Formation and Cyclization of Acyl Thioamides. A Novel β-Lactam Forming Process

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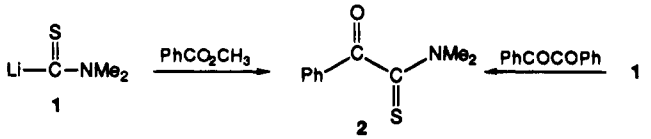
Received December 19, 1994

We have been interested in the chemistry of (*N,N*-dimethylthiocarbamoyl)lithium, **1**, and its potential to serve as an acyl anion equivalent. This reagent has been generated by Seebach at −100 °C by deprotonation of dimethylthioformamide with LDA, and it can be reacted with electrophiles.[1] Reagent **1** is not stable at −78 °C, but it can be easily generated "in situ" and trapped as it is formed by aldehydes and ketones at this temperature.[2] A single case of reaction of this reagent with an ester (methyl benzoate) has been reported, and a good yield of acyl thioamide **2** was obtained.[1] We now report the use of this reagent, **1**, in the construction of β-lactam systems in a simple two-step procedure.



In conjunction with other studies, we have attempted to add anion **1** to benzil. To our surprise, a significant amount (30%) of acyl thioamide **2** was obtained. This unusual and unexpected product led to mechanistic speculation involving an ester intermediate. Our mechanistic speculation on the origin of this acyl thioamide, **2**, led us to react methyl benzoate with in situ generated **1**. As with the previously reported reaction of preformed **1** with methyl benzoate, the addition of a mixture of methyl benzoate and dimethylthioformamide to a solution of LDA at −78 °C led to a good yield of **2**.[3] However, also formed was a trace amount of a new product, β-thiolactam **3**. We have found that the origin of this new product is acyl thioamide **2**, which reacts with the LDA present to generate **3**. Indeed, when a pure sample of **2** is treated with LDA at −78 °C, it is converted to β-thiolactam **3** in good yield.

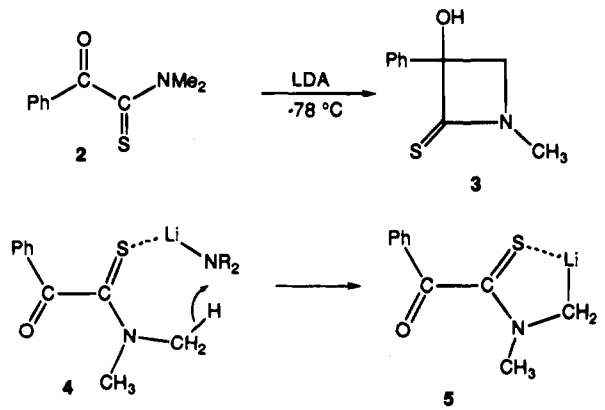
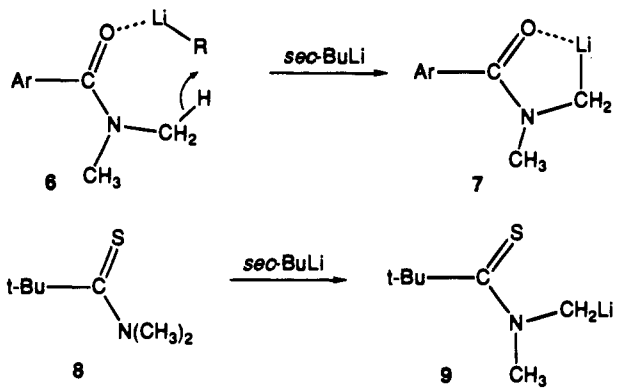


Table 1. Products and Yields (%) in Conversion of Esters RCO_2CH_3 to β-Lactams

R	$RCOCSNMe_2$	β-thiolactam	β-lactam
C_6H_5	68	81	62
4-$CH_3C_6H_4$	67	86	47
4-$CH_3OC_6H_4$	70	90	34[a]
4-$CF_3C_6H_4$	80	86	55
t-Bu	96	99	57
1-adamantyl	84	98	*b*
$CH_3C(OCH_3)_2$	96	40	*b*
i-pr	90	0	*b*

[a] *m*-Chloroperoxybenzoic acid oxidation. Ozone gave no β-lactam product. [b] Not attempted.

Table 1 gives yields of analogous β-thiolactams produced by reaction of a variety of acyl thioamides with LDA. The reaction presumably involves deprotonation of the *N*-methyl group of the acyl thioamide, followed by intramolecular cyclization of anion **5**. Precedent for this type of reaction comes from the studies of Beak, who has observed deprotonation of certain dialkylamides **6** with alkyllithium reagents.[4] Prior coordination of the lithium with the carbonyl group was proposed, and this activates certain hydrogens with respect to deprotonation. Seebach[5] has also successfully deprotonated



thioamide **8** with *sec*-BuLi. We propose an analogous type of prior coordination of LDA with sulfur as in **4**. This would account for the enhanced kinetic acidity of the methyl hydrogens in **2**. The reaction is not completely general, but is restricted to acyl thioamides containing no acidic hydrogens adjacent to the carbonyl group. However, the role of sulfur appears to be crucial in this cyclization. Thus the analogous reaction of acyl amides gives no cyclized products. LDA reacts with the $PhCOCONMe_2$ to give the reduction product $PhCHOHCONMe_2$, where LDA presumably serves as the hydride donor.[6,7] Intramolecular cyclization of a dipole-stabilized anion such as **5** is expected to be rapid. In certain instances, when more than 2 equiv of LDA is employed, conversion of esters to β-thiolactams can be carried out in a single-pot reaction.[8]

Conversion of the β-thiolactams to the corresponding β-lactams proved to be a simple procedure in most cases. While *m*-chloroperbenzoic acid has been used for C=S to C=O

(1) (a) Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309. (b) Seebach, D.; Lubosch, W.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 1014.

(2) (a) Banhidai, B.; Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 836. (b) Lien, M. H.; Ablenas, F. J.; George, B. E.; Maleki, M.; Jain, R.; Hopkinson, A. C. *Can. J. Chem.* **1987**, *65*, 1800. (c) Creary, X.; Hatoum, H. N.; Barton, A.; Aldridge, T. E. *J. Org. Chem.* **1992**, *57*, 1887. (d) Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 7115.

(3) Previously, certain acyl thioamides have been prepared by reaction of ketones $RCOCH_3$ with $SOCl_2$ followed by reaction with secondary amines. See: Adiwidjaja, G.; Günther, H.; Voss, J. *Liebigs Ann. Chem.* **1983**, 1116.

(4) For leading references, see: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(5) (a) Seebach, D.; Lubosch, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 313. (b) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102.

(6) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

(7) $PhCOCONMe_2$ gives no reaction with $LiN(SiMe_3)_2$.

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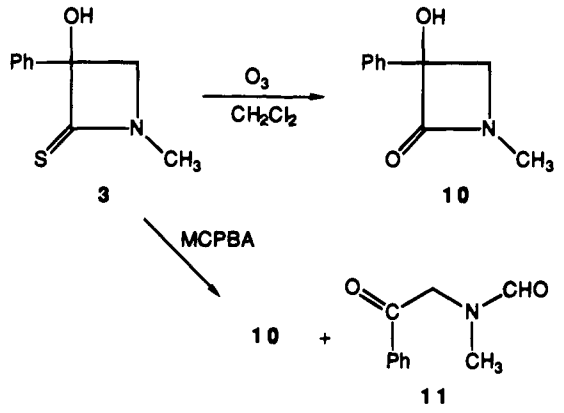
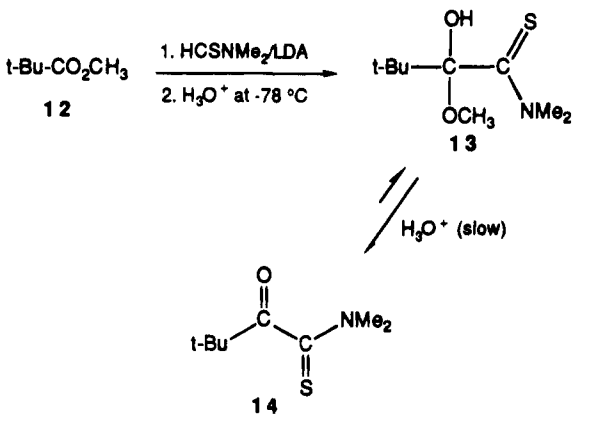
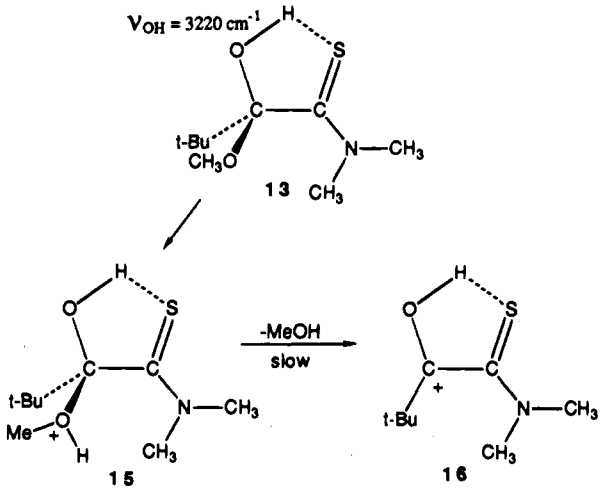
conversions in the past,[9] this procedure led to low yields in the case of β-thiolactam **3**. Also produced was a significant amount of the ring-opened product **11**.[10] There is limited precedent in the literature on the use of ozone to effect C=S to C=O conversions.[11] We have therefore resorted to cleavage of the C=S bond of **3** using ozone, and this procedure gives good yields of β-lactam **10**.[12,13]



Of further interest is the reaction of (*N,N*-dimethylthiocarbamoyl)lithium, **1**, with methyl pivalate, **12**, which was used in the preparation of acyl thioamide **14**. Quenching the reaction with acetic acid at −78 °C leads to an excellent yield of hemiacetal **13**, which is a *stable compound at room temperature.*



This hemiacetal is stable even in the presence of Et_3N. Conversion of **13** to the keto form requires treatment with acid of moderate strength. This represents, to our knowledge, a unique example of a kinetically "stable" hemiacetal where the keto form predominates at equilibrium. We speculate that the relatively large barrier to loss of methanol from **13** is due to a combination of conformational and steric effects. Infrared and NMR studies[14] suggest that **13** exists as a strongly intramolecularly hydrogen bonded species. The rate-limiting step in conversion of **13** to **14** should involve loss of methanol from the protonated form **15**. Steric factors may well slow the loss of methanol since the *tert*-butyl group must move into the same plane as the dimethylamino group in **16**.



In summary, certain β-lactams can be produced by a simple procedure starting with readily available esters and *N,N*-dimethyl thioformamide (which is also commercially available and inexpensive). LDA-promoted condensation gives acyl thioamides, and further LDA-promoted cyclization, followed by ozonolysis, gives reasonable overall yields of β-lactams. Further studies are underway on the scope of this novel base-promoted cyclization process, which gives a facile entry into a ring system of much interest with respect to antibacterial activity.[15]

Supplementary Material Available: ^1H and ^{13}C NMR spectra of β-thiolactams, β-lactams, and **9** (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(8) In a typical procedure, a solution of LDA prepared by addition of 35 mL of 1.6 M *n*-butyllithium (56 mmol) to 6.00 g of diisopropyl amine (59 mmol) in 20 mL of THF was cooled to −78 °C. A mixture of 3.26 g of methyl benzoate (24 mmol) and 2.13 g of *N,N*-dimethylthioformamide (24 mmol) in 50 mL of THF was added dropwise. After 1 h at −78 °C, the mixture was slowly warmed to room temperature and then water was added. After a standard aqueous workup with CH_2Cl_2 extraction, the organic solvents were removed using a rotary evaporator. The solid which slowly formed was slurried with a small amount of cold ether and collected to give 3.125 g (68%) of β-thiolactam **3**, mp 108−9 °C: ^1H NMR ($CDCl_3$) δ 7.60−7.53 (m, 2 H), 7.43−7.30 (m, 3 H), 4.126 (d, J = 6.9 Hz, 1 H), 4.011 (d, J = 6.9 Hz, 1 H), 3.672 (br s, 1 H), 3.222 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 204.76, 138.27, 128.50, 128.44, 125.54, 82.29, 66.61, 31.72. Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.10; H, 5.89; N, 7.23; S, 16.64.

(9) Kochhar, K. S.; Cottrell, D. A.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 1323.

(10) Amide **11** is formally a retro-benzoin condensation product of **10**. It is not formed directly from **10** since this product is stable under the reaction conditions.

(11) (a) Zwanenburg, B.; Janssen, W. A. J. *Synthesis* **1973**, 617. (b) Nilsson, N. H.; Jacobsen, C.; Sørensen, O. N.; Haunsøe, N. K.; Senning, A. *Chem. Ber.* **1972**, *105*, 2854.

(12) In a typical procedure, a solution of 1.115 g of β-thiolactam **3** in 20 mL of CH_2Cl_2 was cooled to −78 °C and ozone was bubbled through the solution until the blue color persisted. The mixture was warmed to room temperature, and the solvent was removed using a rotary evaporator. The residue was chromatographed through a short silica gel column and eluted with ether. Solvent removal left 0.633 g (62%) of β-lactam **10**, mp 102−3 °C: ^1H NMR ($CDCl_3$) δ 7.49−7.41 (m, 2 H), 7.36−7.25 (m, 3 H), 5.17 (br, 1 H), 3.582 (d, J = 5.4 Hz, 1 H), 3.480 (d, J = 5.4 Hz, 1 H), 2.867 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.31, 138.58, 128.64, 128.38, 125.53, 86.17, 59.32, 28.47. Exact mass (FAB) calcd for $C_{10}H_{11}NO_2$: 178.0868. Found: 178.0864.

(13) Analogs of **10** have been prepared previously via photocyclization of α-ketoamides of the type $RCOCONR_2$. See: Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958 and references therein.

(14) Hemiacetal **13** shows a strong, concentration independent, intramolecularly hydrogen bonded OH at 3220 cm^{-1}. Exchange of the acidic hydrogen with D_2O is relatively slow, and extensive shaking with D_2O is needed to effect complete exchange.

(15) (a) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3.