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Studies of Heteroaromaticity. XX.[1] Novel Thermal 1,3-Dipolar Cycloaddition of 5-Nitrofuran-2-carbohydroxamoyl Chloride with Diketene and Dicyclohexylcarbodiimide

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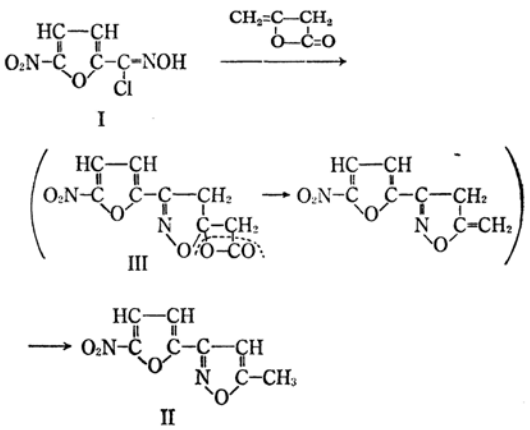
Ketenes sometimes undergo 1,3-dipolar cycloaddition reactions, but with such typical 1,3-dipoles as nitrones[2] and *N*-oxides,[3] diphenylketene reacts in a different manner, affording an isoxazolone derivative.[4] However, there have been no reports concerning the similar reactions of nitrile oxides with diketene, presumably because of its inertness. Since ketene is generally generated by the pyrolysis of diketene,[5] we attempted the thermal 1,3-dipolar cycloaddition of 5-nitrofuran-2-carbohydroxamoyl chloride (I)[6] to diketene. I was heated in toluene with an equivalent amount of diketene until the evolution of hydrogen chloride gas had ceased; this afforded a crystalline product, II, in a 20% yield, in addition to the recovered I, after purification on a silica-gel (Mallinckrodt, 100 mesh) column. The yield of II was improved to 60% by adding excess amounts of diketene at intervals. The results of elemental analysis and the spectral data support the identification of II as 3-(5-nitro-2-furyl)-5-methylisoxazole, an isomer of 3-(5-nitro-2-furyl)-4-methylisoxazole,[7] mp 146—149°C; it could unambiguously be discriminated from II by an NMR spectral comparison.[8] It is noteworthy that the thermal procedure proceeded, presumably through an expectable intermediate adduct, III, followed by the elimination of carbon dioxide, thus affording an isoxazole derivative, II, instead of isoxazolone. 5-Nitrofuran-2-carbonitrile *N*-oxide did not react at all with diketene under the reaction conditions given by Minami and Matsumoto.[7] Similar treatments of *m*- and *p*-nitrobenzcarbohydroxamoyl chloride with diketene afforded only intractable tars, though the evolution of hydrogen chloride gas was observed in the course of the reactions.



Another interesting example was observed in the 1,3-dipolar cycloaddition reaction of I with carbodiimides. Carbodiimides as dipolarophilic heterocumulenes are known to react with dipolar compounds like hydrazoic acid, diazomethane, and nitrile imines,[9] and quite recently, the addition of aromatic nitrile oxides to diphenylcarbodiimide in the presence of boron trifluoride etherate as a catalyst has been reported to afford a spiro-1,2,4-oxadiazole, IV, *via* a 1 : 1 adduct, V.[10]

I was heated in toluene with an equivalent amount of dicyclohexylcarbodiimide (DCC) until the evolution of hydrogen chloride gas had ceased. The worked-up product (VI) consisted of yellow crystals; the results of the elemental analysis and the spectral data support the idea that VI is 1,4-dicyclohexyl-3-(5-nitro-2-furyl)-4,5-dihydro-5-oxo-1*H*-triazole. This was further confirmed by its chemical conversion to the known *N*,*N'*-dicyclo-

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[1] Part XIX of this series: T. Sasaki and T. Yoshioka, This Bulletin, **41**, 2212 (1968).

[2] C. H. Hassall and A. E. Lippman, *J. Chem. Soc.*, **1953**, 1059; H. Staudinger and K. Miescher, *Helv. Chim. Acta*, **2**, 554 (1919).

[3] T. Koenig, *Tetrahedron Letters*, **1965**, 3127.

[4] R. Scarpati and P. Sorrentino, *Gazz. Chim. Ital.*, **89**, 1525 (1959).

[5] S. Andreades and H. D. Carlson, *Org. Synth.*, **45**, 50 (1965).

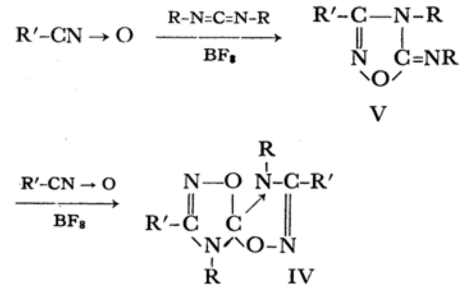
[6] T. Sasaki and T. Yoshioka, This Bulletin, **40**, 2604 (1967).

[7] S. Minami and J. Matusmoto, *Chem. Pharm. Bull.* (*Tokyo*), **15**, 366 (1967).

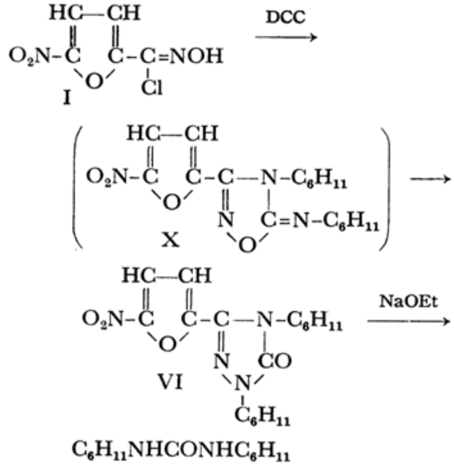
[8] NMR ($CDCl_3$) τ: 1.67 (doublet, 5-C–H).

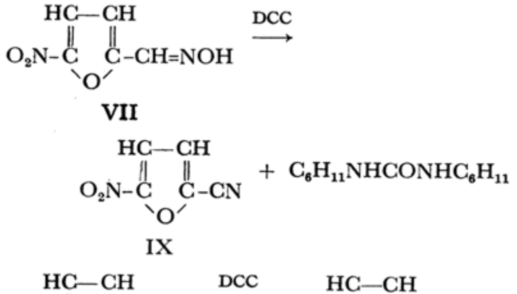
[9] H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y. (1967), p. 260, and the references cited therein.

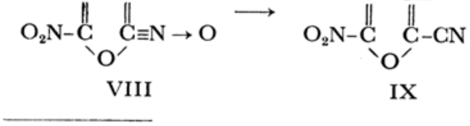
[10] C. Grundman and R. Richter, *Tetrahedron Letters*, **1968**, 963.



hexylurea[11] when its ethanolic solution was refluxed with sodium ethoxide. The similar thermal treatment of 5-nitrofuran-2-carboxaldehyde oxime (VII) with DCC and the normal treatment of 5-nitrofuran-2-carbonitrile oxide (VIII) with DCC in ether at room temperature both afforded 5-nitrofuran-2-carbonitrile (IX),[12] and no cyclization occurred. Considering the results given by Grundman and Richter,[10] it seems reasonable to assume, in the reaction of I with DCC, that a 1 : 1 adduct like X might be produced as the first step and that this might then be thermally rearranged to VI. However, such a thermal rearrangement of oxadiazole to triazole has never been documented. Therefore, further investigation is necessary before the mechanism can be discussed in detail; this investigation is now being undertaken.







Experimental[13]

3-(5-Nitro-2-furyl)-5-methylisoxazole (II). I (0.88 g; 0.4 mmol) was treated with 1.0 g of diketene and 20 m*l* of toluene at reflux temperature for 18 hr, until the evolution of hydrogen chloride gas had ceased. After the removal of the solvent, the residue was dissolved in chloroform and chromatographed on a silica-gel column. 0.17 g (20%) of yellow crystals, mp 143—144°C, was obtained from the first fraction*[1] after recrystallization from ethanol. UV λ_{max}^{EtOH} mμ (ε): 320 (14500). NMR ($CDCl_3$) τ: 2.56 (doublet, $J=3.8$ cps, 4-C–H of nitrofuran), 2.96 (doublet, $J=3.8$ cps, 3-C–H of nitrofuran), 3.53 (quartet, $J=0.2$ cps, 4-C–H), 7.46 (doublet, $J=0.2$ cps, 5-C–CH_3).

Found: C, 49.38; H, 3.17; N, 14.25%. Calcd for $C_8H_6O_4N_2$: C, 49.47; H, 3.12; N, 14.43%.

1,4-Dicyclohexyl-3-(5-nitro-2-furyl)-4,5-dihydro-5-oxo-1*H*-triazole (VI). I (0.95 g; 0.5 mmol) was refluxed with 1.0 g (0.5 mmol) of DCC in 20 m*l* of toluene for 7 hr, until the evolution of hydrogen chloride gas had ceased. After the removal of the solvent under reduced pressure, the residue was dissolved in chloroform and chromatographed on a silica-gel column. 0.7 g (40%) of VI, mp 146—148°C, was obtained from the first fraction after recrystallization from ethanol. UV λ_{max}^{EtOH} mμ (ε): 350 (3400, shoulder), 295 (9000). IR (KBr) cm^{-1}: 1700 (ν_{CO}). NMR ($CDCl_3$) τ: 2.58 (doublet, $J=3.8$ cps, 4-C–H of nitrofuran), 2.86 (doublet, $J=3.8$ cps, 3-C–H of nitrofuran), around 6.2 and 8.5 (multiplet, –CH_2).

Found: C, 60.10; H, 6.63; N, 15.71%. Calcd for $C_{18}H_{24}O_4N_4$: C, 59.68; H, 6.71; N, 15.55%.

Conversion of VI to *N,N′*-Dicyclohexylurea. A mixture of 0.23 g of VI, 0.1 g of sodium ethoxide, and 20 m*l* of ethanol was refluxed for 6 hr. After the ethanol had been removed under reduced pressure, the residue was made acidic by adding dilute hydrochloric acid, and then it was extracted with chloroform. After drying a chloroform layer over sodium sulfate, a chloroform solution was chromatographed on a silica

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[11] Mp 242°C. Found: C, 69.82; H, 11.04; N, 11.92%. Calcd for $C_{13}H_{24}ON_2$: C, 69.60; H, 10.78; N, 12.49%. IR (KBr) cm^{-1}: 3350 (νNH), 1630 (νCO). *Cf.* C. A. Dekker and H. G. Khorana, *J. Org. Chem.*, **76**, 3522 (1954).

[12] Mp 62—64°C. T. Sasaki and T. Yoshioka, *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem. Japan*), **25**, 665 (1967).

[13] All melting points were determined on a Yanagimoto micromelting-point apparatus and have not been corrected. The ultraviolet spectra were run on a JASCO Model ORD/UV-5 optical rotary dispersion recoder, while the infrared spectra were measured on a JASCO Model IR-S spectrophotometer. The NMR spectra were taken on a Varian A-60 apparatus, with tetramethylsilane as an internal standard, and their chemical shifts are presented in terms of τ values.

*[1] From the second fraction, I was recovered in a 56% yield.

column. 0.05 g (50%) of dicyclohexylurea[11] was obtained from the first fraction after recrystallization from benzene - petroleum ether.

***N*-Nitrofuran-2-carbonitrile (IX).** *From 5-Nitrofuran-2-carboxaldehyde Oxime (VII).* A solution of 0.8 g of VII and 1.03 g of DCC in 25 m*l* of toluene was refluxed for 10 hr. After cooling, the resulting precipitates were filtered and washed with hot benzene to afford 1.0 g (87%) of dicyclohexylurea,[11] which was identified by infrared spectral comparison with an authentic specimen. The filtrate was condensed, redissolved in chloroform, and then chromatographed on a silica-gel column. 0.6 g (85%) of VIII[12] was obtained from the first fraction; it was identified by infrared spectral comparison with an authentic specimen.

From 5-Nitrofuran-2-carbonitrile Oxide (VIII). To a stirred solution of 0.8 g of I and 0.91 g of DCC in 30 m*l* of ether, there was added a solution 1 m*l* of triethylamine in 10 m*l* of ether at room temperature. Stirring was continued for 1 hr, after which the resultant triethylamine hydrochloride was filtered and washed with ether. The ether washings were combined with the filtrate and chromatographed on a silica-gel column, using chloroform as an eluent. From the first fraction a very small amount of IX was obtained, while from the third fraction, 0.5 g of dicyclohexylurea[11] was obtained; the other parts were intractable tars hard to characterize.