medium consists of one
or more solvents which are inert towards the reagents,
chosen from amongst chlorinated aliphatic solvents, cyclic
25 or non-cyclic ethers, acetone, pyridine, acetonitrile,
dimethylformamide and alcohols.

18. Use according to Claim 17, characterized in that
the solvent medium contains water.

19. Use according to Claim 18, characterized in that
30 the solvent medium is a dioxane-water mixture in the
ratio 1:1.

20. Use according to any one of Claims 10 to 19,
characterized in that the acid-binding agent is an organic
or inorganic base.

35 21. Use according to Claim 20, characterized in that
the base is chosen from amongst sodium or potassium hy-
droxide, sodium or potassium carbonate or bicarbonate,
magnesium oxide and tertiary amines.



22. Use according to Claim 21, characterized in that the tertiary amine is pyridine or triethylamine.
23. Use according to any one of Claims 10 to 22, characterized in that the reaction is carried out at a temperature of between 0° and 30°C.
24. Use according to any one of Claims 10 to 23, characterized in that the pH value is maintained constant.