Phototransformation of 1,2,4-Triazolo[1,2-*a*]pyridazine-1,3-dione to Pyrrolo[1,2-*a*]-1,3,5-triazine-2,4-dione

Tuvia Sheradsky* and Reuven Moshenberg

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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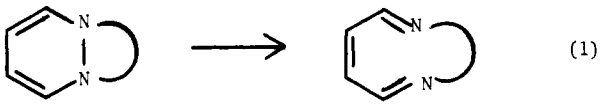
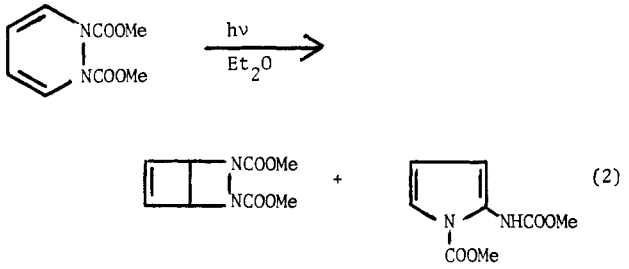
5-(Methoxycarbonyl)-2-phenyl-1,2,4-triazolo[1,2-*a*]pyridazine-1,3-dione (3) was obtained by a Diels–Alder reaction of 3-(methoxycarbonyl)-2-pyrone (1) with 4-phenyl-1,2,4-triazoline-2,5-dione (2). The photolysis of 3 in methanol yielded the 6-methoxy-9-methoxycarbonyl and 6-methoxycarbonyl derivatives of 3-phenylpyrrolo[1,2-*a*]-1,3,5-triazine-2,4-dione (7 and 8, respectively) while photolysis in dichloromethane yielded the 8-methoxycarbonyl derivative 10. All the photoproducts were formed via a triazonine (5) which underwent either transannular addition of methanol to give 7, addition–elimination of methanol to 8, or further photolysis to 10.

Cleavage of the N–N bond in bicyclic systems containing bridgehead hydrazine presents a facile route to medium-sized heterocycles containing two or more heteroatoms. This approach has been employed previously[1] by using the Hoffman elimination. An attractive unexplored application is the electrocyclic ring opening, generalized in eq 1.

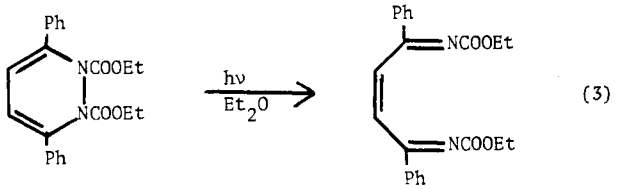


(1)

The photolysis of monocyclic 1,2-dihydropyridazines has been reported in two particular cases and showed high substituent dependency. When carbon substituents were lacking, the main pathway was intramolecular [2 + 2] cycloaddition, accompanied by some ring opening which led through further photolysis to a pyrrole[2] (eq 2). On the other hand, the 3,6-diphenyl derivative underwent ring opening only and the product was photochemically stable[3] (eq 3).



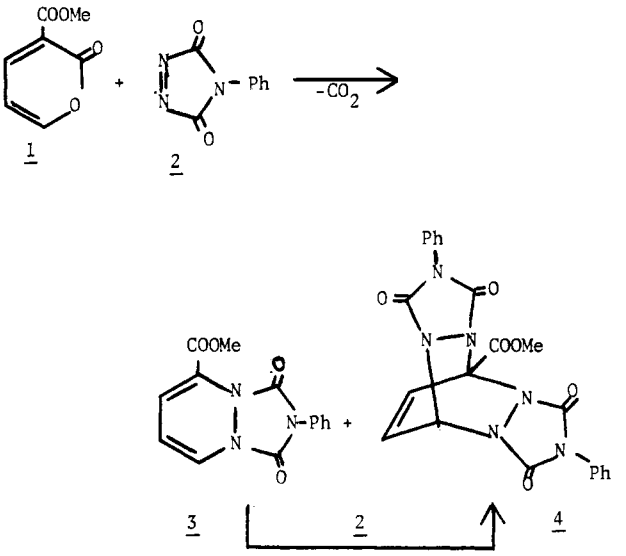
(2)



(3)

Our attempts to prepare bicyclic 1,2-dihydropyridazines by analogy with the published syntheses of the monocyclic derivatives (bromination–dehydrobromination[4] or selenium dioxide oxidation[5] of tetrahydropyridazines) were unsuccessful. An alternative approach which should give the requisite derivatives in one operation is the Diels–Alder reaction of α-pyrones with cyclic azo dienophiles.[6] Indeed, the reaction of 3-(methoxycarbonyl)-2-pyrone (1) with 4-phenyl-1,2,4-triazoline-3,5-dione (2) afforded compound 3 in 42% yield, together with 20% of the 1:2 adduct 4, formed by further Diels–Alder reaction of 3 with 2 (Scheme I).

Scheme I



The diene 3 was obtained as orange crystals, λ_{max} = 406 nm. Its reaction with 2 gave 4 quantitatively, but it was inert toward carbon dienophiles (dimethyl acetylenedicarboxylate or maleic anhydride) even on prolonged heating. Compound 4 was obtained as a mixture of stereoisomers, as was evident from its NMR spectrum which was very complex and exhibited three methyl peaks.

The photolysis of 3 was carried out in methanol, as the expected initial photoproduct was the triazonine 5 (Scheme II) which contains two acylimino linkages. Acyl imines are unstable, highly electrophilic, and usually isolated as addition products with alcohols.[7,8] Normal bis addition of methanol to 5 would lead to 6, which was not detected. The reaction yielded two products in a ratio of 3:1. The major one (35%) was a methanol monoadduct and was identified as 7. The minor one (12%) was isomeric with 3 and was identified as 8.

(1) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1969**, *34*, 2715.
(2) Altman, L. J.; Semmelhack, M. F.; Hornby, R. B.; Vederas, J. C. *Chem. Commun.* **1968**, 686.
(3) Rigaudy, J.; Breliere, J. C. *Bull. Soc. Chim. Fr.* **1968**, 455.
(4) Altman, L. J.; Semmelhack, M. F.; Hornby, R. B.; Vederas, J. C. *Org. Prep. Proced. Int.* **1975**, *7*, 35.
(5) Alder, K.; Niklas, H. *Justus Liebigs Ann. Chem.* **1954**, *585*, 81.
(6) Arora, P. C.; Mackay, D. *Chem. Commun.* **1969**, 677.
(7) Suen, Y. H.; Horeau, A.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1965**, 1454.
(8) Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron* **1967**, *23*, 2869.

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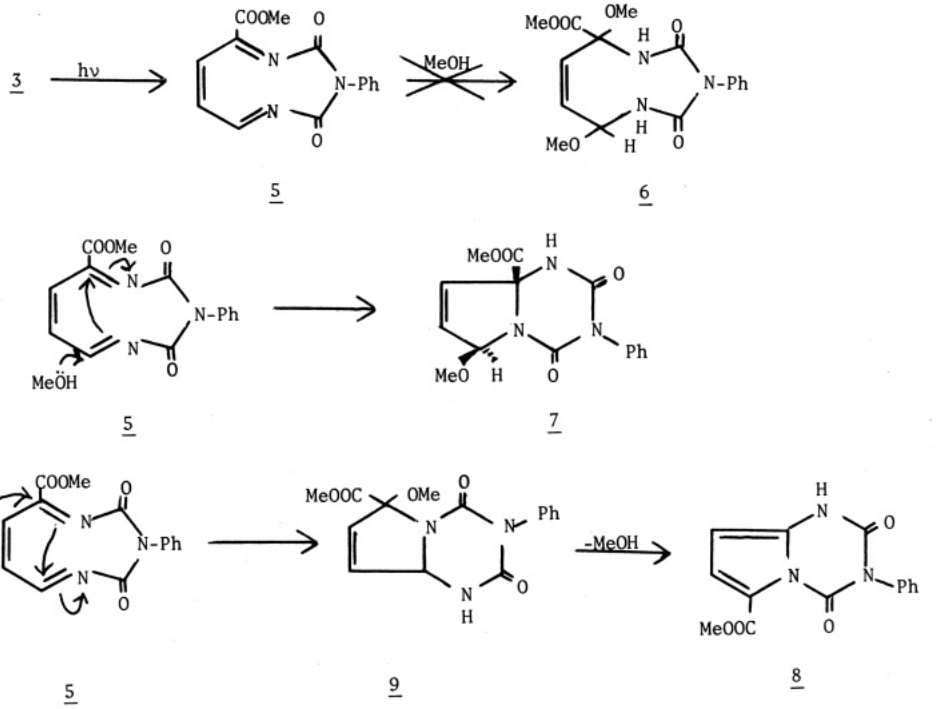
Scheme II



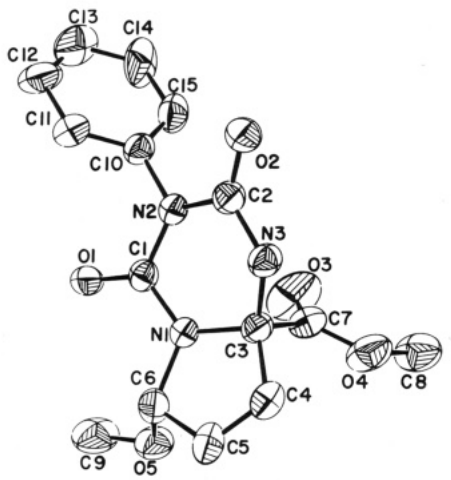
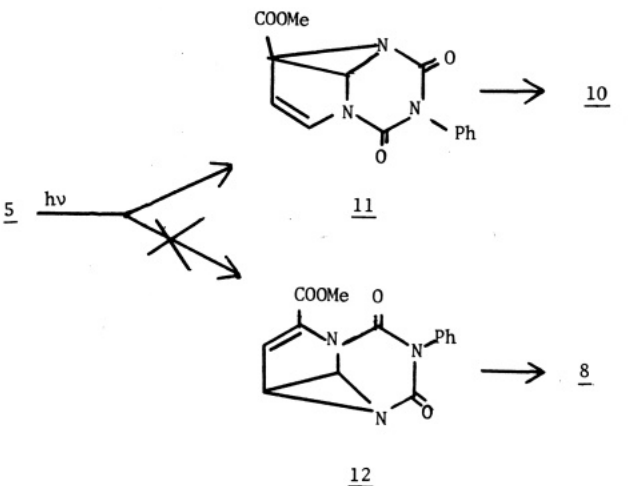


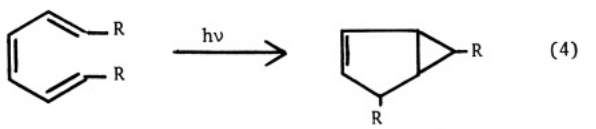
Figure 1. Perspective drawing of the molecular structure of **7**.

Scheme III

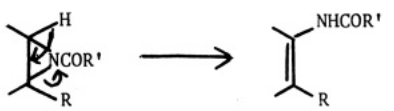


A resonable mechanism for the formation of both products (**7** and **8**) involves the expected N–N bond cleavage with electrocyclic ring opening to **5**, followed by the formation of the new C—N bond through transannular addition of methanol across the two C=N bonds. The addition occurs in two directions to give **7** and **9**. Aromatization through elimination of methanol is possible only in **9** to give **8**.

The mechanism of the formation of **7** is supported by the stereospecifity. The transannular bridging has to occur at the side of the molecule opposite the methanol attack, with back-side attack on the methoxycarbonyl-bearing carbon. Thus the methoxy and methoxycarbonyl groups in **7** should come out on the same side. Indeed compound **7** was obtained as a single stereoisomer, and X-ray analysis (see Figure 1) showed that the methoxy and methoxycarbonyl groups (bonds C3–C7 and C6–O5 in Figure 1) are in a cis relationship. The transformation **5** → **8** can, however, be interpreted as a photochemical process involving two steps. The first is analogous to the known photoisomerization of 1,3,5-hexatrienes to bicyclo[3.1.0]-hexenes[9] (eq 4) followed by ring opening of the aziridine intermediate[10] (eq 5).



(4)

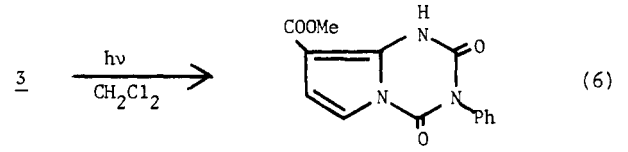


(5)

(9) The photochemistry of hexatrienes has been reviewed. Dauben, W. G.; McInnis, E. L.; Michno, D. M. In "Rearrangements in Ground and Excited States"; DeMayo, P., Ed.; Academic Press: New York, 1980; Vol. III, p 91.

(10) Formation of such aziridine intermediates and their opening is frequently encountered on addition of carbonyl or sulfonyl nitrenes to aromatics. Cf.: Lwowski, W., Ed. "Nitrenes"; Interscience: New York, 1970, Chapters 6 and 8.

For clarification of this point, compound **3** was photolized in dichloromethane. Compound **8** was not formed, and the only isolated product (40%) was another isomer, identified as **10** (eq 6).

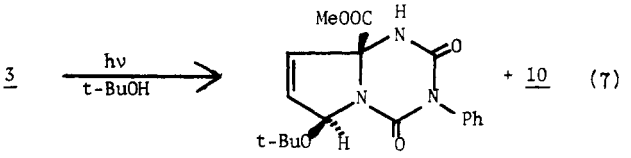


(6)

10

The exclusive formation of **10** indicates that the photochemical process is completely regiospecific and proceeds only through the intermediate **11** and not through **12** (Scheme III). The photoisomerization is generally interpreted as an intramolecular $_{\pi}4_s + _{\pi}2_a$ cycloaddition, and although the effect of substituents on its direction has not been systematically studied, it has been shown in several cases to be considerable.[11] In the present case, the formation of **11** would put the electron-attracting methoxycarbonyl group on the $_{\pi}2$ component, and that may make this pathway favorable. Photochemical interconversions of bicyclo[3.1.0]hexenes which lead to a single isomer were also reported.[12]

A confirmation of the mechanistic interpretation was obtained from the photolysis of **3** in *tert*-butyl alcohol. The addition of the weakly nucleophilic solvent was slow and occurred only at the more reactive and less hindered aldimine linkage to give **13** (6%, eq 7). The main product was **10**, however, through the competing photochemical process.



(7)

13

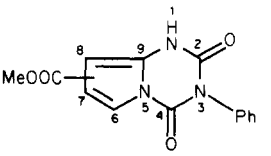
The structural assignments of all the reported compounds are based on spectral evidence (see Experimental Section). The NMR spectra of the isomers **8** and **10** are given for comparison in Table I. They are of the same shape and indicate the pyrrolo[1,2-a]-1,3,5-triazine structure, in which two adjacent pyrrole carbons are unsubstituted. The assignment of the position of the methoxycarbonyl group is supported by the IR spectra. In the spectrum of **8** the ester carbonyl absorption appears at the normal position (1730 cm^{-1}) while in that of **10** it is shifted to 1700 cm^{-1} as it is conjugated to two nitrogens. The NH group in **8** is free and absorbs at 3370 cm^{-1}, while in **10** it is associated through intramolecular hydrogen bonding to the ester carbonyl and absorbs at 3200 cm^{-1}.

In this work we have made the first attempt to prepare a medium-sized heterocycle according to eq 1. The high electrophilic and photolytic reactivities of the product did not allow its isolation. However, in view of the present availability of a variety of cyclic azo dienophiles,[13] the method can be useful for the preparation of some unusual bicyclic systems containing a bridgehead nitrogen.

Experimental Section

General Methods. Melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. Spectra were obtained on the following instruments: IR (Nujol mulls) on a Perkin-Elmer 157 spectrometer, UV on a Varian-Techtron 635 spectrophotometer, and NMR on a Bruker WH-300 spectrometer. Mass spectra (70 eV) were recorded on a Varian MAT 311 instrument. Photolyses were carried out (under nitrogen) by using a Hanovia 450-W high-pressure mercury immersion lamp in a water-cooled Pyrex vessel. E. M. Merck silica gel 60 (70–230 mesh) was used for chromatography. Petroleum either refers to the fraction with a boiling range of 40–60 °C.

Table I. ^1H and ^{13}C NMR Data (Solvent $[CD_3]_2SO$)



atoms	shift, ppm 8	10
	Hydrogen	
H-6		6.65 (d)[a]
H-7	7.08 (d)[b]	7.12 (d)
H-8	5.65 (d)	
CH_3	3.70 (s)	3.77 (s)
C_6H_5	7.42-7.53 (m)	7.40-7.49 (m)
	Carbon	
C-2 and C-4	147.81, 144.52	147.71, 145.18
C-6	116.69	110.86 (d)
C-7	89.45 (d)	96.20 (d)
C-8	123.40 (d)	117.71
C-9	134.01	133.12
$COOCH_3$	159.65, 51.43 (q)	162.88, 50.72 (q)
C_6H_5	134.89, 129.63 (d), 128.78 (d)	134.44, 128.93 (d), 128.70 (d), 128.5 (d)

[a] $J_{6,7} = 3.8$ Hz. [b] $J_{7,8} = 3.8$ Hz.

5-(Methoxycarbonyl)-2-phenyl[1,2,4]triazolo[1,2-a]-pyridazine-1,3-dione (3). A cooled (0–5 °C) solution of 4-phenyl-1,2,4-triazoline-3,5-dione[14] (**2**; 1.75 g, 0.01 mol) in acetone (30 mL) was added in one portion to a cooled (0–5 °C) stirred solution of 3-(methoxycarbonyl)-2-pyrone[15] (**1**; 1.54 g, 0.01 mol) in acetone (40 mL). The ice bath was removed, and when the temperature reached 15 °C, the color changed from red to orange, and a precipitate began to form. Stirring was continued for 1 h, and the solid (0.92 g, mp 214–216 °C) was removed by filtration. It was identified as the 1:2 adduct **4** (see below). The filtrate was evaporated, and the oily residue (1.85 g) was chromatographed on silica gel (70 g). Elution with chloroform yielded an orange oil which solidified on standing and was crystallized from chloroform–petroleum ether to give 1.2 g (42%) of **3** as orange crystals: mp 136–137 °C; IR ν_{max} 1760, 1710, 1680 cm^{-1} (C=O); UV (EtOH) λ_{max} 406 nm (ϵ 1700); NMR ($CDCl_3$) δ 3.75 (s, 3 H, OCH_3), 5.28 (dd, J = 7 Hz, 1 H), 6.08 (d, 1 H), 6.87 (d, 1 H), 7.33 (s, 5 H); mass spectrum, *m/e* (relative intensity) 285 (55, M^+), 138 (30), 119 (100), 108 (52), 91 (45). Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.69; H, 3.94; N, 15.00.

Reaction of equimolar amounts of **2** and **3** (acetone solutions, room temperature) gave a quantitative yield of **4**: mp 215–216 °C; IR 1760, 1730, 1710, 1690 cm^{-1} (C=O); NMR [$(CD_3)_2SO$] δ 3.76, 3.79, 3.82 (s, 3 H combined, OCH_3), 5.70–6.48 (m, 3 H), 7.40–7.57 (m, 10 H). Anal. Calcd for $C_{22}H_{16}N_6O_6$: C, 57.39; H, 3.50; N, 18.26. Found: C, 57.36; H, 3.63; N, 18.32.

Photolysis of 3. (a) In Methanol. A solution of 1 g of **3** in 450 mL of methanol was irradiated as described above. The reaction progress was monitored by disappearance of the 406-nm band and was nearly complete after 7 h. The solution, which turned light yellow and contained some precipitate, was concentrated under reduced pressure to a volume of 50 mL, and the precipitated solid was separated by filtration and triturated with

(11) Padwa, A.; Brodsky, L.; Claugh, S. *J. Am. Chem. Soc.* **1972**, *94*, 6767 and references cited therein.
(12) Prinzbach, H.; Druckrey, E. *Tetrahedron Lett.* **1965**, 2959. Prinzbach, H.; Hagemann, H.; Hartenstein, J. H.; Kitzing, R. *Chem. Ber.* **1965**, *98*, 2201.
(13) Moody, C. J. *Adv. Heterocycl. Chem.* **1982**, *30*, 1.
(14) Wamhoff, H.; Wald, K. *Org. Prep. Proced. Int.* **1975**, 7, 251.
(15) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 2303.

Table II. Crystallography Data for Compound 7

formula	$C_{15}H_{15}O_5N_3$	V, Å^3	1487.8 (5)
M_r	317.3	Z	4
space group	$P2_1/c$	d(calcd), g cm^{-3}	1.42
a, Å	9.158 (1)	μ (Mo Kα), cm^{-1}	0.68
b, Å	14.214 (2)	no. of unique data	2579
c, Å	11.498 (2)	no. of data ($I \geq 3\sigma(I)$)	1897
β, deg	96.25 (4)	R	0.052
		R_w	0.070

ethyl acetate to give pure 6-(methoxycarbonyl)-5-phenylpyrrolo[1,2-*a*]-1,3,5-triazine-2,4-dione (8; 0.12 g, 12%); mp 279–280 °C dec; IR 3370 (NH), 1770, 1730, 1690 cm^{-1} (C=O). NMR, see Table I. Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.98; H, 4.16; N, 14.87.

The filtrate was evaporated and the residue chromatographed on silica gel (30 g). Elution with chloroform–petroleum ether and with chloroform gave small oily fractions which were not identified. Chloroform–ethyl acetate (8:2) eluted a solid which was crystallized from methanol to give 6,9-dihydro-6-methoxy-9-(methoxycarbonyl)-3-phenylpyrrolo[1,2-*a*]-1,3,5-triazine-2,4-dione (7): 0.39 g (35%); mp 173–174 °C; IR 3240 (NH), 1750, 1725, 1665 cm^{-1} (C=O). NMR [$(CD_3)_2SO$] δ 3.54, 3.80 (s, 3 H each, OCH_3), 5.73 (d J = 6.2 Hz, 1 H), 5.92 (d, J = 1.6 Hz, 1 H), 6.04 (dd, 1 H), 7.24–7.47 (m, 5 H), 7.42 (s, 1 H, exchangeable with D_2O); mass spectrum, m/e (relative intensity) 258 (100, $M^+ - CH_3COO$), 226 (10), 139 (65), 119 (30), 107 (27), 96 (27). Anal. Calcd for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.77; N, 13.24. Found: C, 56.86; H, 4.88; N, 12.89.

(b) In Dichloromethane. Irradiation of a solution of 1 g of **3** in 450 mL of dichloromethane was nearly complete after 8 h (UV monitoring). The solution was evaporated, and chloroform (50 mL) was added. Filtration and trituration with ethyl acetate yielded 8-(methoxycarbonyl)-3-phenylpyrrolo[1,2-*a*]-1,3,5-triazine-2,4-dione (**10**): 0.4 g (40%); mp 299–300 °C dec; IR 3200 (NH), 1750, 1700, 1680 cm^{-1} (C=O); NMR, see Table I; mass spectrum, m/e (relative intensity) 285 (100, M^+), 254 (8), 166 (17), 135 (15), 124 (7), 119 (25), 107 (9), 91 (17). Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.85; H, 4.01; N, 14.42. Chromatography of the filtrate did not give identifiable products.

X-ray Crystal Structure Analysis.[16] Data were measured on a PW1100/20 Philips four-circle computer-controlled diffractometer. Mo Kα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by at least-squares fit of 24 centered reflections in the range of $10 \leq \theta \leq 13°$. Intensity data were collected by using the ω–2θ technique to a maximum 2θ of 50°. The scan width, $\Delta\omega$, for each reflection was 1° with a scan time of 20 s. Background measurements were made for other 20 s at both limits of each scan. Three standard reflections were monitored every 60 min. No systematic variations in intensities were found.

Intensities were corrected for Lorentz and polarization effects. All nonhydrogen atoms were found by using the results of the MULTAN direct method analysis.[17] After several cycles of refinements[18] the positions of the hydrogen atoms were calculated and added with a constant isotropic temperature factor of 0.5 Å^2 to the refinement process. Refinement proceeded to converge by minimizing the function $\sum w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(|F_o|)^{-2}$. A final difference fourier synthesis map showed several peaks less than 0.1 e Å^{-3} scattered about the unit cell without a significant feature.

The discrepancy indices, $R = \sum||F_o| - |F_c||\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(|F_o|^2]1/2$, are presented with other pertinent crystallographic data in Table II.

Registry No. 1, 25991-27-9; 2, 4233-33-4; 3, 88180-59-0; 4, 88200-31-1; 5, 88180-60-3; 7, 88180-61-4; 8, 88180-62-5; 9, 88180-63-6; 10, 88180-64-7.

Supplementary Material Available: Complete X-ray data of compound 7, including atomic positional and thermal parameters, bond distances, and angles (5 pages). Ordering information is given on any current masthead page.

(16) We thank Dr. S. Cohen for his help with this analysis.

(17) Main, P.; Hull, S. W.; Lessinger, L.; Germain, G.; DeClercq, J. P.; Woolfson, M. M. "MULTAN 78. A System of Computer Programs for The Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York, England, and Louvain, Belgium; 1978.

(18) All crystallographic computing was done on a Cyber 74 computer at the Hebrew University of Jerusalem by using the SHELX 1977 structure-determination package.

Additions and Cycloadditions of Ketenes to 1,3-Thiazole and Its Alkyl Derivatives

Alessandro Medici, Giancarlo Fantin, Marco Fogagnolo, Paola Pedrini, and Alessandro Dondoni*

Laboratory of Organic Chemistry, Faculty of Sciences, University of Ferrara, Ferrara, Italy

Giovanni Dario Andreetti

Istituto di Strutturistica Chimica, Università, e Centro di Strutturistica Difrattometrica, C.N.R., Parma, Italy

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1,3-Thiazole and its 4-methyl and 5-methyl derivatives react with *tert*-butylcyanoketene (TBCK) and dichloroketene (DCK), affording Michael-type addition products at C_2, viz., 2-acylthiazoles, and 2:1 cycloadducts (with TBCK only) which proved by X-ray analysis to be bicyclic systems constituted by a thiazoline and a piperidine-1,3-dione ring condensed across the C–N bond. 2-Ethyl- and 2-isopropyl-1,3-thiazole undergo acylation by DCK at the C_α of the alkyl chain. The latter thiazole gives also a 2:1 cycloadduct, which X-ray analysis showed to be a bicyclic system constituted by a thiazoline and an oxazinone ring condensed across the C–N bond. A mechanism is envisaged involving the quaternization of the thiazole nitrogen by the ketene to give an *N*-thiazolium enolate system which owing to proton exchange between the C_2 of the ring or the C_α of the 2-alkyl chain and its enolate portion is in equilibrium with an *N*-acylthiazolium ylide or zwitterion, respectively. Subsequent reactions of these active intermediates with the ketene lead to the final products.

Relatively few examples of synthetically valuable reactions leading to carbon–carbon bond formation at the thiazole ring are to be found in the literature.[1] We have recently reported reactions of thiazoles with various C-

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