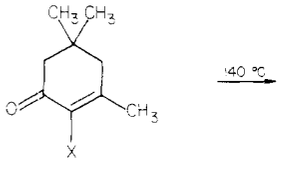
On the Intramolecular Reactivity of Azidoenones

Summary: The thermally induced intramolecular eliminative rearrangements of 2-[(2-azidoethyl)thio]-2-cycloalkenones are described.

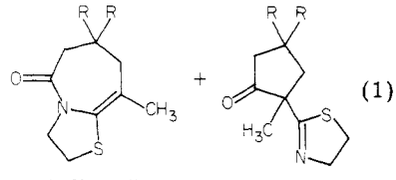
Sir: While 1,3-dipolar cycloadditions of organic azides are well-known, intramolecular examples have been only occasionally reported.[1,2] Systematic data are available for a series of azidoalkenes[3] and intramolecular azide additions to nitriles[4] and perhaps to carbonyl groups[5] have been reported. Herein we describe the thermally induced eliminative rearrangement of 2-[(2-azidoethyl)thio]-2-cycloalkenones, which leads to products of ring expansion and contraction. In certain cases, rearrangement, coupled with a desulfurization step, provides a completely regioselective method for conversion of a 2-cycloalkenone to a homologous enelactam, e.g., **12** → **13** → **14** and **17**. This Beckmann rearrangement-like process may have considerable value in modification of steroids and related natural products.

Azido enone **1c** is prepared from isophorone epoxide[6] by (1) reaction with 2-mercaptoethanol in ethanol-KOH[7] to give **1a** (95% yield), (2) treatment of **1a** with methanesulfonyl chloride in triethylamine-CH_2Cl_2 to give **1b** (100%), and (3) reaction of **1b** with sodium azide in DMF to give **1c**: 84% yield; oil; ^1H NMR ($CDCl_3$) δ 1.02 (6 H, s, *gem*-$(CH_3)_2$), 2.12 (3 H, s, vinyl CH_3), 2.40 (2 H, s, ring CH_2), 2.41 (2 H, s, ring CH_2), 2.91 (2 H, m, SCH_2), 3.40 (2 H, m, NCH_2); IR (neat) 6.25 (s), 5.95 (s), 4.74 μm (s).

When heated in xylene solution, **1c** is converted to **2** and **3** (1:1) in 85% yield (eq 1; separation and isolation by silica



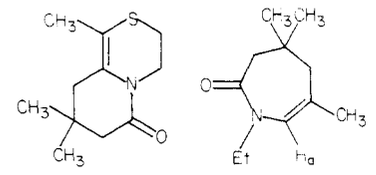
1a, X = SCH_2CH_2OH
b, X = SCH_2CH_2OMS
c, X = $SCH_2CH_2N_3$
d, X = SCH_2CHO



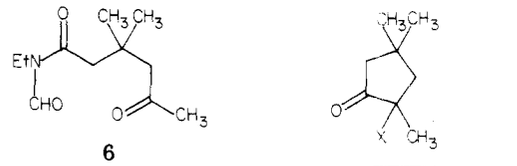
2, R = CH_3 **3**, R = CH_3
2a, R = H **3a**, R = H

(1)

gel chromatography). Structural assignments for **2** and **3** are based on a combination of spectral data and chemical reactivity. Thus, **2** (chemical ionization m/e 212) displays ^1H NMR ($CDCl_3$) signals at δ 1.04 (6 H, s, *gem*-$(CH_3)_2$), 1.89 (3 H, s, vinyl CH_3), 2.08 (2 H, s, ring CH_2), 2.29 (2 H, s, ring CH_2), 3.10 (2 H, m, SCH_2), and 3.96 (2 H, m, NCH_2) and IR absorption ($CHCl_3$) at 6.05 μm. These data are consistent with ene lactams **2** and **4**; unambiguous assignment of the structure as that of **2** is accomplished by nickel boride desulfurization[8] of **2** to give **5**, for which ^1H NMR ($CDCl_3$) for H_a appears at δ 5.80 (1 H, s, weak allylic coupling, $J < 1$ Hz). Furthermore, treatment of **5** with ozone followed by reduction of the ozonide with dimethyl sulfide in CH_2Cl_2 gives the formimide methyl ketone **6**.



4 **5**



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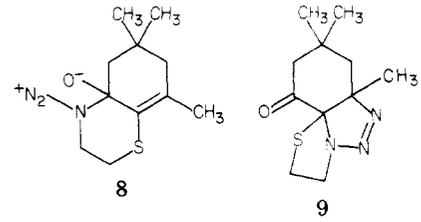
7a, X = CHS(NH)CH_2CH_2
b, X = CHO
c, X = H

Cyclopentanone **3** (chemical ionization m/e 212) gives ^1H NMR completely in accord with the assigned structure and IR absorption (neat) at 5.71 and 6.20 μm. On reduction with aluminum amalgam in wet ether,[9] **3** is converted to **7a**, from which the previously reported[10] keto aldehyde **7b** is formed on hydrolysis with mercuric chloride in aqueous acetonitrile. Deformylation[10] of **7b** produces a product that is identical in every respect with authentic 2,4,4-trimethylcyclopentanone **7c**.

With regard to the mechanism of formation of **2** and **3**, we note that **1c** is recovered unchanged from refluxing ethanolic solution; however, comparable reaction conditions, but in the presence of a catalytic amount of hydrochloric acid, result in complete decomposition of **1c** without the production of **2** and **3**.[11] On the other hand, reaction of a benzene solution of **1c** with concentrated sulfuric acid at room temperature results in rapid evolution of N_2, and within 5 min, aldehyde **1d** is formed in high yield.[12] Thus, an intramolecular acid-catalyzed Schmidt reaction[13] is not involved in the formation of **2**. While it is possible that a carbonyl-azide adduct[4] such as **8** may



8 **9**

be involved in the conversion of **1c** to **2** as shown, we feel that a more reasonable intermediate is the triazoline **9**, which could undergo competitive acyl migrations with loss of N_2 to give both **2** and **3**.

In order to describe some measure of the generality of the azido enone eliminative rearrangement, we present four additional examples. All azido enones were prepared and subjected to thermolysis by the procedures outlined for

(1) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).
(2) An example from our laboratory is recorded in A. G. Schultz and C.-K. Sha, *J. Org. Chem.*, **45**, 2041 (1980).
(3) A. L. Logothetis, *J. Am. Chem. Soc.*, **87**, 749 (1965).
(4) P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).
(5) J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.*, **94**, 4952 (1972).
(6) E. I. Wasson and H. O. House, *Org. Synth.*, **37**, 58 (1957).
(7) A. G. Schultz, *J. Org. Chem.*, **39**, 3185 (1974).
(8) W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
(9) A. I. Meyers and J. L. Durandetta, *J. Org. Chem.*, **40**, 2021 (1975). In this case, aluminum amalgam reduction of **3** is only marginally effective; brief sodium cyanoborohydride reduction in methanol/*p*-toluenesulfonic acid at room temperature is preferable.
(10) G. D. Ryerson, R. L. Wasson, and H. O. House, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, 1963, p 957.
(11) Under these reaction conditions, both **2** and **3** are stable.
(12) For this kind of acid-catalyzed decomposition of alkyl azides, see R. A. Abramovitch and E. P. Kyba in "The Chemistry of the Azido Group", S. Patai, Ed., Interscience, New York, 1971, Chapter 5.
(13) J. H. Boyer and L. R. Morgan, *J. Org. Chem.*, **24**, 561 (1959).

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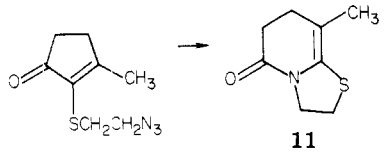
1c. Both 2a and 3a are formed from the azido enone corresponding to 1c in yields nearly identical with those of 1c, indicating that the *gem*-dimethyl group in 1c has no effect on product distribution.

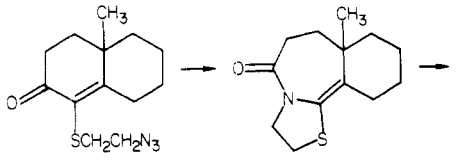
Cyclopentenone 10 undergoes rearrangement to dihydropyridone 11 in 93% yield. Thus, ring contraction of 10 to a cyclobutanone does not compete with ring expanstion to 11 (eq 2).



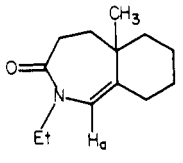
10 11 (2)

In contrast to 1c, we have found that thermolysis of fused-ring azidocyclohexenones results only in products of ring expansion. Thus, octalone 12 cleanly gives 13 (eq 3) in 70% isolated yield: mass spectrum (electron impact) m/e 237; IR ($CHCl_3$) 6.03 μm. Desulfurization of 13 gives 14 [^1H NMR ($CDCl_3$) for H_a δ 5.55 (1 H, s, weak allylic coupling)].

The exclusive formation of 13 at the expense of ring-contracted 16 may be a result of a preferred orientation for azide–olefin cycloaddition to give triazoline 15, rather

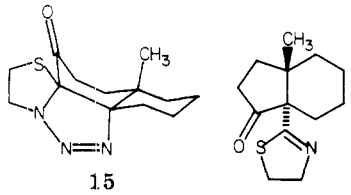


12 13



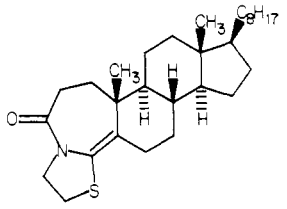
14 (3)

than that with a cis-fused decalone ring system. Carbonyl migration with expulsion of N_2 from 15 would be expected to produce a ring-contracted compound with a relatively strained trans ring fusion, e.g., 16. We intend to test this supposition in future experiments.



15 16

Finally, we note that 4β,5β-epoxycholestan-3-one[14] can be converted to steroid derivative 17 (mp 99–101 °C) in 64% overall yield, suggesting that this methodology will be useful in the construction of a variety of *A*-aza-*A*-homosteroid analogues.[15]



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Supplementary Material Available: Complete experimental details (9 pages). Ordering information is given on any current masthead page.

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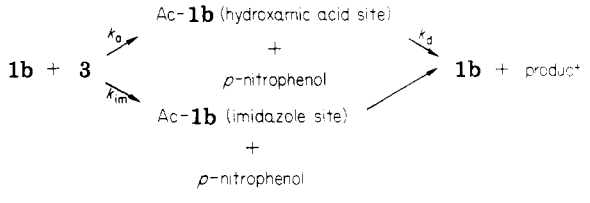
Stereoselective Micellar Bifunctional Catalysis

Summary: The catalytic effect in the hydrolysis of enantiomeric amino acid ester derivatives by an optically active bifunctional catalyst containing the hydroxamic acid and imidazole groups shows high reactivities and pH dependence of stereoselectivity in the presence of CTABr.

Sir: Proteolytic enzymes exhibit a characteristic stereospecificity as well as structural specificity in their catalytic actions toward their various substrates. Optically active micellar catalysts are being increasingly studied as models to gain further insight of stereospecific properties in enzymic reactions.[1-10] In our previous papers,[11,12] it has been shown that mixed micelles of *N*-acyl-L-histidine and the cationic surfactant are effective stereoselective catalysts for cleavage of the enantiomeric substrates.

Recently, it has been reported that micellar bifunctional

Scheme I



Ac-1b = acylated intermediate

(1) C. A. Bunton, L. Robinson, and M. F. Stam, *Tetrahedron Lett.*, 121 (1971).
(2) J. M. Brown and C. A. Bunton, *J. Chem. Soc., Chem. Commun.*, 969 (1974).
(3) R. A. Moss and W. L. Sunshine, *J. Org. Chem.*, **39**, 1083 (1974).
(4) R. A. Moss, T. J. Lukas, and R. C. Nahas, *Tetrahedron Lett.*, 3531 (1977).
(5) R. A. Moss, R. C. Nahas, and T. J. Lukas, *Tetrahedron Lett.*, 507 (1978).
(6) J. Koga, M. Shoshi, and N. Kuroki, *Nippon Kagaku Kaishi*, 1179 (1978).
(7) K. Yamada, H. Shosenji, and H. Ihara, *Chem. Lett.*, 491 (1979).
(8) K. Yamada, H. Shosenji, H. Ihara, and Y. Otsubo, *Tetrahedon Lett.*, 2529 (1979).
(9) R. Ueoka, T. Terao, and K. Ohkubo, *Noppon Kagaku Kaishi*, 462 (1980).
(10) H. Ihara, S. Ono, H. Shosenji, and K. Yamada, *J. Org. Chem.*, **45**, 1623 (1980).
(11) Y. Ihara, *J. Chem. Soc., Chem. Commun.*, 984 (1978).
(12) Y. Ihara, *J. Chem. Soc., Perkin Trans. 2*, in press.

(14) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, 2459 (1967).
(15) Compound 17 can be desulfurized in 96% yield to give *N*-ethyl-3a-aza-*A*-homocholest-4-en-3-one [mp 111–112° C (hexane)]. This compound gave UV and IR spectra completely analogous to those reported for the *N*-methyl derivative; see D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 1764 (1975). The *N*-methyl derivative is prepared by rearrangement of 3-(methylimino)-cholest-4-ene *N*-oxide.

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