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*N*-Alkyl-*N'*-arylcarbodiimides add alkyl and aryl isocyanates to the *N*-alkyl substituted CN double bond to yield 4-arylimino-1,3-diazetidino-2-ones **3**. In the case of bulky alkyl substituents the reaction still proceeds across the sterically hindered CN double bond. *N*-Aryl-*N'*-[(4-dimethylamino)phenyl]carbodiimides form [2 + 2] cycloadducts with aryl isocyanates preferentially across the CN double bond not attached to the electron-rich aryl groups. However, steric crowding on this CN double bond directs the reaction to the adjacent double bond of the heterocumulative system. The rate of the [2 + 2] cycloaddition reaction of *N*-methyl-*N'*-phenylcarbodiimide with 4-nitrophenylisocyanate is about 2.5 times faster in acetonitrile than in benzene.

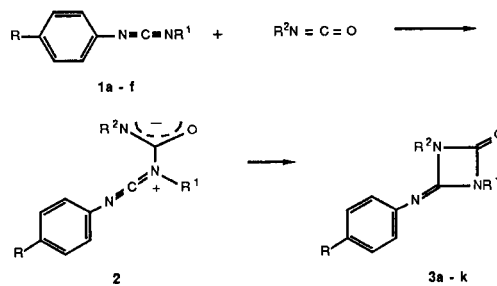
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The [2 + 2] cycloaddition reaction of heterocumulenes, such as carbodiimides, isocyanates and isothiocyanates is well known [1]. For example, carbodiimides react with aryl isocyanates to give four-membered ring [2 + 2] cycloadducts *via* addition across the CN double bonds of both heterocumulenes [2]. In case of unsymmetrically substituted carbodiimides both CN double bonds could participate in this reaction to give mixtures of products, and steric hindrance and electronic effects could influence the product distribution. We had previously observed that the bicyclic *N*-alkyl-*N'*-arylcarbodiimide, 4,5,6,7-tetrahydrobenzo-1,3-diazonine, reacted with phenyl isocyanate exclusively on the "aliphatic" substituted CN double bond [3]. In order to gain further insights into this interesting and synthetically useful reaction we studied the [2 + 2] cycloaddition reactions of several unsymmetrically substituted carbodiimides.

Unsymmetrically substituted carbodiimides **1** are best synthesized by dehydrosulfuration of the corresponding thioureas. *N*-Alkyl-*N'*-arylcarbodiimides have enhanced nucleophilicity on the nitrogen adjacent to the alkyl group, and therefore reaction across this CN double bond is expected. Electron-donating or withdrawing substituents on the aryl groups of unsymmetrically substituted carbodiimides influence the electron density of the cumulative double bonds, and this effect should be more pronounced in *N,N'*-diarylcarbodiimides, where the nucleophilicity of both nitrogens is approximately equal. A further complication could be competition between the CN bonds in both heterocumulenes, which could result in the formation of carbodiimide dimers. Uncatalyzed dimerization of the aryl isocyanates is unlikely under the reaction conditions.

In view of the above considerations we were surprised to find that *N*-alkyl-*N'*-arylcarbodiimides **1** react with alkyl and aryl isocyanates exclusively across the CN double bond attached to the aliphatic substituent to give 4-imino-1,3-diazetidino-2-ones **3**. Even with the highly sterically

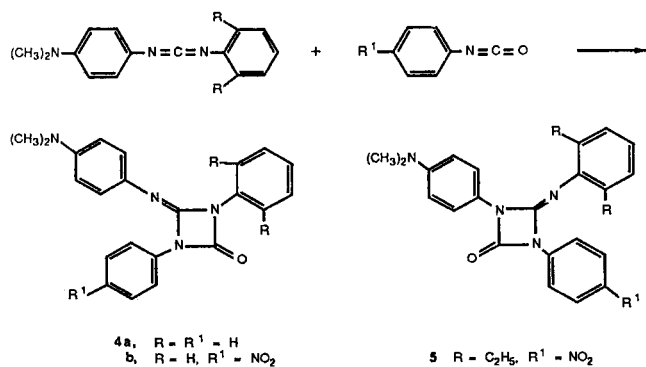
hindered *N*-*t*-butyl-*N'*-phenylcarbodiimide the reaction took place only across this CN double bond. In all cases only one reaction product was obtained. It was further observed that substituents R on the aromatic ring and steric factors caused by enlarging the substituents R<sup>1</sup> on the carbodiimide **1** retard or accelerate the reaction as expected. For example, *N*-alkyl-*N'*-arylcarbodiimides undergo fastest reaction when R = (CH<sub>3</sub>)<sub>2</sub>N and R<sup>1</sup> = CH<sub>3</sub>, and slowest additions were observed when R = NO<sub>2</sub> and R<sup>1</sup> = (CH<sub>3</sub>)<sub>3</sub>C. The reactivity of the aryl isocyanates is fastest when R = 4-nitrophenyl. Aliphatic isocyanates react considerably slower than aromatic isocyanates.



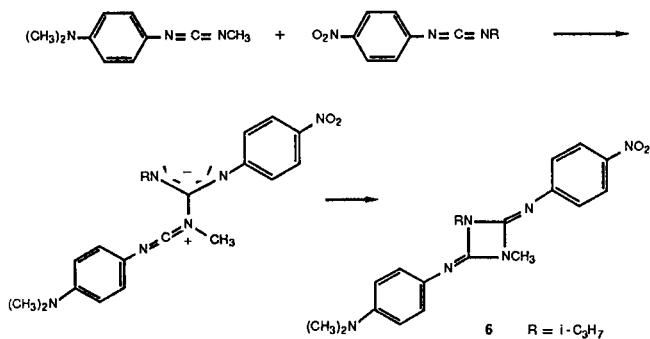
1	3	R	R <sup>1</sup>	R <sup>2</sup>
a	a	H	CH <sub>3</sub>	CH <sub>3</sub>
b	b	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
c	c	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - (4)
b	d	H	C(CH <sub>3</sub> ) <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
c	e	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>
	f	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
d	g	CH <sub>3</sub> O	CH <sub>3</sub>	CH <sub>3</sub>
	h	CH <sub>3</sub> O	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
e	i	NO <sub>2</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - (4)
f	j	NO <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - (4)
g	k	Cl	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>

The [2 + 2] cycloaddition reactions of *N,N'*-diarylcarbodiimides with two differently substituted aryl groups can be influenced by electronic as well as steric factors. For example, the reaction of *N*-[(4-dimethylamino)phenyl]-*N'*-phenylcarbodiimide with phenyl isocyanate or 4-nitrophenyl isocyanate at room temperature yields exclusively cy-

cloadducts with structure **4**, resulting from addition across the CN double bond attached to the unsubstituted phenyl ring. The structure assignment rests on mass spectroscopic evidence, which in case of **4b** gave a mass fragment of 119 for phenyl isocyanate. If the cycloaddition had occurred across the CN double bond next to the 4-(dimethylamino)phenyl group, phenyl isocyanate could not have been one of the major fragments. Adding steric hindrance to the electron-rich CN double bond by substituting the phenyl ring with substituents in the 2 and 6 position changes the course of the cycloaddition reaction. Thus, a cycloadduct **5** was isolated as the sole product from reaction of *N*-(2,6-diethylphenyl)-*N'*-(4-dimethylamino)phenyl carbodiimide and 4-nitrophenyl isocyanate at room temperature. The structural assignment of **5** is also based on mass spectroscopic evidence.



In the [2+2] cycloaddition reaction involving two unsymmetrically substituted carbodiimides with inverse electron demand, such as *N*-[(4-dimethylamino)phenyl]-*N'*-methylcarbodiimide (**1c**) and *N*-(4-nitrophenyl)-*N'*-isopropylcarbodiimide (**1e**) again only one cycloadduct **6** was obtained in 69% yield. This is the first example of a [2+2] cycloaddition reaction between two different carbodiimides.



Attempts to trap ionic intermediates, such as **2**, with dipolarophiles failed. When the reaction of *N*-phenyl-*N'*-methylcarbodiimide with 4-nitrophenyl isocyanate was conducted in diethyl acetylenedicarboxylate as solvent on-

ly cycloadduct **3c** was obtained in 77% yield. Trapping of polar intermediates was observed in the [2+2] cycloaddition reactions of carbodiimides with *p*-toluenesulfonyl isocyanate [4]. However, we found that the reaction rate of *N*-phenyl-*N'*-methylcarbodiimide with 4-nitrophenyl isocyanate was approximately 2.5 times faster in acetonitrile than in benzene. The rate enhancement in the polar solvent, although perhaps too low to account for the formation of dipolar intermediates, does indicate the possibility of solvation of such species.

In summary, unsymmetrically substituted carbodiimides undergo regioselective cycloaddition reactions with isocyanates. The more nucleophilic nitrogen in the carbodiimide attacks the electrophilic carbon center in the isocyanate group giving rise to the formation of only one cycloadduct. Steric hindrance has no influence on the [2+2] cycloaddition reaction of *N*-alkyl-*N'*-arylcarbodiimides with isocyanates, but plays a role in the cycloaddition reaction of unsymmetrically substituted diarylcarbodiimides. Isothiocyanates also react only across one of the CN double bonds in unsymmetrically substituted carbodiimides [5].

Table I

Analytical Data for 4-Imino-1,3-diazetidione-2-ones **3**

	Mp °C	Yield [a]	Formula	Calcd./Found		
				C %	H %	N %
<b>3a</b>	35-36	29	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O	63.48	5.86	22.21
				63.71	6.03	22.06
<b>3b</b>	86-87	54	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O	71.70	5.21	16.72
				71.58	5.30	16.64
<b>3c</b>	130-131	77	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub>	60.81	4.05	18.91
				60.73	4.12	18.73
<b>3d</b>	70-72	58	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O	73.69	6.53	14.32
				73.51	6.57	14.32
<b>3e</b>	145-146	71	C <sub>12</sub> H <sub>10</sub> N <sub>4</sub> O	62.05	6.94	24.12
				62.30	6.91	24.04
<b>3f</b>	120-121	68	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O	69.37	6.16	19.03
				69.59	6.38	18.94
<b>3g</b>	66-67	48	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	60.26	5.94	19.16
				60.23	6.21	19.00
<b>3h</b>	101-102	85	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	68.31	5.37	14.94
				68.02	5.60	14.84
<b>3i</b>	180-181	90	C <sub>15</sub> H <sub>11</sub> N <sub>5</sub> O <sub>5</sub>	52.79	3.25	20.52
				53.01	3.27	20.23
<b>3j</b>	140-142	86	C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O <sub>5</sub>	55.28	4.09	18.96
				55.34	4.27	19.08
<b>3k</b>	92-93	47	C <sub>15</sub> H <sub>12</sub> ClN <sub>3</sub> O	63.05	4.23	14.70
				63.18	4.43	14.66

[a] Yields are for analytically pure samples, the crude yields were high in all cases.

## EXPERIMENTAL

Infrared spectra were recorded on a Beckman Acculab 4 spectrophotometer with chloroform as medium. The  $^1\text{H}$ -nmr spectra were determined on a Varian EM360A spectrometer, and  $^{13}\text{C}$ -nmr spectra on a Varian CFT 20 with deuteriochloroform as solvent and TMS as internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points are uncorrected.

General Procedure for the Preparation of 1,3-Disubstituted 4-Imino-1,3-diazetidene-2-ones **3a-k**.

Equimolar amounts of *N*-alkyl-*N'*-arylcarbodiimides and isocyanates in the range of 0.05 to 0.1 mole are mixed and kept at ambient temperature with exclusion of moisture. Progress of the reaction is monitored by infrared spectroscopy (disappearance of the  $\text{N}=\text{C}=\text{O}$  and  $\text{N}=\text{C}=\text{N}$  bands at  $2280\text{ cm}^{-1}$  and  $2120\text{--}2150\text{ cm}^{-1}$ , respectively). The cycloadducts **3a-k** show a weakly resolved band for  $\text{C}=\text{O}$  and  $\text{C}=\text{N}$  bonds at  $1720\text{ cm}^{-1}$  with a shoulder at  $1705\text{--}1680\text{ cm}^{-1}$ . The reaction duration varies from less than 10 minutes (for **1a** and phenyl isocyanate) to more than 20 days (for **1b** and phenyl isocyanate). Heating of the reaction mixtures to reduce reaction times was deliberately avoided in order to suppress side reactions caused by dissociation of the newly formed cycloadducts **3** and recombination of the resulting heterocumulenes. Work-up of the reaction mixtures is by trituration with cold solvents in which the cycloadducts are sparingly soluble (*i.e.* isooctane), filtration, and recrystallization from isooctane/propanol, diethyl ether, or 2-propanol. Yields of isolated products and analyses for compounds **3** are listed in Table I.

Measurement of the Rate of Reaction of *N*-Methyl-*N'*-phenylcarbodiimide with 4-Nitrophenyl Isocyanate.

To a 0.005 mole solution of 4-nitrophenyl isocyanate in 50 ml of acetonitrile 0.005 mole of *N*-methyl-*N'*-phenylcarbodiimide was added. The rate of disappearance of the carbodiimide absorption at  $2150\text{ cm}^{-1}$  was monitored by infrared spectroscopy, and the time of 50% conversion was found to be 18 minutes at  $23^\circ$ . The half-life of this reaction in benzene at  $23^\circ$  was found to be 46.5 minutes. The reaction followed second order kinetics.

Formation of [2+2] Cycloadducts from *N,N'*-Diarylcarbodiimides and Aryl Isocyanates.

a) *N*-[(4-Dimethylamino)phenyl]-*N'*-phenylcarbodiimide is treated with an equimolar amount of phenyl isocyanate in methylene chloride at room

temperature for 5 days (complete disappearance of  $\text{N}=\text{C}=\text{O}$  at  $2280\text{ cm}^{-1}$  and  $\text{N}=\text{C}=\text{N}$  at  $2150\text{ cm}^{-1}$  signals in the infrared). Solvent removal and trituration of the residue with hot 2-propanol leaves ureas, which were removed by filtration. The cycloadduct **4a** precipitates from the solution on cooling in colorless crystals (60% yield), mp  $94\text{--}96^\circ$  (2-propanol); ir:  $1720\text{ cm}^{-1}$ ,  $1690\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ,  $\text{C}=\text{N}$ ).

Anal. Calcd. for  $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}$ : C, 74.14; H, 5.66; N, 15.72. Found: C, 74.31; H, 5.89; N, 15.74.

b) *N*-[(4-Dimethylamino)phenyl]-*N'*-phenylcarbodiimide is treated similarly with an equimolar amount of 4-nitrophenyl isocyanate in methylene chloride to give 30% of the cycloadduct **4b**, mp  $125\text{--}126^\circ$  (2-propanol).

Anal. Calcd. for  $\text{C}_{22}\text{H}_{18}\text{N}_5\text{O}_3$ : C, 65.83; H, 4.77; N, 17.45. Found: C, 65.94; H, 4.95; N, 17.22.

c) *N*-(2,6-Diethylphenyl)-*N'*-[(4-dimethylamino)phenyl]carbodiimide is treated similarly with 4-nitrophenyl isocyanate in methylene chloride to give 34% of the cycloadduct **5**, mp  $100\text{--}101^\circ$  (diethyl ether).

Anal. Calcd. for  $\text{C}_{26}\text{H}_{27}\text{N}_5\text{O}_3$ : C, 68.25; H, 5.95; N, 15.31. Found: C, 67.93; H, 6.06; N, 15.07.

2-[(4-Dimethylamino)phenylimino]-4-isopropylimino-1-methyl-3-(4-nitrophenyl)-1,3-diazetidene (**6**).

A 0.1 equimolar solution of the carbodiimides **1c** and **1e** in methylene chloride was stored at ambient temperature for ten days. Evaporation of the solvent and trituration of the residue with diethyl ether afforded the crude cycloadduct **6**, which was recrystallized from 2-propanol, yield, 69%, mp  $165\text{--}166^\circ$ ; ir:  $1675\text{ cm}^{-1}$  ( $\text{C}=\text{N}$ ).

Anal. Calcd. for  $\text{C}_{26}\text{H}_{24}\text{N}_6\text{O}_2$ : C, 63.14; H, 6.36; N, 22.09. Found: C, 63.38; H, 6.48; N, 22.18.

## REFERENCES AND NOTES

- [1] H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", Academic Press, New York, 1967.
- [2] W. J. Farrissey, Jr., R. J. Ricciardi, and A. A. R. Sayigh, *J. Org. Chem.*, **33**, 1913 (1968).
- [3] R. Richter, B. Tucker, and H. Ulrich, *J. Org. Chem.*, **48**, 1694 (1983).
- [4] H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Am. Chem. Soc.*, **94**, 3484 (1972).
- [5] H. Ulrich, B. Tucker, and R. Richter, *Chem. Ber.*, **120**, 849 (1987).