5-Norbornene-2,3-dicarboximido Carbonochloridate. A New Stable Reagent for the Introduction of Amino-Protecting Groups

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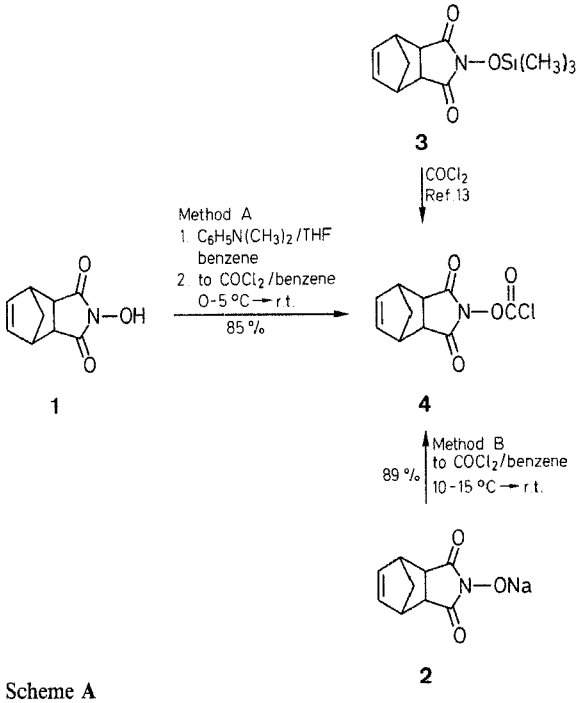
The synthesis of activated carbonates, based on a new carbonochloridate derived from N-hydroxy-5-norbornene-2,3-dicarboximide, is reported. These activated carbonic esters are excellent reagents for the introduction of all currently used urethane protecting groups.

Carbonochloridates (chloroformates) are important starting materials for the introduction of amino-protecting groups, especially in peptide chemistry. After the description of the benzyloxycarbonyl group by Bergmann und Zervas in 1932,[1] several related urethane-type amino-protecting groups were developed.[2,3,4] Common reagents for the introduction of these groups are azides,[5] active esters,[6,7,8] acid chlorides,[9,10] and fluorides.[11,12] However, the use of some of these reagents requires several steps or expensive starting materials, and for each protecting group a different type of reagent is needed.

In our work on protection and coupling reactions in peptide synthesis we tried to unify and simplify the key procedures by using a common precursor. For this purpose activated esters of carbonochloridic acid appeared to be the most appropriate candidates.

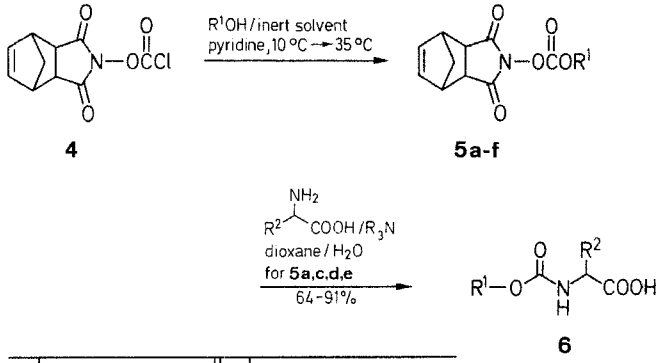
All such active esters should be derived from the new carbonochloridate **4**, which is based on *N*-hydroxy-5-norbornene-2,3-dicarboximide (**1**), a compound first used for the activation of protected amino acids.[13]

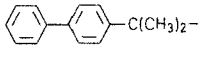
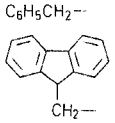
As shown in Scheme **A**, we synthesized 5-norbornene-2,3-dicarboximido carbonochloridate **4** from **1**, its sodium or potassium salts **2** or its trimethylsilyl derivative **3** by means of reaction with phosgene.[14]



Scheme **A**

Although **4** is highly reactive, it can be obtained as a colorless solid, which can be stored with exclusion of air and moisture for extended periods. Carbonochloridate **4** reacts with alcohols in the presence of pyridine to give activated carbonates **5**, which are excellent reagents for the introduction of all currently used urethane protecting groups.



5	R^1	5	R^1
a	t-C_4H_9–	d	
b	$C_6H_5CH_2$–	e	
c		f	$H_3C–SO_2–(CH_2)_2$–

Scheme **B**

Compounds **5a–f** can also be synthesized in a one-pot procedure, in which **4** is produced *in situ* from **1** and phosgene and reacted further with an appropriate alcohol. Benzyl derivative **5b** was also obtained by the reaction of benzyl carbonochloridate and **1**.[15] All carbonates **(5a–f)** are crystalline compounds and can be stored for unlimited periods.

Reaction of carbonates **5a–f** with amino acid salts in dioxane/water gives the corresponding protected amino acids **6** in yields of 64–91%. The *N*-hydroxy-5-norbornene-2,3-dicarboximide **(1)** liberated during the reaction can be easily removed due to its ready solubility in water. No dipeptide by-products were formed, according to HPLC analysis.[16]

Table 1. 5-Norbornene-2,3-dicarboximido Carbonates **5** Prepared.

Product	m.p. (°C)	Molecular Formula[a]	MS (70 eV)[b]
5a	124–26	$C_{14}H_{17}NO_5$ (279.3)	279.3
5b	121–23	$C_{17}H_{15}NO_5$ (313.4)	313.4
5c	143–45	$C_{24}H_{19}NO_5$ (401.1)	401.1
5d	220–21	$C_{20}H_{23}NO_5$ (357.1)	357.1
5e	121–24	$C_{25}H_{23}NO_5$ (417.4)	417.4
5f	124–26	$C_{13}H_{15}NO_7$ (329.3)	329.3

[a] Satisfactory microanalyses obtained: C, H, N ± 0.2.
[b] Recorded on a Kratos AEI MS 902S spectrometer.

Table 2. Urethane-protected Amino Acid Derivatives Prepared[a]

Reagent	Protected Amino Acid	Mp(°C)	Yield (%)
5a	Boc-Ala-OH	82	87
	Boc-Gly-OH	85–87	85
	Boc-Leu-OH	79–83	91
	Boc-Trp-OH	126–38	86
	Boc-Phe-OH	82–84	91
5c	Fmoc-Ala-OH	144	91
	Fmoc-Gly-OH	172–74	81
	Fmoc-Asp(O-*t*-Bu)-OH	148–49	64
	Fmoc-Phe-OH	180–82	87
	Fmoc-Val-OH	142–44	85
5d	Adoc-Phe-OH	60–63	82
	Adoc-Ala-OH	140–41	84
5e	Bpoc-Pro-OH	122–24	81
	Bpoc-Phe-OH	85–87	79

[a] Boc = *t*-butoxycarbonyl; Fmoc = (9-fluorenylmethoxy)carbonyl; Adoc = adamantyloxycarbonyl; Bpoc = [2-(4-biphenylyl)-2-propoxy]carbonyl.

Caution: working with phosgene is extremely hazardous and requires special precautionary measures.[17]

5-Norbornene-2,3-dicarboximido Carbonochloridate 4:

Method A: A solution of *N*-hydroxy-5-norbornene-2,3-dicarboximide (**1**; 17.9 g, 0.1 mol) and *N,N*-dimethylaniline (12 g, 0.095 mol) in tetrahydrofuran/benzene (1:3; 100 ml) is added dropwise to a solution of phosgene (9.9 g, 0.1 mol) in benzene (50 ml) at 0–5 °C. The mixture is stirred for 1 hour at 5 °C and for 3 hours at room temperature. The amine hydrochloric is filtered, and the solution evaporated to dryness *in vacuo*. The residue is dissolved in dichloromethane (50 ml), and a trace of bis(5-norbornene-2,3-dicarboximido) carbonate is removed by filtration. The solvent is removed *in vacuo*, and the residue triturated with ether (50 ml) to give **4**; yield: 20.5 g (85%); m.p. 98–100 °C (dec.)

$C_{10}H_8O_4NCl$ (241.6) calc. Cl 14.69 found 14.74

HRMS: calc. for $C_{10}H_8O_4NCl$, *m/e* = 241.0149; found 241.0142

IR (KBr): ν = 1815, 1795, 1740 cm^{-1} (C=O).

Method B: To a stirred solution of phosgene (247 g, 180 ml, 2.5 mol) in dry benzene (1.5 l), the sodium salt of **1** (201 g, 1 mol; synthesized from **1** and sodium hydroxide in methanol) is added portionwise at 15 °C. Stirring is continued for 2 h at 10–15 °C and the solution concentrated to a volume of 400 ml. After standing overnight the mixture is filtered and the precipitate washed with benzene (2 × 50 ml). Concentration of the benzene solution and trituration of the resultant residue with ether (300 ml) gives 158 g (68%) of **4**. Concentration of the ether filtrate to a volume of 150 ml followed by addition of hexane (150 ml) gives a second crop of **4** (56 g); overall yield: 214 g (89%).

Carbonates 5a–e

5-Norbornene-2,3-dicarboximido carbonochloridate **4** (24.1 g, 0.1 mole) is dissolved in an inert solvent (toluene, benzene tetrahydrofuran or a halogenated hydrocarbon; 150 ml) and a solution of the appropriate alcohol (0.1 mole) and pyridine (8 ml) in an inert solvent (40 ml) is added at 10–15 °C. The reaction mixture is stirred for 1 h at room temperature and for 3 h at 35 °C. The pyridine hydrochloride precipitate is filtered and the solution evaporated to dryness. Further purification is carried out either by recrystallization of the solid from 90% aqueous methanol or by extraction of the impurities from a dichloromethane solution first with 5% aqueous sodium hydrogencarbonate solution and then water at 5 °C, followed by drying with sodium sulfate and evaporation to give the pure carbonates (Table 1).

Urethane-Protected Amino Acids; General Procedure:

To a stirred solution of the amino acid (10 mmol) in a mixture of dioxane/water, 1:1 (20 ml) is added a tertiary amine (12 mmol). After 5 min, **5** (12 mmol) in dioxane (10 ml) is added and stirring continued for 2–3 h. After complete reaction (TLC control) the organic solvent is evaporated and the resultant mixture acidified to pH 2–3. The urethane-protected amino acids are extracted with dichloromethane, dried with sodium sulfate and the solution concentrated. The crude products are collected and recrystallized as indicated in the Table 2.

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