Convenient and Improved Synthesis of Unstable Carbodiimides

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Carbodiimides have been applied in the synthesis of amidines, anhydrides, amides, carboxylic acids, sulfonic acids, esters, and other functional compounds[1,2,3]. Commercially available dicyclohexylcarbodiimide has found widespread application in peptide synthesis[4]. Carbodiimides are also valuable intermediates for the synthesis of isoureas[5,6], substituted guanidines[2,3,7], and a variety of heterocyclic systems[2,3]. Early methods for preparation of carbodiimides were based on the dehydrosulfurization of thioureas by mercury, silver, or lead oxides[2,3]; tedious isolation of the carbodiimides from metallic sulfides is an important short-coming of these methods[8]. Methods of dehydration of ureas by organic sulfur and phosphorus reagents like *p*-toluenesulfonyl chloride[8], triphenylphosphine/carbon tetrachloride[9], and triphenylbromophosphonium bromide[10] overcome the above difficulties, but lead to poor yields of unstable carbodiimides. Some aromatic and aliphatic carbodiimides are liquids and can be distilled, however a large number of them are unstable and, on thermal treatment, decompose or polymerize[2]. Decomposition and polymerization also occur often on prolonged standing. For example, diethylcarbodiimide polymerizes within a few days[11]. Phenylmethylcarbodiimide is extremely unstable, polymerizing even at $-20\,^{\circ}C$[12]. It cannot be distilled, but can be gas chromatographed at 65 °C on a SE 30 column[13]. In general, the stability of carbodiimides increases with the degree of branching of the alkyl substituents attached to the nitrogen atom: $RCH_2 < R_2CH < R_3C$[11].

We report that good yields of carbodiimides **4** can be achieved by a modification of the method described by Bestmann et al.[10]. These authors performed the dehydration of ureas **1** by bromotriphenylphosphonium bromide (**2**)/triethylamine in benzene under reflux. We have found that much better yields, especially for unstable carbodiimides, can be attained by slow addition of

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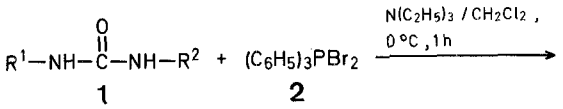
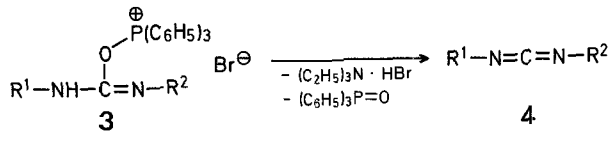
Table. Carbodiimides **4** from Ureas **1**

Product No.	R^1	R^2	Method	Reaction conditions Temperature/time	Yield [%]	b.p. [°C]/torr	Molecular formula[a] or Lit. b.p. [°C]/torr	I.R. (CH_2Cl_2) $\nu_{N=C=N}$ [cm^{-1}]
4a	CH_3	C_6H_5	A	40 °C/120 min	37	—[b]	$C_8H_8N_2$ (132.2)	2130
			B	80 °C/ 90 min	58			
			C	0 °C/ 60 min	90			
4b	CH_3	n-C_4H_9	A	40 °C/120 min	29	—[b]	$C_6H_{12}N_2$ (112.2)	2120
			B	80 °C/ 90 min	57			
			C	0 °C/ 60 min	70			
4c	CH_3	n-C_6H_{13}	C	0 °C/ 60 min	70	—[b]	$C_8H_{16}N_2$ (140.9)	2140
4d	CH_3	Cl—CH_2—CH_2	C	0 °C/ 60 min	80	—[b]	$C_4H_7ClN_2$ (118.5)[7]	2122
4e	CH_3	Br—CH_2—CH_2	C	0 °C/ 60 min	80	—[b]	$C_4H_7BrN_2$ (163.0)	2120
4f	CH_3	2-(2-methyl-1,3,4-thiadiazol-5-yl)-thioethyl	A	40 °C/120 min	27	—[b]	$C_7H_{10}N_4S_2$ (214.1)	2140
			B	80 °C/ 90 min	58			
			C	0 °C/ 60 min	75			
4g	C_6H_5	C_6H_5	C	0 °C/ 60 min	90	178–180°/10	135–138°/2[10]	2125
4h	c-C_6H_{11}	c-C_6H_{11}	B	80 °C/ 90 min	68	158–160°/12	105–107°/1[10]	2130
			C	0 °C/ 60 min	90			
4i	C_2H_5	C_2H_5	B	80 °C/ 90 min	18	36–40°/1	35–40°/1[15]	2130
			C	0 °C/ 60 min	70			
4j	C_6H_5	n-C_4H_9	B	80 °C/ 90 min	70	79–81°/0.1	80°/0.1[10]	2135
			C	0 °C/ 60 min	90			
4k	C_6H_5	c-C_6H_{11}	C	0 °C/ 60 min	90	106–108°/1	104–108.5°/1[16]	2135
4l	n-C_4H_9	n-C_4H_9	C	0 °C/ 60 min	90	84–86°/9	82°/8[11]	2130

[a] Satisfactory microanalyses obtained for compounds **4a–i**: C ±0.02, H ±0.02, N ±0.02, Hal ±0.05, S ±0.01.
[b] Thermally unstable.

the urea to the suspended reagent and triethylamine in cold dichloromethane (Table).





The conversion can be easily monitored by the urea carbonyl (1630–1640 cm^{-1}) and carbodiimide (2120–2130 cm^{-1}) absorptions in the I.R. spectra.

The starting ureas **1** were prepared by conventional methods, and all of them are known, except for methyl-(2-methyl-1,3,4-thiadiazol-5-ylthioethyl)-urea[7]. All carbodiimides are also known and described in our patent[14], except for the phenylbutyl-, phenylcyclohexyl-, and di-*n*-butylcarbodiimides.

Carbodiimides 4; General Procedures:

Method A: Triethylamine (2.8 ml, 20.5 mmol), tetrachloromethane (2.3 ml, 20.7 mmol), and triphenylphosphine (5.35 g, 20.4 mmol) are added to urea (20 mmol) in dichloromethane (8 ml) at room temperature. The mixture is heated under reflux during 2 h, the solvent is removed, and the residue is extracted with *n*-hexane (2 × 15 ml). Evaporation of the solvent gives the crude carbodiimide **4** which is distilled under reduced pressure or chromatographed at 65 °C on an SE 30 column.

Method B: Triethylamine (2.75 ml, 20.2 mmol) is added to bromotriphenylphosphonium bromide (**2**; 4.2 g, 10 mmol) in benzene (15 ml) at room temperature. The urea **1** (8 mmol) is added portionwise to the stirred mixture during 15 min. The mixture is heated under reflux for 1.5 h, and cooled to 10 °C. The solution is filtered, the solvent is evaporated, and the residue extracted with hexane (2 × 15 ml). Evaporation of the solvent gives the crude carbodiimide **4**, which is distilled under reduced pressure or chromatographed at 65 °C on an SE 30 column.

Method C: The substituted urea **1** (8 mmol) is added portionwise during 60 min to a stirred suspension of bromotriphenylphosphonium bromide (**2**; 4.2 g, 10 mmol) and triethylamine (2.75 ml, 20.2 mmol) in dichloromethane (15 ml) at 0 °C. The resulting mixture is washed with water (20 ml) and the organic solvent is dried with sodium sulfate. Evaporation of the solvent gives a residue which is worked up, as described in method B, to give the crude carbodiimide **4**, which is distilled under reduced pressure or chromatographed at 65 °C on an SE 30 column.

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