isomer, (−)-(2*S*,8a*R*)-**2** (entries 7 and 13). Asymmetric enolate oxidation of 2-methyltetralone (**6**) with (+)-(2*R*,8a*S*)-**1** gave much lower stereoselectivities (entries 15–19). Changing the base or solvent failed to increase the asymmetric induction. Asymmetric oxidations using (−)-(*S*,*S*)-**3** also reduced the asymmetric induction for **4a,b** (entries 8 and 14) but nearly doubled it from 16% ee to 23.5% ee for ketone **6** (compare entries 17 with 20).

The results summarized in Table I are best understood in terms of an open transition state, where nonbonded steric interactions are principally responsible for the chiral recognition.[10] Dreiding models and an X-ray crystal structure of the conformationally locked oxaziridine (+)-(2*R*,8a*S*)-**1**, suggest that in the vicinity of the active site oxygen the most sterically demanding region is the bridgehead 5–4a bond.[12] We consider, by analogy with recent studies by Heathcock and co-workers,[13] that the largest enolate group is the "OM" (M = Li, Na) solvent aggregate complex. The two extreme geometries for the oxidation of the si-faces of the metal (*Z*)-enolates of **4a,b** by (+)-(2*R*,8a*S*)-**1** are depicted in Scheme I. From a consideration of the nonbonded interactions, the planar transition-state geometry is favored over the spiro form.[14] The lower enantioselectivities noted for 2-methyltetralone (**6**) are consistent with this hypothesis because all rotational conformations of this enolate are sterically demanding. It is interesting to note that planar transition-state geometry is also preferred for asymmetric epoxidations of alkenes by chiral oxaziridines[18] and certain conformationally restricted peracids.[19]

If our assumptions concerning the factors that control the transition state geometries are correct, then it follows that "NaO" can also be considered as a large group. The higher enantioselectivities associated with sodium vs. lithium enolates of **4a,b** probably reflect the lower temperature of oxidation for the former counterion (Table I).[20] We speculate that the generally lower stereoselectivities seen in the presence of HMPA (entries 2, 4, 10, 12, 16) and for the potassium enolates (entries 5, 13, 18) are the result of a smaller effective size for "OM" group. K^+ is a poorer chelating metal than either Li^+ or Na^+, and HMPA is known to disrupt metal chelation.[21]

Attempts to extend these transition-state ideas to our previous studies of ester and amide lithium enolates are hindered by the lack of regioselective enolate formation and the seemingly contradictory effect of solvent on the stereoselectivity. Nevertheless, the available information is consistent with the spiro transition-state geometry for these enolates. We believe that the differences in the asymmetric oxidation of the ketones and the esters and amides may reflect different solution structures for their enolates.[15]

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(10) No change in the ^1H or ^{13}C NMR spectra of oxaziridine (+)-(2*R*,8a*S*)-**1** and the shift reagent $Pr(fod)_3$ at 1:1 molar ratios could be detected.[11]

(11) Davis, F. A.; Towson, J. T., manuscript in preparation.

(12) Details of the X-ray structure of (+)-(2*R*,8a*S*)-**1** will be published elsewhere.[11]

(13) (a) Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. (b) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022.

(14) In analogy with other studies,[16] the enolate and oxaziridine are considered to approach in a perpendicular fashion. Recent ab initio calculations by Houk and Paddon-Row suggest that the transition state for reaction of MeF with the acetaldehyde enolate is product-like; i.e., MeF approaches the enolate at an angle of 106°.[17] Reduced steric interactions of enolates with the bridgehead bond in (+)-(2*S*,8a*R*)-**1** would be predicted with this transition-state geometry.

(15) The aggregate solution structures of enolates, as well as the actual reacting species have not been clearly established. See, for example: Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. The solid-state enolate structures of ketones (tetramers), esters (dimers and tetramers), and amides (dimers) have been reported. See: Seebach, D.; Amstutz, R.; Laube, W.; Schweizer, B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764 and references cited therein.

(16) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.

(17) Houk, K. N.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1986**, *108*, 2659.

(18) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123.

(19) Rebek, J., Jr.; Marshall, L.; Wolak, R.; McManis, J. *J. Am. Chem. Soc.* **1984**, *106*, 1170.

(20) Attempts to carry out the oxidation of the sodium enolates at higher temperatures (0 °C) resulted in decomposition.

(21) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737 and references cited therein.

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The First Two-Step 1,3-Dipolar Cycloadditions: Interception of an Intermediate†

Summary: The zwitterionic intermediate **4** from thiocarbonyl ylide **2** and tetracyanoethylene undergoes competing cyclizations to give the normal cycloadduct **3** and a seven-membered ketene imine **6** in a 35/65 ratio; **6** is formed reversibly and is intercepted by water and methanol to furnish lactam **7** or lactim ether **5**.

Sir: Normal 1,3-dipolar cycloadditions being concerted,[1] we were guided in our search for transgressions by the PMO considerations[2] in Figure 1. Further strong lifting of the π-MO energies of the 1,3-dipole and lowering those of the dipolarophile should make ΔE_{II} negligibly small, i.e., ΔE_{II} can no longer defray the additional "entropy price" for the highly ordered transition state of the concerted process vs. that of *zwitterion formation* which results from *one* HO–LU interaction.

Thiocarbonyl ylides[3] are the 1,3-dipoles with the highest π-MO energies. We recently described the cycloadditions of 2,2,4,4-tetramethyl-1-oxocyclobutane-3-thione *S*-methylide (**2**) and of adamantanethione *S*-methylide to dimethyl 2,3-dicyanofumarate, an ethylene derivative with four electron-attracting substituents.[4] The *nonstereospecificity* implied a zwitterionic intermediate capable of rotation. The following experiments indicate that *two intermediates* are involved in the reaction of **2** with tetracyanoethylene (TCNE).

The extrusion of N_2 from the 1,3,4-thiadiazoline **1**[5,6] ($t_{1/2}$ = 76 min in THF, 40 °C) is a 1,3-dipolar cycloreversion furnishing **2**; in situ, **2** adds to a wide range of dipolarophiles.[6] N_2 elimination from **1** in THF + 1 vol % *water* in the presence of 1.1 equiv of TCNE at 40 °C provided 24% of **3** (mp 213–215 °C dec),[7] the normal cycloadduct of **2**, accompanied by 45% of $C_{15}H_{16}N_4OS$ (mp 171–173 °C) i.e., a compound with one additional H_2O. The reaction

†Dedicated to Professor Siegfried Hünig on the occasion of his 65th birthday.

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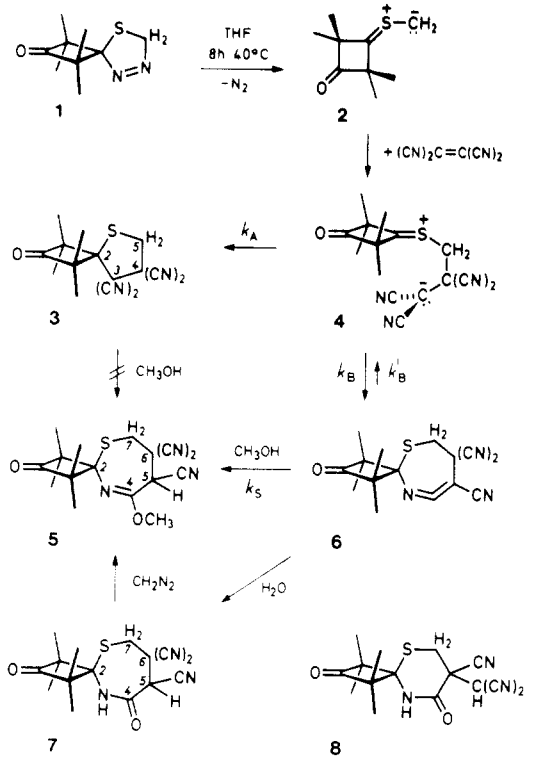


in dry THF afforded 84% of **3**, which was stable to water. The origin of the new compound $C_{15}H_{16}N_4OS$ was ambiguous, since TCNE itself reacts with water.[8]

In contrast, TCNE is resistant to cold pure alcohols; the latter have been used to intercept zwitterionic intermediates in (2 + 2) cycloadditions of TCNE to enol ethers.[9] TCNE remained unchanged when warmed in THF + 2 vol % methanol for 8 h at 40 °C. N_2 extrusion from **1** in this medium provided 36% **3** and 56% of a compound (mp 175–177 °C dec) with an additional molecule of CH_3OH. The spirothiolane **3** was stable to refluxing methanol. This points to partial trapping of an intermediate by water and methanol.

The ^1H and ^{13}C NMR spectra of the cycloadduct **3** indicate a plane of symmetry. On the other hand, four different $\delta_H(CH_3)$, three ^{13}C singlets for CN, and AB spectra for CH_2 establish a lack of symmetry in the interception products. Both afforded after acidic cleavage 2,2,4,4-tetramethylcyclobutane-1,3-dione bis(2,4-dinitrophenylhydrazone) suggesting S,N-acetals at C-3 of the four-membered ring.

IR bands (Nujol) of the aqueous product at 3387, 3277 (N–H), 1785 (C=O), and 1698 cm^{-1} (st, amide I) are in harmony with a carboxamide function. The δ_C values of the ring C atoms fit structure **7** of a seven-membered lactam better than the six-membered ring **8**. The mechanistic considerations below support **7**. The conversion of **7** by diazomethane into the methanol adduct **5** indicates

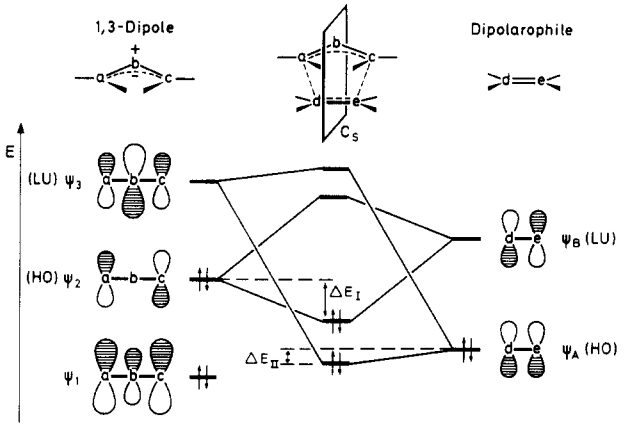


Figure 1. π-HO–LU interaction diagram for 1,3-dipolar cycloaddition.

Table I. Thiadiazoline 1 (0.20 M) and TCNE (0.22 M) in THF (5 h, 45 °C); Influence of Methanol Concentration

CH_3OH		lactim ether **5**/	yield
equiv	vol %	cycloadduct **3**	**5** + **3**, %
0	0	0:100	84
0.62	0.50	60:40	85
1.23	1.0	66:34	97
2.47	2.0	68:32	88
3.70	3.0	63:37	94
6.17	5.0	64:36	95

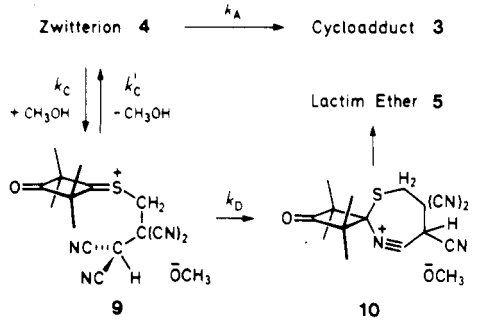
an acidic amide. Besides the NH of **7**, the 5-H of **7** (δ 5.17) and of **5** (δ 5.22) are exchanged by D_2O. The C=N vibration of **5** occurs at 1700 cm^{-1} and C=O at 1771 cm^{-1}. $\delta_H(OCH_3)$ at 3.82 and δ(C-4) at 146.5 agree with an *O*-methyl imidate function.

We assume the *zwitterion* **4** as an intermediate. Resonance distributes the negative charge over C and N atoms of the malononitrile function. The combination of the trisubstituted carbanion with the carbenium–sulfonium center to give thiolane **3** is sterically hindered by the *gem*-dimethyl groups. The barricade is less effective for the anionic nitrogen; the *cyclic ketene imine* **6** emerges from a competing pathway. The reactions of **6** with water or methanol afford the lactam **7** and the lactim ether **5**, respectively. The dichotomy in the *intra*molecular alkylation of the nitrile anion in **4** is known from *inter*molecular analogues. Whenever the electronically preferred alkylation of the carbanion is subject to steric hindrance, N-alkylation furnishing ketene imines becomes prominent.[10]

The cumulated bond system of ketene imines approaches linearity,[11] and its inclusion in a seven-membered ring creates strain. However, the spirocyclic ketene imine **6** need not be stable either; in the absence of water or alcohol it can revert to the zwitterion **4** and flow off to **3**.

In an alternative mechanism, the malononitrile anion function of **4** enters an acid–base equilibrium with the added methanol (or water), producing **9**. An intramolecular Ritter reaction[12] gives rise to nitrilium ion **10**, which probably is not less strained than **6**. The lactim ether **5** would result from ion recombination. This pathway requires methanol concentration to occur in the rate equation for the formation of **5**; the product ratio should be de-

(1) Review: Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, pp 1–176.
(2) Review: Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.
(3) Reviews: Kellogg, R. M. *Tetrahedron* **1976**, *32*, 2165. Huisgen, R.; Fulka, C.; Kalwinsch, I.; Li, X.; Mloston, G.; Moran, J. R.; Pröbstl, A. *Bull. Soc. Chim. Belg.* **1984**, *93*, 511.
(4) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.*, in press.
(5) Diebert, C. D. *J. Org. Chem.* **1970**, *35*, 1501.
(6) Huisgen, R.; Mloston, G.; Fulka, C. *Heterocycles* **1985**, *23*, 2207.
(7) Satisfactory elemental analyses and spectra have been obtained for all new compounds.
(8) Middleton, W. J.; Little, E. L.; Coffman, D. D.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1958**, *80*, 2795.
(9) (a) Huisgen, R.; Schug, R.; Steiner, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 80, 81. (b) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117.
(10) (a) Newman, M. S.; Fukunaga, T.; Miwa, T. *J. Am. Chem. Soc.* **1960**, *82*, 873. (b) Dijkstra, R.; Backer, H. J. *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 575. (c) Parker, C. O.; Emmons, W. D.; Pagano, A. S.; Rolewicz, H. A.; McCallum, K. S. *Tetrahedron* **1962**, *17*, 89.
(11) X-ray analyses: Jochims, J. C.; Lambrecht, J.; Burkert, U.; Zsolnai, L.; Huttner, G. *Tetrahedron* **1984**, *40*, 893 and references therein.
(12) Review: Krimen, L. I.; Cota, D. J. *Org. React. (N.Y.)* **1969**, *17*, 213.



$$(5)/(3) = K_C(CH_3OH)k_D/k_A \quad (1)$$

termined by eq 1. Within the first mechanism, a product ratio independent of the methanol concentration is expected if methanol addition to the ketene imine is fast ($5/3 = k_B/k_A$).

The independence of the product ratio 5/3 from the methanol concentration (Table I) excludes the mechanism via nitrilium ion **10**, and $k_B/k_A = 65/35$ refers to the kinetically controlled formation of **6** and **3** from zwitterion **4**. It is impressive that in the experiment with 0.62 equiv of methanol 90% is consumed by the ketene imine **6**, the yield of **5** being only slightly diminished. Analogous reactions in THF + 0.5 or 1.0 vol % water afforded **7** and **3** in the same ratio 65/35; thus, k_B/k_A is independent of the *nature* of the trapping reagent. We are unaware of an alternative for the ketene imine **6** which fits the data equally well, but some variations in the kinetic scheme are conceivable.[13]

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(13) (a) **2** + TCNE enter competing *concerted* (3 + 2) and (3 + 4) cycloadditions in the ratio 35:65, furnishing **3** and **6**, the latter reversibly. A concerted [$_\pi4_s + _\pi4_s$] cycloaddition violates orbital control and has not been observed for 1,3-dipoles. (b) The concerted formation of **3** from **2** + TCNE and the formation of **6** via **4** compete in the ratio 35:65; in the absence of water or methanol **6** returns via **4** to **2** + TCNE. Schemes a and b fail to explain the nonstereospecificity of a related cycloaddition.[4] (c) As in b but with **6** slowly returning to **4** and channeled to **3**. In this more complex scheme, there is a concerted and a nonconcerted pathway leading to **3**.

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A Novel Preparation of Cyclohepta[*b*]pyrrol-2-ones

Summary: A novel synthesis of the title compounds has been achieved by the base-promoted reaction of diethyl (diazomethyl)phosphonate (**3**) and 2-oxopropanamides **4**.

Sir: The study of enzymatic reactions has stimulated interest in the synthesis of analogues of naturally occurring nucleic acid bases. The interest is driven by the possible consequences of various types of inhibition or induction of enzymatic reactions.[1] In this context, cyclohepta[*b*]-

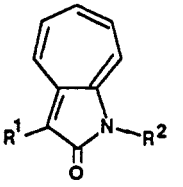
(1) (a) *Burger's Medicinal Chemistry*, 4th ed; Wolff, M. E., Ed.; Wiley Interscience: New York, 1979; Part 2. (b) Baker, B. R. *Design of Active-Site-Directed Irreversible Enzyme Inhibitors*; Wiley: New York, 1967. (c) Leonard, N. J.; Hiremath, S. P. *Tetrahedron* **1986**, *42*, 1917.

Table I. Products Isolated by Reaction of 3 with 4 in Acetonitrile

entry	4	X	2[a,b]	recovered 3[a]
1	a	H	82	34[c]
2	b	Cl	63	36
3[d]	c	CH_3	76	37

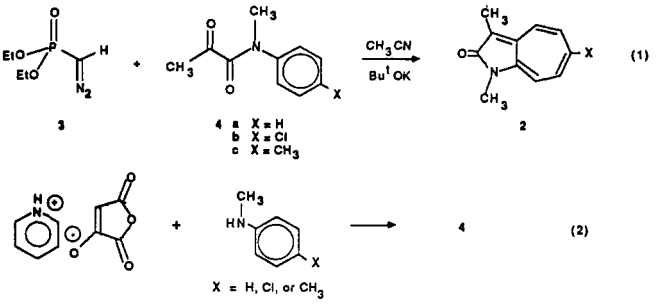
[a] Isolated yield (%). [b] Yield based on recovered starting material. [c] See footnote 7. [d] See footnote 8.

pyrrol-2-one (**1a**) and its derivatives can be considered as nonbenzenoid analogues of indoles and have been investigated for both their pharmaceutical applications[2] and their chemical and physical properties.[3] The parent compound **1a** has been shown to have inhibitory effects on ascites hepatoma,[2d,e] and the diacid **1b** has recently been found to have potential as an antidiabetic agent as a result of its inhibitory action on aldose reductase.[2c]



1 a $R^1, R^2 = H$
b $R^1 = CO_2H$, $R^2 = CH_2CO_2H$

We report herein a novel and facile synthesis of substituted cyclohepta[*b*]pyrrol-2-ones **2**. The synthetic route involves the base-promoted reaction between diethyl (diazomethyl)phosphonate (**3**)[4] and 2-oxopropanamides **4** (eq 1), themselves prepared by reaction of pyridinium hydroxymaleic anhydride[5] with the appropriately substituted *N*-methylaniline (eq 2).[6]



(2) (a) Abe, N.; Nighiwaki, T. *J. Chem. Res. Synop.* **1984**, 264. (b) Helsley, G. C.; Effland, R. C.; Davis, L. U.S. Patent 3 997 557; *Chem. Abstr.* **1977**, *86*, P139850w. (c) Treasurywala, A.; Palameta, B.; Bogri, T.; Bagli, J. U.S. Patent 4 337 265; *Chem. Abstr.* **1982**, *97*, P162818c. (d) Mirura, Y.; Okamoto, N.; Katayama, H. *J. Biochem.* **1961**, *49*, 502. (e) Mirura, Y.; Okamoto, N.; Goto, M. *Ibid.* **1961**, *49*, 508. (f) Mirura, Y.; Okamoto, N.; Shimanune, A. *Seikagaku* **1960**, *32*, 744; *Chem. Abstr.* **1964**, *60*, 7312f.

(3) (a) Wu, C.; Yang, P. *Hua Hsueh* **1977**, 45. (b) Toda, T.; Ryu, S.; Hagiwara, Y.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 82. (c) Sato, A.; Nozoe, S.; Toda, T.; Seto, S.; Nozoe, T. *Ibid.* **1973**, *46*, 3530. (d) Toda, T.; Seto, S.; Nozoe, T. *Ibid.* **1968**, *41*, 590. (e) Toda, T. *Ibid.* **1967**, *40*, 590. (f) Nakao, H.; Soma, N.; Sunagawa, G. *Chem. Pharm. Bull.* **1965**, 828. (g) Sunagawa, G.; Nakao, H. *Ibid.* **1965**, 450. (h) Ogura, K.; Sasaki, H.; Seto, S. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 306. (i) Seto, S.; Nozoe, T. *Proc. Jpn. Acad.* **1956**, *32*, 756. (j) Nozoe, T.; Seto, S.; Nozoe, S. *Ibid.* **1956**, *32*, 172. (k) Nozoe, T.; Seto, S.; Matsumura, S.; Terasawa, T. *Chem. Ind. (London)* **1954**, 1356.

(4) Seyferth, D.; Mormar, R. M.; Hilbert, P. H. *J. Org. Chem.* **1971**, *36*, 1379.

(5) Ireland, R. E.; Thompson, W. J.; *J. Org. Chem.* **1979**, *44*, 3014.

(6) Wohl, A.; Osterlin, C. *Chem. Ber.* **1907**, *40*, 2312.

0022-3263/86/1951-4087$01.50/0