Halogenated Ketenes. IX. Ketene Carbodiimide Cycloadditions[1,2]

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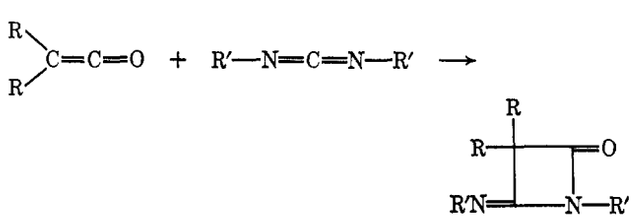
Received February 4, 1969

The cycloaddition of various types of ketenes with dicyclohexyl- and diisopropylcarbodiimides to produce imino-β-lactams has been investigated. A large difference in the ketene reactivities was found. The ketenes studied include fluoro-, chloro-, dibromo-, methylchloro-, phenylchloro-, diphenyl-, phenylethyl-, butylethyl-, and dimethylketenes as well as ketene itself. The mechanism of this reaction is discussed in terms of a dipolar intermediate. The preparation of phenylethyl- and phenylchloroketenes and cycloaddition of the latter with cyclopentadiene are also described.

There are many reports which date back to the early investigations of Staudinger on the reaction of ketenes with imino compounds across the C=N linkage to give β-lactams.[3] However, the cycloaddition with carbodiimides has only recently appeared; and in the first two reports no structures were given and, furthermore, one report indicated that the adducts were not isolated owing to decomposition.[4,5] Hull has more recently described the reaction of dichloroketene with a couple of carbodiimides to yield the corresponding azetidinones (β-lactams).[6] In connection with a study of monohaloketenes, one of us has quite recently communicated on the cycloaddition of fluoroketene and diisopropylcarbodiimide.[7]

We now wish to report on a study of the reaction of dicyclohexyl- and diisopropylcarbodiimides with different types of ketenes, with particular emphasis on halogenated ketenes. As a part of this study, the previously unknown phenylethyl- and phenylchloroketenes were synthesized; and cycloaddition of the latter with cyclopentadiene is also described.

The reaction of ketenes and carbodiimides is a 1,2-cycloaddition reaction and can be generally represented as follows.

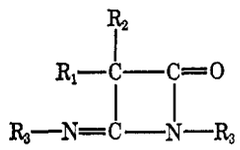


The imino-β-lactams and the yields of the preparations are shown in Table I. The infrared spectra of the cycloadducts revealed the carbonyl absorptions at 1810–1832 cm^{-1} and the C=N absorptions at 1690–1716 cm^{-1}.

Since we have been unable to isolate the halogenated ketenes, these materials were generated by dehydrohalogenation of the appropriately substituted acid halide with triethylamine in the presence of the carbodiimide. The optimum conditions for these cycloadditions appears to be in refluxing hexane. At lower temperatures, the rate of cycloaddition is considerably slower, and the more unstable ketenes undergo polymerization rather than cycloaddition. Diphenylketene is an exception, as a benzene solution of this ketene and diisopropylcarbodiimide at room temperature loses the characteristic yellow color due to ketene after only about 30 min. Difficulty was experienced in the isolation and purification of the adducts from chloro- and butylethylketenes, but the spectral data established that these β-lactams were produced.

TABLE I

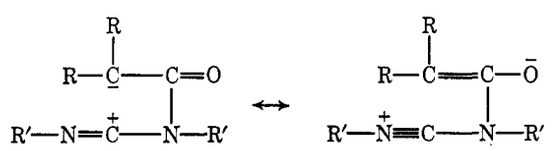
CYCLOADDUCTS FROM KETENES AND CARBODIIMIDES



Compd	Registry No.	R_1	R_2	R_3	Yield, %
I	20452-63-5	C_6H_5	C_6H_5	C_6H_{11}	90
II	20452-64-6	C_6H_5	C_6H_5	i-C_3H_7	88
III	20452-65-7	C_6H_5	Cl	C_6H_{11}	65
IV	20452-66-8	Br	Br	C_6H_{11}	59
V	20452-68-0	C_6H_5	C_2H_5	i-C_3H_7	57
VI	20452-69-1	F	H	i-C_3H_7	40
VII	20452-70-4	CH_3	CH_3	i-C_3H_7	32
VIII	20452-71-5	CH_3	Cl	C_6H_{11}	25
IX	20452-72-6	Cl	H	i-C_3H_7	20
X	20452-73-7	C_4H_9	C_2H_5	i-C_3H_7	15
XI	20452-74-8	H	H	i-C_3H_7	5

The treatment of dicyclohexylcarbodiimide with an excess of diphenylketene did not produce a detectable amount of the 2:1 adduct, nor was there any evidence of such an adduct in any of the other preparations.

We have already presented evidence which indicates that the mechanistic pathway for this reaction involves a dipolar intermediate represented below.[8]



It is interesting to note that the phenyl-substituted ketenes and the dihaloketenes give considerably better yields of the β-lactams than the other ketenes. This is apparently a result of these ketenes having substituents capable of stabilizing or smearing out the negative charge on the α carbon, thus making these materials

(1) Paper VIII. W. T. Brady, W. L. Vaughn, and E. F. Hoff, *J. Org. Chem.*, **34**, 843 (1969).

(2) Support of this investigation by The Robert A. Welch Foundation and a National Science Foundation Grant (GP-7386) is gratefully acknowledged.

(3) R. N. Lacey, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1207.

(4) Fabrenfabriken Bayer Akt. Ges., British Patent 797,972 (1958); *Chem. Abstr.*, **53**, 3059 (1959).

(5) R. Hofmann, E. Schmidt, K. Wamsler, A. Reichle, and F. Moosmuller, German Patent 960,458 (1957); *Chem. Abstr.*, **53**, 16077 (1959).

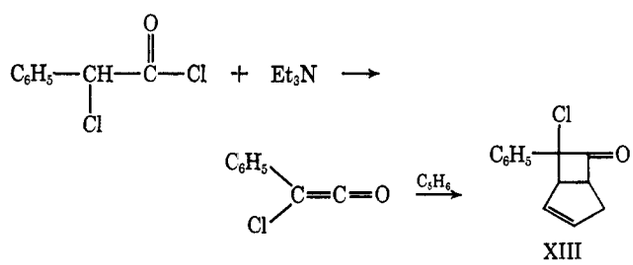
(6) R. Hull, *J. Chem. Soc., C*, 1967, 1154.

(7) W. T. Brady and E. F. Hoff, *J. Amer. Chem. Soc.*, **90**, 6256 (1968).

(8) W. T. Brady and E. D. Dorsey, *Chem. Comm.*, 1638 (1968).

more reactive than the others studied. Ketene itself is less reactive than all of the ketenes investigated, and this is certainly consistent with the dipolar mechanism. It should be emphasized that all of these reactions are uncatalyzed, and that cycloadditions effected in the presence of Lewis acid catalysts would be expected to show a decrease in the reactivity differences.

Phenylchloroketene is readily prepared by the dehydrochlorination of α-chloro-α-phenylacetyl chloride with triethylamine. When the dehydrochlorination is effected in the presence of the reactive cyclopentadiene, the corresponding 1,2 cycloadduct, XII, is obtained in 80% yield along with a quantitiative amount of amine salt.



XIII

Cycloaddition of phenylchloroketene with cyclohexene, an unactivated olefin, proceeded with difficulty as expected. The adduct was obtained in about 20% yield, but difficulty was experienced in purification.

Phenylethylketene was readily obtained by the dehydrochlorination of α-phenylbutyryl chloride with triethylamine and was easily distilled under reduced pressure.

Experimental Section

The solvents employed in these preparations were benzene and hexane, which were previously dried by refluxing and distilling from calcium hydride. Diphenylketene was obtained by the dehydrochlorination of diphenylacetyl chloride with triethylamine.[9] α-Chloro-α-phenylacetyl chloride was prepared from *dl*-mandelic acid and phosphorus pentachloride according to the method of Walden.[10] All of the other acid halides were also prepared from the corresponding acids and an appropriate reagent according to standard procedures. Dimethylketene was obtained by the pyrolysis of the commercially available ketene dimer, tetramethyl-1,3-cyclobutanedione, and ketene was prepared by the pyrolysis of acetone.[11,12] We are grateful to Eastman Chemical Products, Inc., for supplying us with butylethylketene in the form of a 20% solution in toluene.

1-Cyclohexyl-4-cyclohexylimino-3,3-diphenylazetidin-2-one (I).—A 13.2-g (0.068-mol) portion of diphenylketene was added to a stirred solution containing 14 g (0.068 mol) of dicyclohexylcarbodiimide in 100 ml of hexane at room temperature. After several hours, the reaction mixture was filtered to yield 23.6 g (90%) of I: mp 158–159°; ir 1810 (C=O) and 1695 cm^{-1} (C=N); nmr (CCl_4) δ 1.57 (m, 20 H), 3.4 (m, 2 H), and 7.12 ppm (m, 10 H).

Anal. Calcd for $C_{27}H_{32}N_2O$: C, 80.9; H, 8.05; N, 6.95. Found: C, 80.8; H, 8.35; N, 6.71.

3,3-Diphenyl-1-isopropyl-4-isopropyliminoazetidin-2-one (II).—A solution containing 6.4 g (0.033 mol) of diphenylketene and 4.2 g (0.033 mol) of diisopropylcarbodiimide in 100 ml of benzene was allowed to stand at room temperature for 2 hr. Upon removal of the solvent and recrystallization of the solid residue from ether, II was obtained in 88% yield: mp 108.5–109.5°; ir 1810 (C=O) and 1690 cm^{-1} (C=N); nmr (CCl_4) δ 0.80 (d, 6 H), 1.45 (d, 6 H), 3.66 (m, 1 H), 4.03 (m, 1 H), and 7.3 ppm (m, 10 H).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.7; H, 7.56; N, 8.75. Found: C, 79.0; H, 7.58; N, 8.74.

3-Chloro-1-cyclohexyl-4-cyclohexylimino-3-phenylazetidin-2-one (III).—A solution of 13.3 g (0.070 mol) of α-chloro-α-phenylacetyl chloride in 30 ml of hexane was added dropwise to a refluxing solution of 14.5 g (0.070 mol) of dicyclohexylcarbodiimide and 14.2 g (0.141 mol) of triethylamine in 200 ml of dry hexane. After the addition was complete, the mixture was allowed to continue refluxing for 2 hr. The amine salt was removed by filtration and the hexane was evaporated to yield 16 g (65%) of III, recrystallized from methanol: mp 86–88°; ir 1822 (C=O) and 1700 cm^{-1} (C=N); nmr (CCl_4) δ 1.5 (m, 20 H), 3.4 (m, 2 H), and 7.42 ppm (m, 5 H).

Anal. Calcd for $C_{21}H_{27}ClN_2O$: C, 70.30; H, 7.52; Cl, 9.90; N, 7.81. Found: C, 70.53; H, 7.83; Cl, 9.82; N, 8.08.

3,3-Dibromo-1-cyclohexyl-4-cyclohexyliminoazetidin-2-one (IV).—To a refluxing solution of 12.2 g (0.059 mol) of dicyclohexylcarbodiimide and 6.55 g (0.065 mol) of triethylamine in 100 ml of hexane was added over a period of 2 hr a solution of 16.6 g (0.059 mol) of dibromoacetyl chloride in hexane. After refluxing an additional 30 min, the solution was cooled and filtered and the solvent was evaporated on a rotatory evaporator. The residue was recrystallized from 95% ethanol to yield 14.5 g (59%) of IV: mp 121.5–122°; ir 1822 (C=O) and 1716 cm^{-1} (C=N); nmr (CCl_4) δ 1.7 (m, 20 H), and 3.7 ppm (m, 2 H).

Anal. Calcd for $C_{15}H_{22}N_2OBr_2$: C, 44.3; H, 5.42; N, 6.90. Found: C, 44.5; H, 5.63; N, 6.73.

Phenylethylketene.—A solution of 11.1 g (0.11 mol) of triethylamine in 20 ml of hexane was added dropwise to 18.2 g (0.10 mol) of α-phenylbutyryl chloride in 50 ml of hexane at room temperature. Stirring was continued for several hours after the addition was complete. The salt was removed by filtration, the solvent was evaporated, and the phenylethylketene was distilled at 32–34° (0.04 mm) to yield 7 g (48%) of product: ir 2110 cm^{-1} (ketene absorption).

3-Ethyl-1-isopropyl-4-isopropylimino-3-phenylazetidin-2-one (V).—A 4.2-g (0.029 mol) portion of phenylethylketene was added to 20 ml of dry benzene containing 3.62 g (0.029 mol) of diisopropylcarbodiimide at room temperature. The solution was allowed to stand at this temperature for 48 hr, after which time the yellow color of the ketene had disappeared. The solvent was evaporated and the residue was recrystallized from ether to yield 4.5 g (57%) of V: mp 35–36°; ir 1830 (C=O) and 1710 cm^{-1} (C=N); nmr (CCl_4) δ 0.95 (d, 3 H), 1.10 (d, 3 H), 1.12 (t, 3 H), 1.45 (d, 6 H), 2.28 (m, 2 H), 3.42 (heptet, 1 H), 4.05 (heptet, 1 H), and 7.25 ppm (m, 5 H).

Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.25; H, 8.93; N, 10.23.

3-Fluoro-1-isopropyl-4-isopropyliminoazetidin-2-one (VI).—A solution containing 11.4 g (0.12 mol) of fluoroacetyl chloride in 60 ml of hexane was added dropwise to a refluxing solution containing 24 g (0.24 mol) of triethylamine and 15.5 g (0.12 mol) of diisopropylcarbodiimide in 100 ml of hexane. Refluxing was continued for 2 hr after the addition. The amine salt was removed by filtration and the filtrate was vacuum distilled to yield 8.9 g (40%) of VI: bp 50–51° (0.7 mm); ir 1832 (C=O) and 1710 cm^{-1} (C=N); nmr (CCl_4) δ 1.32 (m, 12 H). 3.85 (m, 2 H), and 5.94 ppm (d, 1 H, J_{HF} = 55 cps).

Anal. Calcd for $C_9H_{15}FN_2O$: C, 58.1; H, 8.07; N, 15.5. Found: C, 58.37; H, 8.26; N, 15.21.

3,3-Dimethyl-1-isopropyl-4-isopropyliminoazetidin-2-one (VII).—To a solution of 40 ml of hexane containing 18.2 g (0.144 mol) of diisopropylcarbodiimide was added 10.1 g (0.144 mol) of dimethylketene. This solution was refluxed for 8 hr, and then the solvent and unreacted carbodiimide were removed by vacuum distillation. The residue was recrystallized from ligroin to yield 9.1 g (32%) of VII. The cycloadduct was further purified by sublimation at room temperature and 0.01-mm pressure: mp 75–76°; ir 1815 (C=O) and 1695 cm^{-1} (C=N); nmr (CCl_4) δ 1.10 (d, 6 H), 1.35 (s, 6 H), 1.35 (d, 6 H), and 3.7 ppm (m, 2 H).

Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.3; H, 10.2; N, 14.3. Found: C, 67.06; H, 9.99; N, 14.45.

3-Chloro-3-methyl-1-cyclohexyl-4-cyclohexyliminoazetidin-2-one (VIII).—A 11.3-g (0.066-mol) portion of α-chloropropionyl bromide in 50 ml of hexane was added to a stirred refluxing solution of 13.6 g (0.066 mol) of dicyclohexylcarbodiimide and 13.3 g (0.132 mol) of triethylamine in 150 ml of hexane over 2 hr. After refluxing for an additional 5 hr. and cooling, the amine

(9) H. Staudinger, *Ber.*, **44**, 1619 (1911).
(10) P. Walden, *ibid.*, **28**, 1287 (1895).
(11) W. E. Hanford and J. C. Sauer, *Org. Reaction*, **3**, 136 (1946).
(12) W. E. Hanford and J. C. Sauer, *ibid.*, **3**, 108 (1946).

salt was removed. The solvent was removed on a rotatory evaporator and the residue was recrystallized from 95% ethanol to yield 4.8 g (25%) of VIII. Further purification was obtained by sublimation at 56° *in vacuo:* mp 61–62°; ir 1825 (C=O) and 1705 cm^{-1} (C=N); nmr (CCl_4) δ 1.6 (m), 1.85 (s), and 3.55 ppm (m). The singlet was superimposed on the 1.6 multiplet. The areas were in the ratio of 2:23.

Anal. Calcd for $C_{16}H_{25}N_2OCl$: C, 64.8; H, 8.45; N, 9.46. Found: C, 64.8; H, 8.77; N, 9.40.

3-Chloro-1-isopropyl-4-isopropyliminoazetidin-2-one (IX).—A 10.1-g (0.065 mol) portion of chloroacetyl bromide in 25 ml of hexane was slowly added to a refluxing solution of 8.2 g (0.065 mol) of diisopropylcarbodiimide and 6.5 g (0.13 mol) of triethylamine in 100 ml of hexane. The reaction mixture was refluxed for 2 hr after the addition was completed. Upon removal of the salt by filtration and evaporation of the solvent, the residue was distilled to yield 2.4 g (20%) of impure IX: ir 1820 (C=O) and 1705 cm^{-1} (C=N).

3-*n*-Butyl-3-ethyl-1-isopropyl-4-isopropyliminoazetidin-2-one (X).—To a refluxing solution consisting of 9.95 g (0.079 mol) of diisopropylcarbodiimide in 50 ml of hexane was slowly added 9.95 g (0.079 mol) of butylethylketene in 50 ml of hexane. This solution was refluxed for an additional 2 hr. The solvent was evaporated and the residue was distilled at 80–89° (0.025 mm) to yield 2.3 g (12%) of impure X: ir 1810 (C=O) and 1690 cm^{-1} (C=N).

1-Isopropyl-4-isopropyliminoazetidin-2-one (XI).—An excess of ketene was bubbled into a solution of 8.1 g (0.07 mol) of diisopropylcarbodiimide over a period of 8 hr. The solvent was evaporated to yield predominantly unreacted carbodiimide with only a very small amount (5%) of XI: ir 1820 (C=O) and 1700 cm^{-1} (C=N).

7-Chloro-7-phenylbicyclo[3.2.0]hept-2-en-6-one (XII).—A 17.25-g (0.17 mol) portion of triethylamine in 30 ml of benzene was added dropwise with stirring to a solution containing 29.35 g (0.155 mol) of α-chloro-α-phenylacetyl chloride, 102.5 g (1.55 mol) of cyclopentadiene, and 100 ml of dry benzene. After the addition was complete, the mixture was refluxed for 1 hr. The amine salt was removed by filtration and the filtrate was concentrated and distilled *in vacuo* to yield 27 g (80%) of XII: bp 113–113.5° (0.9 mm); ir 1784 (C=O) and 1600 cm^{-1} (C=C); nmr (CCl_4) δ 2.55 (m, 2 H), 4.18 (m, 2 H), 5.6 (m, 2 H), and 7.4 ppm (m, 5 H).

Anal. Calcd for $C_{13}H_{11}ClO$: C, 71.40; H, 5.08. Found: C, 71.3; H, 5.07.

Registry No.—Phenylethylketene, 20452-67-9; XII, 20452-75-9.

Thermal Cleavage Reactions of N-Chloroketimines. Behavior of Imino Radicals

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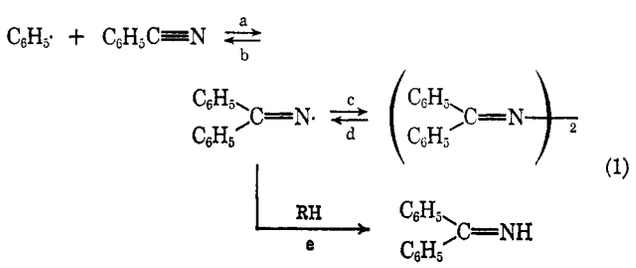
Received November 27, 1968

In contrast to the relatively stable diphenyl N-chloroketimine (**1**), phenyl benzyl N-chloroketimine (**2**) in chlorobenzene solution (<0.04 *M*) undergoes cleavage at 130° to form benzonitrile and benzyl chloride along with small amounts of bibenzyl. The reaction is accelerated by slow addition of benzoyl peroxide and inhibited by oxygen. A radical chain sequence is postulated involving β scission of phenyl benzyl ketimino radical (**13**) as the key step. The intermediate benzyl radical has been trapped by added 1-octene to form 1-phenyl-3-chlorononane (**12**) and by added tri-*n*-butyltin hydride (Bu_3SnH) to form toluene. At 35–40°, radical **13** can be partially intercepted by Bu_3SnH before cleavage. Phenyl α-methylbenzhydryl N-chloroketimine (**3**) gives benzonitrile, 1,1-diphenylethylene, and hydrogen chloride on thermolysis, the latter two products apparently derived from 1,1-diphenyl-1-chloroethane (**10**). In concentrated solution, additional products from the thermolysis of **2** included ammonium chloride and 2,3,4,5-tetraphenylpyrrole (**9**). The reduction of **1** with Bu_3SnH at 50–60° could be inhibited by oxygen and accelerated by di-*t*-butyl peroxyoxalate as anticipated for a radical chain process. Silver ion catalyzed Beckmann rearrangement of **2** gave N-phenylphenylacetamide (**4**) free from N-benzylbenzamide (**5**), so that chlorine appears to be *syn* to the benzyl group. Similar treatment of **3** gave no amides but only benzonitrile and 1,1-diphenylethylene. Attempts to prepare the N-chloroketimine from phenyl benzhydryl ketimine by the same procedures which were successful for **1**, **2**, and **3** gave initial chlorination on carbon rather than on nitrogen.

The methylenimino radical ($H_2C{=}N\cdot$), produced by addition of hydrogen atoms to hydrogen cyanide in a low-temperature matrix, has been observed by esr spectroscopy.[1] However, methods of formation and typical reactions of substituted ketimino radicals ($RR'C{=}N\cdot$) are not well known. We wish to report some reactions of N-chloroketimines which involve the intermediacy of such radicals.

Generation of cyclohexyl or phenyl radicals in the presence of benzonitrile gives small amounts of ketimines;[2] a ketimino radical produced by addition of the carbon radical to the nitrile group (step 1a) is a reasonable intermediate if it is assumed to be able to abstract hydrogen (step 1e) to give the observed product. Among the products from pyrolysis of benzophenone azine at 375–500° are benzene, biphenyl, benzonitrile, and benzophenone ketimine;[3] initial N–N bond homolysis (step 1d) followed by β scission of a ketimino radical (step 1b) was invoked to explain nitrile formation. A similar scheme would rationalize the



(1)

pyrolysis of acetone azine to form acetonitrile and ethane[4] as well as the use of certain azines as polymerization initiators.[5,5a] Other reactions which apparently involve radical addition to the nitrile function and the intermediacy of ketimino radicals [$R(X)C{=}N\cdot$] which either undergo β scission (X = Cl) or abstract hydrogen

(1) E. L. Cochran, F. J. Adrian, and V. A. Bowers, *J. Chem. Phys.*, **36**, 1938 (1962).

(2) J. R. Shelton and C. W. Uzelmeier, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

(3) S. S. Hirsch, *J. Org. Chem.*, **32**, 2433 (1967).

(4) J. L. Anderson, U. S. Patent 2,770,643 (1956).

(5) M. J. Roedel, U. S. Patent 2,439,528 (1948).

(5a) NOTE ADDED IN PROOF.—Photolysis of benzalazine has also been postulated to proceed through imino radicals: R. W. Binkley, *J. Org. Chem.*, **34**, 2072 (1969).