A New Observation of Limiting Case 1,3-Dipolar Cycloaddition. Evidence for a Highly Unsymmetrical Transition State Structure with the Reactions of Mesoionic Compounds

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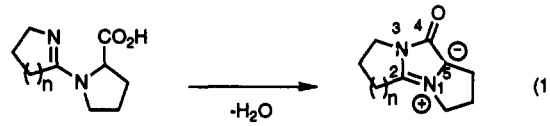
Summary: Torsional restriction and a highly unsymmetrical transition state for a 1,3-dipolar cycloaddition divert a portion of the reaction through a stepwise pathway.

Huisgen[1] has proposed two criteria for observing limiting case 1,3-dipolar cycloaddition reactions, where products derived from the zwitterionic intermediate of stepwise bond formation are observed. These criteria are (1) a wide HOMO/LUMO gap between the dipole and the dipolarophile and (2) a great deal of steric hindrance at one of the reacting dipolar termini. Two reported examples fit these criteria. Both Huisgen's $HOMO_{dipole}$-controlled thiocarbonyl ylide cycloadditions[2] and Quast's $HOMO_{dipolarophile}$-controlled azide reactions[3] show low stereospecificity with olefinic dipolarophiles as well as products derived from the intramolecular trapping of initial, singly-attached products. In the latter case, the structure of the isolated zwitterionic intermediate was determined by crystallography and analyzed by computational methods.[4] Stepwise processes involving 1,3-dipoles have also been used to explain [3 + 3] cycloaddition reactions,[5] and products from some nitrile oxide reactions have been attributed to a partition via diradical intermediates.[6] Huisgen and Hall propose to have detected diradical intermediates via the polymerization amplification technique.[7] Understanding transition state structural requirements, one important result from studying stepwise reactions, is receiving a great deal of attention as a mediator for evaluating FMO and steric effects on the regioselectivity of 1,3-dipolar cycloadditions.[8] The regioselectivities observed for reactions with mesoionic compounds,[9] in particular, have defied any unified description, and the usual assumptions about the structure of the cycloaddition transition state have been questioned recently.[10] During the course of an investigation into the regioselectivity of münchnone cycloadditions[11] we had cause to prepare the *N*-iminoylproline[12] precursors **1a–c** that would give rise to the three tricyclic mesoionic 1,3-imidazolium-4-olates[13] **2a–c** (eq 1). We wish



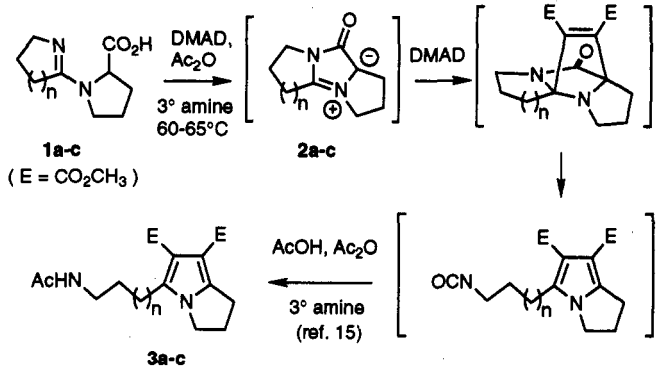
(1)

1a: n=1 **1b:** n=2 **1c:** n=3 **2a:** n=1 **2b:** n=2 **2c:** n=3

to report a striking difference in reactivity between these three compounds based on cycloadditions with acetylenic dipolarophiles. We propose that this difference uncovers a new criterion for limiting case cycloadditions and reveals a unique experimental insight into the transition state structural requirements in the 1,3-dipolar cycloaddition reactions of a mesoionic compound.

Formation and reaction of the mesoionic compounds were carried out *in situ*. Cyclodehydrations of the *N*-iminoylprolines were accomplished with acetic anhydride,[14] along with 1–5 equiv of the dipolarophile and 0.03–0.05 equiv of diisopropylethylamine (or triethylamine).[15] In all three cases (**1a–c**), the cycloadduct derived from reaction with dimethyl acetylenedicarboxylate (DMAD) could be readily isolated (Scheme I).

Scheme I



The differences in product distribution upon reaction of **1a–c** with DMAD and methyl propiolate are summarized in Table I.[16] As the size of the iminoyl-derived ring is decreased, the amount of 1,3-dipolar cycloaddition reaction

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(6) (a) Baran, J.; Mayr, H. *J. Org. Chem.* **1989**, *54*, 5774–5783. (b) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603–4607.

(7) Huisgen, R.; Penelle, J.; Mloston, G.; Padias, A. B.; Hall, H. K., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 266–274.

(8) Sustmann, R.; Sicking, W.; Huisgen, R. *J. Org. Chem.* **1993**, *58*, 82–89.

(9) Gingrich, H. L.; Baum, J. S. In *Oxazoles*; Turichi, I. J., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 45; Wiley: New York, 1986; pp 731–961.

(10) Texier, F.; Mazari, M.; Yebdri, O.; Tonnard, F.; Carrié, R. *Bull. Soc. Chim. Fr.* **1991**, *128*, 962–967.

(11) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Abdon, R. L.; Trost, B. M. Intramolecular 1,3-Dipolar Cycloadditions of Münchnones with Acetylenic Dipolarophiles: Sorting out the Regioselectivity. *Tetrahedron*, in press.

(12) Prepared via the iminoylation method reported for primary amino acids: Dunn, A. D.; Kinnear, K. I.; Norrie, R. *Z. Chem.* **1986**, *26*, 290–292.

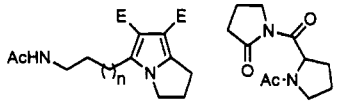
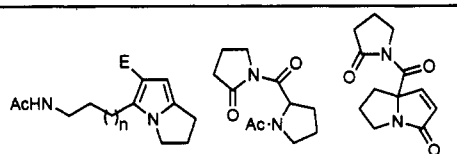
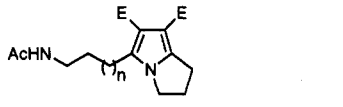
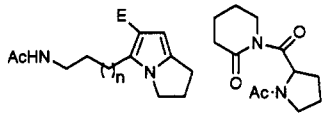
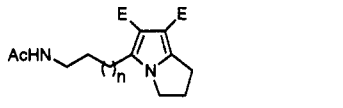
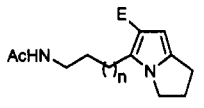
(13) Generally, except for aryl-substituted or otherwise stabilized compounds that allow isolation, the occurrence of mesoionic intermediates such as **2a–c** is inferred from their reaction products. See: (a) Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965–3011. (b) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239–2329.

(14) For the preparation of representative 1,3-imidazolium-4-olates, see: Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2; pp 39–41.

(15) Addition of a tertiary amine is required to cause the derivatization of the isocyanate function that is liberated in the cycloreversion step. For the isocyanate chemistry, see: Blagbrough, I. S.; Mackenzie, N. E.; Ortiz, C.; Scott, A. I. *Tetrahedron Lett.* **1986**, *27*, 1251–1254.

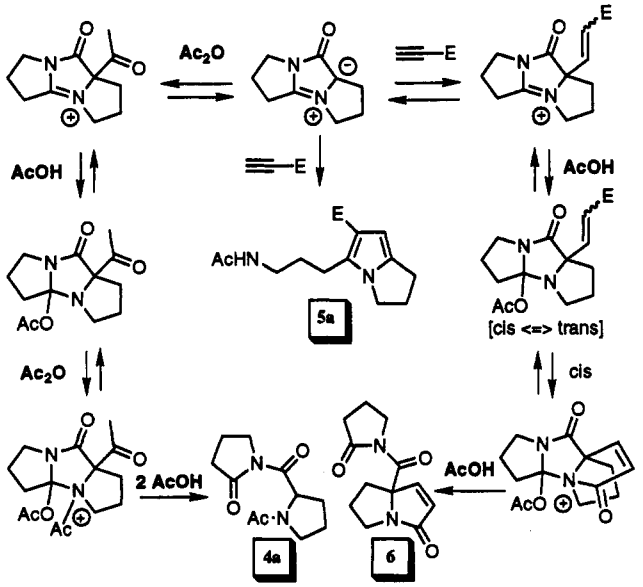
0022-3263/93/1958-7324$04.00/0

Table I. Reactions of 1a–c with DMAD and Methyl Propiolate

dipole precursor	reaction with DMAD[a,b]	yield[c]	reaction with methyl propiolate[a,b,d]	yield[c]
1a (n=1)	 3a (13%) 4a	(90%)	 5a (8%) 4a 6 (22%)	(80%)
1b (n=2)	 3b (59%)		 5b (16%) 4b	(52%)
1c (n=3)	 3c (63%)		 5c (89%)	

[a] The percentages listed alongside specific compound numbers refer to unoptimized yields of purified materials. [b] Samples of **4a** and **4b** were identified in the crude reaction mixtures. Samples of these materials were isolated from the reaction mixtures and compared with independently prepared authentic samples (see ref 17). [c] The percentages listed under this heading refer to estimated yields based on the masses of the reaction products. The product ratios for **3a:4a**, **5a:4a:6**, and **5b:4b** depend on the concentration of dipolarophile used. Under comparable conditions, the product ratios are 1:1 (**3a:4a**), 1:3:3 (**5a:4a:6**), and 2:1 (**5b:4b**). Also, see Figure 1 and the accompanying discussion. [d] The regiochemical assignments for **5a–c** are based on homonuclear ^{1}H-NMR decoupling experiments, and in the case of **5a** and **5b**, comparison with the regioisomeric ester prepared by the elimination reaction of the (toluenesulfonyl)acrylate adduct described in ref 30. In addition, up to 25% of the regioisomeric cycloadduct is observed if the dipole is formed at high temperature in the presence of methyl propiolate rather than by slowing warming the premixed reagents.

Scheme II. Proposed Mechanism for the Products Formed from 2a and Methyl Propiolate



of the mesoionic intermediate **2a–c** decreases, as evidenced by the formation of **4a**,[17] **4b**,[17] and **6**.[18] The pyrrolizidinone **6** is proposed to be derived from a stepwise pathway (Scheme II). The formation of **6** from **2a** is most significant because it represents a stepwise reaction pathway competing for the dipolarophile along with the cycloaddition pathway to form **5a**. The two ring-opened products **4a** and **4b** are derived from independent, competing reaction pathways of the mesoionic compounds with acetic anhydride.[19]

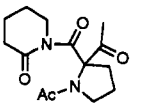
A series of concentration studies (Figure 1) affirms the competition between acetic anhydride and methyl propiolate for the mesoionic compound **2a** in the mechanistic picture presented in Scheme II. As the concentration of methyl propiolate increases, more of the dipole is diverted toward the formation of the cycloaddition and stepwise products **5a** and **6**, respectively. A 1:3 ratio of **5a:6** is constant in all of the runs. Some of the mechanistic steps proposed in Scheme II are precedented on established features of the Dakin–West reaction.[20] The α-carbon of a 1,3-oxazolium-5-olate (münchnone) is nucleophilic toward acylating agents, which, by analogy, allows for either an acylation or a conjugate addition of the 1,3-imidazolium-4-olate **2a** as a first step. In a Dakin–West reaction, addition of acetate to the atom corresponding to C-2 (see eq 1 for numbering) or to the carbonyl carbon ultimately results in a decarboxylation reaction.[21] Addition to C-2, which is the next step proposed for the formation both **4a** and **6**, is observed under low acetic acid conditions in the Dakin–West reaction.[22] This overall pattern of reactivity has also been proposed for the reaction between a tricyclic

(16) All new compounds exhibit satisfactory NMR, IR, and accurate mass MS data.

(17) The structures for the ring-opened products **4a** and **4b** were confirmed by their independent syntheses. The butyllithium-generated anions derived from 2-pyrrolidinone and δ-valerolactam were acylated with the 4-nitrophenolate ester of *N*-acetylproline to give a pair of compounds that were identical with **4a** and **4b**, respectively, by all spectroscopic and physical criteria.

(18) The structure of the dehydropyrrolizidinone **6** was confirmed by X-ray analysis. The product crystallized in the orthorhombic space group $Pna2_1$ with a = 6.201(1) Å, b = 12.332(4) Å, c = 14.606(7) Å, Z = 4, V = 1116.9(6) Å^3. The structure was solved by direct methods and refined to an R-index = 0.0308 with a final R_w of 0.0394; GOF = 1.16.

(19) When **2a** and **2b** are formed in acetic anhydride without dipolarophile present, the ring-opened products are formed. Compound **1a** gives **4a** in 34% isolated yield (unoptimized), while **1b** gives 45% of **4b**. The latter crude reaction mixture contains a 1:2 mixture of **4b** and what we have assigned, by NMR, to be the acetylated version of **4b**: **7**. Attempts to isolate **7** from this mixture give only **4b**, which would result from the anticipated facile de-acetylation.

7: 

(20) Buchanan, G. L. *J. Chem. Soc. Rev.* **1988**, *39*, 91–109.
(21) Knorr, R.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2598–2610.

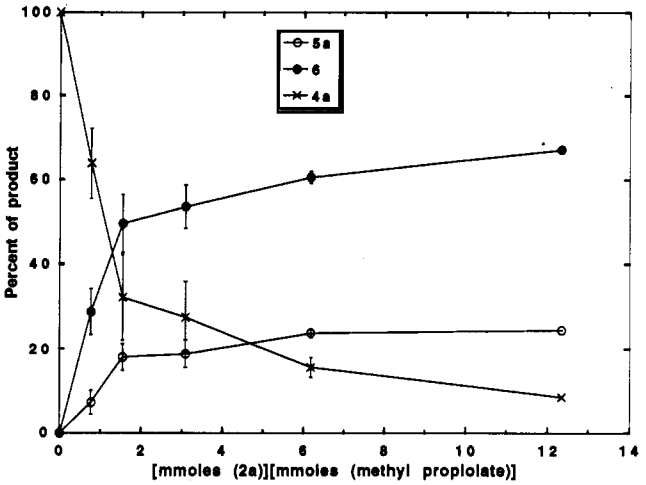


Figure 1. Distribution of products for reactions of **2a** with increasing concentration of methyl propiolate. The data points in this figure are the averages from multiple runs, with the high/low range indicated by the bars.

münchnone with molecular oxygen.[23] We have not seen evidence for the oxazoles observed from some *N*-acylprolines,[24] which is a result that is consistent with the structure of the mesoionic compounds **2a–c**. We postulate an intermolecular or intramolecular acylation then forms a cationic intermediate that fragments to form **4a** or **6**, respectively, which is similar to a deacylative fragmentation proposed by Kawase.[25] While we have not yet isolated any of the proposed intermediates, we have evidence for the compound that is deacetylated to give **4b**.[19]

In contrast with both Huisgen's[2] and Quast's[3] limiting case examples, this series of reactions involves partners having neither a large HOMO/LUMO gap nor an extreme steric prejudice. We interpret the diminishing amount of cycloaddition product as the ring contracts from **2c** to **2a** as the inability of the 1,3-dipole to achieve the necessary bending for the cycloaddition transition state.[26] The decreased flexibility of the dipole causes the cycloaddition pathway to slow down, allowing the alternative reaction pathways to become more productive. Another possible interpretation is that the ring-opening reactions proposed to form **4a**, **4b**, and **6** are accelerated in the more strained tricyclic systems, thereby diverting the reaction toward these pathways. We prefer the cycloaddition deceleration hypothesis. First, the DMAD cycloadditions are more productive than those derived from methyl propiolate. This is consistent with the higher dipolarophilic reactivity of DMAD[27] allowing for an earlier transition state which would require less bending of the 1,3-dipole. By the Hammond postulate,[28] the less reactive methyl propiolate requires a higher degree of bending at the transition state, and this pathway is more easily diverted as the rigidity of the dipole increases. We propose that the degree of dipole bending required to cause cycloaddition with the triple bond is the contributing factor responsible for inhibiting the cycloaddition. Second, we find support for this picture in that **2a** is observed to react efficiently with olefinic dipolarophiles, such as methyl acrylate, that are usually less reactive than DMAD and methyl propiolate. In addition, the reactions of **2a** with diethyl maleate and diethyl fumarate are stereospecific[29] and that with methyl (E)-β-toluenesulfonylacrylate[30] is completely stereoselective, regioselective, and apparently stereospecific.[31] While we cannot determine whether the cycloaddition reactions in the case of the acetylenic dipolarophiles proceed via concerted or nonconcerted pathways, the reactivity observed with the olefinic dipolarophiles demonstrates the usual behavior of these compounds as mesoionic 1,3-dipoles. We infer that the transition state structure for reactions with olefinic dipolarophiles does not require the same degree of bending in the dipole as with the acetylenic dipolarophiles. Third, none of the ring-opened products (**4a**, **4b**) were observed with olefinic dipolarophile cycloadditions under the same conditions where they were observed with acetylenic dipolarophiles. This is consistent with our proposal that the transition state energies for the latter reactions have been elevated due to the required torsional strain, allowing the acylation of the dipole, running at a rate that is independent of the identity of the dipolarophile, to become competitive with dipolarophilic reactions.

(22) (a) Knorr, R.; Staudinger, G. K. *Chem. Ber.* **1971**, *104*, 3621–3632. (b) Knorr, R. *Chem. Ber.* **1971**, *104*, 3633–3643.

(23) Kawase, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1328–1329.

(24) Kawase, M.; Miyamae, H.; Narita, M.; Kurihara, T. *Tetrahedron Lett.* **1993**, *34*, 859–862.

(25) Kawase, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1076–1077.

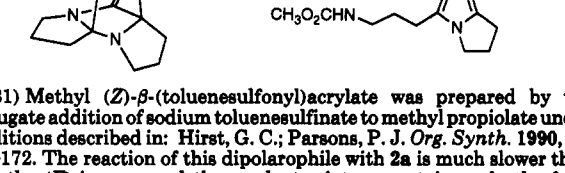
(26) For leading discussions of 1,3-dipolar cycloaddition transition state geometries, see: (a) Reference 6. (b) Sustman, R.; Sicking, W. *Tetrahedron* **1988**, *44*, 379–387. (c) Sustman, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1471–1480. (d) Sustman, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1653–1658. (e) Dewar, M. J. S.; Hwang, J. C.; Kuhn, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735–741. (f) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 428–433. (g) Leroy, G.; Sana, M. *Tetrahedron* **1976**, *32*, 709–717. (h) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2; pp 37–47.

(27) (a) Huisgen, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 1059–1071. (b) Eckell, A.; George, M. V.; Huisgen, R.; Kende, A. S. *Chem. Ber.* **1977**, *110*, 578–595.

(28) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 215–216.

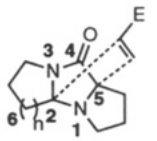
(29) The regiochemical and stereochemical distributions from the reactions of **2a** with methyl acrylate, diethyl fumarate, and diethyl maleate are not completely assigned. Spectroscopic analysis of the reaction mixtures reveals that the cycloadditions with fumarate and maleate are stereospecific. The dipolarophiles remain unisomerized under the reaction conditions. The reaction with fumarate is reasonably stereoselective (ca. 10:1), and only a single stereoisomer is detectable from the reaction with maleate. The spectral features from all three diastereomers compare very favorably with the analogous compound **8a**.

(30) We thank L. Jungheim for the experimental details for preparing the dipolarophile reported in: Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepard, T. A.; Sigmund, S. K. *Tetrahedron* **1988**, *44*, 3119–3126. The structure of the cycloadduct (**8a**) was confirmed by X-ray analysis. The cycloadduct crystallized in the monoclinic space group $P2_1/n$, with a = 14.151(4) Å, b = 9.647(2) Å, c = 14.735(5) Å, β = 99.64(2)°, Z = 4, V = 1983.1(9) Å^3. The structure was solved by direct methods and refined to an R-index = 0.0578 with a final R_w of 0.0604; GOF = 2.34. This compound was treated with a 0.1 M methanol solution of sodium methoxide to give **9a**, the dihydropyrrolinecarboxylate regioisomeric to **5a**, derivatized in the side chain as a methylcarbamate rather than as an acetamide. A 9:1 mixture of carbamates homologous to **9a** was observed from the elimination/cycloreversion of the cycloadduct of this dipolarophile with **1b**, where the major regioisomer compares favorably with **9a** and the minor regioisomer compares favorably with **5a–c**.



(31) Methyl (*Z*)-β-(toluenesulfonyl)acrylate was prepared by the conjugate addition of sodium toluenesulfinate to methyl propiolate under conditions described in: Hirst, G. C.; Parsons, P. J. *Org. Synth.* **1990**, *69*, 169–172. The reaction of this dipolarophile with **2a** is much slower than with the (*E*)-isomer, and the product mixture contains only the fragmentation product, **4a**, and the unchanged (*Z*)-isomer. Thus, we have only a difference in reactivity as evidence to support the stereospecificity of the reaction, which seems more likely to support a cycloaddition pathway.

Table II. Summary of Calculated Torsion Angles for Transition-State Structures



torsion angle for atoms	**2a** (deg) (n = 1)	**2b** (deg) (n = 2)
1–2–3–4	2.84	3.21
2–3–4–5	8.23	9.36
3–4–5–1	10.07	11.31
4–5–1–2	9.19	10.34
5–1–2–3	4.10	4.61
5–1–2–6	3.59	5.69

We have performed a computational search for the transition-state structures of the cycloaddition reactions of **2a** and **2b** with methyl propiolate. Transition-state geometries were located with the SADDLE option using the MNDO parameters[32] of MOPAC (Version 6.0) and refined via Baker's method.[33] Both of these transition states were characterized by one negative force constant and gradient values of 0.009 (**2a** reaction) and 0.007 (**2b** reaction). The calculated transition-state geometries for both of the tricyclic partners are roughly planar, reflecting the anticipated early transition states that look like the planar mesoionic nucleus.[34] The degree of pyramidalization in the five atoms of the mesoionic heterocycle, as measured by the five different torsion angles, is slightly greater in the **2b** transition state relative to the **2a** transition state (Table II). The pyramidalization is most pronounced for the C-2 terminus of the 1,3-dipole, as measured by the exocyclic torsion angle labeled 5–1–2–6 in Table II. These results are consistent with intuition about the degree of flexibility that the six-membered ring would have relative to the five-membered ring. This small absolute difference is reasonable, considering that the cycloaddtion to give **4a** is still a competitive pathway for **2a** and not completely diverted toward the formation of **6**.

The observed product distribution from the less flexible dipole **2a** also supports the picture of a concerted asynchronous transition state for the cycloaddition.[35] If we assume that a concerted to nonconcerted continuum characterizes the changeover, then the initial conjugate addition reaction anticipated for the formation of **6** occurs alongside an asynchronous cycloaddition transition state with a high Michael-like component (advanced bond formation at the β-terminus of propiolate relative to the α-terminus).[36] As the cycloaddition becomes more difficult (**2b** to **2a**), then the balance is tipped toward the Michael pathway. The structure of the transition states formulated by the MNDO searches are highly asynchronous in this direction (see Figure 2). We note with great interest that the bond distances located in these searches are very comparable to the values reported for Quast's stepwise azide reaction product (3.11 and 1.97 Å)[4] and also in our work with münchnones.[11] Unfortunately, we have not yet been able to identify an acceptable transition-state structure leading to the alternative regioisomer.

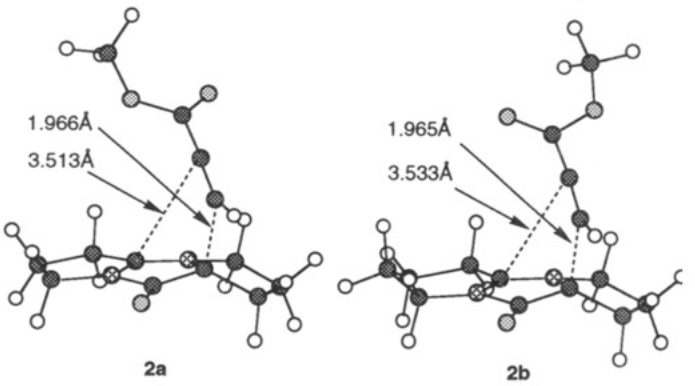


Figure 2. Calculated transition-state geometries for **2a** and **2b** with methyl propiolate.

The competitive formation of products derived from stepwise and cycloaddition pathways has provided a new example of a limiting case 1,3-dipolar reaction. Because this observation has been made for a mesoionic system that does not fit either of the criteria for other limiting case examples, and is rather more typical of many other 1,3-dipoles, we add our support to the notion that concerted, asynchronous bond formation plays a significant role in the selectivity of these cycloaddition reactions. In this context, we have also addressed theoretical and synthetic questions about the regioselectivity problem in the cycloaddition of other mesoionic compounds, and these results will be reported in due course. We are also investigating the scope of this torsional restriction as a probe for borderline and limiting case cycloaddition reactions, as well as a regiocontrol element for 1,3-dipolar cycloaddition reactions.

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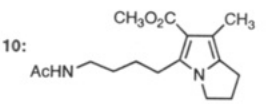
Supplementary Material Available: Experimental and spectroscopic data for new compounds (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

(32) Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917.
(33) Baker, J. *J. Comput. Chem.* **1986**, *7*, 385–395.
(34) An X-ray analysis structure has been determined for *N*-(*p*-bromophenyl)sydnone; see: Bärnighausen, H.; Jellinek, F.; Munnik, J.; Vos, A. *Acta Crystallogr.* **1963**, *16*, 471–475.
(35) (a) Reference 26. (b) A concerted, asynchronous transition state for nitrile oxide/olefin cycloaddition reactions has been proposed: Houk, K. N.; Firestone, R. A.; Monchausen, L. L.; Mueller, P. H.; Arison, B. H.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227–7228 and has been used to rationalize experimental results reported in ref 3.

(36) The reactions of **2a** and **2b** with methyl 2-butynoate provide additional evidence that is consistent with the demands of Michael-like character in the transition state. With **2a**, none of either a cycloaddition product nor a Michael-derived stepwise product (analogous to **6**) are observed, only the fragmentation byproduct **4a**. In the case of **2b**, a 70% chromatographed yield of a 1:1 mixture of the cycloaddition product **10** and the fragmented byproduct **4b** are observed.



(37) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.