Carbon–Carbon Bond Formation via Intramolecular Cycloadditions: Use of the Thiocarbonyl Ylide Dipole in *anhydro*-4-Hydroxythiazolium Hydroxides

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The mesoionic systems resulting from the introduction of 2-(allyloxy)phenyl substituents into the 2-, 3-, and 5-positions of *anhydro*-4-hydroxythiazolium hydroxide undergo intramolecular cycloaddition under different reaction conditions, the ease of cycloaddition diminishing in the order 2-substituted > 5-substituted ≫ 3-substituted. These cycloadditions were highly regio- and stereospecific, and rationalizations in terms of transition-state intermediates account for this behavior. The rate of cycloaddition was influenced appreciably by the electronic nature of the 2-, 3-, and 5-substituents, by the number of atoms separating the dipole and the dipolarophile, and by the degree of substitution of the dipolarophile. Alkynic and cyano dipolarophilic side chains also undergo extremely facile cycloaddition, leading to ring-fused thiophenes, thiazoles, and pyridinones, and with the alkynic dipolarophile, the N-substituent in the thiazole ring was found to control the decomposition of the initial cycloadduct. These intramolecular cycloadditions are in notable contrast to intermolecular cycloadditions with this mesoionic system where highly activated, electron-deficient dipolarophiles are required.

Introduction

Intramolecular 1,3-dipolar cycloadditions, in addition to their intrinsic theoretical interest, offer a viable synthetic approach to a variety of heterocyclic systems,[2] and this area of 1,3-dipole chemistry is one of continuing, current interest.[2] The thiocarbonyl ylide 1,3-dipole has received very little attention in these intramolecular cycloadditions, despite the potential for the initial cycloadduct to extrude sulfur to form arenes or heteroarenes. Difficulties encountered in constructing substrates containing the thiocarbonyl ylide may be avoided to some extent by utilizing the "masked" thiocarbonyl ylide present in the mesoionic 1,3-thiazole[3] or 1,3-dithiole[4] systems, and in this paper we describe the use of mesoionic *anhydro*-4-hydroxythiazolium hydroxides in intramolecular cycloadditions.

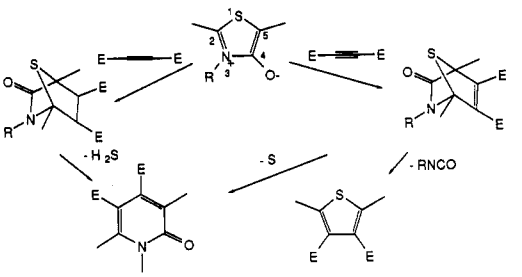
Intermolecular cycloadditions of *anhydro*-4-hydroxythiazolium hydroxides require electron-deficient alkenes and alkynes, giving initial 1:1 cycloadducts, which either lose H_2S, sulfur, or a substituted isocyanate, leading to 2(1*H*)-pyridinones or thiophenes.[2] These reactions are illustrated in Scheme I. For intramolecular cycloadditions, the dipolarophilic side chain can be attached at the 2-, 3-, and 5-positions of the nucleus. In principle this led to the consideration of four transition states for each point of attachment, designated as 2-endo, 2-exo, etc., in Figure 1. These cycloadditions provide a useful, direct synthetic approach to a number of ring-fused heterocycles.

Results and Discussion

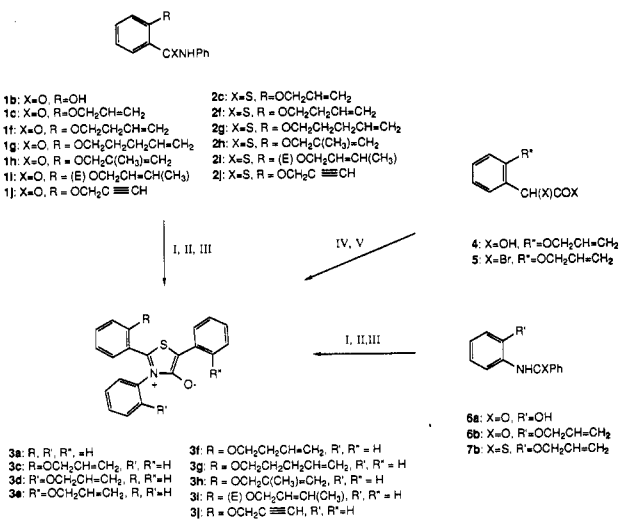
I. Synthesis of the Three [2-(Allyloxy)phenyl]-Substituted *anhydro*-4-Hydroxythiazolium Hydroxides 3. The two methods usually used for the synthesis of mesoionic thiazoles **3** involve either cyclodehydration of a thioglycolic acid intermediate or the reaction of a binucleophile (thioamide) with a bielectrophile (α-bromoacyl chloride). The three possible isomers of **3** containing an allyl ether substituent were synthesized via the latter method and differed in that the terminal dipolarophile was incorporated into either the binucleophilic or bielectrophilic portion of the molecule. The thioglycolic acid route, however, was used in the synthesis of those systems with no substituent in the 5-position.

Alkylation of salicylanilide (**1b**) with allyl bromide in hot acetone/K_2CO_3 gave 2-(allyloxy)benzanilide (**1c**), and replacement of the amide oxygen with sulfur in **1c** with Lawesson's reagent resulted in **2c**. Ring closure of **2c** with

Scheme I



Scheme II[a]



[a] (I) Allyl bromide, K_2CO_3; (II) Lawesson's reagent; (III) PhCH(Br)COCl/Et_3N; (IV) PBr_3; (V) PhCSNHPh/Et_3N.

(1) Abstracted in part from the M.S. Thesis of W.A.J. and the Ph.D. Dissertation of M.O.D., Rensselaer Polytechnic Institute, 1988. Part of this material has appeared as a preliminary communication: Potts, K. T.; Dery, M. O. *J. Chem. Soc., Chem. Commun.* **1986**, 561.

(2) For recent reviews and references, see: Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 8. Newton, C.; Ramsden, C. *Tetrahedron* **1982**, *38*, 1241. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894. Sammes, P. G.; Bromidge, S. M.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725.

(3) Potts, K. T.; Houghton, E.; Singh, U. P. *J. Org. Chem.* **1974**, *39*, 3627. Potts, K. T.; Baum, J.; Houghton, E. *J. Org. Chem.* **1974**, *39*, 3631.

(4) Gotthardt, H.; Huss, O. *Justus Liebigs Ann. Chem.* **1981**, 347.

0022-3263/89/1954-1077$01.50/0

Table I. ^{1}H NMR Data (200 MHz, $CDCl_3$) for Cycloadducts Derived from Mesoionic Systems 3c,f,h,i, 19, and 20

	chemical shifts δ (TMS)					coupling constants, J (Hz)					
compd no.	H_{5b}	H_{5a}	H_6	H_{7b}	H_{7a}	H_{5gem}	H_{5b}, H_6	H_{5a}, H_6	H_{7b}, H_6	H_{7a}, H_6	H_{7gem}
					Exo Adducts						
8a	2.28	2.94	3.42	4.31	4.60	12.9	4.2	7.9	11.5	4.5	11.1
10	2.53	3.04	3.26	4.31	4.62	12.1	4.3	7.82			
11	2.33–2.45	3.11	3.77	4.17	4.44	12.1	3.8	7.9			
13	2.53	2.65		4.47	4.78	13.0					10.5
14		2.78	2.98	4.38	4.68			4.1	11.1	7.5	11.5
16	2.66	3.65				13.5					10.5
					Endo Adducts						
8b	2.30	2.94	3.60	4.48	4.75	12.8	5.7	10.3	12.3	4.9	11.1
9	2.75	3.11	4.01	4.20	4.43	12.6	3.1	9.5	5.2	3.3	12.9
15		3.34	3.60		4.74			8.2		2.1	

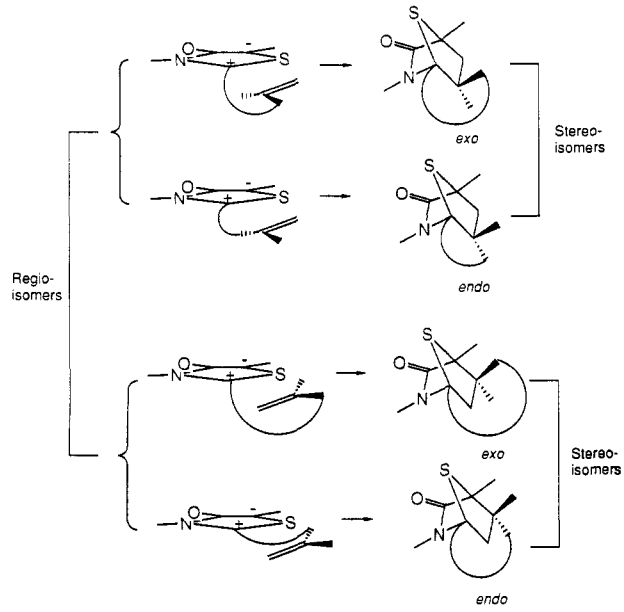
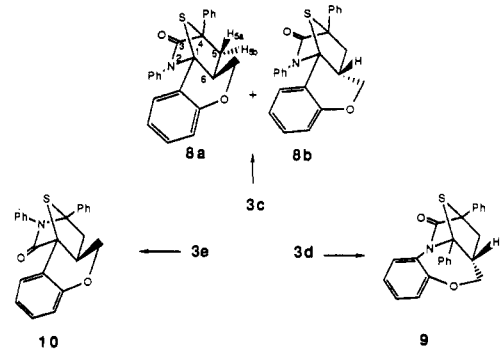


Figure 1. Possible orientations of the dipolarophile in cycloadditions of the 2-substituted systems.

α-bromophenacyl chloride/Et_3N gave the mesoionic system **3c**. Partial cycloaddition during isolation prevented the isolation of this mesoionic system in a pure state. It underwent a very facile regio- and stereoselective cycloaddition at room temperature to a 6:1 mixture of cycloadducts **8a** and **8b** (determined by 200-MHz ^{1}H NMR spectroscopy). The structure of **8a** was assigned principally from ^{1}H NMR data and confirmed by single-crystal X-ray analysis.[3] We attribute the preferred formation of **8a** over **8b** to a lower conformational energy requirement in the transition state of **8a** when compared to that required for the formation of **8b** (Scheme III). In the *anhydro*-4-hydroxy-1,3-dithiolium hydroxide system studied by Gotthardt and Huss,[4] an analogous adduct with the same stereochemistry as **8a** was obtained, but no minor isomer was observed.

The isomeric mesoionic system **3d** with the dipolarophilic side chain attached to nitrogen was prepared in a similar manner to **3c** above, starting in this instance with *N*-(2-(allyloxy)phenyl)benzamide (**6b**), obtained from *N*-(2-hydroxyphenyl)benzamide (**6a**) and allyl bromide. In contrast to **3c**, the mesoionic system **3d** was isolated in the pure state and was fully characterized. The intramolecular cycloaddition of **3d** occurred only at elevated temperatures (130 °C) and gave, in a regio- and stereospecific cycloaddition, cycloadduct **9** whose structure was assigned on the basis of its characteristic ^{1}H NMR spectrum (Table I). The stereospecificity of this cycloaddition is readily

Scheme III

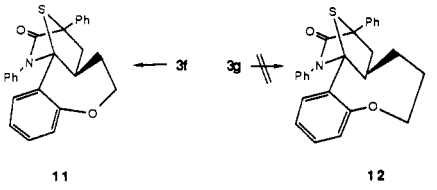


explained by considering molecular models of the transition states involved. The transition state leading to the exo analogue of **9** cannot be modeled because it is conformationally impossible for the dipole and dipolarophile to attain parallel plane overlap; thus, the exo adduct was not observed. In contrast to **3c** in which the terminal alkene carbon atom is seven atoms removed from the positive terminus of the dipole (C-2 of the thiazole nucleus), the corresponding centers in **3d** are separated by eight atoms, the additional atom apparently having an appreciable effect on the relative positions of the reactive centers.

The syntheses of the isomeric mesoionic systems **3c** and **3d** above followed the conceptually common pathway of reaction of the appropriate binucleophile and α-bromophenacyl chloride, and in each of these two cases the olefinic side chain was preattached to the binucleophile. In order to prepare the isomeric mesoionic system **3e**, however, it was necessary to incorporate the alkenic side chain into the bielectrophile. Readily available[5] 2-(allyloxy)benzaldehyde was converted[6] into the mandelic acid derivative **4**, which, when treated with 2 equiv of PBr_3, gave 2-(allyloxy)-α-bromophenylacetyl bromide (**5**). This material was not purified but reacted in situ with thiobenzanilide[7]/triethylamine to give the mesoionic system **3e**. This isomeric system also could not be isolated in a pure state due to partial cycloaddition occurring under these reaction conditions, and the cycloaddition was completed in refluxing benzene, resulting in a single cycloadduct **10**. This structure was assigned on the basis of the ^{1}H NMR data (Table I), and ^{1}H NMR (200 MHz) analysis

(5) (a) Potts, K. T.; Bordeaux, K. G.; Kuehnling, W. R.; Salsbury, R. L. *J. Org. Chem.* **1985**, *50*, 1666, 1677. (b) Claise, L.; Eisleb, O. *Justus Liebigs Ann. Chem.* **1917**, 401.
(6) Compere, E. L., Jr. *J. Org. Chem.* **1968**, *33*, 2565.
(7) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 299.

Scheme IV



11 12

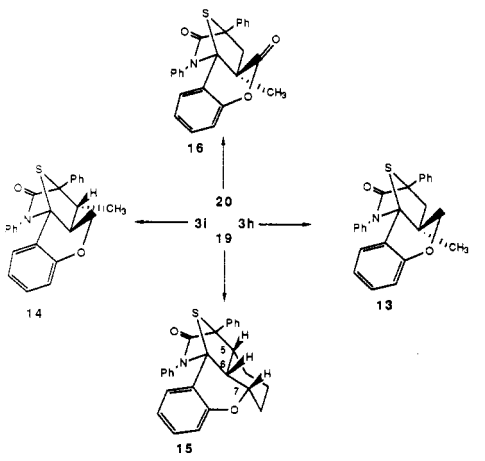
of the crude reaction mixture showed no other cycloadduct formation.

It should be noted that in **3e** seven atoms also separate the terminal carbon of the alkene and a reactive terminus of the dipole. Since the structures of cycloadducts **8a** and **8b** were established from X-ray data, structural assignments for the other cycloadducts were made by correlation of the ^1H NMR chemical shifts and coupling constants of the C_5, C_6, and C_7 protons with the corresponding protons in **8a** and **8b**. In general it was found that the exo protons were deshielded by the sulfur bridge and that the corresponding ^1H signals occurred downfield relative to those of the endo protons. In this manner it was possible to assign all chemical shifts to appropriate protons.

B. Variations in Dipolarophile Chain Length. Isomers of **3** in which R was replaced by a variety of terminal alkenic groups were studied extensively. All were readily prepared and were characterized by the ease with which the cycloaddition occurred. Via the synthetic sequence used for the preparation of isomer **3c**, the use of 4-bromo-1-butene as the alkylating agent gave the mesoionic compound **3f**. Cycloaddition occurred only after extended heating and resulted in a single cycloadduct **11** (Scheme IV). In this instance the terminal carbon of the alkene and a reactive center of the dipole are separated by eight atoms, giving a 7-membered ring as in **11**. Using 5-bromo-1-pentene in the above alkylation yielded **3g**, which failed to undergo cycloaddition on heating for extended periods in a variety of solvents, extensive decomposition occurring. We attribute the unreactivity of **3g** in the cycloaddition process to be due to the difficulty of the alkene moiety to attain a parallel plane approach with the thiocarbonyl ylide dipole, and this steric constraint is evident upon examination of molecular models with nine atoms separating the terminal alkene carbon atom and the reactive center of the dipole. A similar difficulty in obtaining parallel plane approach was also evident in **3f**, although in this instance cycloaddition was not prevented but only impaired when compared to the highly reactive allyl isomer **3c**. In general, as the length of the side chain was increased, or as the alkene was substituted (see below), considerably higher reaction temperatures were required for cycloaddition to occur. In each of these cases some decomposition of the mesoionic system resulted, accounting for the low yields obtained. Similar dependence on the number of atoms separating reactive centers in analogous cycloadditions has been observed.[8,9]

C. Cycloaddition with Methyl-Substituted Alkenic Dipolarophiles. In some intramolecular dipolar cycloadditions alkene substitution has been shown to retard cycloaddition,[10] and to determine the influence of this type of substitution on the present mesoionic system, we next studied systems containing methyl-substituted alkenes. Alkylation of **1b** with crotyl chloride gave, after repeated

Scheme V



16 20 19 14 13 15

recrystallization, the trans amide **1i** in pure form. Conversion into the thioamide **2i** occurred smoothly with Lawesson's reagent, and ring closure of **2i** with α-bromophenacetyl chloride occurred readily to give **3i**. The mesoionic compound **3i** could not be isolated in a pure state, undergoing cycloaddition at room temperature to give a single cycloadduct **14** (Scheme V). In this system the preferred isomer is the exo adduct, which was also observed in the unsubstituted alkene system.

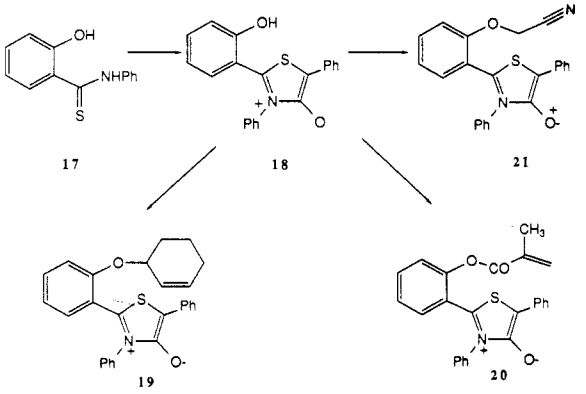
An additional mesoionic compound **3h**, containing a methallyl group, was prepared from **1b** and methallyl bromide by the same two-step, synthetic sequence used for the isomer **3i**. Heating **3h** in boiling toluene gave a single cycloadduct **13** whose stereochemistry could not be determined unambiguously from its ^1H NMR data since the diagnostic proton on carbon 6 is absent in this compound. An NOE experiment failed to produce any signal enhancement, but by examination of molecular models one is able to exclude with reasonable certainty on steric grounds the isomer with an exo methyl group.

Several of the benzamides used in our study could not be converted cleanly into the corresponding thioamides with Lawesson's reagent[7] or with other more recently developed O/S exchange reagents.[11] The desired thioamides are the common precursor to the mesoionic system **3**, and to circumvent this problem an alternative synthesis was carried out as described below.

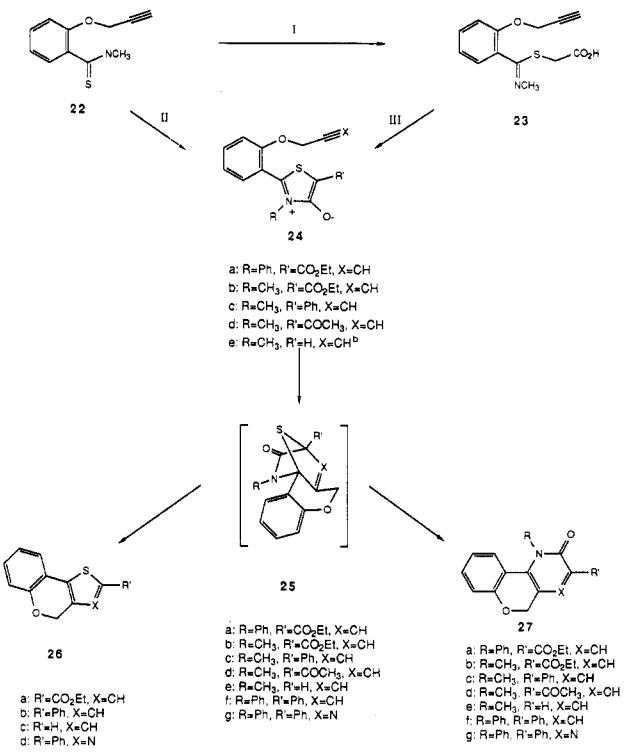
D. More Complex Alkenic Dipolarophiles. An attractive, practical synthesis of the mesoionic system **3** would be to append the dipolarophilic side chain to the hydroxyl group in the last step after the formation of the mesoionic system. Treatment of salicylanilide **1b** with Lawesson's reagent gave the thioamide **17**, which, when treated with α-bromophenacetyl chloride, gave the mesoionic system **18** as a stable, high-melting, red crystalline product. Although the aromatic hydroxyl group present in thioamide **17** could have been involved in the ring closure reaction, no evidence for products arising from any of these competing pathways was found. Purification of **18** was difficult because of its low solubility in organic solvents at moderate temperatures, but it could be recrystallized from DMF. The exocyclic oxygen atom in mesoionic thiazole systems does not undergo alkylation[2] with alkyl halides, etc., and consequently the aromatic hydroxyl group underwent ready acylation and alkylation without effecting the thiazole nucleus. This synthetic approach enabled a variety of systems that had previously

(8) Garanti, L.; Sala, A.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 2403.
(9) Gilchrist, T. L.; Wasson, R. C.; King, F. D.; Wooton, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2511.
(10) For example, see: Armstrong, R.; Grigg, R.; Jordan, M. W.; Malone, J. F. *Tetrahedron* **1985**, 41. Padwa, A.; Gingrich, H. L.; Lim, R. *J. Org. Chem.* **1982**, *47*, 2447.
(11) Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T. *Synthesis* **1984**, 827.

Scheme VI



Scheme VII[a]



[a] (I) $BrCH_2CO_2H$, Et_3N; (II) R'CHBrCOCl, Et_3N; (III) DCC or $(CH_3CO)_2O$. [b] Underwent spontaneous cycloaddition.

been unattainable to be prepared as described below.

Treatment of **18** with 3-bromocyclohexene/K_2CO_3 in refluxing acetone gave the mesoionic system **19**, which also could not be isolated in a pure state due to partial cycloaddition occurring under these reaction conditions. The cycloaddition was completed in boiling xylene, giving the cycloadduct **15**, which was the only isomer observed in the crude reaction mixture. The facial selectivity of this reaction allows the stereochemistry at three centers to be simultaneously constructed. Material balance was accounted for by the considerable amount of material of low R_f found in the reaction mixture. This material retained the olefinic protons and was probably formed by an allyl ether rearrangement of the initial olefinic ether and subsequent decomposition of the resultant mesoionic system. The structure of the cycloadduct **15** was assigned on the basis of its ^1H NMR spectrum, and additional evidence in support of this structure came from an NOE of 0.16 observed between protons H_6 and H_7, establishing the cis relationship of these protons.

Compound **18** was acylated with methacryloyl chloride/triethylamine, giving the acyl derivative **20**. This product also could not be isolated in a pure condition because partial cycloaddition had occurred under these reaction conditions. The cycloaddition was completed in boiling toluene and gave a single cycloadduct assigned structure **16**. Even though the diagnostic proton on carbon 6 was absent in this adduct, the structure of adduct **16** could be assigned from its ^1H NMR data due to an observed NOE enhancement of 0.10 between the endo hydrogen on carbon 5 and the endo methyl group attached to carbon 6. There was no observed NOE enhancement between the methyl group and the signal for the exo hydrogen on carbon 5. The formation of the cycloadduct **16** is interesting in that, despite the demonstrated spatial requirements necessary for cycloaddition, the sp^2 hybridized carbon in the side chain did not interfere with these requirements, either spatially or electronically, further extending the utility of this cycloaddition approach.

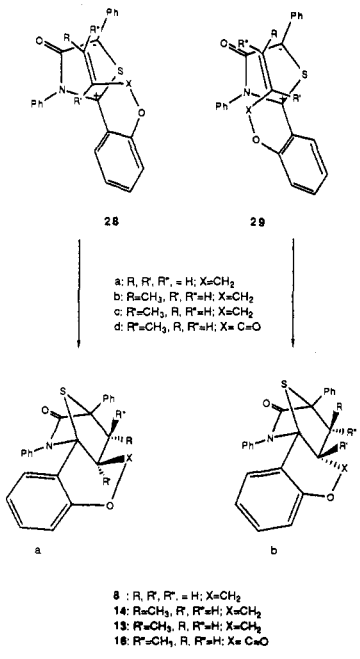
II. Cycloaddition with Alkynes. By utilization of propargyl bromide in the synthetic sequence leading to the intermediate **3c**, the acetylenic thioamide **2j** was obtained. Ring closure with α-bromophenacyl chloride gave the mesoionic compound **3j**, which also could not be isolated due to its facile cycloaddition. The initial cycloadduct was not isolated; it immediately lost PhNCO to give the fused thiophene **26b**. Thermal extrusion of sulfur from the intermediate cycloadduct is also a possibility and would give rise to ring-fused pyridone. However, we did not observe any of this product, and a similar result was obtained by Gotthardt and Huss[4] in the 1,3-dithiole system.

Intramolecular cycloaddition of **3** was also studied with a terminal nitrile as dipolarophile. Treatment of **18** with K_2CO_3 in refluxing acetone followed by the addition of α-chloroacetonitrile gave **21**, which underwent partial cycloaddition under these reaction conditions. The cycloaddition was completed in boiling toluene, giving the cycloadduct **26d** (Scheme VII). The formation of the thiazole **26d** is readily rationalized as occurring in a similar manner to the thiophene **26b**, with the intermediate cycloadduct **25g** losing PhNCO to give the fused thiazole **26d**. An alternative decomposition pathway would be via the initial cycloadduct **25g** undergoing thermal extrusion of sulfur to give a ring-fused pyrazinone, but none of this product was observed. The nitrile group is seldom used as a dipolarophile, and this present utilization of an alkyl cyanide illustrates the potential for the synthesis of fused thiazoles via an intramolecular cycloaddition approach.

Ring closure of the substituted thioglycolic acid **23**, which was obtained from **22** and α-bromophenylacetic acid, with DCC gave the 5-unsubstituted system **24c**, which could not be isolated in a pure state. It underwent a spontaneous cycloaddition (12 h, 20 °C) to give the α-pyridinone **27e**. Treatment of the thioamide **22** with α-bromophenacyl chloride gave **24e** whose presence was detected from its red color. It also could not be isolated in a pure state, with contamination by its cycloadduct always occurring. The resultant product was shown to be the α-pyridinone **27c**, which arose by extrusion of sulfur from the initial cycloadduct.

In intermolecular cycloadditions with mesoionic systems, introduction of an acetyl substituent into the mesoionic ring at a position α to the carbonyl group always resulted in loss of cycloaddition ability. Ring closure of the substituted thioglycolic acid **23** with acetic anhydride gave directly the acetyl-substituted mesoionic system **24d**, reflecting the high degree of negative charge at the 5-position. The acetyl compound **24d** could be recrystallized without cycloaddition occurring, but on reflux in toluene for 12 h, cycloaddition resulted to give the α-pyridinone **27d** (77%)

Scheme VIII



formed from the initial cycloadduct by extrusion of sulfur. Introduction of an ethoxycarbonyl substituent into the 5-position by treatment of **22** with α-bromo(ethoxycarbonyl)acetyl chloride to give **24b** also resulted in a stable mesoionic system, which similarly underwent intramolecular cycloaddition to give the α-pyridinone **27b** with a 3-ethoxycarbonyl substituent. In marked contrast to this last reaction is the cycloaddition behavior of the mesoionic system **24a** with a *N*-phenyl substituent. Heating **24a** in boiling toluene for 12 h resulted in cycloaddition occurring with the formation of the ring-fused thiophene **26a**. In this instance phenyl isocyanate was eliminated from the initial cycloadduct. Similar elimination of phenyl isocyanate from the initial cycloadducts occurred with the mesoionic systems **3j** and **21**, which gave **26f** (X = CH) and **26d** (X = N), respectively.

These results indicate that the N-substituent in the mesoionic system **3** is controlling the decomposition of the initial cycloadducts derived from alkynic dipolarophilic side chains. With a *N*-phenyl substituent, cycloreversion was favored, apparently due to the formation of the conjugated system present in phenyl isocyanate.

III. Stereochemical Aspects. Examination of the transition state in these cycloadditions provides a rationalization of the stereochemical results observed, with two transition state factors being important: conformational practicality, i.e., the conformation of the molecule must be such that the dipole and dipolarophile can readily attain a parallel plane approach; and steric demand, i.e., if there are several possible conformations in which parallel plane approach is possible, then the least sterically demanding transition state will be favored. The experimentally observed stereochemistry in the above cycloadditions can be explained by considering the outcome of cycloadditions of these types.[12]

(1) 2-Substituted Thiazoles. The stereochemistry of the cycloadducts in these systems is consistent with an exo approach of the alkene in the transition state. There were two exceptions: in one instance a minor isomer was produced by an endo approach, and, in the other case, the alkene was contained in a cyclohexene ring, which, for reasons explained later, approaches from the endo face.

Cycloadducts **8a** and **8b** must arise from the transition states **28a** and **29a**, respectively (Scheme VIII). The transition state **28a** is much less sterically demanding than transition state **29a** in which there is interaction between the thiazole N-substituent and the dipolarophilic side chain, and this was reflected experimentally in the 6:1 ratio of cycloadduct **8a**:**8b**. Both transition states must be relatively close in conformational energy since both adducts were formed.

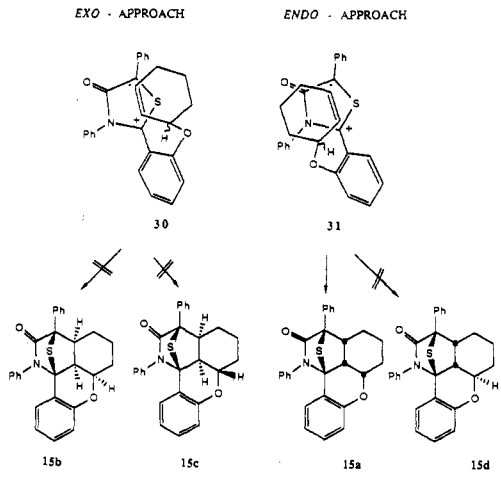
Formation of cycloadduct **11** is favored for the same reasons as cycloadduct **8a**, but in this instance a minor isomer was not observed. Overall **3f** is much less reactive toward cycloaddition than the isomeric system **3c**, requiring higher reaction temperatures for the cycloaddition and resulting in lower yields of cycloadduct, and the additional carbon atom in the olefinic side chain makes it sterically more difficult for the system to obtain parallel plane approach. It must also raise the relative conformational energy of an exo vs an endo approach, resulting in exclusion of the endo isomer. One also needs to consider thermal decomposition of the mesoionic systems at these higher reaction temperatures.

A methyl-substituted alkene in the dipolarophilic side chain does not affect the stereoselectivity of the cycloaddition. The relative conformational energy differences between the exo and endo approach, however, must be increased, and thus isomers arising from the endo transition state are excluded. Thus cycloadducts **14a**, **13a**, and **16a** are formed from the transition states **28b**, **28c**, and **28d**, respectively, and the cycloadducts **14b**, **13b**, and **16b**, which would arise from an endo approach in the transition state **29b**, **29c**, and **29d**, respectively, are not formed.

Cycloadduct **15** is particularly interesting (Scheme IX). There are four possible reaction products, and the only one observed is **15a**, arising from an endo approach. Rationalization of this stereochemical result is more complicated than with the other systems studied above since, in this instance, the dipolarophilic side chain contains a chiral carbon atom, and the possible conformers of the cyclohexenyl ring as well as the conformers of the overall molecule, i.e., exo vs endo approach, must be considered. The assumptions made, however, are the same as those previously used.

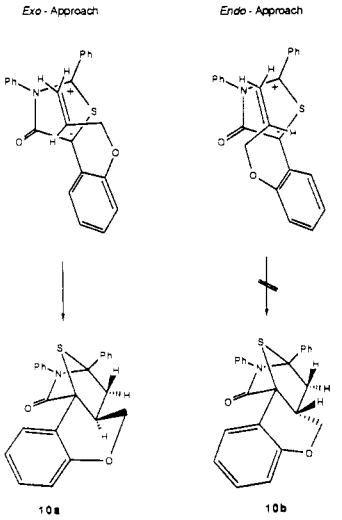
The two possible approaches, endo and exo, and the four possible products are summarized in Scheme IX. Examination of molecular models indicates that when the cyclohexenyl ring approaches from the exo face **30**, this is not a conformation that allows the dipole and dipolarophile

Scheme IX



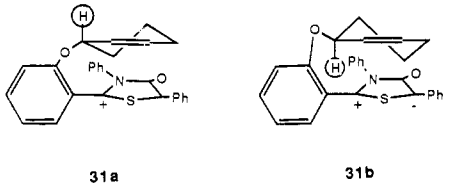
(12) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754; Gilchrist, T. L.; Wasson, R. C.; King, F. D.; Wooton, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2517.

Scheme X



to obtain good overlap. Much better overlap results from an endo approach. Thus the products **15b** and **15c**, which would arise from an exo approach, are not formed.

There are two possible orientations **31** for endo approach in which **31a** is favored over **31b** because of the steric interactions present in **31b**, which are absent in **31a**. These interactions arise from the indicated hydrogen atom, which points directly into the mesoionic ring in **31b** and is far removed from the mesoionic ring in **31a**. Thus the reaction gives only a single product **15**.

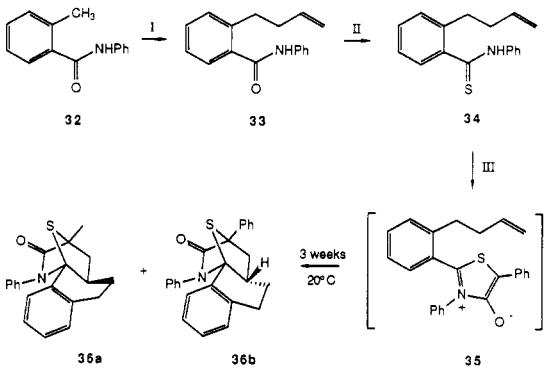


(2) 3-Substituted Thiazoles. The resultant stereochemistry of the cycloadducts resulting from this system is readily explained by molecular models. These show that it is impossible to construct a transition state that would lead to an exo adduct; in addition, it is also impossible to construct a reasonable model of the exo adduct of this cycloadduct. It is also important to note that in this system the resultant adduct will contain a 7-membered ring.

(3) 5-Substituted Thiazoles. The stereochemistry of the cycloadduct from this system is explained by an analogous argument, which also provides a rationalization of the observed stereochemistry of the cycloadducts **8a** and **8b**. The cycloadduct is formed from the least sterically demanding transition state (Scheme X).

We have also looked at the role of product stability[13,14] in determining the course of these cycloadditions. Table IV lists the minimized total energy[15] for the various cycloadducts described above. It is interesting to note the close correlation of the experimental results with those predicted on the basis of these calculations. The one exception is adduct **15**; experimentally adduct **15a** was isolated whereas our calculations indicate this adduct to be of higher energy than adduct **15d**. We attribute this difference to steric approach control in the transition state governing product formation.

Scheme XI[a]



[a] (I) 2 *n*-BuLi, allyl bromide, THF, 0 °C; (II) Lawesson's reagent, toluene; (III) α-bromophenyl acetyl chloride, Et_3N, C_6H_6.

One question still remaining to be considered is the effect of the oxygen atom in the dipolarophilic side chain on the cycloaddition. Evidence indicates that bimolecular cycloadditions with these types of systems are HOMO dipole–LUMO dipolarophile controlled,[16a] and the 5-position of the mesoionic ring has the highest HOMO coefficient.[16b] Any group that influences the electron density at the 5-position should have an effect on the cycloaddition. Electron-withdrawing substituents in the 5-position, such as the acetyl and ethoxycarbonyl derivatives, have been shown to retard cycloaddition when compared to 5-phenyl-substituted systems. The oxygen atom in the 2-position of the phenyl ring is in direct conjugation with the 5-position of the thiazolium ring and, as an electron-donor group, should enhance the reactivity of the system toward intramolecular cycloaddition. To confirm this effect, we synthesized the mesoionic compound **35** via the route shown in Scheme XI. As anticipated, replacement of the oxygen atom with a methylene group slowed significantly the rate of cycloaddition, to the extent that in comparable compounds (**3c** and **35**), the cycloaddition of **3c** required 36 h at room temperature for the cycloaddition to be completed after generation of **3c**; the cycloaddition of **35** required 3 weeks under comparable reaction conditions. The structures of the cycloadducts **36a** and **36b**, isolated in a 34:1 ratio, were assigned on the basis of the compatibility of their ^1H NMR data with that of the cycloadducts **8a** and **8b** described above. A similar activating effect of an ortho oxygen atom has been noted[17] in related intramolecular 1,3-dipolar cycloadditions of *o*-(cyanomethyleneoxy)phenylazide.

Experimental Section[18]

General Procedure for the Preparation of Benzanilide Ethers 1c,f–j. 2-Hydroxybenzanilide (1 equiv), potassium carbonate (2 equiv), and the alkyl bromide (1 equiv) were stirred and heated under reflux in acetone for 12 h. The reaction mixture was cooled and filtered, and the solvent was then removed under reduced pressure, leaving a brown residue. This residue was

(13) Marshall, J. A.; Grote, J.; Andia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186.
(14) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, 4609.
(15) PC Model/MMX Software was used (Serena Software, Bloomington, Indiana).
(16) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, Chapter 1. Garanti, L.; Zeechi, G. *J. Org. Chem.* **1975**, *40*, 1906. (b) Baudy, M.; Robert, A.; Guimon, G. *Tetrahedron* **1982**, *38*, 1241.
(17) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 1906.
(18) Spectral characterizations were carried out on the following instruments: infrared spectra, Perkin-Elmer Model 298 or 337 grating infrared spectrophotometer; ^1H NMR, Varian XL-200 with TMS as an internal standard; mass spectra, Hewlett Packard GC-MS system, Model 5987A spectrometer. All melting points were determined in capillaries using a Mel-temp apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or Robertson Laboratory, Inc., Madison, NJ.

Table II. Precursor Benzanilide Ethers 1 and Thiobenzanilide Ethers 2

compd no.	X	mp, °C	yield, %	crystalline form[a]	molecular formula	analytical data: calcd/found C	H	N	spectral data [M + 1] (rel intensity)[b]	IR Data cm^{-1} (KBr)	^1H NMR ($CDCl_3$) δ
1c	O	50–52	94	prisms	$C_{16}H_{15}NO_2$	75.87/75.86	5.97/5.99	5.53/5.49	253 (70)	3340 (NH) 1655 (CO)	4.76 (d, 2, $J_{OCH_2,CH}$ = 4.8 Hz, OCH_2), 5.39 (d, 1, $J_{CH,CH}$ = 11.2 Hz, CH_2), 5.58 (d, 1, $J_{CH,CH}$ = 17.6 Hz, CH_2), 6.34 (m, 1, CH), 6.97–8.41 (m, 9, aromatic), 10.0 (s, 1, NH)
1f	O	58–60	80[c]	prisms	$C_{17}H_{17}NO_2$	76.38/76.30	6.41/6.42	5.24/5.19	268 (100)	3350 (NH) 1660 (CO)	2.74 (m, 2, $J_{CH,CH}$ = 6.4 Hz, $OCH_2CH_2CHCH_2$), 4.29 (t, 2, $J_{OCH_2,CH}$ = 6.4 Hz, OCH_2), 5.23 (m, 2, $CHCH_2$), 5.96 (m, 1, CH), 7.01–8.33 (m, 9, aromatic), 9.90 (s, 1, NH)
1g	O	37–39	85	microprisms	$C_{18}H_{19}NO_2$	76.84/76.91	6.81/6.86	4.98/4.97	282 (100)	1655 (CO)	2.10 (m, 2, CH_2), 2.35 (m, 2, CH_2), 4.23 (t, 2, OCH_2), 5.09 (m, 2, $CHCH_2$), 5.87 (m, 1, CH), 6.99–8.34 (m, 9, aromatic), 10.04 (s, 1, NH)
1j	O	120–122	85	needles	$C_{16}H_{13}NO_2$	76.48/76.50	5.21/5.24	5.58/5.57	252 (100)	1715 (CO) 2121 (C≡C)	2.70 (t, 1, CH), 4.91 (d, 2, OCH_2), 6.84–8.50 (m, 9, aromatic), 9.82 (s, 1, NH)
1h	O	41–42	72	microneedles	$C_{17}H_{17}NO_2$	76.38/76.29	6.41/6.46	5.24/5.19	268 (100)	1650 (CO)	1.93 (s, 3, CH_3), 4.65 (s, 2, OCH_2), 5.19 (d, 2, $C(CH_3)CH_2$), 6.99–8.34 (m, 9, aromatic), 9.95 (s, 1, NH)
1i	O	77–78	66	long needles	$C_{17}H_{17}NO_2$	76.36/76.38	6.41/6.43	5.24/5.22	268 (37)	1660 (CO)	1.85 (d, 3, $J_{CH,CH}$ = 6.5 Hz, CH_3), 4.67 (d, 2, J_{CH,OCH_2} = 5.6 Hz, OCH_2), 5.98 (m, 2, $J_{CH,CH}$ = 15.6 Hz, CHCH), 6.06–8.34 (m, 9, aromatic), 10.17 (br s, 1, NH)
2c	S	90–92	71	irregular prisms	$C_{16}H_{15}NOS$	71.34/69.99	5.62/5.67	5.20/5.02	269 (100)	1585 (C=C)	4.74 (d, 2, $J_{OCH_2,CH}$ = 4.8 Hz, OCH_2), 5.41 (d, 1, $J_{CH,CH}$ = 11.2 Hz, CH_2), 5.62 (d, 1, $J_{CH,CH}$ = 17.6 Hz, CH_2), 6.24 (m, 1, CH), 6.17–8.63 (m, 9, aromatic), 10.70 (s, 1, NH)
2f	S	57–60	53	fine needles	$C_{17}H_{17}NOS$	72.05/72.12	6.05/6.06	4.94/4.91	284 (100)	3280 (NH)	2.64 (m, 2, J_{CH,CH_2} = 5.3 Hz, OCH_2CH_2CH), 4.24 (t, 2, $J_{OCH_2,CH}$ = 6.3 Hz, OCH_2), 5.07 (m, 2, $CHCH_2$), 5.86 (m, 1, CH), 6.97–8.56 (m, 9, aromatic), 10.90 (s, 1, NH)
2g	S	52–53	53	plates	$C_{18}H_{19}NOS$	72.69/72.80	6.44/6.50	4.71/4.64	298 (100)	3280 (NH)	1.99 (m, 2, CH_2), 2.24 (m, 2, CH_2), 4.18 (t, 2, OCH_2), 5.01 (m, 2, $CHCH_2$), 5.79 (m, 1, CH), 6.96–8.54 (m, 9, aromatic), 10.82 (s, 1, NH)
2j	S	69–70	40	prisms	$C_{16}H_{13}NOS$	71.88/71.65	4.90/4.98	5.24/5.18	268 (100)	2130 (C≡C)	2.55 (t, 1, CH), 4.81 (d, 2, OCH_2), 6.80–8.13 (m, 9, aromatic), 10.90 (s, 1, NH)
2h	S	52–54	27	prisms	$C_{17}H_{17}NOS$	72.05/71.99	6.06/6.10	4.94/4.91	284 (100)	3220 (NH)	1.85 (s, 3, CH_3), 4.49 (s, 2, OCH_2), 5.10 (d, 2, CH_2), 6.86–8.52 (m, 9, aromatic), 10.72 (s, 1, NH)
2i	S	82–83	27	microneedles	$C_{17}H_{17}NOS$	72.05/71.98	6.05/6.09	4.94/4.93	284 (94)	3280 (NH) 1615 (C=C)	1.78 (d, 3, $J_{CH_3,H}$ = 5.5 Hz, CH_3), 4.64 (d, 2, $J_{OCH_2,CH}$ = 6.0 Hz, OCH_2), 5.72–6.02 (m, 2, $J_{CH,CH}$ = 15.5 Hz, CHCH), 6.98–8.62 (m, 9, aromatic), 11.06 (s, 1, NH)

[a] All crystallized from *n*-hexane except **1d**, **1f**, and **1g**, which separated from *n*-hexane–ether, and **1k**, which separated from ether; all oxygen compounds were colorless and the sulfur analogues light yellow which separated from *n*-hexane–ether. [b] All CI spectra except **1c** and **2c**, which were determined under EI conditions. [c] Based on recovered starting material.

Table III. Isolable Mesoionic *anhydro*-4-Hydroxy-2,3,5-trisubstituted-thiazolium Hydroxides[a]

compd no.	mp, °C	yield, %	crystalline form[b]	molecular formula	analytical data: calcd/found			M^+ (rel intensity)	IR data ν_{CO} (KBr), cm^{-1}	^1H NMR ($CDCl_3$) δ
					C	H	N			
3d	136–137	64	red rosettes/ $CHCl_3$–Et_2O	$C_{24}H_{19}NO_2S$	74.74/74.65	4.97/4.99	3.63/3.59	385 (100)	1635	4.31 (d, 2, OCH_2), 5.00 (m, 2, CH_2CH_2), 6.02 (m, 1, CH), 6.87–8.10 (m, 14, aromatic)
3f	122–124	85	bright red microneedles/ CH_2Cl_2–Et_2O	$C_{25}H_{21}NO_2S$	75.16/75.22	5.30/5.32	3.51/3.49	400 (8) [M + 1][c]	1615	2.41 (m, 2, OCH_2CH_2), 3.84 (t, 2, OCH_2), 5.12 (m, 2, $CHCH_2$), 5.76 (m, 1, CH), 6.79–8.03 (m, 14, aromatic)
3g	102–103	84	bright red microneedles/ *n*-hexane	$C_{26}H_{23}NO_2S$	75.52/75.40	5.61/5.66	3.39/3.38	414 (78) [M + 1]	1615	1.78 (m, 2, CH_2), 2.12 (m, 2, CH_2), 3.79 (t, 2, OCH_2), 4.97 (m, 2, $CHCH_2$), 7.58 (m, 1, CH), 6.78–8.04 (m, 14, aromatic)
3h	100–101	82	red microneedles/ *n*-hexane	$C_{25}H_{21}NO_2S$[d]				399 (35)[e]	1610	1.71 (s, 3, CH_3), 4.21 (s, 2, OCH_2), 4.88 (d, 2, CH_2), 6.76–8.03 (m, 14, aromatic)
18	294–295	63	red plates/ DMF	$C_{21}H_{15}NO_2S$[f]				345 (7)[g]	1600	6.70 (m, aromatic)[h]

[a] Similar mesoionic systems **3c,e,j,i, 19, 20,** and **21** underwent partial cycloaddition at room temperature or on attempted purification. [b] Low-temperature recrystallization was used to retard cycloaddition. [c] Other principal ions *m/z* 121 (78) [PhCS], 119 (100) [PhNCO]. [d] Always contaminated with a trace amount of cycloadduct. [e] Other principal ions *m/z* 280 (100) [M – PhNCO], 121 (14) [PhCS], 119 (20) [PhNCO]. [f] Always contained a trace amount of DMF. [g] Other ions *m/z* 313 (7) [M^+ – S], 196 (100) [M^+ – PhCSCO], 121 (19) [PhCS]. [h] DMSO-d_6.

dissolved in diethyl ether and distilled water. The separated organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure, leaving a brown oil. The product crystallized from an appropriate solvent and its physical characteristics are described in Table II.

General Procedure for the Preparation of Thiobenzanilide Ethers 2. The Preparation of 2-(Allyloxy)thiobenzanilide (2c). 2-(Allyloxy)benzanilide (20.2 g, 80 mmol) and Lawesson's reagent (19.1 g, 47 mmol) were stirred and heated under reflux in dry toluene for 12 h. The reaction mixture was cooled and extracted with 1 M KOH solution (3 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and removed under reduced pressure to give a brown residue. The residue crystallized from *n*-hexane as yellow, irregular prisms: 15.2 g (71%), mp 90–92 °C. The physical characteristics of **2c** and the other thioethers prepared by this method are described in Table II.

General Procedure for the Preparation of (a) Isolable *anhydro*-4-Hydroxythiazolium Hydroxides. Preparation of *anhydro*-3-(2-(Allyloxy)phenyl)-2,4-diphenyl-4-hydroxythiazolium Hydroxide (3d). α-Bromophenylacetyl chloride (2.4 g, 10.0 mmol) was added dropwise to a solution of 2-(2-allyloxy)thiobenzanilide (2.8 g, 10 mmol) in dry benzene (50 mL). After 80 min Et_3N (2.0 g, 20 mmol) was added, and stirring was continued for 5 h. The separated material was collected and washed with benzene, and the benzene was removed from the filtrate under vacuum to give a red solid, which separated from $CHCl_3$–Et_2O as red rosettes: 2.5 g (64%), mp 136–137 °C. Products prepared in this manner are described in Table III.

(b) Nonisolable *anhydro*-4-Hydroxythiazolium Hydroxides 3c,e,i,j. The reaction was carried out as above, and the benzene was removed from the filtrate to give a red residue, usually as a gum, which was shown by ^1H NMR data to be the desired mesoionic system mixed with varying amounts of the cycloadduct. Heating this residue in an inert solvent, usually benzene, toluene, xylene, or 1,2-dichlorobenzene, resulted in the cycloaddition being completed as described below.

Preparation of *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-hydroxyphenyl)thiazolium Hydroxide (18). α-Bromophenylacetyl chloride (1.78 g, 8.32 mmol) was added dropwise to a solution of 2-hydroxythiobenzanilide (1.91 g, 8.32 mmol) and dry dichloromethane. The reaction mixture was stirred for 4 h before triethylamine (1.69 g, 16.6 mmol) was added dropwise with continued stirring. The following morning the separated materials were filtered; the collected material was washed with dichloromethane and then recrystallized from DMF forming red plates: 1.82 g (63%), mp 294–295 °C (Table III).

Preparation of *anhydro*-2-(2-(Cyclohexenyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (19). *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-hydroxyphenyl)thiazolium hydroxide (18) (0.25 g, 0.72 mmol), potassium carbonate (0.20 g, 1.44 mmol), and 3-bromocyclohexene (0.12 g, 0.72 mmol) in acetone (50 mL) were heated under reflux with stirring for 24 h. The cooled reaction mixture was filtered, and the collected material was washed with acetone. Removal of the solvent under reduced pressure gave a red gum, which was dissolved in a mixture of diethyl ether–distilled water. The separated organic layer was dried over Na_2SO_4, filtered, and removed under reduced pressure, leaving a red solid, which underwent cycloaddition upon attempted further purification.

Preparation of *anhydro*-2-(2-((Cyanomethyl)oxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (21). *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-hydroxyphenyl)thiazolium hydroxide (18) (0.25 g, 0.72 mmol), potassium carbonate (0.20 g, 1.4 mmol), and chloroacetonitrile (0.05 g, 0.72 mmol) in acetone (50 mL) were heated under reflux for 24 h. The cooled reaction mixture was filtered, and the collected material was washed with acetone. Removal of the solvent gave a red gum, which was dissolved in a mixture of diethyl ether–distilled water. The separated organic layer was dried, filtered, and removed under reduced pressure to give a red gum, which was used without further purification.

Preparation of *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-(methacryloyloxy)phenyl)thiazolium Hydroxide (20). Triethylamine (0.03 g, 0.29 mmol), *anhydro*-3,5-diphenyl-4-hydroxy-2-(2-hydroxyphenyl)thiazolium hydroxide (18) (0.10 g, 0.29 mmol), and dry benzene were stirred together at room tem-

Table IV. Minimum Energies (kcal mol^{-1}) for Cycloadducts Derived from *anhydro*-4-Hydroxythiazolium Hydroxides

cycloadduct	configuration	minimum energy	difference	minimum energy	configuration
8	exo[a]	56.53	5.72	62.25	endo[c]
13	exo[b]	59.08	7.42	66.50	endo[d]
14	exo[b]	59.26	3.99	63.25	endo[d]
16	exo[b]	63.88	6.03	69.91	endo[d]
10	exo[b]	57.33	3.45	60.78	endo[d]
11	exo[b]	64.46	0.62	65.08	endo[d]
36	exo[a]	56.02	4.79	60.81	endo[c]
9	endo[b]	67.22	36.42	103.64	exo[d]
15a	endo[b]	76.44	5.64	70.80	endo[d] (15d)

[a] Major isomer. [b] Exclusive product. [c] Minor isomer. [d] Product not formed.

perature for 2 h before methacryloyl chloride (0.03 g, 0.29 mol) was added dropwise. The reaction mixture underwent a gradual color change from orange to a deep, dark-red, and, after 5 h, the separated materials were filtered and washed with dry benzene, and the filtrate was removed under reduced pressure to give a red residue. Crystallization of this material from diethyl ether–*n*-hexane at −80 °C gave red microneedles, which underwent a facile cycloaddition upon attempted further purification: 0.06 g (50%).

Cycloadducts 8a,b of *anhydro*-2-(2-(Allyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (3c). A solution of *anhydro*-2-(2-(allyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium hydroxide (prepared as above) in dry benzene (50 mL) was stirred at ambient temperature for 36 h. Removal of the solvent under reduced pressure gave a colorless solid, which was purified by column chromatography (silica gel with elutent being 60% *n*-hexane, 38% CH_2Cl_2, 2% EtOAc) and gave three fractions. The first fraction crystallized from *n*-hexane (0.03 g) and was identified as unreacted thioamide. The exo isomer was found in the second fraction and separated as colorless prisms from ethanol: 0.38 g (and additional amounts were recovered upon further workup), total yield 0.43 g (73%); mp 212–213 °C; IR (KBr) 1695 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (dd, 1, J_{H_{5b},H_6} = 4.2 Hz, $J_{H_{5gem}}$ = 12.9 Hz, H_{5b}), 2.94 (dd, 1, J_{H_{5a},H_6} = 7.9 Hz, H_{5a}), 3.42 (m, 1, H_6), 4.31 (dd, 1, J_{H_7,H_6} = 11.5 Hz, $J_{H_{7gem}}$ = 11.1 Hz, H_7), 4.60 (dd, 1, J_{H_7,H_6} = 4.6 Hz, H_7), 6.67–7.57 (m, 14, aromatic); mass spectrum (CI pos) [M$^+$ + 1] 386 (100). Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.66; H, 4.99; N, 3.61.

The third fraction was determined (200-MHz NMR) to be an enriched mixture of minor (endo) and major (exo) isomers. Column chromatography (silica gel eluted with a mobile phase containing 60% *n*-hexane, 35% CH_2Cl_2, 5% Et_2O) gave two fractions. An additional amount (0.04 g) of the major isomer was recovered in the first fraction. The second fraction contained the minor isomer, which was finally separated by silica gel preparative chromatography (eluted with a mobile phase containing 30% CH_2Cl_2, 65% *n*-hexane, 3% Et_2O, four developments being necessary to obtain a complete separation) and gave colorless prisms from methanol: 0.05 g (9%); mp 159–160 °C; IR (KBr) 1695 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (dd, 1, J_{H_{5b},H_6} = 5.7 Hz, $J_{H_{5gem}}$ = 12.8 Hz, H_{5b}), 3.06 (dd, 1, J_{H_{5a},H_6} = 10.3 Hz, H_{5a}), 3.59 (m, 1, H_6), 4.48 (dd, 1, J_{H_7,H_6} = 12.3 Hz, $J_{H_{7gem}}$ = 11.1 Hz, H_7), 4.75 (dd, 1, J_{H_7,H_6} = 4.9 Hz, H_7), 6.66–6.75 (m, 14, aromatic); mass spectrum (CI pos) [M$^+$ + 1] 386 (100). Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.51; H, 5.10; N, 3.49.

Preparation of *N*-(2-(Allyloxy)phenyl)benzamide (6b). *N*-(2-Hydroxyphenyl)benzamide (43.0 g, 200 mmol) and potassium carbonate (55.3 g, 400 mmol) in acetone (100 mL) were stirred and heated under reflux. Allyl bromide (24.2 g, 200 mmol) was added to the mixture, and heating was continued for 2 h. The cooled reaction mixture was filtered, and the collected material was washed with acetone. Concentration of the acetone gave a colorless solid, which was dissolved in a distilled water–chloroform mixture. The organic phase was separated, dried over Na_2SO_4, and removed under reduced pressure. The resultant solid was recrystallized from ethanol, forming light-orange, irregular prisms: 26.8 g (53%), mp 57–59 °C; IR (KBr) 1640 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.64 (d, 2, OCH_2), 5.30 (m, 2, $CHCH_2$), 6.04 (m, 1, CH), 6.84–8.64 (m, 10, aromatic and NH); mass spectrum (EI) (M$^+$) 253 (32). Anal. Calcd for $C_{16}H_{15}NO_2 \cdot {}^1/_4H_2O$: C, 74.54; H, 6.06; N, 5.43. Found: C, 74.79; H, 6.06; N, 5.38.

Preparation of *N*-(2-(Allyloxy)phenyl)thiobenzamide (7b). *N*-(2-(Allyloxy)phenyl)benzamide (26.8 g, 110 mmol) and Lawesson's reagent (26.7 g, 66 mmol) in toluene (50 mL) were stirred and heated under reflux for 18 h. The cooled reaction mixture was washed with NaOH (10%) and HCl (10%). Removal of the solvent under reduced pressure left an orange oil, which crystallized from *n*-hexane. Recrystallization from ethanol afforded light orange rhombs: 6.7 g (23%); mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 4.69 (d, 2, OCH_2), 5.30 (m, 2, $CHCH_2$), 6.20 (m, 1, CH), 6.90–7.98 (m, 10, aromatic and NH); mass spectrum (EI) (M$^+$) 269 (7). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.20; H, 5.65; N, 5.19.

Preparation of the Cycloadduct 9 of *anhydro*-2,4-Diphenyl-4-hydroxy-3-(2-(allyloxy)phenyl)thiazolium Hydroxide (3d). *anhydro*-2,4-Diphenyl-4-hydroxy-3-(2-(allyloxy)-phenyl)thiazolium hydroxide (2.2 g, 5.7 mmol) in xylene (50 mL) was stirred and heated under reflux for 8 days. A colorless precipitate formed, which was collected and air-dried. Recrystallization from chloroform gave colorless rhombs of **9**: 1.43 g (65%); mp 245–248 °C; IR (KBr) 1700 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.75 (dd, 1, J_{H_{5b},H_6} = 3.07 Hz, $J_{H_{5gem}}$ = 12.6 Hz, H_{5b}), 3.11 (dd, 1, J_{H_{5a},H_6} = 9.6 Hz, H_{5a}), 4.01 (m, 1, H_6), 4.20 (dd, 1, $J_{H_{6gem}}$ = 12.9 Hz, J_{H_9,H_6} = 9.6 Hz, H_9), 4.43 (dd, 1, J_{H_9,H_6} = 3.3 Hz, H_9), 6.89–7.71 (m, 14, aromatic); mass spectrum (EI) (M$^+$) 385 (67). Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.70; H, 4.98; N, 3.58.

Preparation of 2-(Allyloxy)mandelic Acid (4). A slurry of lithium chloride (2.12 g, 0.05 mol), potassium hydroxide (5.16 g, 0.1 mol), ice (20 g), and dioxane (20 mL) was stirred at 5 °C. A solution of 2-(allyloxy)salicylaldehyde (4.10 g, 0.025 mol) and bromoform (6.32 g, 0.025 mol) was added to this slurry, and stirring was continued for 24 h at 5 °C. After an additional 24 h at ambient temperature, the separated material was collected by filtration. The mother liquor was acidified with concentrated HCl and extracted with diethyl ether (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give a pale orange oil, which crystallized upon standing. The solid materials were combined and recrystallized from carbon tetrachloride, separating as colorless prisms: 1.43 g (27%); mp 101–103 °C; IR (KBr) 3400 (OH), 2900 (OH), 1710 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.60 (d, 2, OCH_2), 5.34 (m, 2, $CHCH_2$), 5.38 (s, 1, CH(OH)), 6.02 (m, 1, $CHCH_2$), 6.88–7.42 (m, 4, aromatic); mass spectrum (CI pos) [M$^+$ + 1] 209 (8), 191 (100) {[M$^+$ + 1] − H_2O}. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.43; H, 5.85.

Cycloadduct 10 of *anhydro*-5-(2-(Allyloxy)phenyl)-2,3-diphenyl-4-hydroxythiazolium Hydroxide (3e). A solution of 2-(allyloxy)mandelic acid (0.70 g, 3.34 mmol) in dry benzene was treated with phosphorus tribromide (0.60 g, 2.26 mmol), and the reaction mixture was stirred at ambient temperature for 3 days. Thiobenzanilide (0.72 g, 3.34 mol) and triethylamine (0.68 g, 6.76 mmol) were added, and the stirring was continued for an additional 48 h. The separated materials were collected and washed with benzene. The mother liquor was removed under reduced pressure to give an orange oil, which was dissolved in toluene and then heated under reflux for 12 h. The reaction mixture was cooled, and the solvent was removed under reduced pressure to give a yellow oil, which crystallized from methanol as colorless plates: 0.43 g (33%, based on the starting α-hydroxy acid 4); mp 224–226 °C; IR (KBr) 1700 (CO) cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 2.53 (dd, 1, $J_{H_{5gem}}$ = 12.1 Hz, J_{H_{6b},H_5} = 4.3 Hz, H_{6b}), 3.04 (m, 1, H_5), 3.26 (dd, 1, J_{H_{6a},H_5} = 7.8 Hz, H_{6a}), 4.31 (t, 1, $J_{H_{7gem}}$ = 10.8 Hz, J_{H_7,H_5} = 11.1 Hz, H_7), 4.62 (dd, 1, J_{H_7,H_5} = 4.4 Hz, H_7), 6.80–7.66 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 386 (100). Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.85; H, 4.99; N, 3.63.

Preparation of the Cycloadduct 11 of *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-(butenyloxy)phenyl)thiazolium Hydroxide (3f). A solution of *anhydro*-3,5-diphenyl-4-hydroxy-2-(2-(butenyloxy)phenyl)thiazolium hydroxide (0.20 g, 0.50 mmol) in toluene (20 mL) was stirred under reflux for 5 days. Removal of the solvent under reduced pressure gave a colorless solid, which separated from ethanol as colorless prisms: 0.11 g (55%); mp 231–233 °C; IR (KBr) 1685 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (dd, 1, $J_{H_{7b},H_{8b}}$ = 14.9 Hz, $J_{H_{7b},H_{8a}}$ = 7.1 Hz, H_{7b}), 2.33–2.45 (m, 2, H_{7a},H_{5b}), 3.11 (dd, 1, $J_{H_{5gem}}$ = 12.2 Hz, J_{H_{5a},H_6} = 7.9 Hz, H_{5a}), 3.77 (m, 1, $J_{H_6,H_{5b}}$ = 3.8 Hz, H_6), 4.17 (m, 1, $J_{H_{8b},H_{7a}}$ = 5.4 Hz, H_{8b}), 4.45 (m, 1, $J_{H_{8a},H_{7b}}$ = 7.1 Hz, H_{8a}), 6.95–7.70 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 400 (100). Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.16; H, 5.30; N, 3.51. Found: C, 75.28; H, 5.32; N, 3.48.

Preparation of the Cycloadduct 15 of *anhydro*-2-(2-(Cyclohex-2-enyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (19). A solution of the mesoionic compound **19** in xylenes was refluxed for 30 min. Removal of the solvent under vacuum gave a tan gum, which crystallized from diethyl ether as colorless needles: 0.07 g (23% based on **18**); mp 228–229 °C; IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–2.06 (m, 6, aliphatic), 3.34 (q, 1, J_{H_5,H_6} = 8.2 Hz, H_5), 3.60 (t, 1, H_6), 4.74 (m, 1, J_{H_6,H_7} = 2.1 Hz, H_7), 6.69–7.44 (m, 14, aromatic); (CI pos) [M^+ + 1] 426 (100). Anal. Calcd for $C_{27}H_{23}NO_2S$: C, 76.20; H, 5.45; N, 3.29. Found: C, 76.13; H, 5.50; N, 3.24.

Preparation of 2-Phenyl-4*H*-thieno[3,2-*c*][1]benzopyran (26b). A solution of *anhydro*-3,5-diphenyl-4-hydroxy-2-(2-(propargyl)phenyl)thiazolium hydroxide (prepared as above) in benzene (50 mL) was stirred at ambient temperature for 4 days. Removal of the solvent under reduced pressure gave an orange oil, which separated from ethanol as colorless needles: 0.18 g (69%); mp 67–68°C (lit.[4] mp 74–75 °C); ^1H NMR ($CDCl_3$) δ 5.23 (s, 2, OCH_2), 6.73–7.77 (m, 10, aromatic); mass spectrum (CI pos), [M^+ + 1] 265 (100).

Preparation of 2-Phenyl-4*H*-thiazolo[3,2-*d*][1]benzopyran (26g). The mesoionic system **31** (0.50 g, 1.30 mmol) was refluxed in anhydrous toluene for 6 days. Removal of the solvent under reduced pressure left a brown solid, which crystallized from *n*-hexane as tan needles: 0.24 g (71%); mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 5.50 (s, 2, OCH_2), 6.95–7.97 (m, 9, aromatic); mass spectrum (EI) (M^+) 265 (100), 162 (44) [M^+ – PhCN]. Anal. Calcd for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.35; H, 4.22; N, 5.25.

Preparation of the Cycloadduct 13 of *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-(methallyloxy)phenyl)thiazolium Hydroxide (20). A solution of *anhydro*-3,5-diphenyl-4-hydroxy-2-(2-(methallyloxy)phenyl)thiazolium hydroxide (prepared above) in toluene (50 mL) was stirred and heated under reflux for 48 h. Removal of the solvent under reduced pressure gave an oil that would not crystallize. The product was separated from the original material by silica gel short-column chromatography (chloroform as the eluent) and crystallized from diethyl ether as colorless prisms: 0.58 g (45%); mp 143–144 °C; IR (KBr) 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3, CH_3), 2.53 (d, 1, $J_{H_{5gem}}$ = 13.1 Hz, H_{5b}), 2.65 (d, 1, H_{5a}), 4.47 (d, 1, $J_{H_{7gem}}$ = 10.5 Hz, H_7), 4.78 (d, 1, H_7), 6.67–7.58 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 400 (100). Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.16; H, 5.30; N, 3.51. Found: C, 75.27; H, 5.35; N, 3.48.

Cycloadduct 14 of (*E*)-*anhydro*-2-(2-(Crotyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (3i). A solution of (*E*)-*anhydro*-2-(2-(crotyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium hydroxide and dry benzene was stirred at ambient temperature for 6 days. Removal of the solvent under reduced pressure gave a brown oil, which crystallized on standing. Purification of this material by column chromatography (silica gel, eluent 60% *n*-hexane, 40% CH_2Cl_2) gave two fractions. The first fraction crystallized from *n*-hexane (0.05 g) and was identified as unreacted thioamide. The cycloadduct was found in the second fraction and formed colorless microprisms from diethyl ether: 0.39 g (56% based on recovered thioamide); mp 174–175 °C; IR (KBr) 1685 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3, J_{CH_3,H_5} = 6.3 Hz, CH_3), 2.78 (m, 1, J_{H_5,H_6} = 4.1 Hz, H_5), 2.98 (m, 1, H_6), 4.38 (t, 1, $J_{H_6,H_{7b}}$ = 11.1 Hz, H_{7b}), 4.68 (dd, 1, $J_{H_6,H_{7a}}$ = 7.5 Hz, $J_{H_{7gem}}$ = 11.5 Hz, H_{7a}), 6.64–7.81 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 400 (100). Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.16; H, 5.30; N, 3.51. Found: C, 75.14; H, 5.29; N, 3.47.

Preparation of the Cycloadduct 16 of *anhydro*-3,5-Diphenyl-4-hydroxy-2-(2-(methacryloyloxy)phenyl)thiazolium Hydroxide (3h). A solution of *anhydro*-3,5-diphenyl-4-hydroxy-2-(2-(methacryloyloxy)phenyl)thiazolium hydroxide (prepared above) in toluene (50 mL) was heated under reflux for 3 days. Removal of the solvent under reduced pressure gave a colorless solid, which crystallized from diethyl ether as colorless prisms: 0.30 g (49%), mp 225–226 °C; IR (KBr) 1770 (CO), 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (s, 3, CH_3), 2.67 (d, 1, $J_{H_{5gem}}$ = 13.5 Hz, H_{5b}), 3.65 (d, 1, H_{5a}), 6.88–7.55 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 414 (100). Anal. Calcd for $C_{25}H_{19}NO_3S$: C, 72.62; H, 4.63; N, 3.39. Found: C, 72.55; H, 4.63; N, 3.36.

***N*-Methyl-2-(propargyloxy)thiobenzamide (22).** A mixture of *N*-methyl-2-(propargyloxy)benzamide (1.13 g, 5.97 mmol) in THF (50 mL) was heated under reflux with stirring for 30 min. Upon the reaction mixture being cooled, a small amount of precipitate formed, which was removed by filtration. The mother liquor was concentrated under reduced pressure to a yellow oil which was dissolved in ethyl acetate and purified by silica gel column chromatography (eluted with ethyl acetate), and the yellow band was collected. After removal of the solvent the resultant yellow oil crystallized upon standing, and crystallized from diethyl ether–*n*-hexane as yellow prisms: 0.61 g (50%); mp 54–55 °C; IR (KBr) 2110 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (t, 1, C≡CH), 3.38 (d, 3, NCH_3), 4.79 (d, 2, OCH_2), 7.02–8.43 (m, 4, aromatic), 9.07 (s, 1, NH); mass spectrum (EI) (M^+) 205 (18), 172 (64) [M^+ – H – S], 166 (15) [M^+ – C_3H_3], 134 (100) [M^+ – C_3H_3 – S]. Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.34; H, 5.40; N, 6.79.

2-(Ethoxycarbonyl)-4*H*-thieno[3,2-*c*][1]benzopyran (26a). *anhydro*-5-(Ethoxycarbonyl)-4-hydroxy-3-phenyl-2-(2-(propargyloxy)phenyl)thiazolium hydroxide (0.30 g, 0.86 mmol) was stirred and heated under reflux in toluene for 12 h. Concentration of the solvent under reduced pressure gave a brown solid, which was purified by column chromatography (silica gel, and eluted with a solution of 25% ethyl acetate–*n*-hexane). The yellow fraction was collected and concentrated under reduced pressure to give a pale yellow solid, which formed pale-yellow microneedles from pentane: 0.16 g (73%); mp 93–94 °C; IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3, CH_2CH_3), 4.35 (q, 2, CH_2CH_3), 5.72 (s, 2, OCH_2), 6.80–7.54 (m, 5, aromatic); mass spectrum (CI pos) [M^+ + 1] 261 (100). Anal. Calcd for $C_{14}H_{14}O_3S$: C, 64.59; H, 4.65. Found: C, 64.85; H, 4.58.

***anhydro*-5-(Ethoxycarbonyl)-4-hydroxy-3-phenyl-2-(2-(propargyloxy)phenyl)thiazolium Hydroxide (24a).** α-Bromo-α-(ethoxycarbonyl)acetyl chloride (0.85 g, 3.7 mmol) was added dropwise to a solution of 2-(propargyloxy)thiobenzanilide (1.0 g, 3.7 mmol) and triethylamine (0.75 g, 7.4 mmol) in dry benzene (25 mL). After this solution was stirred overnight, the separated materials were collected by filtration and then extracted twice with benzene (50 mL). Concentration of the benzene under reduced pressure gave an orange oil, which crystallized from acetone as bright-yellow prisms: 0.92 g (71%); mp 170–172 °C; IR (KBr) 3210 (C≡CH), 2105 (C≡C), 1705, 1635 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, 3, CH_2CH_3), 2.49 (t, 1, C≡CH), 4.35 (m, 4, CH_2CH_3 and OCH_2), 6.89–7.40 (m, 9, aromatic); mass spectrum (CI pos) [M^+ + 1] 380 (4), 348 (24) {[M^+ + 1] – S}, 260 (100) {[M^+ + 1] – H – PhNCO}. Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.29; H, 4.21; N, 3.45.

***anhydro*-5-(Ethoxycarbonyl)-4-hydroxy-3-methyl-2-(2-(propargyloxy)phenyl)thiazolium Hydroxide (24b).** α-Bromo-α-(ethoxycarbonyl)acetyl chloride (0.43 g, 1.9 mmol) was added dropwise to a solution of *N*-methyl-2-(propargyloxy)thiobenzamide (0.35 g, 1.71 mmol) and triethylamine (0.38 g, 3.71 mmol) in dry benzene (25 mL). After this solution was stirred overnight, the separated materials were removed by filtration and extracted three times (or until the extract was colorless) with benzene. Con-

centration of the solvent under reduced pressure gave a yellow solid, which underwent cycloaddition upon attempted further purification: 0.48 g (89%); mp 156 °C; IR (KBr) 3200 (CCH), 2110 (CC), 1705, 1625 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3, CH_2CH_3), 2.56 (t, 1, C≡CH), 3.45 (s, 1, NCH_3), 4.33 (q, 2, CH_2CH_3), 4.78 (d, 2, OCH_2), 7.18–7.70 (m, 4, aromatic); mass spectrum (CI pos) [M^+ + 1] 318 (4), 286 (100) {[M^+ + 1] – S}.

3-Acetyl-1-methyl-5*H*-benzo[*h*]pyrano[4,3-*h*]-1*H*-pyrid-2-one (27d). *anhydro*-5-Acetyl-4-hydroxy-3-methyl-2-(2-(propargyloxy)phenyl)thiazolium hydroxide (0.03 g, 0.104 mmol) was stirred and heated under reflux in toluene (25 mL) for 12 h. Concentration of the solvent under reduced pressure gave a yellow solid, which was purified by column chromatography (silica gel, eluted with a solution of 20% ethyl acetate–*n*-hexane and then a solution of 40% ethyl acetate–*n*-hexane). The yellow band was collected and concentrated under reduced pressure to give a yellow solid, which formed yellow needles from *n*-hexane: 0.02 g (77%); mp 137–138 °C; IR (KBr) 1650 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74 (s, 3, $COCH_3$), 3.86 (s, 3, NCH_3), 4.86 (s, 2, OCH_2), 7.12–8.05 (m, 5, aromatic); mass spectrum (EI) (M^+) 255 (89), 240 (100) [M^+ – CH_3], 212 (11) [M^+ – CH_3CO]. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.38; H, 5.10; N, 5.66.

3-(Ethoxycarbonyl)-1-methyl-5*H*-benzo[*h*]-1*H*-pyrano-[4,3-*b*]pyrid-2-one (27b). *anhydro*-5-(Ethoxycarbonyl)-4-hydroxy-3-methyl-2-(2-(propargyloxy)phenyl)thiazolium hydroxide (0.50 g, 1.6 mmol) was stirred and heated under reflux in toluene (25 mL) for 3 h. Concentration of the solvent under reduced pressure gave a yellow solid, which crystallized from methanol as colorless, irregular prisms: 0.32 g (71%); mp 181–183 °C; IR (KBr) 1775, 1630 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3, CH_2CH_3), 3.86 (s, 3, NCH_3), 4.42 (q, 2, CH_2CH_3), 4.87 (s, 2, OCH_2), 7.13–8.06 (m, 5, aromatic); mass spectrum (CI pos) [M^+ + 1] 268 (100), 240 (53) {[M^+ + 1] – CO}. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.15; H, 5.17; N, 4.80.

***anhydro*-5-Acetyl-4-hydroxy-3-methyl-2-(2-(propargyloxy)phenyl)thiazolium Hydroxide (24d).** α-Bromoacetic acid (0.26 g, 1.9 mmol) was added in small portions to a solution of *N*-methyl-2-(propargyloxy)thiobenzamide (0.25 g, 1.22 mmol) and triethylamine (2.3 g, 22.4 mmol) in dry benzene (25 mL). After this solution was stirred for 5 h at room temperature, an additional portion of α-bromoacetic acid (0.26 g, 1.9 mmol) was added, and the stirring was continued overnight. The separated materials were removed by filtration and washed well with dry benzene. Acetic anhydride (1 mL) and triethylamine (1 mL) were then added to the mother liquor, and the resultant solution was kept at room temperature for 72 h. Concentration of the solvent under reduced pressure gave a brown residue, which was purified by column chromatography (alumina, eluent 50% dichloromethane–ethyl acetate). The yellow band was collected and concentrated under reduced pressure to give a yellow solid, which finally separated from dichloromethane–diethyl ether as yellow microneedles: 0.05 g (14%); mp 207–208 °C; IR (KBr) 1610, 1655 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (s, 4, $COCH_3$ and C≡CH), 3.42 (s, 3, NCH_3), 4.76 (d, 2, OCH_2), 7.04–7.66 (m, 4, aromatic); mass spectrum (CI pos) [M^+ + 1] 288 (100). Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.56; N, 4.88. Found: C, 62.63; H, 4.40; N, 4.71.

Preparation of *anhydro*-3-Methyl-5-phenyl-2-(2-(propargyloxy)phenyl)thiazolium Hydroxide (24c). α-Bromophenylacetyl chloride (0.5 g, 2.3 mmol) was added dropwise to a solution of *N*-methyl-2-(propargyloxy)thiobenzamide (0.47 g, 2.3 mmol), triethylamine (0.47 g, 4.6 mmol), and dry benzene. After 3 h the separated materials were removed by filtration and washed well with benzene; this material underwent facile cycloaddition on attempted further purification.

Preparation of 1-Methyl-3-phenylbenzo[*h*]-1*H*-pyrano-[4,3-*b*]pyridin-2-one (27c). A solution of *anhydro*-3-methyl-5-phenyl-2-(2-(propargyloxy)phenyl)thiazolium hydroxide (**24c**) (prepared above) was stirred and heated under reflux in benzene for 30 min. Concentration of the solvent under reduced pressure gave a yellow solid, which crystallized from diethyl ether as yellow needles: 0.34 g (52%); mp 144–145 °C; IR (KBr) 1615 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3, NCH_3), 4.87 (s, 2, OCH_2), 7.10–7.78 (m, 10, aromatic and vinyl); (CI pos) [M^+ + 1] 290 (100). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.81; H, 5.25; N, 4.78.

2-(1-Butenyl)benzanilide (33). *n*-Butyllithium (40 mL, 2.2 M, 0.088 mol) was added dropwise to a solution of 2-methylsalicylanilide (9.3 g, 0.044 mol) in THF (100 mL) stirred at 0 °C. After addition of about half the base, the brilliant, violet color of the dianion formed instantaneously. The resultant solution was stirred for 30 min before allyl bromide (5.3 g, 0.044 mol) was added dropwise. Upon final addition of the allyl bromide the violet color of the dianion disappeared, resulting in a colorless reaction mixture. The reaction mixture was then poured onto crushed ice and extracted with diethyl ether (3 × 100 mL). The ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a colorless oil, which was boiled in *n*-hexane (300 mL) and filtered from any insoluble material. The desired amide **33** crystallized as colorless prisms, and concentration of the mother liquor gave an additional amount of amide: 7.44 g (67%); mp 52–54 °C; IR (KBr) 3300 (NH), 1655 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (q, 2, CH_2CH_2CH), 2.94 (t, 2, CH_2CH_2), 4.98 (m, 2, $CHCH_2$), 5.82 (m, 1, $CHCH_2$), 7.12–7.62 (m, 10, aromatic and NH); mass spectrum (CI pos) [M^+ + 1] 252 (100). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.23; H, 6.86; N, 5.54.

***anhydro*-2-(2-(1-Butenyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide (35).** α-Bromophenylacetyl chloride (0.47 g, 2.2 mmol) was added dropwise to a solution of 2-(1-butenyloxy)thiobenzanilide (0.58 g, 2.2 mmol) and triethylamine (0.44 g, 4.4 mmol) in dry benzene (50 mL). After this solution was stirred for 12 h, the separated material was removed by filtration and washed well with benzene. The mother liquor contained a relatively pure solution of **35**, which underwent a facile cycloaddition upon attempted further purification.

Cycloadducts 36a and 36b of *anhydro*-2-(2-(1-Butenyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium Hydroxide. A solution of *anhydro*-2-(2-(1-butenyloxy)phenyl)-3,5-diphenyl-4-hydroxythiazolium hydroxide (**35**) (prepared as above) in benzene (50 mL) was heated under reflux with stirring for 72 h. Concentration of the solvent under reduced pressure left a colorless solid, which was purified by column chromatography (silica gel, eluent dichloromethane). The first fraction was collected, a great deal of intractable tarry material being removed from the origin, and removal of the solvent left a colorless solid, which was a mixture of diastereoisomers. The major isomer **36a** separated from methanol as colorless needles: 0.52 g (64%); mp 207–209 °C; IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20–2.43 (m, 3, aliphatic), 2.95–3.22 (m, 4, aliphatic), 6.98–7.59 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 384 (100). Anal. Calcd for $C_{25}H_{21}NOS$: C, 78.30; H, 5.52; N, 3.65. Found: C, 78.15; H, 5.49; N, 3.60.

Concentration of the above mother liquor under reduced pressure gave a solid, which was a mixture of unreacted thioamide and diastereoisomers. Purification of this material by column chromatography (silica gel, eluent 50% dichloromethane–*n*-hexane) resulted in two fractions being collected. The first fraction contained unreacted thioamide. The second fraction was an enriched mixture of the major and minor diastereoisomers which was separated by PLC (silica gel preparative plate, 1 mm); four developments with a solution of 75% dichloromethane–*n*-hexane were required to effect separation, the minor isomer eluting second), giving the minor isomer as a pale-yellow oil, which crystallized upon standing and formed colorless prisms from diethyl ether: 0.01 g (1%); mp 143 °C; IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02–2.48 (m, 3, aliphatic), 2.96–3.42 (m, 4, aliphatic), 6.82–7.65 (m, 14, aromatic); mass spectrum (CI pos) [M^+ + 1] 384 (100). Anal. Calcd for $C_{25}H_{21}NOS$: C, 78.30; H, 5.52; N, 3.65. Found: C, 78.06; H, 5.35; N, 3.56.

2-(1-Butenyl)thiobenzanilide (34). 2-(1-Butenyl)benzanilide (8.6 g, 34.2 mmol), Lawesson's reagent (9.9 g, 24.5 mmol), and toluene (150 mL) were heated together with stirring under reflux for 2 h. The solvent was decanted from any insoluble, tarry residue and then concentrated under reduced pressure to an orange oil. Purification of this material by column chromatography (silica gel, eluent 25% ethyl acetate–*n*-hexane) gave an initial orange band, which was collected and concentrated under reduced pressure to an orange oil, which separated from pentane as pale yellow microprisms: 5.68 g (62%); mp 71–72 °C; IR (KBr) 3130 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (q, 2, CH_2CH_2CH), 2.91 (t, 2, CH_2CH_2CH), 5.00 (m, 2, $CHCH_2$), 5.77 (m, 1, $CHCH_2$), 6.68–7.83

(m, 9, aromatic), 8.77 (s, 1, NH), 9.74 (s, 1, NH); mass spectrum (CI pos) [$M^+ + 1$] 268 (100). Anal. Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24. Found: C, 76.37; H, 6.39; N, 5.16.

1-Methyl-5*H*-benzo[*h*]-1*H*-pyrano[4,3-*h*]pyrid-2-one (27e). α-Bromoacetic acid (0.23 g, 1.66 mmol) was added to a solution of *N*-methyl-2-(propargyloxy)thiobenzamide (0.28 g, 1.38 mmol) and triethylamine (1.00 g, 9.93 mmol) in benzene (50 mL). The reaction mixture was stirred for 6 h before an additional amount of α-bromoacetic acid (0.23 g, 1.66 mmol) was added and stirring continued overnight. The separated materials were collected by filtration and washed well with benzene. DCC (0.28 g, 1.38 mmol) was added in small portions to the above mother liquor, and the resultant solution was stirred at ambient temperature overnight, filtered, and concentrated under reduced pressure to a brown oil. This material was purified by column chromatography (alumina, eluent 50% ethyl acetate–dichloromethane) and gave a yellow oil, which crystallized from methanol: 0.06 g (21%); mp 100–102 °C; IR (KBr) 1620 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3, NCH_3), 4.80 (s, 2, OCH_2), 6.54–7.68 (m, 6, aromatic); mass spectrum (CI pos) [$M^+ + 1$] 214 (100). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.22; H, 5.07; N, 6.32.

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Synthesis of Isoxazoles and Isothiazoles from α-Oxo Ketene Dithioacetals

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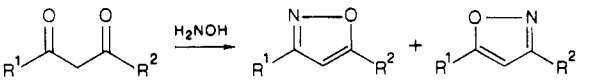
α-Oxo ketene dithioacetals derived from cyclohexanone, cyclopentanone, and 3-pentanone and 3,3-bis(methylthio)propenal afforded oximes **5–8**, respectively, upon treatment with hydroxylamine in ethanol at reflux. Oximes **5**, **7**, and **8** were converted into isoxazoles upon treatment with Amberlyst 15 ion exchange resin and gave isothiazoles by reaction with thionyl chloride and pyridine in methylene chloride. Oxime **6** gave isothiazole **13** with both procedures. Carbon NMR data are reported for the oximes, isoxazoles, and isothiazoles.

The α-oxo ketene dithioacetal functionality has proven to be a versatile three-carbon synthon[1] that is particularly useful in the synthesis of heterocyclic compounds. During the course of our studies on this functionality, we have endeavored to develop regiospecific transformations involving either initial reaction at the ketone carbonyl[2] or at the β-carbon[2b,3] of the enone system. Although a few isoxazoles have been prepared from α-oxo ketene dithioacetals,[4] it seemed curious that the ketene dithioacetals were derived only from aryl cyanomethyl ketones. The literature reports contained no indication of the generality of the synthetic method with α-oxo ketene dithioacetals derived from aliphatic ketones.

We now report that hydroxylamine reacts with α-oxo ketene dithioacetals derived from aliphatic ketones to afford the corresponding oximes, which can be converted into either isoxazoles or isothiazoles depending upon the reaction conditions employed for ring closure. The methodology provides the first synthesis of isoxazoles from α-oxo ketene dithioacetals in a process not involving initial conjugate addition of the hydroxylamine and this aspect greatly extends the synthetic route to a range of ketones other than β-keto nitriles. The method also provides the first reported synthesis of isothiazoles from α-oxo ketene dithioacetals. The reactions are clean and afford the heterocycles in good to excellent yields.

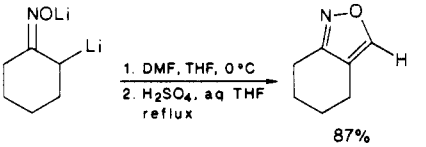
Background

Isoxazoles are most frequently prepared by reaction of 1,3-diketones with hydroxylamine (eq 1).[5] The procedure



(1)

works well for symmetrical 1,3-diketones and can be extended to unsymmetrical 1,3-diketones that have alkyl groups of moderately different steric bulk attached to the carbonyl carbons. If the two alkyl groups are of similar steric bulk, a mixture of regioisomers is obtained.[5,6] More recently, Olofson[7a] has addressed this limitation by formylation of oxime dianions with *N*,*N*-dimethylformamide (eq 2). Subsequent acid-catalyzed cyclization affords the



87%

(2)

desired isoxazole. The procedure can afford 5-aryl-substituted isoxazoles but cannot be employed for the synthesis of 5-alkyl-substituted derivatives since *N*,*N*-dimethylacetamide or higher amide homologues tend to undergo deprotonation under the reaction conditions. The

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