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A DITHIOL ESTER VERSION OF DIECKMANN CONDENSATION

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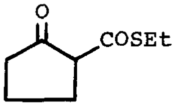
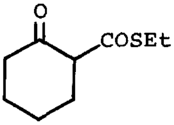
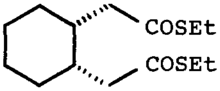
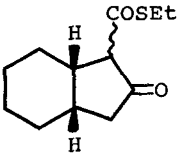
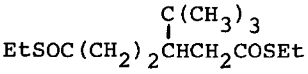
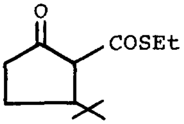
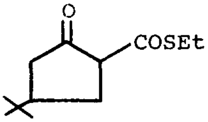
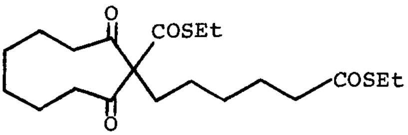
The Dieckmann condensation[1] is an important cyclization process whereby esters of dicarboxylic acids are converted into versatile cyclic β-keto esters. The commonly used procedures involve prolonged treatment of diesters under strongly basic conditions, often at elevated temperature. We wish to report a dithiol ester version of the Dieckmann condensation, which proceeds readily under markedly milder conditions to give, in good yields, cyclic β-keto thiol esters (Eq. 1).

Eq. 1

In sharp contrast to the crucial conditions required to induce the Dieckmann condensation of diethyl adipate[2], the cyclization of the sulfur analogue, di-S-ethyl hexanedithioate (**1**)[3,5], occurred smoothly within 2 hr when treated with 1.3 equivalents of sodium hydride[6] and a catalytic amount (0.1 equivalent) of ethanethiol in 1,2-dimethoxyethane (20 ml/g of **1**) at room temperature. Acidification of the reaction mixture with 1 N hydrochloric acid followed by the usual work-up with ether extraction and bulb-to-bulb distillation of the crude product at 100°C (oven temperature)/1 Torr gave a 91% yield of partially enolized S-ethyl 2-cyclopentanonecarboxylthioate (**2**): homogeneous by glc and tlc; ir (film) 3300 (enol), 1745 (cyclopentanone), 1670 (thiol ester), 1615 and 1575 cm^{-1} (β-hydroxy

Table 1. Condensation of Dithiol Esters

Dithiol ester	Time (hr)[a]	Product(s)	Isolated Yield (%)
$EtSOC(CH_2)_4COSEt$ 1	2	 2	91%
$EtSOC(CH_2)_5COSEt$ 3	3	 4	86%
 5	5	 6	96%
 $EtSOC(CH_2)_2CH(C(CH_3)_3)CH_2COSEt$ 7	6	 +  8a 8b (~1:2)	93%
$EtSOC(CH_2)_6COSEt$ 9	20	b	--
	20[c]	 10	78%

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[a] Except for one case specified below, all the reactions were carried out at room temperature in 1,2-dimethoxyethane using 1.3 eq. of sodium hydride and 0.1 eq. of ethanethiol.

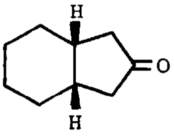
[b] Recovery of starting material.

[c] The reaction was performed in refluxing 1,2-dimethoxyethane.

α,β-unsaturated thiol ester); nmr (CCl_4) δ 3.22 (t, ~1/2 H, J = 7 Hz, -COCHCO-), 2.91, 2.87 (~1:1, both q, total 2 H, J = 7 Hz each, $-COSCH_2-$), 1.30 and 1.28 (~1:1, both t, total 3 H, J = 7 Hz each, $-CH_3$); ms M^+ 172.0563 (calcd. for $C_8H_{12}O_2S$: 172.0568). The formation of a six-membered β-keto thiol ester was shown to be equally facile; under similar conditions, pimelthioate 3 was cyclized to afford S-ethyl 2-cyclohexanonecarboxylthioate (4) in 86% yield. Additional examples are illustrated in Table 1. The cyclization of di-S-ethyl suberthioate (9) was also studied. The complete recovery of the starting material however indicated that the described reaction conditions were ineffective to induce seven-membered ring formation. Interestingly, when the reaction mixture was brought to reflux, a 78% yield of the dimeric compound 10 was isolated.

One observation of these studies, which promises wide synthetic utility, was the relative ease of removal of the thiol ester group from the cyclization products. Unlike the decarbalkoxylation of β-keto esters which often requires severe acid or base treatment,[7] removal of the thiol ester group from β-keto thiol esters could be easily achieved by brief treatment with Raney nickel under virtually neutral conditions. Thus, when treated with an excess (ca. 10 times by weight) of W-2 Raney nickel[8] in ethanol at room temperature for 15 min, both keto thiol esters 2 and 4 underwent clean removal of the carboxylthioate moiety resulting in exclusive formation (glc analysis) of cyclopentanone and cyclohexanone respectively. Similar treatment (each for 2 hr) of 6 and a mixture of 8a and 8b afforded the corresponding ketones 11 (82% yield) and 12 (85% yield) of analytical purity.

We are currently investigating alkylation and annelation reactions using the β-keto thiol ester system.



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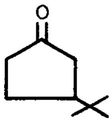

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Acknowledgment. We are grateful to the National Research Council of Canada and the University of Alberta for financial support.

References and Notes

1. For reviews, see C. R. Hauser, and B. E. Hudson, Org. Reactions, 1, 274 (1942); J. P. Schaefer, and J. J. Bloomfield, ibid., 15, 1 (1967).
2. P. S. Pinkney, Org. Syn., Coll. Vol., 2, 116 (1943).
3. All dithiol esters with the exception of 5[4] were synthesized from the corresponding acid chloride by ethanethiol-pyridine treatment.
4. Compound 5 was prepared from the corresponding acid by treatment with phenyl dichlorophosphate, ethanethiol and pyridine in 1,2-dimethoxyethane analogous to a reported procedure using N,N-dimethylphosphoramidic dichloride as the activating agent (H. J. Liu, S. P. Lee, and W. H. Chan, Synth. Commun., in press).
5. All new compounds were adequately characterized by spectroscopic methods (ir, nmr and ms) and by exact mass measurement and/or elemental analysis.
6. Sodium hydride was washed with n-pentane prior to use.
7. For example, see H. O. House, "Modern Synthetic Reactions," 2nd Ed., W. A. Benjamin, Inc., Menlo Park, Ca. 1972, pp. 511-516.
8. R. Mozingo, Org. Syn., Coll. Vol., 3, 181 (1955).

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