Intramolecular 1,4-Dipolar Cycloaddition of Cross-Conjugated Heterocyclic Betaines. A New Route to Hexahydrojulolidines and Related Peri-Fused Ring Systems

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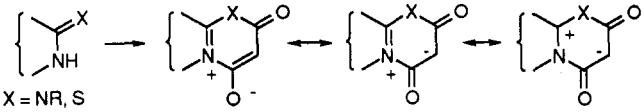
Summary: Alkenyl-substituted bicyclic anhydro-4-hydroxy-2-oxo-1,3-thiazinium hydroxides prepared from 3,3-disubstituted thiolactams and 1,3-bielectrophiles formed thermally-induced intramolecular cycloadducts which underwent loss of carbonyl sulfide, followed by a 1,5-hydrogen shift, to hexahydrojulolidines and related ring systems.

The importance of the bimolecular 1,3-dipolar cycloaddition reaction in organic synthesis derives, in large part, from its ability to generate five-membered heterocyclic rings containing several contiguous stereogenic centers in one synthetic operation.[1] The intramolecular version of the reaction has proven equally valuable as a route to complex heterocyclic systems.[2] In contrast, much less is known about the cycloaddition behavior of 1,4-dipoles whose transient existence was first postulated[3] in 1967.



This class of reactive intermediates, while of considerable theoretical interest, attracted little synthetic attention until the elements of a 1,4-dipole were incorporated into a cross-conjugated heteroaromatic betaine[4] by the cyclocondensation of an appropriately substituted monoprotic amidine or thioamide with a 1,3-bielectrophile derived from malonic acid.[5] Intramolecular 1,4-dipolar cycloadditions of these betaines,[6] or their tautomeric equivalents,[7] have resulted in ring annulations leading to bi- and tricyclic heterocycles which are not readily accessible by cyclocondensation routes. The overall convenience of this method, the ease of access to starting materials, and the relatively high yields and purity of the products obtained suggested its application to the preparation of a number of polycyclic ring systems of interest in natural products chemistry. This paper establishes the synthetic utility of the intramolecular cycloaddition of a series of bicyclic anhydro-4-hydroxy-2-oxo-1,3-thiazinium hydroxides[8] and their successful application in the synthesis of hexahydrojulolidines[9] and related ring systems and also the corresponding linear, ring-fused systems.[10]

The overall synthetic approach leading to *peri* ring-fused systems is shown in Scheme I. The 1,4-dipolar cycloaddition always results in a ring-fused 3,4-dihydropyridin-2-one, but three variables may be introduced into the reaction sequence, allowing appreciable control over the nature of the final products. Variation of the ring size in the initial thiolactam, the position and length of the dipolarophilic tether relative to the thiazinium sulfur atom, and the nature of the 1,3-bielectrophilic species used to generate the thiazinium betaine have all been successfully exploited in our synthetic work. Collectively, they illustrate the synthetic potential of this methodology.

The 3,3-disubstituted thiolactams **3** were synthesized by two procedures: from the lactam **1** by an initial introduction[11] of the alkenyl side chain at the 3-position to give **2a** followed by sulfuration of the lactam with Yokoyama's reagent[12] (or Lawesson's reagent[13]) to form **2b** or **2d**, followed by introduction of the ethyl group to give **3**, employing essentially the same alkylation conditions utilized for the introduction of the alkenyl group. The alternative, complementary procedure started with the 3-methyl substituted lactam[14] **4**. Introduction of the alkenyl side chain was carried out as above, and the resultant disubstituted lactam was converted into **3c** or **3d** by sulfuration with Lawesson's reagent. The following illustrates the procedures used for the conversion of **1** or **4** into the final products **8**. In many instances, the

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(1) Padwa, A. Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vols. I and II.
(2) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. Padwa, A.; Schoffstall, A. M. *Advances in Cycloaddition*; JAI Press, Inc.: Greenwich, CT, 1990; Vol. 2, p 1. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(3) The classification of a number of reactions as 1, 4-dipolar cycloadditions was initially introduced by Professor R. Huisgen at the First International Congress of Heterocyclic Chemistry, University of New Mexico, in 1967; see: Huisgen, R. In *Topics in Heterocyclic Chemistry*; Castle, R., Ed.; John Wiley & Sons: New York, 1969; Chapter 8.
(4) For reviews on this heterocyclic class see: Friedrichsen, W.; Kappe, T. *Heterocycles* **1982**, *19*, 1083. Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.
(5) Potts, K. T.; Sorm. M. *J. Org. Chem.* **1971**, *36*, 8; **1972**, *37*, 1422. Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem.* **1975**, *40*, 2596. See also ref 18.
(6) Potts, K. T.; Dery, M. O. *J. Org. Chem.* **1990**, *55*, 2884.
(7) For examples see: Sammes, P. G.; Watt, R. A.; *J. Chem. Soc., Chem. Commun.* **1976**, 367; **1975**, 502. Davies, L. B.; Greenburg, S. G.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1909. Gotthardt, H.; Riegels, M. *Chem. Ber.* **1968**, *121*, 1143. For a related system see: Rougeot, E.; Muskowitz, H.; Miocque, M. *J. Heterocycl. Chem.* **1983**, *20*, 1407.
(8) The Chemical Abstracts name of, e.g., **5a**, is anhydro-9-ethyl-4-hydroxy-2-oxo-9-(penten-5-yl)-3-phenyl-6,7,8,9-tetrahydropyrido[2,1-*a*][1,3]thiazinium hydroxide. For ease of discussion and for comparision with monocyclic betaines they are referred to as thiazinium betaines, but the peripheral numbering shown in **5** is used for substituent location.
(9) For a selection of synthetic routes see: Martin, S. F.; Desai, S. K.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294. Weisner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433 and references cited in these papers.
(10) Sheehan, J. C.; Young, R. L.; Cruickshank, D. A. *J. Am. Chem. Soc.* **1960**, *82*, 6147. Inubushi, Y.; Tsuda, Y.; Katarao, E. *Chem. Pharm. Bull.* **1965**, *13*, 1482.
(11) The general procedure used was that described earlier by: Durst, T.; Labelle, M. J. *Can. J. Chem.* **1972**, *50*, 3196.
(12) Yokoyama, M.; Hasegawa, Y.; Hatenaka, H.; Kawazoe, Y.; Imamoto, T. *Synthesis* **1984**, 827.
(13) Lawesson, S. O.; Shabana, R.; Scheibye, S.; Clausen, K.; Oleseh, S. O. *Nouv. J. Chem.* **1980**, *47*, 4. Lawesson, S. O.; Thompson, I.; Clausen, K.; Scheibye, S. *Org. Synth.* **1990**, *7*, 372.
(14) Kariyone, K. *Chem. Pharm. Bull (Tokyo)* **1960**, *8*, 1110. Schäffler, A.; Ziegenbein, W. *Chem. Ber.* **1955**, *88*, 1374.

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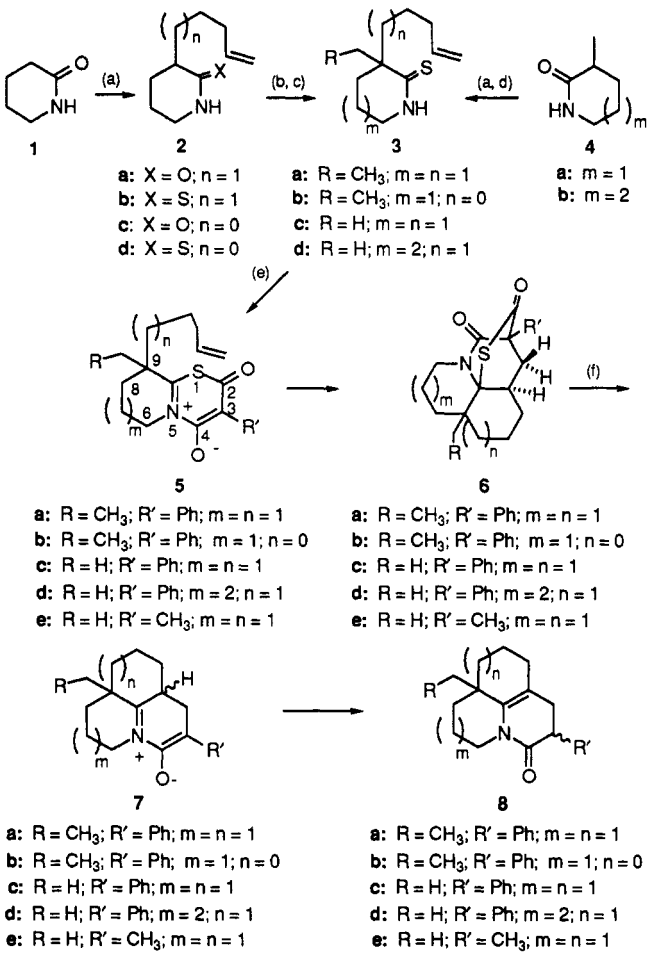
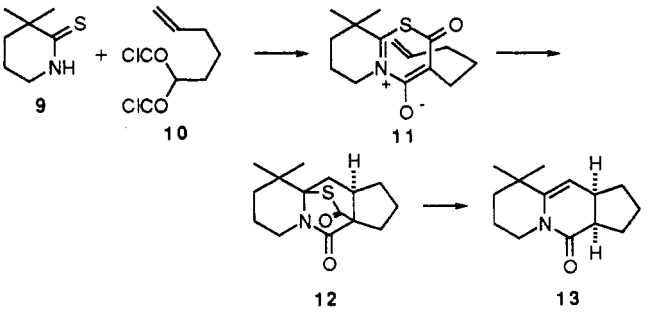
Scheme I[a]



[a] Key: (a) 2 × *n*-BuLi, Et_2O, 0 °C, 5-bromopent-1-ene; (b) Yokoyama's reagent, THF, rt, 24 h; (c) 2 × *n*-BuLi, THF, 0 °C, EtI; (d) Lawesson's reagent, benzene, rt; (e) (chlorocarbonyl)phenyl ketene, toluene, or xylene, reflux; (f) toluene, or xylene, reflux.

thiolactam **3** may be directly converted into **8** without isolation of any of the intermediates, *a process that involves the making and breaking of seven bonds in a sequential fashion.* 3-(Penten-5-yl)-2(1*H*)-piperidinone[15] (**2a**), prepared from **1** (70%), was treated with an excess of Yokoyama's reagent to give 3-(penten-5-yl)piperidine-2(1*H*)-thione (**2b**). This compound was readily converted into 3-ethyl-3-(penten-5-yl)piperidine-2(1*H*)-thione (**3a**). Heating a sample of thiolactam **3a** in toluene/triethylamine with (chlorocarbonyl)phenyl ketene[16] at 110°C for 2h gave cycloadduct **6a**. The intermediate betaine **5a** was not isolated under these reaction conditions. Further heating of **6a** in xylene induced the loss of carbonyl sulfide,[17] and two epimeric products were isolated from the crude reaction mixture by silica gel chromatography, the minor epimer **8a** (β-R′, 12%), and the major epimer **8a** (α-R′, 24%). These structures were assigned on the basis of their characteristic ^1H NMR data. The intermediate zwitterionic species **7a** was not isolated as it rapidly underwent a nonconcerted 1,5-hydrogen shift to form **8a**. Formation of the [6,6,5]-system **8b** started with thiolactam **2d**, obtained from lactam **2c** as above, which was converted into **3b**. Treatment of this thioamide with (chlorocarbonyl)phenyl ketene in toluene/triethylamine for 2 h at 110 °C gave cycloadduct **6b**. Use of refluxing xylene as the solvent (24 h) and workup of the reaction mixture by silica gel chromatography gave the minor epimer of **8b** (β-R′, 12%)and the major epimer **8b** (α-R′, 33%).

Scheme II



Lactam **4a** was readily converted into thiolactam **3c** (74%) which was then treated with (chlorocarbonyl)phenyl ketene in benzene at 25 °C to give **5c** (93%). When **5c** was heated at reflux in toluene for 20 h, two products were obtained; the cycloadduct **6c** (42%) and the 2,3-dihydropyridinone **8c** (β-R′, 48%). It should be noted that **5c** or **6c** could also be converted into **8c** in quantitative yield by heating in boiling xylene for 1 h. Similarly, lactam **4b** was converted into thiolactam **3d** (54%) which upon treatment with (chlorocarbonyl)phenyl ketene in benzene at 25 °C gave **5d** (94%). Thermolysis of **5d** in toluene for 20 h afforded cycloadduct **6d** (14%) as the minor product and a 1:1-diastereomeric mixture of **8d** (71%) as the major product. In the above examples, the R′ group is a phenyl group which stabilizes the dipole by charge delocalization. Substituted malonyl dichlorides provide[6] an effective way of extending the generality of the reaction, and we studied the cycloaddition of betaine **5e** with a 5-methyl substituent. Betaine **5e** (71%) was prepared by the dropwise addition of methyl malonyl dichloride to 3-methyl-3-(penten-5-yl)-2-valerothiolactam. Heating **5e** in toluene at 120°C for 2 h gave cycloadduct **6e** (80%) which produced **8e** (95%) on further thermolysis. It should be noted that the above cycloadditions require 3,3-disubstitution in the betaine **5**. With monosubstitution, no cycloaddition occurred in numerous examples studied. Rather, a 1,5-hydrogen shift of the 9-hydrogen in **5** took place, and the resultant 1,3-thiazine-4,6-dione did not undergo cycloaddition under the reaction conditions.

The formation of a linear ring-fused system is shown in Scheme II. Thiolactam **9** (98%) with penten-5-yl malonyl dichloride[18] (**10**) resulted in the betaine **11** (37%) which, when heated in xylene at 150°C for 22 h, gave **13** directly[19] (62%).

In conclusion, we have developed an efficient ring annulation procedure leading to hexahydrojulolidines and related ring systems. The intramolecular 1,4-dipolar cycloaddition of bicyclic anhydro-1,3-thiazinium hydroxides can now be exploited to prepare a variety of azapolycyclic ring systems found in nature. Work along these lines is in progress and will be reported in due course.

(15) All new compounds prepared had satisfactory analytical or HRMS data, as well as other spectral data which are described in the Experimental Section (supplementary material).
(16) Nakanishi, S.; Butler, K. *Org. Prep. Proc. Int.* **1977**, 155.
(17) Carbonyl sulfide may be conveniently identified by trapping in an alcoholic solution of piperidine when it formed the corresponding salt; see: Seibert, W. *Angew. Chem.* **1959**, *71*, 194.
(18) Kappe, T.; Gosler, W. *Synthesis* **1972**, 312.
(19) The *cis*-configuration at the 5,6-ring junction was assigned on the basis of the NMR data and steric considerations.

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Supplementary Material Available: Experimental procedures and characterization data (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.