Preparation of Carbodiimides Using Phase-Transfer Catalysis

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A new method is described for the preparation of carbodiimides by dehydration of ureas with arenesulfonyl chlorides under solid-liquid phase-transfer catalytic (PTC) conditions using solid potassium carbonate as a base and a lipophilic quaternary ammonium salt as a catalyst. The method is generally applicable for the synthesis of disubstituted carbodiimides, but is especially useful for unsymmetrically substituted carbodiimides. The basic carbodiimides prepared were identified in the form of the more stable, crystalline quaternary salts.

In connection with a program aimed at the synthesis of new carbodiimides with basic side chains, an efficient method was sought to produce the sensitive target molecules in good yield and high purity.

The synthesis of carbodiimides have recently been reviewed.[1,2] Although a number of new reagents[3-8] have been suggested from disubstituted ureas or thioureas, the most frequently used method for the synthesis of unsymmetrically substituted carbodiimides is still the desulfurization of thioureas by means of heavy metal salts[9] or by the dehydration of ureas with *p*-toluenesulfonyl chloride in pyridine[10] or in triethyl amine/dichloromethane solution.[11] The latter seemed to be most promising, yet because of purification difficulties, it was not satisfactory enough for our purposes.

Table 1. Carbodiimides **3** Prepared by the PTC Method

Product	Reagent	Reaction Time (h)	Yield (%)	b.p./torr (°C)	Molecular Formula[a] or Lit. b.p. (°C)/torr	IR (neat) ν_{NCN} (cm^{-1})
3a	**2a**	4[b], 2[c]	91[b], 88[c]	120/0.1	145/0.2[12]	2180
	2b	3.5[b], 1.5[c]	92[b], 87[c]			
3b	**2a**	4[b]	83[b]	dec.	$C_{14}H_{25}N_3O$ (251.4)	2210
3c	**2a**	1[d]	85[d]	105/0.1	89.5–91.5/0.4[11]	2200
	2b	0.75[d]	91[d]			
3d	**2a**	3[b], 1.2[c]	88[b], 86[c]	dec.	$C_{15}H_{27}N_3$ (249.4)	2200
3e	**2a**	2.5[b], 1.5[c]	66[b], 68[c]	dec.	$C_{15}H_{28}N_4$ (264.4)	2180
	2b	2[b]	71[b]			
3f	**2a**	4[b]	68[b]	90–95/0.08	$C_{12}H_{17}N_3$ (203.3)	2195
	2b	3[b]	75[b]			
3g	**2a**	2[b]	90[b]	97/0.07	$C_{11}H_{21}N_3O$ (211.3)	2180
3h	**2a**	1[b]	81[b]	66–70/0.07	$C_{10}H_{21}N_3$ (183.3)	2190
3i	**2a**	1[b]	71[b]	52–3/0.2	$C_7H_{15}N_3$ (141.2)	2210
3j	**2a**	2[b]	65[b]	88/0.07	$C_{10}H_{20}N_4$ (196.3)	2180
3k	**2a**	5[b], 3[c]	98[b], 94[c]	90–92/0.1	$C_{14}H_{18}N_2$ (214.3)	2190
		3[b]	97[b]			
3l	**2a**	4[b]	96[b]	88–89/0.15	$C_{12}H_{16}N_2$ (188.3)	2200
3m	**2a**	11[c]	35[c]	76–79/0.3[f]	98–100/0.5[16]	2120
	2b	8[c]	50[c]			
3n	**2b**	13[c]	30[c]	60–65/13[f]	52–53/10[17]	2100

[a] New compounds; satisfactory microanalyses obtained: C ±0.31, H ±0.37, N ±0.35; except **3e** (C −0.45) and **3i** (C −0.58).
[b] in benzene.
[c] in toluene.
[d] in benzene/chloroform, 2:1.
[e] in chloroform.
[f] Contaminated with the arenesulfonyl chloride.

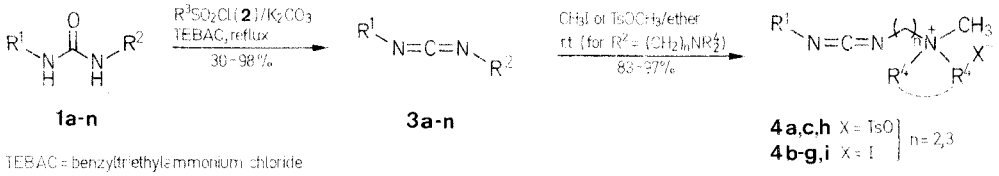
Table 2. Water Soluble Quaternary Salts **4** of Carbodiimides **3**

Carbodiimide	Salt	Yield (%)	m.p. (°C)	Molecular Formula[a] or Lit. m.p. (°C)	IR (KBr) ν_{NCN} (cm^{-1})
3a	**4a**	83[b]	113–114	113–115[12]	2120
3b	**4b**	91[c]	115–117	$C_{15}H_{28}IN_3O$ (393.3)	2090
3c	**4c** (X = I)	88[c]	160–162	161.5–163[11]	2105
	4c (X = TsO)	95[b]	164–166	164.4–165.4[11]	2160
3d	**4d**	87[c]	—[d]	$C_{16}H_{30}IN_3$ (391.3)	2175
3e	**4e**	93[c]	168–170	$C_{16}H_{31}IN_4$ (406.35)	2105
3f	**4f**	88[c]	170–172	172.4–173.4[17]	2110
3g	**4g**	86[c]	89–91	$C_{12}H_{24}IN_3O$ (353.2)	2100
3h	**4h**	94[b]	127–128	$C_{18}H_{31}N_3O_3S$ (369.5)	2150
3i	**4i**	97[c]	126–127	$C_8H_{18}IN_3$ (283.15)	2110

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.21, N ±0.12.
[b] Alkylating agent: p-$CH_3C_6H_4SO_2OCH_3$.
[c] Alkylating agent: CH_3I.
[d] Oily crystals.

We report here a new method for preparation of carbodiimides with general structure **3** by dehydration of ureas **1** with arenesulfonyl chlorides **2** under solid-liquid phase-transfer catalytic (PTC) conditions. Solid potassium carbonate is used as base and a lipophilic quaternary ammonium salt, triethyl benzyl ammonium chloride (TEBAC), as catalyst.

For the preparation of compounds of type **3**, the PTC technique proved to be superior to any other method tried: no side reactions have been detected, the yields are high, the reaction and working up procedures are very simple, and the raw products are for the most part analytically pure, such that no further purification is required.



TEBAC = benzyltriethylammonium chloride
Ts = *p*-toluenesulfonyl

1, 3	R^1	R^2
a	*cyclo*-C_6H_{11}	$-(CH_2)_3N$(morpholino)
b	*cyclo*-C_6H_{11}	$-(CH_2)_2N$(morpholino)
c	*cyclo*-C_6H_{11}	$-(CH_2)_3N(CH_3)_2$
d	*cyclo*-C_6H_{11}	$-(CH_2)_3N$(pyrrolidino)
e	*cyclo*-C_6H_{11}	$-(CH_2)_3N$(4-methylpiperazino)
f	C_6H_5	$-(CH_2)_3N(CH_3)_2$
g	*n*-C_4H_9	$-(CH_2)_3N$(morpholino)
h	*n*-C_4H_9	$-(CH_2)_3N(CH_3)_2$
i	CH_3	$-(CH_2)_3N(CH_3)_2$
j	CH_3	$-(CH_2)_3N$(4-methylpiperazino)
k	*cyclo*-C_6H_{11}	$-CH_2C_6H_5$
l	*n*-C_4H_9	$-CH_2C_6H_5$
m	*cyclo*-C_6H_{11}	*cyclo*-C_6H_{11}
n	*t*-C_4H_9	*t*-C_4H_9

2	R^3
a	4-$CH_3C_6H_4$
b	4-BrC_6H_4

4	n	NR_2^4	4	n	NR_2^4
a	2	N(morpholino)	f	3	$N(CH_3)_2$
b	3	N(morpholino)	g	2	N(morpholino)
c	3	$N(CH_3)_2$	h	3	$N(CH_3)_2$
d	3	N(pyrrolidino)	i	3	$N(CH_3)_2$

4e: n = 3; $CH_3\overset{+}{N}R_2^4$ = N(4-methylpiperazino)-CH_3

Although the method seems to be generally applicable for the synthesis of **3**, it is especially suitable for making unsymmetrically substituted carbodiimides having a tertiary amino group in the molecule. Quaternary ammonium salts of these compounds play an important role in peptide chemistry.[12] The results for the preparation of carbodiimides are summarized in Table I.

When the urea starting materials are hardly or not soluble in the solvents commonly used in PTC technique, the reaction is slow and the yield is usually poor. This is the situation in the transformation of the symmetrically substituted urea derivatives like dicyclohexyl- and di-*tert*-butylurea (Table I; **3m, 3n**). The synthesis of 1,3-diphenylcarbodiimide from 1,3-diphenylurea could not be effected under this circumstances, probably for electronic reasons. The synthesis of these symmetrically substituted carbodiimides, however, can be effected by a number of excellent routes, starting from non-ureas.[13–15]

The new method is carried out starting from 1,3-disubstituted ureas **1**, which are reacted with one equivalent of *p*-toluenesulfonyl chloride **(2a)** or *p*-bromobenzenesulfonyl chloride **(2b)**, 4 equivalents of potassium carbonate, and 0.1 equivalent TEBAC in benzene, toluene or in some cases in a mixture of chloroform and benzene, refluxing for 60–180 minutes. The reaction proceeds smoothly with liberation of carbon dioxide to give the carbodiimides **3**, which were isolated by filtration of the solid materials and evaporation of the filtrate. The resultant oily residue was generally pure enough not to require destillation.

The basic carbodiimides **3a–j** prepared were identified in the form of the more stable, crystalline quaternary salts **4**. Data for the salts is given in Table II.

Carbodiimides 3; General Procedure:
A solution of disubstituted urea **1** (10 mmol) and arenesulfonyl chloride **2** (10 mmol) in the solvent specified in Table I (70 ml), is stirred at reflux temperature in the presence of potassium carbonate (3.53 g, 40 mmol) and benzyltriethylammonium chloride (0.23 g, 1 mmol). The reaction is monitored by TLC. The resultant precipitate is filtered off, and the filtrate is washed with water (2 × 10 ml). The organic layer is dried with magnesium sulfate and evaporated to give **3** as an oily residue, which is generally pure or can be destilled *in vacuo*. See Table 1.

Carbodiimide Quaternary Salts 4; General Procedure:
To a solution of carbodiimide **3a–i** (10 mmol) in dry ether (20 ml), the alkylating agent [methyl iodide (10 mmol), or methyl *p*-toluenesulfonate (10 mmol)] is added, and the mixture is allowed to stand overnight. The white precipitate is filtered off and washed with dry ether to give the carbodiimide quaternary salt. See Table 2.

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