Tetrahedron Letters, Vol. 33, No. 40, pp. 5877-5880, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Generation and Cycloaddition Reactions of Transient Alkyl-Substituted Anhydro-4-hydroxythiazolium Hydroxides

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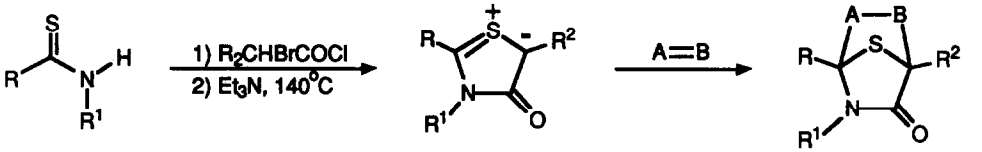
Abstract: Transient alkyl-substituted anhydro-4-hydroxythiazolium hydroxides undergo efficient inter- and intramolecular cycloaddition to provide the corresponding 1,3-dipolar cycloadducts in high yield.

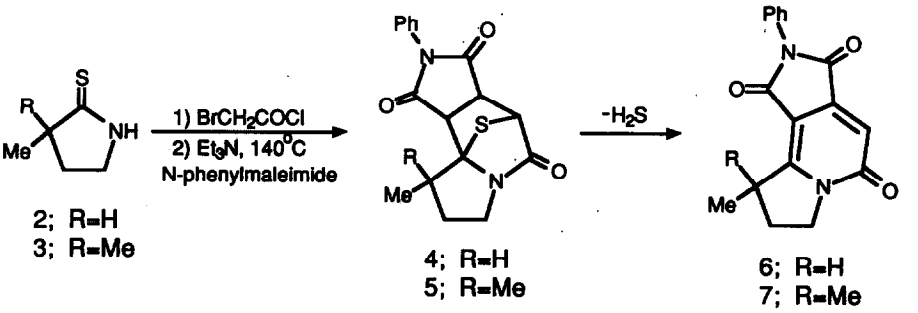
The anhydro-4-hydroxythiazolium hydroxide ring system (1) is a mesoionic species which has received considerable attention by Potts and co-workers over the past two decades.[1] Interest in this ring system may be attributed to 1) its ease of preparation from simple thioamides[2], 2) the interesting physical properties it possesses, and 3) the propensity for its thiocarbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a wide range of dipolarophiles to produce complex heterocyclic ring systems.[3,4] Despite the considerable amount of research dealing with the chemistry of anhydro-4-hydroxythiazolium hydroxides, the range of their structural variation has remained somewhat narrow. In particular, in virtually every investigation to date, at least one of the substituents R, R^1, or R^2 is an aryl moiety presumably due to electronic stabilization of the dipole to a sufficient degree to allow for its isolation. In order to broaden the utility of these mesoionic compounds for synthesis, we thought it worthwhile to investigate the possibility of generating transient anhydro-4-hydroxythiazolium hydroxides in which the peripheral substituents R, R^1, and R^2 were of the alkyl, rather than aryl, variety. The results of this investigation are reported herein.



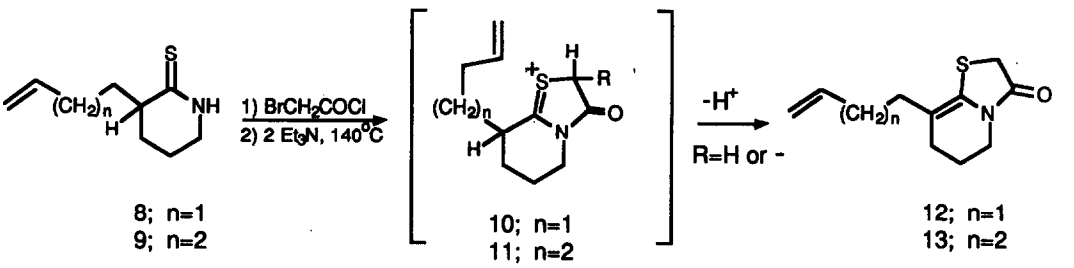
1

Our study commenced with an examination of simple cyclic thiolactams as mesoionic precursors. Sequential treatment of thiolactams **2** and **3** with bromoacetyl chloride and triethylamine in the presence of one equivalent of N-phenylmaleimide afforded pyridones **6** and **7** in good yield.[5] These compounds are derived by dipolar cycloaddition of the mesoionic species **1** with the added dipolarophile to give cycloadduct **4** or **5** as a transient intermediate which subsequently eliminates hydrogen sulfide.[6]

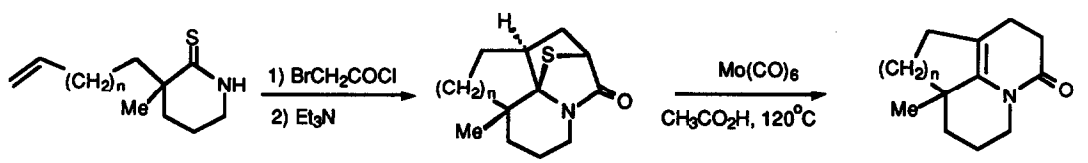
Intramolecular 1,3-dipolar cycloaddition reactions represent one of the most efficient methods for the generation of complex ring systems.[7] In connection with our continuing interest in this area,[8] we decided to investigate the cycloaddition behavior of anhydro-4-hydroxythiazolium hydroxides which possess tethered alkenes.[9] Thiolactams **8** and **9** were therefore treated under the aforemen-



tioned conditions for dipole formation-cycloaddition. In both these cases, cycloaddition was not observed. Instead, compounds **12** and **13** were isolated as the exclusive products and arise by elimination of the proton alpha to the thiocarbonyl ylide dipoles of **10** and **11**.[10] Apparently, proton loss to give a S,N-ketene acetal is faster than intramolecular dipolar cycloaddition across the unactivated pi-bond.

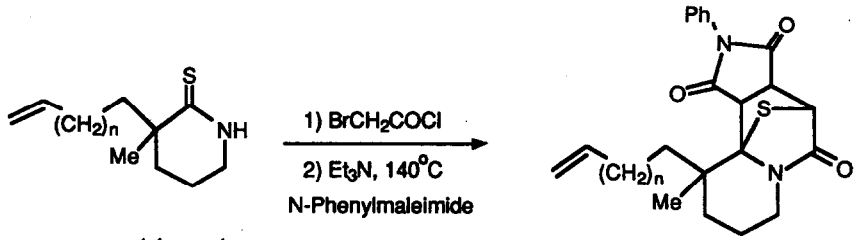


We sought to prevent this elimination pathway by introducing an alkyl group in the alpha position of the intermediate dipole. With the deprotonation pathway blocked, we reasoned that intramolecular dipolar cycloaddition should become a viable process. The methylated thiolactams **14** and **15** were prepared to test this hypothesis. Gratifyingly, high yields of intramolecular cycloadducts were obtained (76% and 92%) when these compounds were subjected to the standard reaction conditions. The depicted stereochemistry for cycloadducts **16** and **17** is the result of *endo* cycloaddition with regard to the dipole and this assignment is based on our related work with intramolecular isomünchnone cycloaddition, for which X-ray crystallographic analysis was performed.[11] Additional support for the stereochemical assignment is found from molecular mechanics calculations[12] which show that the *endo* isomers are 5.73 and 3.96 kcal/mol more stable than their respective *exo* isomers.



The bridging sulfur atom of the cycloadducts could be efficiently removed by using a set of conditions similar to that employed by Alper and Blais for the reduction of thiols.[13] In this manner, enamides **18** and **19** were isolated in 73% and 84% yield, respectively.

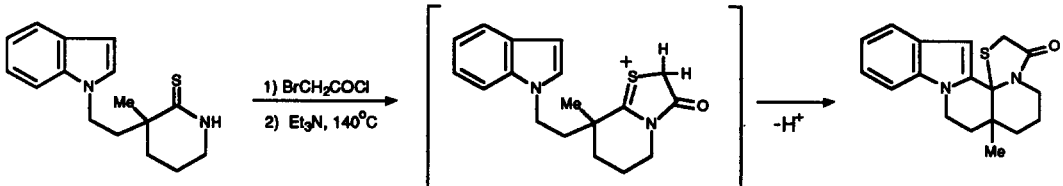
In order to ascertain the relative reactivity of intra- *vs* intermolecular cycloaddition of anhydro-4-hydroxythiazolium hydroxides, competition experiments were performed using the dipoles derived from thiolactams **14** and **15** in the presence of 1.1 equiv. of N-phenylmaleimide. In both cases, only products of bimolecular cycloaddition were observed. This result helps to rationalize the willingness of lactam **2** to participate in bimolecular cycloaddition with N-phenylmaleimide while the elimination pathway is the predominate route in the case of thiolactams **8** and **9**. Clearly, the use of electron deficient dipolarophiles[14] enhances the FMO interactions thereby facilitating the rate of cycloaddition.



14; n=1
15; n=2

20; n=1
21; n=2

Finally, we thought it worthwhile to determine whether heteroaromatic π systems could also act as useful dipolarophiles with the anhydro-4-hydroxythiazolium hydroxide system. With this in mind, thiolactam **22** was treated under the standard conditions for dipole formation and cycloaddition. No product of dipolar cycloaddition across the indole π bond was detected in the reaction mixture. Instead, indole **24** was isolated in 89% yield.[15] Compound **24** is derived by cyclization of the dipole precursor **23** onto the 2-position of the indole ring.[16] With this system, attack by the nucleophilic pi-bond onto the reactive N-acyl iminium ion present in **23** occurs prior to proton loss to give the mesoionic dipole.



22 23 24

We believe that compound **24** and structures related to it will prove useful for the synthesis of a variety of annulated indoles. Work in this area is in progress and will be reported in due course.

Acknowledgment: We gratefully acknowledge support of this work by the National Institute of Health. Use of the high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

References and Notes

† Recipient of a Graduate Fellowship from the Organic Chemistry Division of the American Chemical Society sponsored by Pfizer, Inc.

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5. NMR **7**: ($CDCl_3$, 300 MHz) δ 1.64 (s, 6H), 2.17 (t, 2H, J=7.5 Hz), 4.22 (t, 2H, J=7.5 Hz), 6.95 (s, 1H), and 7.37-7.50 (m, 5H).
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12. We thank Professor Kosta Steliou of the University of Montreal for providing a copy of Model 2.98.
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14. Sustmann, R. *Tetrahedron Lett.* **1971**, 2721. *Angew Chem., Int. Ed. Engl.* **1972**, *11*, 838.
15. NMR **23**: ($CDCl_3$, 300 MHz) δ 1.28 (s, 3H), 1.43-1.53 (m, 2H), 1.65 (dt, 1H, J=13.2 and 3.7 Hz), 1.74-1.84 (m, 1H),1.92 (dd, 1H, J=14.6 and 5.0 Hz), 2.35 (dt, 1H, J=13.5 and 6.9 Hz), 2.98 (dt, 1H, J=13.1 and 3.7 Hz), 3.64 (d, 1H, J=15.5 Hz), 3.82 (d, 1H, J=15.5 Hz), 3.89 (dt, 1H, J=12.5 and 5.4 Hz), 4.22 (dd, 2H, J=12.6 and 6.4 Hz), 6.29 (s, 1H), 7.09-7.30 (m, 3H), and 7.54-7.57 (m, 1H).
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(Received in USA 22 June 1992)