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Bimolecular 4+2-Cycloaddition Reactions of Cross Conjugated Betaines with Electron Rich π-Systems

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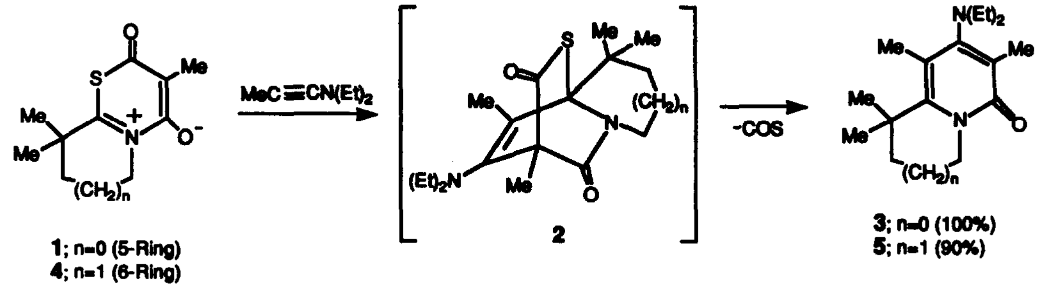
Abstract: Bicyclic anhydro-2-oxo-4-hydroxy-1,3-thiazinium hydroxides undergo 1,4-dipolar cycloadditions with various electron rich π-systems to give 4+2-cycloadducts which on further heating, extrude carbonyl sulfide producing substituted α-pyridones.

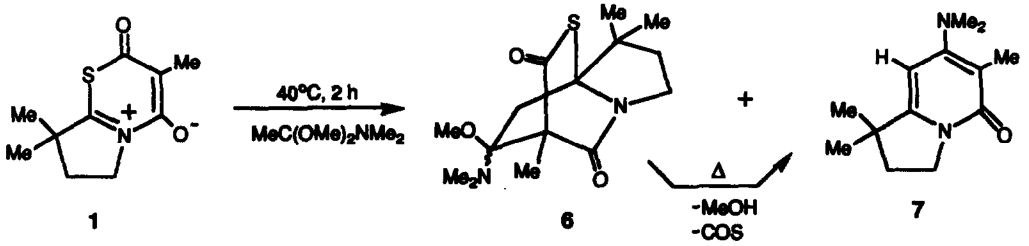
Current efforts to develop new cycloaddition approaches to stereodefined five and six-membered heterocyclic rings have been stimulated by the ever increasing number of important natural products which contain these ring systems.[1,2] The 1,3-dipolar cycloaddition reaction has long been recognized as a favored strategy for the synthesis of five-membered ring heterocycles, often proceeding with a high degree of stereochemical control.[3] In contrast to 1,3-dipoles, much less is known about the cycloaddition behavior of 1,4-dipoles.[4] This class of reactive intermediates has been prepared by cyclocondensation of an appropriate amide or thioamide with alkyl malonyl dichlorides or carbon suboxide.[5] Although a few examples of intramolecular 1,4-dipolar cycloadditions have been reported in the literature,[4,5] little is known about the bimolecular cycloaddition behavior of this class of reactive intermediates.[5-10] In this communication, we describe the 4+2-cycloaddition chemistry of several anhydro-2-oxo-4-hydroxy-1,3-thiazinium hydroxides with a number of electron rich dipolarophiles as a method for preparing substituted α-pyridones.[11]

In order to broaden the utility of these cross-conjugated heterocyclic betaines for organic synthesis, we thought it worthwhile to investigate the cycloaddition behavior of several 1,4-dipoles in which the peripheral substituents were part of a cyclic system. With this in mind, 3,3-dimethyl-2-thiopyrrolidinone was treated with methyl malonyl dichloride[12] so as to generate betaine 1 (n=o). Stirring a sample of 1 with 1-diethylamino-1-propyne at 0°C in CH_2Cl_2 for 10 min afforded α-pyridone 3 in quantitative yield. An analogous reaction occurred with the homologous betaine 4 (n=1) producing cycloadduct 5 in 90% yield. Formation of the pyridone ring presumably involves an initial 1,4-dipolar



cycloaddition of the betaine across the triple bond to give the initial cycloadduct **2**, which is followed by a rapid cheletropic extrusion of carbonyl sulfide. No signs of the initial adduct **2** could be detected, even at temperatures as low as -20°C.

When the reaction of **1** was carried out in the presence of N,N-dimethylacetamide dimethyl acetal in CH_2Cl_2 at 40°C for 2 h, two compounds were isolated in a combined 85% yield. The major product corresponded to α-pyridone **7** (75%) while the minor component was the initial cycloadduct **6**. When **6** was allowed to stand in solution at 25°C, it was quantitatively converted to **7** over a period of several hours.

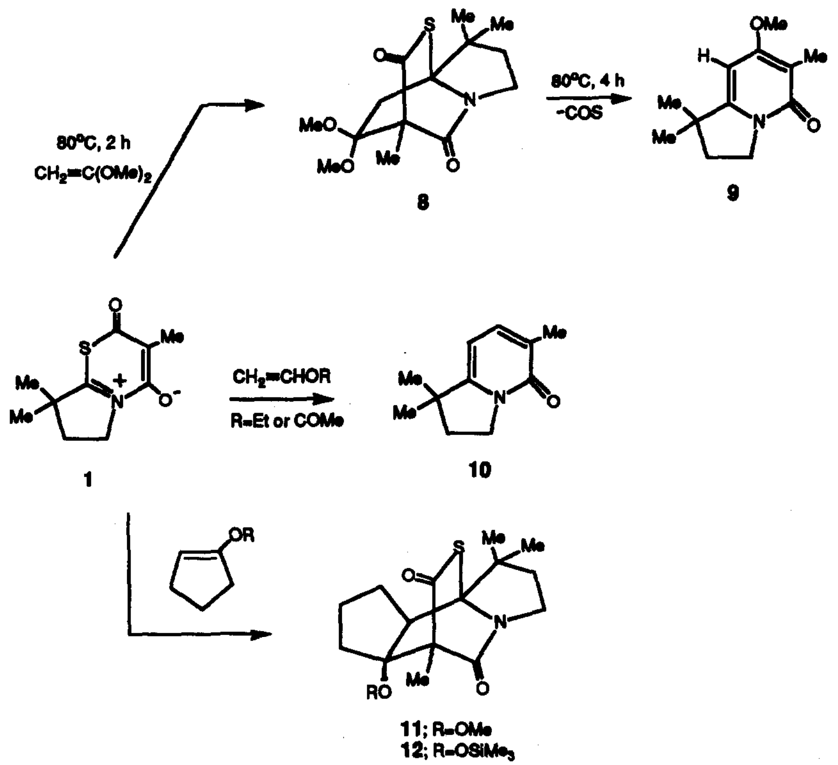


1

6

7

Betaine **1** was found to require higher temperatures and prolonged reaction times for bimolecular cycloadditions with less activated π-systems.[13,14] For example, it was necessary to heat a



8

9

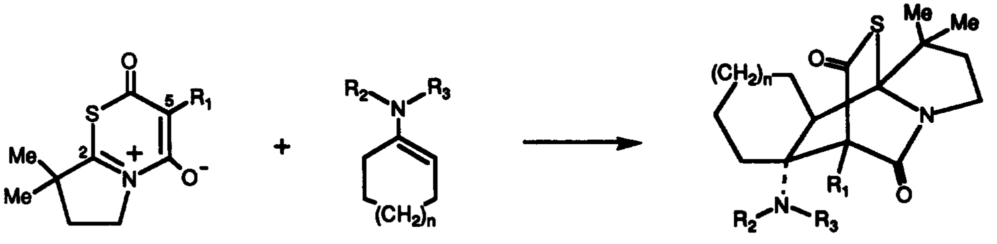
1

10

11; R=OMe
12; R=OSiMe$_3$

sample of 1 with 1,1-dimethoxyethylene in benzene at 80°C for 2 h in order for cycloaddition to occur. The initial cycloadduct 8 was isolated in 83% yield, which on further heating (80°C, 4 h) extruded carbonyl sulfide to give α-pyridone 9. In order to induce cycloaddition of 1 with ethyl vinyl ether or vinyl acetate, it was necessary to carry out the reaction in toluene (sealed tube) at 135°C for 16 h. Under these conditions, only α-pyridone 10 was isolated in 60 and 65% yield, respectively. An analogous cycloaddition reaction occurred with both the methyl and silyl enol ethers of cyclopentanone producing cycloadducts 11 (75%) and 12 (90%) as stable crystalline solids.

High yields of bimolecular cycloadducts (*ca* 85%) were also obtained when betaine 1 (or 13) was allowed to react with several cyclic enamines. Structural assignments were made on the basis of their analytical and spectral properties. In the case of cycloadduct 16, its structure was unequivocally established by an X-ray crystal analysis. The regioselectivity observed in the above cycloadditions was examined in the light of frontier molecular orbital theory.[15] With these systems, the dominant interaction is the *LUMO-dipole* (-1.86 ev) *HOMO-dipolarophile* (type III).[16] The frontier orbital coefficients at the reacting centers of the betaine were calculated using the MOPAC program with the PM3 Hamiltonian. MNDO calculations indicate that the atomic coefficient at the thioamide carbonyl center (*i.e.*, C_2) is larger (0.73) than the enolate substituted center (*i.e.*, C_5 (0.18)) in the LUMO. It is well known that the C_β-coefficient of the HOMO of an electron rich alkene is larger than the C_α-coefficient[17] and consequently cycloadducts related to 16 are predicted to be the major regioisomers.



1; R_1=Me
13; R_1=H

14; R_1=Me; R_2=R_3=$(CH_2)_2$; n=1
15; R_1=Me; R_2=$(CH_2)_2$; R_3=$O(CH_2)_2$; n=0
16; R_1=H; R_2=R_3=$(CH_2)_2$; n=1

One final point has to do with the stereochemistry of these bimolecular reactions. 4+2-Cycloadditions can proceed either through *exo* or *endo*-transition states. The very high *endo* selectivity (relative to the pyrrolidine ring) encountered with these systems can be understood by noting that, in the transition state leading to the *exo* isomer, there is a severe nonbonding interaction between the α-methyl group on the betaine with the allylic hydrogens on the enamine. This interaction is absent in the transition state leading to cycloadduct 16.

In conclusion, the bimolecular cycloaddition of bicyclic anhydro-2-oxo-4-hydroxy-1,3-thiazinium hydroxides proceeds smoothly with a very high degree of regio and diastereoselectivity. Other aspects of this reaction and its application to more complex natural product synthesis will be reported in due course.

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