Sulfur-Extrusive Rearrangement of α-Acylthio Ester by Lithium Amide

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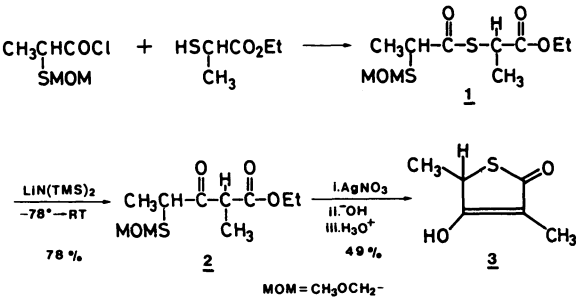
Synopsis. α-Acylthio esters readily undergo facile rearrangement to give β-keto esters on treatment with lithium amide at −78 °C. Thiolactone **3**, a key intermediate for thiolactonic antibiotics, was synthesized by utilizing the rearrangement.

In the course of synthetic studies[1] on the thiolactonic antibiotics, thiotetromycin[2] and thiolactomycin,[3] we treated ethyl 2-(benzoylthio)propanoate in dry tetrahydrofuran with 1.1 equiv lithium diisopropylamide at −78 °C (20 min) to obtain the corresponding β-keto ester [*m/z* 206(M^+), ν (neat) 1740 and 1690 cm^{-1}, δ ($CDCl_3$) 1.50 (3H, d, *J*=7 Hz) and 4.39 (1H, q, *J*=7 Hz)] in 93% yield. These spectral data suggest that it is ethyl 2-benzoylpropanoate. A similar reaction, using potassium *tert*-amylate and triphenylphosphine as a desulfurating agent which removes sulfur atom of the thiirane intermediate, was reported by Eschenmoser *et al.*[4] However, in our case the additive effect of desulfurating agent was not detected completely. In order to prove the generality and limitation of this rearrangement, several *S*-acyl derivatives obtained by *S*-acylation of 2-mercaptopropanoate and mercaptoacetate were treated with lithium amide and the results are summarized in Table 1. α-Acylthio esters except the *S*-acetyl (R^1=CH_3) derivative undergo facile rearrangement to yield the corresponding β-keto esters without a desulfurating agent in synthetically acceptable yield.

Attention was then turned to the application of this reaction to the synthesis of a key intermediate **3** containing the latent C-2 symmetry for thiolactonic antibiotics. Compound **1**[5] obtained by acylation of 2-mercaptopropanoate, on exposure at −78 °C with 1.1 equiv of lithium hexamethyldisilazanide for 20 min and then warming to room temperature in 1.5 h, provided β-keto ester **2**[5] as a mixture of diastereoisomers in 78% yield. Conversion of **2** to thiolactone **3**[5] was successfuly achieved in 49% yield by the following sequence: (1) deprotection of methoxymethyl group with $AgNO_3$; (2) hydrolysis of ester group; (3) thiolac-



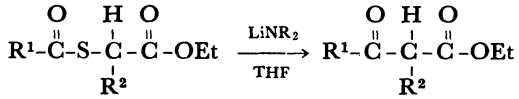
tonization by acidic work-up.

The ease of obtaining α-acylthio esters and the relatively mild conditions required for the rearrangement reaction might provide a useful tool for the construction of natural products.

References

1) K. Tsuzuki and S. Ōmura, *J. Antibiot.*, **36**, 1589 (1983).
2) S. Ōmura, Y. Iwai, A. Nakagawa, R. Iwata, Y. Takahashi, H. Shimizu, and H. Tanaka, *J. Antibiot.*, **36**, 109 (1983).
3) H. Oishi, T. Nato, H. Sasaki, K. Suzuki, T. Hayashi, H. Okazaki, K. Ando, and M. Sawada, *J. Antibiot.*, **35**, 391 (1982).

Table 1. Sulfur-extrusive rearrangement of α-acylthio esters by lithium amide



Entry[a]	R^1	R^2	R^3	Reaction conditions[b]	Yield/%[c]
1	Ph	Me	-Pr	−78 °C, 20 min	93
2	Ph	H	-Pr	−78 °C RT, 1 h	76
3	$Me(CH_2)_2$	Me	Me_3Si	−78 °C RT, 1.5 h	58
4	$Me(CH_2)_2$	H	Me_3Si	−78 °C RT, 2 h	54
5	Me_3C	Me	Me_3Si	−78 °C RT, 1.5 h	58
6	Me_3C	H	Me_3Si	−78 °C RT, 2 h	59

a) Satisfactory MS, ^1H NMR and IR spectroscopic data were obtained for all compounds. b) All reactions were carried out in THF under nitrogen at −78 °C for 20 min, and then warmed to room temperature. c) Isolated yield after silica-gel column chromatography.

4) M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).

5) **1**: MS *m/z* 266 (M^+); IR (neat) ν 1735, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, t, J=7 Hz), 1.50 (6H, d, J=7 Hz), 3.33 (3H, s), 3.70 (2H, q, J=7 Hz), 4.15 (2H, q, J=7 Hz), 4.67 (2H, AB, J=12 Hz). **2**: MS *m/z* 234 (M^+); IR (neat) ν 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (3H, t, J=7 Hz), 1.34 (3H, d, J=7 Hz), 1.44 (3H, d, J=7 Hz), 3.34 (3H, s), 3.78 (1H, q, J=7 Hz), 4.13 (2H, q, J=7 Hz), 4.15 (1H, q, J=7 Hz), 4.81 (2H, s). **3**: MS *m/z* 144 (M^+); IR (neat) ν 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.63 (3H, d, J=7 Hz), 1.77 (3H, d, J=2 Hz), 4.20 (1H, qq, J=2 and 7 Hz).