ORGANIC LETTERS

2008
Vol. 10, No. 21
4975−4978

Hydroxy-β-Thiolactams to Oxazole-2-thiones. A Novel DMSO-Promoted Oxidation

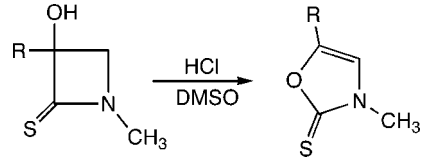
Xavier Creary* and Andrea Losch

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

creary.1@nd.edu

Received September 2, 2008

ABSTRACT



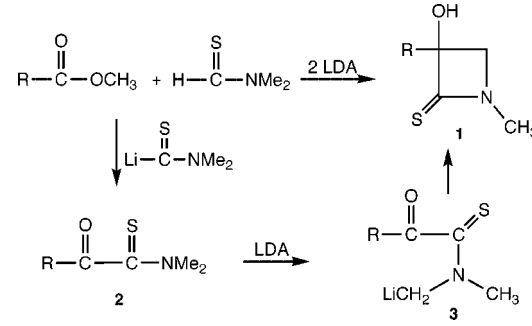
3-Aryl-3-hydroxy-1-methylazetidine-2-thiones react with HCl in DMSO to give 3-methyl-5-aryloxazole-2-thiones. Substituent effects correlate with rate effects on hydrolyses of acetals of benzaldehyde. An ^{17}O labeling experiment indicates that the oxygen atom of the product is derived from the hydroxyl group. Trifluoroacetic anhydride/DMSO in CH_2Cl_2 can also promote the reaction. Mechanisms involving a Grob-type fragmentation of an activated substrate, followed by recyclization, or a cyclopropylcarbinyl type of rearrangement can account for this oxidative rearrangement.

A number of years ago we reported on the synthesis of 3-hydroxy-1-methylazetidine-2-thiones (hydroxy-β-thiolactams) **1** by reaction of esters with *N*,*N*-dimethylthioformamide promoted by excess lithium diisopropylamide (LDA).[1] This transformation proceeds via deprotonation of the *N*,*N*-dimethylthioformamide by the LDA followed by condensation with the ester to form the intermediate acylthioamide **2**. In situ deprotonation of **2** by the excess LDA leads to **3**, and subsequent cyclization gives the observed product **1**.

These hydroxy-β-thiolactams **1** were readily converted to β-lactams by ozonolysis.[1] They could also be converted to mesylate derivatives and solvolytic reactions of these mesylates have been studied in detail.[2] During the course of related studies we have discovered a novel oxidative rearrangement of **1** that occurs under acidic conditions in DMSO.

We have prepared the chloride derivative **4** (An = *p*-$CH_3OC_6H_4$) from the corresponding hydroxy-β-thiolactam and carried out solvolytic studies in DMSO-d_6 containing a trace of water as well as triethylamine to neutralize the byproduct HCl. Under these conditions the hydroxy-β-thiolactam **5** is formed via a carbocation mechanism.[3] However, if the byproduct HCl is not neutralized as it is formed, further warming smoothly converts **5** to the oxazoline-2-thione **6**. Indeed, when pure **5** is dissolved in a freshly prepared solution of 2 M HCl in DMSO, conversion to **6**

Scheme 1. Formation of Hydroxy-β-thiolactams from Esters



(1) Creary, X.; Zhu, C. *J. Am. Chem. Soc.* **1995**, *117*, 5859.
(2) Creary, X.; Zhu, C.; Jiang, Z. *J. Am. Chem. Soc.* **1996**, *118*, 12331.
(3) Creary, X.; Burtch, E.; Jiang, Z. *J. Org. Chem.* **2003**, *68*, 1117.

10.1021/ol802050a CCC: $40.75
Published on Web 10/10/2008

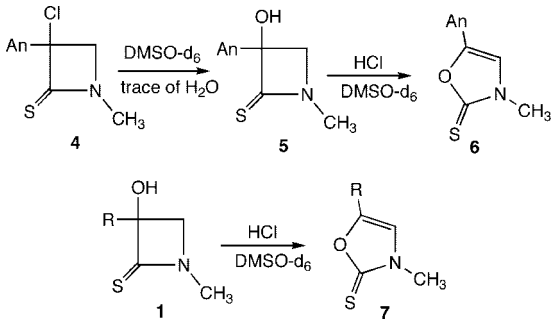
proceeds readily at room temperature. This process has some generality and examination of Table 1 shows that other aryl-

Table 1. Product Yields and Relative Rates of conversion of **1** to **7** with HCl in DMSO

entry	R	% yield	relative rate
1	*p*-$CH_3OC_6H_4$	84	14
2	*p*-$CH_3C_6H_4$	70	3.2
3	C_6H_5	62	1.0
4	*p*-ClC_6H_4	40	0.26
5	*t*-Bu	71	1.1
6	1-adamantyl	81	5.3

and alkyl-substituted hydroxy-β-thiolactams **1** also undergo this oxidative rearrangement to give *N*-methyl oxazoline-2-thiones of general structure **7**. Although the reduced product was not characterized by spectroscopic methods, it is quite apparent from the smell of reaction mixture that dimethyl sulfide is formed. Compounds of general type **7** have been previously prepared by reaction of tetraazapentalene derivatives with α-haloketones.[4] The substrate **7** (R = Ph) has also been prepared by a multistep process starting with the hydrochloride salt of α-aminoacetophenone and $CSCl_2$ or CS_2.[5] This novel oxidative ring expansion of **1** in DMSO promoted by HCl compliments these existing methods for preparation of compounds of type **7**.

Scheme 2. Conversion of Hydroxy-β-thioalctams to Oxazole-2-thiones

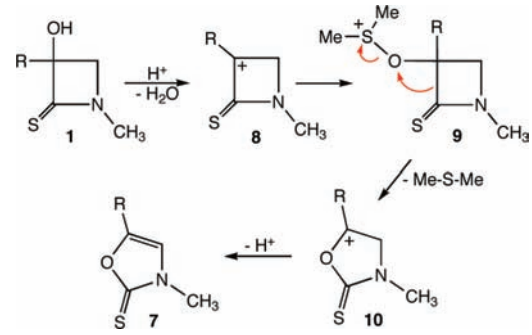


The origin of these oxidized products **7** is of interest. A number of reasonable mechanisms come to mind, the first of which is illustrated in Scheme 3. The first process involves HCl catalyzed ionization of **1** and capture of the intermediate carbocation **8** by DMSO to generate the oxosulfonium ion **9**. The adduct **9** could lose dimethyl sulfide (the oxidation process) with concomitant ring expansion via thiocarbonyl migration to the developing electron-deficient oxygen. This would give an aryl stabilized (as well as oxygen stabilized) carbocation **10**. Deprotonation of **10** would give the observed product **7**.

(4) Matsumura, N.; Tomura, M.; Mori, O.; Takamura, Y.; Yoneda, S. *Tetrahedron Lett.* **1989**, *30*, 2259–62.

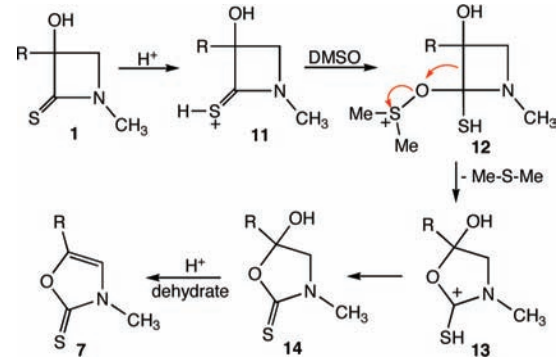
(5) Kjellin, G.; Sandstrom, J. *Acta Chem. Scand.* **1969**, *23*, 2879–87.

Scheme 3. Mechanism 1 for Formation of Oxazole-2-thiones



A second mechanistic suggestion shown in Scheme 4 involves protonation of the thiocarbonyl group of **1** followed

Scheme 4. Mechanism 2 for Formation of Oxazole-2-thiones



by trapping of **11** with DMSO. Loss of dimethyl sulfide and ring expansion to the electron-deficient oxygen would generate highly stabilized cation **13**. Proton loss would give **14**, which would be expected to rapidly dehydrate under the acidic conditions.

Rate data can often give insight into a reaction mechanism. Therefore relative rates of reaction of **1** were determined by competition methods and are summarized in Table 1. Immediately apparent is the fact that overall rate effects are small. The *p*-CH_3O derivative, although the fastest reacting substrate, is only 4.5 times more reactive than the *p*-CH_3 derivative. The *p*-CH_3 derivative is only 3.2 times faster than the unsubstituted *p*-H system. By way of contrast, relative solvolysis rates of mesylate derivatives of **1** show large substituent effects, with relative rates of *p*-CH_3O, *p*-CH_3, and *p*-H derivatives being 4.6×10^5, 73, and 1.0, respectively ($\rho^+ = -6.6$).[2]

Simple correlation of reaction rates of **1** with σ or σ^+ substituent constants is not satisfactory. However, Figure 1 shows an excellent correlation between reactivity of **1** and the rate of acid catalyzed hydrolysis of acetals of general structure **15**,[6] which proceed by way of extensively delocalized cations **17**. This linear free energy relationship

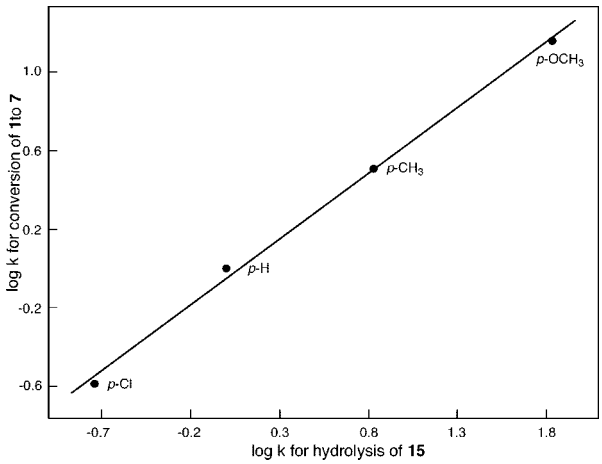


Figure 1. Correlation of rates of reaction of **1** in HCl/DMSO-d_6 with rates of acid-catalyzed hydrolyses of **15**.

suggests a similar stabilization demand in the transition state for the reaction of **1**, i.e., neighboring oxygen stabilization of a cationic intermediate as well as aryl stabilization.

In order to determine the source of the oxygen atom in the oxazoline-2-thione **7**, the reaction was carried out on the labeled substrate ^{17}O-**1** (R = Ph). The product of this reaction shows an ^{17}O NMR signal (Figure 2) at δ 250 ($H_2{}^{17}O$ as an

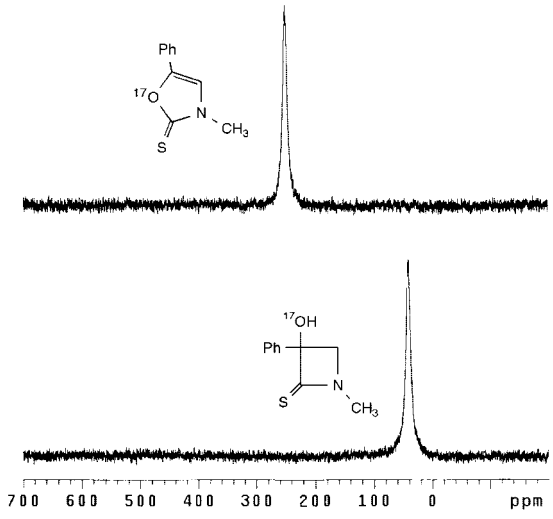
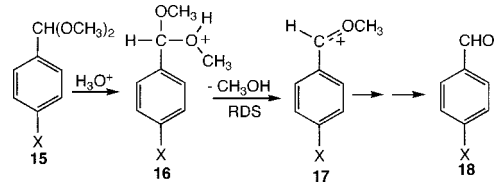


Figure 2. ^{17}O NMR spectra of ^{17}O-**1** (R = Ph) and the product ^{17}O-**7** (R = Ph) formed on reaction in HCl/DMSO-d_6.

external standard). The ^{17}O of the starting material (δ 42) has therefore been incorporated into the product ^{17}O-**7** (R = Ph). Hence the DMSO, as in Mechanisms 1 and 2, cannot be the source of the oxygen atom in **7**. Therefore the more obvious Mechanisms 1 and 2 can be eliminated.

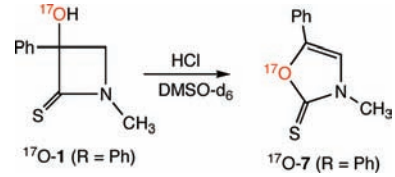
With the failure of Mechanisms 1 and 2 to survive labeling scrutiny, other suggestions are worthwhile. Three such possibilities are shown in Scheme 7. Mechanism 3 involves

Scheme 5. Acetal Hydrolysis Mechanism



the same intermediate thiocarbonyl adduct **12** suggested in Mechanism 2. Loss of dimethyl sulfide, with simultaneous Grob-type fragmentation[7] could generate the protonated ketone **19**. Subsequent proton transfer, followed by cyclization of **20**, would ultimately generate the appropriately labeled product **7**.

Scheme 6. ^{17}O Labeling Study



^{17}O-**1** (R = Ph) ^{17}O-**7** (R = Ph)

While protonation of the thioamide by $(CH_3)_2SOH^+$ seems reasonable, the possibility exists that the electrophilic sulfur atom in this species is the actual catalytic species. Reaction of such an electrophile at the sulfur atom of **1** could generate **21** (Mechanism 4). Grob-type fragmentation would generate the thio-acylium ion **22**. Subsequent proton loss and cyclization would lead to the appropriately ^{17}O-labeled **7**. Alternatively, cyclization of **21** to the strained system **24**, as in Mechanism 5, could lead to the observed product via a cyclopropylcarbinyl-homoallylic cation type of rearrangement of **24**.[8]

In order to support or rule out the suggestion that electrophilic sulfur of $(CH_3)_2SOH^+$ promotes the rearrangement, hydroxythiolactams **1** were added to a mixture of trifluoroacetic anhydride and DMSO in methylene chloride at −78 °C. This mixture is known to generate $(CH_3)_2SOCOCF_3{}^+$, a reagent known to be a source of electrophilic sulfur.[9] Reaction of **1** (R = Ph) gave a complex mixture from which **7** (R = Ph) could be isolated in 35%

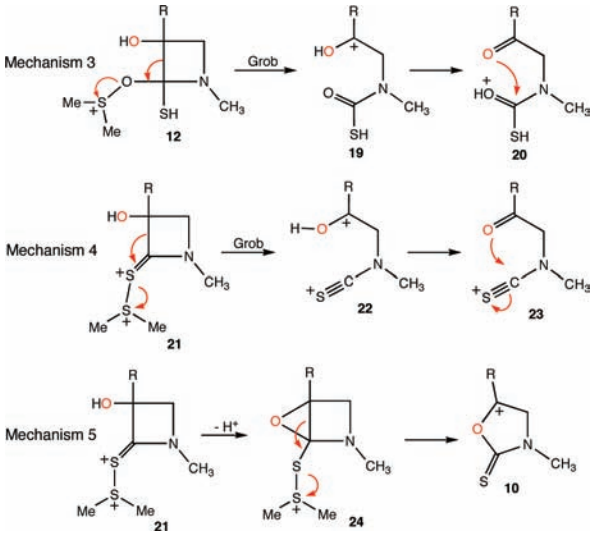
(6) (a) Young, R. P.; Bogseth, R. C.; Rietz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268. (b) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672.

(7) (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594. (b) Weyerstahl, P.; Marsshall, H. *Comp. Org. Syn.* **1991**, *6*, 1044.

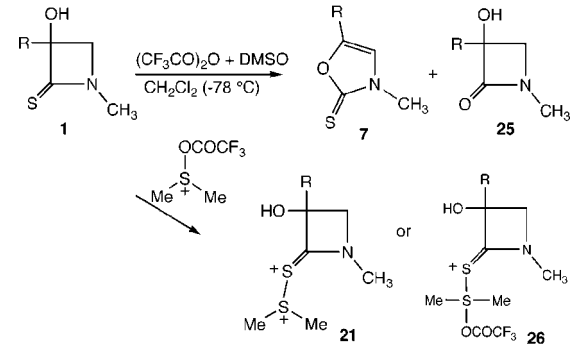
(8) For a discussion of this type of rearrangement, see: (a) Story, P. R.; Clark, B. C., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; *Vol. III*, pp 1007−1098. (b) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69. (c) Olah, G. A.; Reddy, V.; Prakash, In *Chemistry of the Cyclopropyl Group, Part 2*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1995; pp 813−859.

(9) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

Scheme 7. Alternative Mechanisms for Formation of Oxazole-2-thiones



Scheme 8. $(CF_3CO)_2O$/DMSO-Promoted Rearrangement of **1**



yield after chromatography. Also formed was 12% of the β-lactam **25** (R = Ph), another oxidation product.

The hydroxy-β-thiolactam **1** (R = *p*-ClC_6H_4) also gave **7** (R = *p*-ClC_6H_4) and **25** (R = *p*-ClC_6H_4) in 28% and 27% yields respectively after chromatography. The thiolactam **1** (R = *p*-$CH_3OC_6H_4$) gave an extremely complex product mixture in which a small amount of **7** (R = *p*-$CH_3OC_6H_4$) could be identified spectroscopically. In contrast to these aryl substituted thiolactams, the alkyl-substituted systems **1** (R = 1-adamantyl) and **1** (R = *t*-Bu) gave reasonably clean reactions from which **7** could be isolated in 58% and 57% yields respectively after chromatography. It is suggested that reaction of **1** with trifluoroacetic anhydride/DMSO results in formation of **21** (or the equivalent hypervalent sulfur intermediate **26**). Subsequent rearrangement, as in Mechanism 4 or Mechanism 5, gives the product **7**. While these results suggest that electrophilic sulfur in $[Me_2SX]^+$ can indeed promote the oxidative rearrangement of **1** to **7**, they do not rule out the protic acid promoted mechanisms (such as Mechanism 3).

In summary, hydroxy-β-thiolactams **1** undergo an oxidative ring expansion promoted by HCl in DMSO to give oxazoline-2-thiones **7**. An ^{17}O-labeling study shows that the hydroxyl oxygen ends up in the oxazoline-2-thione ring. The oxidative rearrangement of **1** to **7** can also be promoted by $(CF_3CO)_2O$/DMSO mixtures. Grob type fragmentation mechanisms as well as cyclopropylcarbinyl to homoallylic rearrangement type mechanisms are consistent with the available data. Investigations continue into the scope and mechanism of this unusual reaction.

Acknowledgment. This work was partially supported by the National Science Foundation. We thank Professor Richard Taylor (University of Notre Dame) for helpful discussions and the suggestion of the possibility of electrophilic sulfur promoted processes.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802050A