Preparation of Carbodiimides from Phosphoramidates

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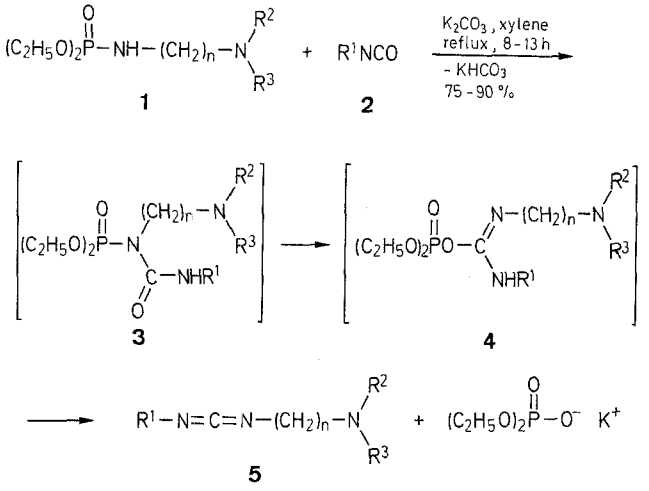
ω-Dialkylaminoalkylphosphoramidates are converted to ω-dialkylaminoalkyl(alkyl)carbodiimides in good yield in a two-phase system by reaction with isocyanates.

Water-soluble carbodiimides are valuable reagents in peptide chemistry and biochemistry,[1] usually as quaternary ammonium salts. They do not decompose in water and can therefore be used in aqueous solution for peptide coupling or to link enzymes to a solid support.

Though several methods are available for the synthesis of unsymmetrically substituted carbodiimides,[2,3] none of them is quite suitable for the preparaton of water-soluble carbodiimides. Recently, we reported a method for the synthesis of such carbodiimides starting from disubstituted ureas.[4] We describe here another simple method for the preparation of ω-dialkylaminoalkyl(alkyl)carbodiimides **5** from phosphoramidates **1** and isocyanates **2**.

This method is already known,[5] but it requires sodium hydride for the generation of the anion of phosphoramidate **1**, and the product so obtained is never sufficiently pure. Our method does not require either the presence of strong bases or strictly anhydrous conditions, and the product is usually obtained in analytically pure form without any destillation or crystallization steps. The reaction is carried out by stirring phosphoramidate **1** with isocyanate **2** in boiling xylene in the presence of solid potassium carbonate as a base.



4	R^1	R^2	R^3	n
a	c-C_6H_{11}	CH_3	CH_3	2
b	c-C_6H_{11}	CH_3	CH_3	3
c	n-C_4H_9	CH_3	CH_3	3
d	c-C_6H_{11}	C_2H_5	C_2H_5	3
e	C_6H_5	CH_3	CH_3	3
f	c-C_6H_{11}	$-CH_2CH_2OCH_2CH_2-$		2
g	c-C_6H_{11}	$-CH_2CH_2N(CH_3)CH_2CH_2-$		3
h	c-C_6H_{11}	$-(CH_2)_5-$		3
i	c-C_6H_{11}	$-(CH_2)_4-$		3

Although the reaction is heterogenous, it does not require a phase-transfer catalyst. We assume that the role of the latter is taken over by the phosphoramidate anion. In contrast to the sodium hydride method, phosphoramidate anion is not present in large amounts in the reaction mixture, because its generation and reaction with the isocyanate molecule may take place simultaneously on the surface of potassium carbonate resulting in the phosphorylated urea intermediate **3**. This is followed by rearrangement (N → O 1,3-phosphoryl migration) to **4** and elimination of the phosphate anion.[5]

The reaction can be monitored by GLC. The carbodiimides are isolated by filtering the solid potassium carbonate and potassium diethyl phosphate. The filtrate, after evaporation, gives the pure carbodiimide as a pale oil, which can be destilled under reduced pressure. The results are summarized in Table 1.

The carbodiimides can best be isolated by quaternization giving colorless, water-soluble crystalline products. For this purpose any alkylating agent such as methyl iodide, benzyl bromide or methyl *p*-toluenesulfonate may be used[4] (Table 2).

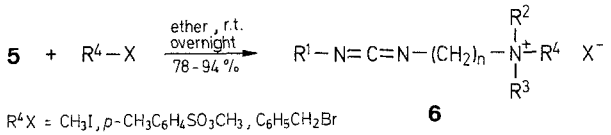


Table 1. Carbodiimides **5** Prepared

Product	Reaction Time (h)	Yield (%)	bp (°C)/Torr	Molecular Formula[a] or Lit. bp (°C)/Torr	IR (neat) ν_{NCN} (cm^{-1})
5a	8	90	85–86/0.25	84–86/0.5[8]	2190
5b	8	89	105/0.1	89.5–91.5/0.4[9]	2200
5c	10	75	75–79/0.1	$C_{10}H_{21}N_3$ (183.3)	2190
5d	8	83	102/0.1	$C_{14}H_{27}N_3$ (223.4)	2205
5e	9	78	91–95/0.08	$C_{12}H_{17}N_3$ (203.3)	2195
5f	13	82	120–122/0.1	145/0.2[1]	2180
5g	12	80	dec[b]	$C_{15}H_{28}N_4$ (196.3)	2180
5h	10	84	dec[b]	$C_{15}H_{27}N_3$ (249.4)	2200
5i	10	86	125–127/0.2	$C_{14}H_{25}N_3$ (235.4)	2200

[a] Microanalyses obtained: C ±0.49, H ±1.82, N ±1.44; except **1h** (H −2.38) and **1i** (H −3.08, N −2.69).
[b] The filtrate is stirred over 2 g silica gel.

Table 2. Quaternary Salts **6** of Carbodiimides **5**

Product	Carbodiimide	Quaternizing Agent	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν_{NCN} (cm^{-1})
6a	**5a**	CH_3I	86	161–163	129–132[8]	2105
		CH_3OTs	92	149–151	$C_{19}H_{31}N_3O_3S$ (381.5)	2120
6b	**5b**	CH_3I	86	161–163	161.5–163[9]	2105
		$PhCH_2Br$	78	142–145	$C_{19}H_{30}BrN_3$ (380.4)	2130
6c	**5c**	CH_3OTs	90	127–128	$C_{18}H_{31}N_3O_3S$ (369.5)	2150
6d	**5d**	CH_3I	82	168–169	$C_{15}H_{30}IN_2$ (365.3)	2110
6e	**5e**	CH_3I	86	171–172	172.4–173.4[10]	2110
6f	**5f**	CH_3OTs	89	113–114	113–115[1]	2120
6g	**5g**	CH_3I	94	177–181	$C_{16}H_{31}IN_4$ (406.35)	2105
		CH_3OTs	89	154–156	$C_{23}H_{38}N_4O_3S$ (450.6)	2108
6h	**5h**	CH_3I	83	–[b]	$C_{16}H_{30}IN_3$ (391.3)	2175
6i	**5i**	CH_3I	81	–[b]	$C_{15}H_{28}IN_3$ (377.3)	2170

[a] Microanalyses obtained: C ±0.72, H ±1.41, N ±1.05; except **6a**B (H −2.12), **6c**B (H −2.48), **6h**A (C −1.18, H −1.81, N +4.37) and **6i**A (H +4.41, N +4.69).
[b] Oily crystals.

The *N*-substituted diethyl phosphoramidates **1** are prepared from diethyl phosphite and the appropriate diamine in an 1:1 mixture of benzene and 2N sodium hydroxide in the presence of carbon tetrachloride and a quaternary ammonium salt.[6,7]

ω-Dialkylaminoalkyl(alkyl)carbodiimides 5; General Procedure:
The appropriate *N*-substituted diethyl phosphoramidate **1** (0.01 mol) is dissolved in xylene (40 mL) and K_2CO_3 (5.5 g, 0.04 mol) and isocyanate **2** (0.011 mol) are added. The mixture is stirred under reflux for 8–13 h. After the disappearance of phosphoramidate (GLC), the mixture is cooled and filtered. The filtrate is evaporated and the remaining oil is generally the pure carbodiimide **5**. It can be destilled in high vacuum.

In the case of **5g** and **5h** the xylene solution stirred over silica **(2g)** before evaporation.

Quaternary Salts 6 of Carbodiimides 5; General Procedure:
To the solution of the appropriate carbodiimide (0.01 mol) in dry ether (20 mL), the alkylating agent [methyl iodide (1.4 g, 0.01 mol), or methyl *p*-toluenesulfonate (1.9 g, 0.01 mol), or benzyl bromide (1.6 g, 0.01 mol)] is added. The mixture is allowed to stand overnight at r.t. The precipitate is filtered off and washed with dry ether to give the carbodiimide quaternary salt (Table 2).

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