Cycloadditions of Ketenes with Cyclic Carbodiimides

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The cycloaddition of ketenes with cyclic carbodiimides yields β-lactams in good to excellent yields. The cycloaddition of equal molar amounts of diphenyl-, phenylethyl- and phenylketenes with cyclic carbodiimides produced a 1:1 cycloaddition product, the expected β-lactams. However, the cycloaddition of a 2:1 molar ratio of diphenyl- and phenylketenes with 1,3-diazacycloocta-1,2-diene respectively, gave the 2:1 cycloadducts, the tricyclodi-β-lactams. The cycloaddition of methylchloro- and dichloroketenes yielded β-lactams that were very susceptible to hydrolysis to the *N*-substituted cycloureas. A trapping experiment suggests that these reactions proceed through a stabilized dipolar intermediate.

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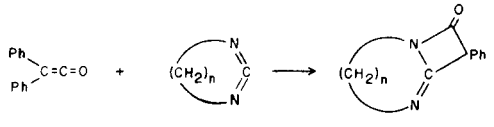
There are many reports in the literature on the (2 + 2) cycloaddition reaction of ketenes with imines to yield β-lactams [1-5]. However, the cycloaddition of ketenes with carbodiimides has not received much attention. We have described the cycloaddition of ketenes with diisopropyl- and dicyclohexylcarbodiimides to yield the monocycloaddition products, the β-imino-β-lactams [6,7]. These reactions were demonstrated to occur by a two-step process involving a dipolar intermediate as the intermediate was successfully trapped. A new synthesis for cyclic carbodiimides has recently been reported and as expected the ring size of the cyclic carbodiimides effects the stability and the reactivity of the carbodiimide moiety [8-10]. This work prompted us to investigate the reaction of these new cyclic carbodiimides with ketenes and this paper describes these reactions and the bicyclo-β-lactams and the tricyclo-β-lactams produced.

The reaction of equal molar amounts of freshly distilled diphenylketene with cyclic carbodiimides occurred readily at room temperature to give (2 + 2) cycloaddition products, **1a, 1b, 1c** in 90+% yields as shown in Scheme I.

Scheme I

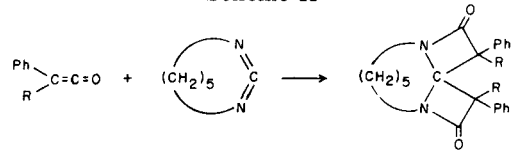


1a, n = 5
1b, n = 6
1c, n = 11

These solid products were easily isolated and purified by recrystallization. The ir spectra revealed a strong band for the carbonyl group at 1790-1800 cm^{-1} and a strong band for the imino function at 1660-1698 cm^{-1}. The ^{13}C-nmr spectra revealed a pair of carbon signals at 39.73-46.72, 43.5-45.3 and 39.13-49.23 ppm for the methylene carbons adjacent to the nitrogen atoms. The ^{1}H-nmr and elemental analyses were also consistent with the assigned structures.

The reaction of a 2:1 molar ratio of diphenylketene with 1,3-diazacycloocta-1,2-diene slowly gave a 2:1 cycloaddition product, **2a**, in 91% yield as illustrated in Scheme II. The structure of **2a** was assigned on the basis of the carbonyl band at 1720 cm^{-1} and no band in the 1600-1700

Scheme II

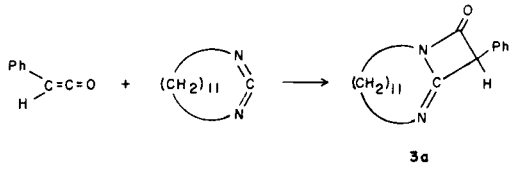


2a, R = Ph
2b, R = Et

cm^{-1} range for the imino group. The ^{13}C-nmr revealed only one signal at 39 ppm for the two methylene groups adjacent to the nitrogen atoms. Phenylethylketene also reacts with this cyclic carbodiimide in a molar ratio of 2:1 to give the corresponding tricyclodi-β-lactam, **2b**, in 91% yield as shown in Scheme II. It is interesting to note that the reaction of a 2:1 molar ratio of diphenylketene and 1,3-diazacyclotetradeca-1,2-diene resulted in only the 1:1 cycloaddition product, **1c**. Apparently, the greater ring strain in **1a** is manifested in a greater reactivity of the residual carbon nitrogen double bond toward a second mole of ketene as compared to **1c**.

The *in situ* generation of an equimolar amount of phenylketene by the triethylamine dehydrochlorination of phenylacetyl chloride in the presence of 1,3-diazacyclotetradeca-1,2-diene resulted in the formation of the 1:1 cycloaddition product, **3**, as shown in Scheme III. The reaction of **3** with additional phenylketene did not give any isolable 2:1 adduct.

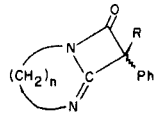
Scheme III



3a

Table I

Cycloadducts of Diphenyl- and Phenylketenes with Cyclic Carbodiimides



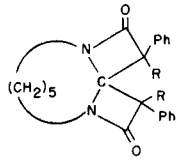
Compound	n	R	Mp °C	Molecular Formula	Analyses % Calcd./Found C		H	
1a	5	Ph	112-114	$C_{20}H_{20}N_2O$	78.95/	79.08	6.58/	6.01
1b	6	Ph	128-130	$C_{21}H_{22}N_2O$	79.25/	79.11	6.92/	6.92
1c	11	Ph	156-157	$C_{26}H_{32}N_2O$	80.40/	80.28	8.35/	8.11
3	11	H	75-76	$C_{20}H_{28}N_2O$	80.00/	79.86	8.64/	8.79

IR, ^1H and ^{13}C NMR Spectral Data

Compound	IR, cm^{-1} (deuteriochloroform)	^1H NMR (deuteriochloroform)	^{13}C NMR (deuteriochloroform)
1a	2920, 1795, 1665, 1370	1.3-2.2 (m, 6H), 3.45-4.0 (m, 2H), 7.1-7.8 (m, 10H)	21.9 (t), 27.7 (t), 29.4 (t), 39.7 (t), 46.7 (t), 71.0 (s), 126.6 (d), 127.4 (d), 128.4 (d), 137.4 (s), 155.3 (s), 170.6 (s)
1b	2920, 1795, 1680, 1350	0.9-1.95 (m, 8H), 3.3-3.9 (m, 4H), 6.7-7.7 (m, 10H)	22.3 (t), 25.9 (t), 30.2 (t), 31.5 (t), 43.5 (t), 45.3 (t), 70.8 (s), 126.6 (d), 127.7 (d), 128.3 (d), 137.3 (s), 152.6 (s), 171.8 (s)
1c	2900, 2840, 1790, 1665, 1430, 1380	0.3-3.0 (m, 18H), 3.2-3.6 (m, 4H), 7.2-7.4 (m, 10H)	22.9 (t), 24.6 (t), 24.8 (t), 25.0 (t), 25.4 (t), 25.8 (t), 26.0 (t), 28.8 (t), 39.1 (t), 49.3 (t), 76.1 (s), 127.9 (d), 128.1 (d), 128.7 (d), 136.1 (s), 153.1 (s), 170.8 (s)
3	2890, 2840, 1790, 1660, 1430, 1380	0.8-2.2 (m, 18H), 2.9-3.05 (m, 2H), 3.35 (t, 2H), 4.87 (s, 1H), 7.1-7.4 (m, 5H)	23.5 (t), 24.5 (t), 24.9 (t), 25.5 (t), 25.8 (t), 26.2 (t), 28.7 (t), 39.1 (t), 50.4 (t), 62.2 (d), 127.6 (d), 127.9 (d), 128.9 (d), 131.5 (s), 152.1 (s), 168.7 (s)

Table II

2:1 Cycloadducts of Phenylethyl- and Diphenylketenes with 1,3-Diazacycloocta-1,2-diene



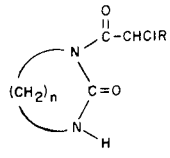
Compound	R	Mp °C	Molecular Formula	Analyses % Calcd./Found C		H	
2a	Ph	236-238	$C_{34}H_{30}N_2O_2$	81.92/	82.04	6.02/	5.85
2b	Et	271.5-273	$C_{26}H_{30}N_2O_2$	77.61/	77.32	7.46/	7.38

IR, ^1H and ^{13}C NMR Spectral Data

Compound	IR, cm^{-1} (deuteriochloroform)	^1H NMR (deuteriochloroform)	^{13}C NMR (deuteriochloroform)
2a	3020, 3010, 2920, 1720, 1430, 1380, 1160	1.0-1.6 (m, 6H), 1.8-2.2 (m, 2H), 3.2-3.7 (m, 2H), 6.6-8.0 (m, 10H)	23.8 (t), 25.1 (t), 41.01 (t), 72.99 (s), 90.7 (s), 126.5 (d), 127.5 (d), 127.6 (d), 127.9 (d), 128.3 (d), 128.5 (d), 135.3 (s), 136.2 (s), 169.7 (s)
2b	2920, 2860, 1740, 1440	1.03 (t, 6H), 1.2-1.6 (m, 8H), 2.1-2.7 (m, 4H), 2.96-3.4 (m, 2H), 7.2-7.5 (m, 10H)	9.29 (q), 24.4 (t), 24.8 (t), 31.3 (t), 39.4 (t), 70.06 (s), 87.7 (s), 127.4 (d), 128.5 (d), 136.2 (s), 169.96 (s)

Table III

Hydrolysis Products of Chloroketene Cycloadducts with Cyclic Carbodiimides



Compound	n	R	Mp °C	Molecular Formula	Analyses % Calcd./Found C		H	
5a	5	Cl	267-268	$C_8H_{12}Cl_2N_2O_2$	40.16/	40.19	5.02/	5.12
5b	11	Cl	109.5-110	$C_{14}H_{24}Cl_2N_2O_2$	52.01/	52.13	7.43/	7.60
5c	11	Me	122.5-123	$C_{15}H_{27}ClN_2O_2$	59.50/	59.34	8.93/	8.95

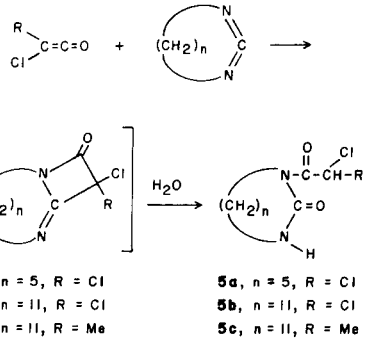
IR, ^1H and ^{13}C NMR Spectral Data

Compound	IR, cm^{-1} (deuteriochloroform)	^1H NMR (deuteriochloroform)	^{13}C NMR (deuteriochloroform)
5a	2920, 2860, 1660, 1500, 1250	1.0-1.6 (m, 6H), 2.9-3.3 (m, 4H), 7.9-8.3 (m, 2H)	[a]
5b	3320, 2920, 2845, 1688, 1510, 1455	1.1-2.1 (m, 18H), 3.4 (t, 2H), 3.88 (t, 2H), 6.6 (s, 1H), 7.5-8.3 (broad, 1H)	23.3 (t), 24.02 (t), 24.94 (t), 25.6 (t), 25.9 (t), 26.5 (t), 26.8 (t), 40.22 (t), 45.04 (t), 65.8 (d), 153.7 (s), 166.5 (s)
5c	3300, 2920, 2845, 1682	1.0-2.2 (m, 21H), 2.93-4.34 (m, 4H), 4.8 (q, 1H), 8.2-8.7 (broad, 1H)	20.9 (q), 23.2 (t), 24.02 (t), 25.37 (t), 26.08 (t), 26.89 (t), 39.95 (t), 44.28 (t), 41.8 (d), 154.4 (s), 172.5 (s)

[a] This compound was not soluble in any available organic solvents. The ms data is as follows, m/e 238, 155, 140, 127, 112, 110, 100, 70, 68.

The *in situ* generation of dichloro- and methylchloroketenes in the presence of 1,3-diazacyclotetradec-1,2-diene and 1,3-diazacycloocta-1,2-diene resulted in the formation of only the 1:1 cycloadducts, **4a, 4b**, and **4c** in yields ranging from 60-80% as shown in Scheme IV. The ir spectra of these crude products revealed a β-lactam carbonyl band at 1780 cm^{-1}. However, in an attempt to purify these compounds by recrystallization from benzene and 95% ethyl alcohol, the ring opening hydrolysis products, **5a, 5b**, and **5c** were formed.

Scheme IV



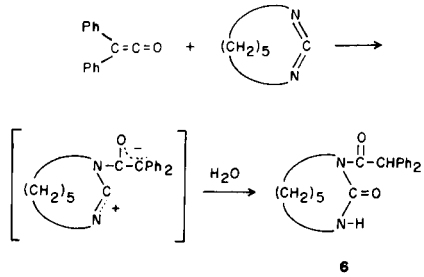
4a, n = 5, R = Cl
4b, n = 11, R = Cl
4c, n = 11, R = Me

5a, n = 5, R = Cl
5b, n = 11, R = Cl
5c, n = 11, R = Me

Standing exposed to the atmosphere at ambient temperature results in this hydrolysis. The ring opened products do not have a band around 1790 cm^{-1} but do have a broad band at 1680-1690 cm^{-1}. The ^{13}C-nmr spectra reveal a pair of triplets at 39-45 ppm and a doublet at 51-65 ppm, which are the two methylene groups adjacent to the two nitrogen atoms and the carbon adjacent to the halogen atom respectively. Surprisingly, all the chloroketene cycloaddition products, including the 1,3-diazacyclotetradeca-1,2-diene, were susceptible to hydrolysis. Apparently, the activating influence of the chlorine atom(s) coupled with the strain involved in the carbon nitrogen double bond provided the impetus for the hydrolysis reaction.

In an attempt to trap the dipolar intermediate in these cycloaddition reactions, we quenched the reaction of diphenylketene with 1,3-diazacycloocta-1,2-diene in benzene at 0° after four minutes by the addition of water. *N*-Diphenylacetal-1,3-diazacyclooctan-2-one, **6** was isolated in a 17% yield. Diphenylacetic acid and **1a** were also isolated from this reaction mixture. Control experiments demon-

Scheme V



6

strated that **6** was not produced from **1a** under identical reaction conditions. Also, it was demonstrated that **6** was not formed from the reaction of the ketene hydrolysis product, diphenylacetic acid, and the cyclic carbodiimide. Thus, the reaction of diphenylacetic acid and 1,3-diazacycloocta-1,2-diene resulted in the formation of 1,3-diaza-2-diphenylacetoxy-1-cyclooctene and diphenylacetic anhydride but no evidence for the formation of **6**. The high yield of the trapped compound, **6**, is probably a reflection of the resonance stabilization of the dipolar intermediate.

In conclusion the cycloadditions involving the 8-membered ring cyclic carbodiimide, 1,3-diazacycloocta-1,2-diene, with ketenes yields both 1:1 and 2:1 cycloaddition products depending on the ratio of ketene and carbodiimide. However, the cycloadditions of the larger ring cyclic carbodiimide, 1,3-diazacyclotetradeca-1,2-diene, yielded only the 1:1 adducts even in the presence of an excess of ketene. We have previously reported that the cycloaddition of acyclic carbodiimides with ketenes yields only the 1:1 cycloaddition products. Clearly, these results suggest that the ring strain in the 1:1 cycloadducts of 1,3-diazacycloocta-1,2-diene is responsible for the addition of the second ketene molecule to the residual carbon nitrogen double bond.

EXPERIMENTAL

Proton nmr spectra were recorded on a Perkin-Elmer R-24B nuclear magnetic resonance spectrometer, employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. The ^{13}C-nmr spectra were obtained on a JEOL FX-90Q FT nuclear magnetic resonance spectrometer.

Hexane, ether and triethylamine were dried and purified by distillation from sodium-potassium alloy prior to use. Diphenylketene was prepared from diphenylacetyl chloride as previously described. All of the cyclic carbodiimides were prepared from commercially available lactams by the Tiemann rearrangement with ring enlargement as described [8,9].

Typical Procedure for Diphenylketene Cycloadditions.

a) Equal Molar Amounts of Ketene and Carbodiimide.

A 0.01 mole portion of diphenylketene was added to a stirred solution of 0.01 mole of the cyclocarbodiimide in 10 ml of ether under a nitrogen atmosphere. The reaction mixture was stirred for an additional hour and the solvent removed under reduced pressure and the residue recrystallized from benzene and hexane to yield the β-lactams.

b) 2:1 Molar Ratio of Ketene and Carbodiimide.

A solution of 0.01 mole of 1,3-diazacycloocta-1,2-diene in 30 ml of ether was added to a stirred solution of 0.02 mole of diphenylketene in 5 ml of ether under a nitrogen atmosphere. The reaction mixture was stirred overnight and the solvent removed under reduced pressure. The residue was recrystallized from chloroform and hexane to give the 2:1 cycloaddition products.

Typical Procedure for the Cycloaddition of *in situ* Generated Ketenes with Cyclic Carbodiimides.

A solution of 0.02 mole of freshly distilled acid chloride in 100 ml of dry hexane was added over a 2 hour period to a stirred solution of 0.02 mole of the cyclic carbodiimide and 0.04 mole of triethylamine in 150 ml of hexane under a nitrogen atmosphere. The resulting mixture was stirred an additional hour and the amine salt removed by filtration. The solvent was removed under reduced pressure and the residue recrystallized from benzene and hexane or benzene and 95% ethanol.

N-Diphenylacetyl-1,3-diazacycloocta-2-one, **6** [11].

A solution containing 0.01 mole of diphenylketene in 50 ml of benzene was added to a solution of 0.01 mole of 1,3-diazacycloocta-1,2-diene in 100 ml of benzene at 0° under a nitrogen atmosphere. This reaction solution was quenched with 100 ml of water after 4 minutes. The solvent and water were evaporated under reduced pressure and the residue dissolved in 100 ml of chloroform. The chloroform solution was extracted several times with dilute sodium hydroxide solution. The chloroform solution was then evaporated to dryness with a rotatory evaporator and the residue was fractionally recrystallized from chloroform and hexane to yield 0.55 g (17%), mp 178-180°; ir (DMSO): 1640 (broad, C=O), cm^{-1}; ^1H-nmr: δ 1.2-1.9 (m, 6H), 3.0-3.7 (m, 4H), 5.0 (s, 1H), 5.2-5.6 (m, 1H), 7.0-7.4 (m, 10H).

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88. Found: C, 74.83; H, 7.23.

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[11] These compounds were not soluble in any available organic solvents except for some limited solubility in hot DMSO.