Solvent removal produced crystals which were purified by recrystallization from hexane–EtOH. Drying under high vacuum afforded 857 mg (69%) of the desired product as white crystals: mp 156–159 °C; NMR ($D_2O$) δ 4.33–3.95 (m, 1), 3.63–2.97 and 3.14 (br m plus s, 10), 2.30 (t, 2, $J$ = 6 Hz), 1.78 (t, 2, $J$ = 6 Hz), 1.33 (br s, 24), 0.90 (t, 3, $J$ = 2.5 Hz); IR (KBr) 3400 (br s), 1566 (s), 1460 (m), 1392 (m) $cm^{-1}$; mass spectrum (FD) $m/e$ 314 [$(M + H - CO_2)^+$], 325 [$(M - MeOH)^+$], 340 [$(M + H_2O)^+$], 358 [$(M + H)^+$], 372 [$(M + CH_3)^+$].

Anal. Calcd for $C_{21}H_{43}NO_3 \cdot 0.14H_2O$: C, 70.0; H, 12.1; N, 3.9. Found: C, 69.6; H, 12.5; N, 3.7.

**6-(Docosyldimethylammonio)-5-hydroxyhexanoate (3e).** To a solution of epoxy ester **6b** (3.00 g, 19.0 mmol) in 50 mL of 70% aqueous EtOH was added docosyldimethylamine (6.71 g, 19.0 mmol). The mixture was stirred at 80 °C for 42 h. The solvent was removed under vacuum, and the resulting crystals were purified by recrystallization from hexane–EtOH. Drying under high vacuum afforded 5.70 g (62%) of **3e** as white crystals: mp 188–190; NMR ($D_2O$) δ 4.35–4.00 (m, 1), 3.60–3.03 and 3.16 (br m plus s, 10), 2.37–2.80 (m, 2), 1.30 (br s, 44), 0.84 (t, 3, $J$ = 6 Hz); IR (KBr) 3330 (s), 1571 (s), 1462 (m), 1386 (m); mass spectrum (FD), $m/e$ 440 [$(M + H - CO_2)^+$], 451 [$(M - MeOH)^+$], 484 [$(M + H)^+$], 498 [$(M + CH_3)^+$].

Anal. Calcd for $C_{30}H_{61}NO_3 \cdot 0.86H_2O$: C, 72.2; H, 12.7; N, 2.8. Found: C, 72.6; H, 12.7; N, 2.8.

**$^{13}C$ NMR Spectra.** Spectral data are given in Table II. Assignments are based upon off-resonance-decoupling experiments and comparison with values for unhydroxylated ammoniohexanoates[19] and other known systems.[20]

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**Registry No. 2a**, 73697-53-7; **2b**, 73697-54-8; **2c**, 73697-55-9; **3a**, 73697-56-0; **3b**, 73697-57-1; **3c**, 73712-26-2; **3d**, 73697-58-2; **3e**, 73697-59-3; **4a**, 591-80-0; **4b**, 1577-22-6; **5a**, 1968-40-7; **5b**, 54653-25-7; **6a**, 73697-60-6; **6b**, 73697-61-7; $Et_3N$, 121-44-8; $Me_3N$, 75-50-3; $Bu_3N$, 102-82-9; $PhCH_2NMe_2$, 103-83-3; $Me_2N(CH_2)_{13}CH_3$, 112-75-4; $Me_2N(CH_2)_{21}CH_3$, 21542-96-1.

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# Acylations of Thiol Ester Enolate Anions

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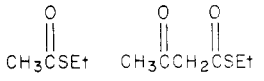
The synthetic utility of thiol ester enolate anions has been explored. Claisen condensations of thiol esters with isopropylmagnesium bromide base proceed in good yield. The Dieckmann reaction of diethyl thiolpimelate to form a six-membered ring proceeds in 74% yield, but the corresponding reaction of diethyl thioladipate to provide a five-membered ring gives only 26% yield. Neither alkylation of ethyl thiolacetate nor a Michael-type adduct with methyl vinyl ketone could be achieved. The mechanism of the Claisen condensation as it applies to thiol esters is discussed.

Chain elongation in fatty acid biosynthesis proceeds by a succession of thiol ester Claisen condensations.[1b-3] By contrast to the ubiquitous nature of the biochemical transformation, thiol ester condensation studies in organic chemistry are rare,[4-6] having been reported only three times. In 1929, Baker and Reid induced ethyl thiolacetate to condense with itself at 50 °C using sodium as a base.[4] These authors obtained a 15% yield of ethyl acetothiolacetate, but in the Experimental Section they made note of the fact that a solid residue, identified as dehydracetic acid, was obtained from the vacuum distillation. A mixed ester condensation of ethyl thiolacetate and ethyl acetate with sodium was also carried out, giving 93% ethyl acetothiolacetate and 2% ethyl acetoacetate.

Cronyn, Chang, and Wall[5] reported a 67% yield of ethyl acetothiolacetate (**2**) from the self-condensation of ethyl thiolacetate (**1**) using isopropylmagnesium bromide at 0 °C and a 20% yield of *tert*-butyl acetothiolacetate from the self-condensation of *tert*-butyl thiolacetate.



**1** **2**

Sheehan and Beck[6] allowed phenyl thiolacetate to condense at 0 °C using isopropylmagnesium bromide and obtained a 49% yield of phenyl acetothiolacetate. In addition, they allowed *N*,*S*-diacetylcysteamine to condense using mesitylmagnesium bromide at room temperature and obtained a 32% yield of *N*-acetyl-*S*-(acetoacetyl)cysteamine.

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Table I. Comparative Yields of β-Keto Esters and β-Keto Thiol Esters from Claisen Condensations

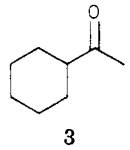
| ester | base | solvent | temp, °C | time, h | yield, % | ref |
|---|---|---|---|---|---|---|
| $CH_3COSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 1.7 | 90 | 5 |
| $CH_3CO_2Et$ | NaOEt | neat | 78 | 8 | 75-76 | 7 |
| $CH_3CO_2Me$ | NaOMe | neat | 60 | 6 | 43 | 8 |
| | NaOMe | neat | *a* | 6 | 50 | 8 |
| $CH_3COS$-*t*-Bu | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 2 | 59 | |
| $CH_3CO_2$-*t*-Bu | $(CH_3CH_2)_2NMgBr$ | $Et_2O$ | 36 | 2 | 55 | 9 |
| | NaH | neat | *a* | 5.5 | 66 | 10 |
| | $LiN(CH_2CH_3)_2$ | $Et_2O$ | 36 | 2 | 58.5 | 11 |
| | $(CH_3)_2CHMgCl$ | $Et_2O$ | | | 20-85 | 12 |
| $CH_3CH_2COSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 1.5 | 84.4 | |
| $CH_3CH_2CO_2Et$ | $(CH_3CH_2)_2NMgBr$ | $Et_2O$ | 36 | | 76 | 9 |
| | $[(CH_3)_2CH]_2NMgBr$ | | *b* | 4 | 73 | 13 |
| | NaOEt | neat | 95 | 16 | 46-47 | 7 |
| | $LiN[CH(CH_3)_2]_2$ | $Et_2O$ | 36 | 0.5 | 21.3 | 11 |
| | NaH | neat | *a* | 12 | 44 | 14 |
| $CH_3CH_2CO_2Me$ | NaOMe | neat | 80 | 6 | 42 | 8 |
| | NaOMe | neat | *a* | 6 | 71 | 8 |
| $CH_3CH_2CH_2COSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 2.8 | 74.2 | |
| $CH_3CH_2CH_2CO_2Et$ | $[(CH_3)_2CH]_2NMgBr$ | | *b* | 4 | 66 | 13 |
| | NaOEt | neat | 95 | 32 | 42 | 7 |
| $CH_3CH_2CH_2CO_2Me$ | NaOMe | neat | *a* | 6 | 79 | 8 |
| $(CH_3)_2CHCOSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | *b* | 18 | 41 | |
| $(CH_3)_2CHCO_2Et$ | $[(CH_3)_2CH]_2NMgBr$ | | *b* | 4 | 55 | 13 |
| | $LiN[CH(CH_3)_2]_2$ | $Et_2O$ | 36 | 3 | 49.3 | 11 |
| $EtSCO(CH_2)_4COSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 2.5 | 26 | |
| $EtO_2C(CH_2)_4CO_2Et$ | NaOEt | benzene | 80 | 12 | 81 | 15 |
| | | | | 12 | 90 | 16 |
| | NaH | $Me_2SO$ | 90-100 | 1+ | 75 | 17 |
| | Na | toluene | | 4 | 89 | 18 |
| | Na | benzene | 80 | 12 | 81 | 15 |
| | NaOEt | $Me_2SO$ | *a* | 8 | 89.3 | 19 |
| $EtSCO(CH_2)_5COSEt$ | $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 1.5 | 74 | |
| $EtO_2C(CH_2)_5CO_2Et$ | Na | benzene | 80 | 2 | 76 | 20 |

[a] Forcing conditions used. [b] Ambient temperature.

## Results and Discussion

**Claisen Condensations of Thiol Esters.** Claisen condensations of thiol esters were carried out at various temperatures and with several bases in an effort to delineate the range of synthetically useful reactions and gain mechanistic insights.

Ethyl thiolacetate (1) was condensed by using isopropylmagnesium chloride as base and following the procedure of Cronyn, Chang and Wall.[5] In our hands, however, only dehydracetic acid (3) could be obtained upon



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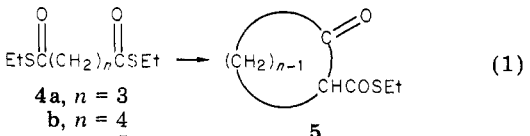
fractional distillation, so the reaction mixture was subjected to preparative gas chromatography to give a 90% yield of ethyl acetothiolacetate (2). The yields, as illustrated by the condensation employing isopropylmagnesium chloride as the base, increased from 70% for the 1:2 base–thiol ester reaction to 90% for the reaction using equimolar proportions of base and thiol ester.

Dieckmann condensations of diethyl thioladipate (**4b**) and diethyl thiolpimelate (**4c**) with isopropylmagnesium chloride proceeded normally to provide **5b** and **5c**, respectively, in good yields (eq 1). However, when attempts



(1)

**4a**, $n = 3$
**b**, $n = 4$
**c**, $n = 5$
**d**, $n = 6$

5

were made to carry out Dieckmann condensations of diethyl thiolglutarate and diethyl thiolsuberate by following the procedure given by Cronyn et al.[5] for the Claisen condensation, the former diester failed to give ethyl 2-oxothiolcyclobutanecarboxylate (**5a**) and the latter gave only a trace of ethyl 2-oxothiolcycloheptanecarboxylate (**5d**) even when the reaction was carried out under high dilution conditions.

On being heated, ethyl acetothiolacetate decomposes to dehydracetic acid,[4] and this makes purification of thiol esters of acetoacetic acid by distillation difficult. Purification by preparative gas chromatography suffered from similar shortcomings but could be realized by resorting to the use of low injection port and detector temperatures.

Table I, which shows a comparison of the yields obtained from the Claisen condensation of some thiol esters using isopropylmagnesium chloride with those obtained previously for the Claisen condensation of esters using various bases, shows that the Claisen condensation of thiol esters with the Grignard reagent gives yields which compare favorably with those obtained from the best reported conditions for condensation of esters. In fact, in two instances, for ethyl thiolacetate and ethyl thiolpropionate, the results are considerably better than those obtained with esters even under forcing conditions. In only one instance, the Dieckmann condensation of diethyl thioladipate (**4b**), are the results much poorer than those obtained by the more traditional methods.

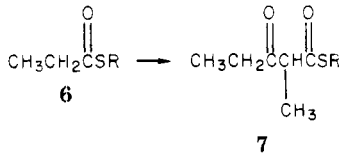
Shorter reaction times are required for the thiol ester Claisen condensation as well as much lower reaction temperatures. These two factors contribute to the ease with which this reaction may be carried out. In addition, they contribute to the utility of the reaction; thermally unstable starting materials should give good yields without the danger of decomposition.

Table II. Claisen Condensation of Ethyl Thiolpropionate with Various Bases To Produce Ethyl 2-Methyl-3-oxothiolvalerate

| base | solvent | temp, °C | yield, % |
|---|---|---|---|
| $(CH_3)_2CHMgCl$ | $Et_2O$ | 0 | 84 |
| *n*-BuLi | $Et_2O$ | 0 | 42 |
| LiSEt | $Et_2O$ | 0 | 13 |
| | $Et_2O$ | 36 | 20 |
| | benzene | 80 | *a* |
| MgClSEt | $Et_2O$ | 0 | 40 |
| | $Et_2O$ | 36 | *a* |
| | benzene | 80 | 50 |
| KSEt | $Et_2O$ | 36 | *a* |
| | benzene | 80 | *a* |
| $Ca(SEt)_2$ | $Et_2O$ | 36 | *a* |
| | benzene | 80 | *a* |

[a] No product could be detected.

In order to optimize the conditions and to study the effects of metal ion and base strength on the Claisen condensation of thiol esters, we carried out the reaction with ethyl thiolpropionate (6) (eq 2) and a number of bases

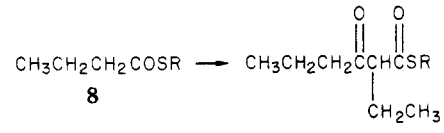


(2)

6 7

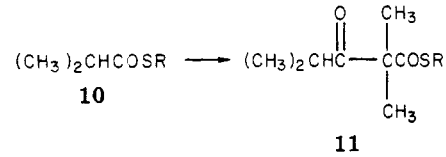
(Table II). The yields of 7 vary with base, but good results were obtained with the magnesium bases isopropylmagnesium chloride and magnesium chloroethyl mercaptide. Both *n*-butyllithium and lithium ethyl mercaptide gave a Claisen condensation product, but the potassium and calcium salts of ethyl mercaptan failed to do so. These results are consistent with the hypothesis that in the presence of weak bases the driving force for the reaction is the formation of a product enolate anion stabilized by chelation.

The NMR spectra of methyl 2-methyl-3-oxothiolvalerate (7), methyl 2-ethyl-3-oxothiolhexanoate (9), and methyl 2,2,4-trimethyl-3-oxothiolvalerate (11) have been reported



(3)

8 9



(4)

10 11

in carbon tetrachloride solution by Demuynck and Thuillier,[21] and our findings in chloroform solutions for the ethyl thiol esters 7 and 9 derived from 6 and 8, respectively, are in agreement. There is, however, considerable disagreement between the spectrum reported here for the ethyl thiol ester 11 and that reported earlier[21] for methyl 2,2,4-trimethyl-3-oxothiolvalerate (11) in which the isopropyl and *gem*-dimethyl groups give rise to a doublet and triplet, respectively. In our hands, the isopropyl methyl groups of 11 show nonequivalence indicative of slow interconversion between rotamers. The doublet nearly coalesces by 80 °C. This restricted rotation probably reflects steric interference between the isopropyl methyl protons and the sulfur atom. Similarly, the *gem*-dimethyl gives rise to two singlets, but these do not coalesce.

**Acylation of Thiol Ester Enolates.** The reaction of ethyl acetate with excess propionyl chloride in the presence of triphenylmethylsodium[23,24] gives both the mono- and diacylated products, with the latter predominating.[23] By contrast, the reaction of the enolate anion of ethyl thiolacetate with propionyl chloride (Table III), when carried out at 0 °C, provides ethyl 2-aceto-3-oxothiolvalerate (12) as the major product. Whether the product arises from the acylation of ethyl acetothiolacetate by propionyl chloride or from the acylation of the ethyl 3-oxothiolvalerate enolate anion by ethyl thiolacetate is unclear. It would not be unreasonable, however, to expect that the ethyl acetothiolacetate is formed first, particularly in view of the fact that a considerable amount of β-keto thiol ester was observed in the reaction mixture. The enolate anion of the β-keto thiol ester, formed by the abstraction of an α-hydrogen atom by an enolate anion of ethyl thiolacetate, could then react with propionyl chloride as shown in eq 5 and 6. This α-hydrogen abstraction is not unexpected

$$CH_3COCH_2COSEt + ClMgCH_2COSEt \rightleftharpoons [CH_3COCHCOSEt]MgCl + CH_3COSEt \quad (5)$$

$$[CH_3COCHCOSEt]MgCl + CH_3CH_2COCl \rightleftharpoons \underset{12}{CH_3COC(COCH_2CH_3)HCOSEt} + MgCl_2 \quad (6)$$

because the $pK_a$ of a β-keto thiol acetate should be lower than that of a thiol ester. What is interesting, however, is the apparently greater susceptibility to nucleophilic attack of the thiol ester.

When the reaction was run at −20 °C, no ethyl 2-aceto-3-oxothiolvalerate was observed. Under these conditions only ethyl acetothiolacetate and ethyl 3-oxothiolvalerate were observed in a ratio of 5:1. Similar results were observed whether the reaction was run for 1.5 or 3.5 h. The fact that only a small amount of ethyl 3-oxothiolvalerate was observed at −20 °C supports the series of steps proposed for ethyl 2-aceto-3-oxothiolvalerate formation.

**Alkylation of Thiol Ester Enolates.** In contrast to the reactions of enolate anions of oxygen esters with alkyl halides from which higher homologues of the starting ester are obtained,[25,26] the enolate anion of ethyl thiolacetate failed to react with methyl iodide at 0 °C when isopropylmagnesium bromide was used as base, giving only the acetoacetic thiol ester (Table III); no ethyl thiolpropionate could be detected.

Several unsuccessful attempts were made to effect Michael reactions (Table III). No ethyl 5-oxothiolcaproate was observed when thiol ester enolate anion was stirred with methyl vinyl ketone (eq 7). From the enolate formed

$$ClMgCH_2COSEt + CH_2{=}CHCOCH_3 \rightarrow NR \quad (7)$$

by the reaction of ethyl thiolpropionate with isopropylmagnesium chloride was obtained only the Claisen con-

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Table III. Alkylation and Acylation Products of Thiol Ester Enolates

| thiol ester | R''X | base | products (rel yield, %) |
|---|---|---|---|
| $CH_3COSEt$ | $CH_3I$ | $(CH_3)_2CHMgCl$ | $CH_3COCH_2COSEt$ |
| $CH_3COSEt$ | $CH_3CH_2COCl$[a] | $(CH_3)_2CHMgCl$ | $CH_3COCH_2COSEt$ (1)<br>$CH_3CH_2COCH(COCH_3)COSEt$ (2.6) |
| $CH_3COSEt$ | $CH_3CH_2COCl$[b] | $(CH_3)_2CHMgCl$ | $CH_3COCH_2COSEt$ (5.3)<br>$CH_3CH_2COCH_2COSEt$ (1) |
| $CH_3COSEt$ | $CH_3CH_2CO_2Et$ | $(CH_3)_2CHMgCl$ | $CH_3COCH(CH_3)CO_2Et$ (1)<br>$CH_3CH_2COCH(CH_3)CO_2Et$ (2.4)<br>$CH_3COCH_2COSEt$ (34.7)<br>$CH_3CH_2COCH_2COSEt$ (14.3) |
| | | NaH | $CH_3COCH(CH_3)CO_2Et$ (1)<br>$CH_3CH_2COCH(CH_3)CO_2Et$ (1)<br>$CH_3COCH_2COSEt$ (12.2)<br>$CH_3CH_2COCH_2COSEt$ (1.4) |
| $CH_3CH_2COSEt$ | $CH_3CO_2Et$ | $(CH_3)_2CHMgCl$ | $CH_3CH_2COCH(CH_3)COSEt$ |
| $CH_3COSEt$ | $CH_3COCH=CH_2$ + EtSH | LiSEt | $CH_3COCH_2CH_2SEt$ |
| $CH_3CH_2COSEt$ | $CH_3COCH=CH_2$ | $(CH_3)_2CHMgCl$ | $CH_3CH_2COCH(CH_3)COSEt$ |

[a] At 0 °C. [b] At −20 °C.

densation product of this thiol ester. When lithium ethyl mercaptide was used as the base for the generation of the ethyl thiolacetate enolate only starting materials were recovered.

These reactions would be expected to proceed to completion only if the enolate ion derived from the product were both stable and nonreactive with respect to subsequent Michael addition, a most unlikely event. In fact, Michael-type additions are generally carried out in the presence of a good proton source to quench the enolate of the product.[27] To facilitate this, generation of the thiol ester enolate anion was attempted by using lithium ethyl mercaptide as the base in the presence of ethyl mercaptan. Neither Claisen condensation product nor Michael addition product of thiol ester was obtained but, rather, a 50% yield of the Michael adduct of the mercaptan 4-(ethylmercapto)-2-butanone (13).

$$CH_3COCH_2CH_2SCH_2CH_3$$
**13**

**Mixed Claisen Condensations.** Mixed-ester Claisen condensations of ethyl thiolacetate and ethyl propionate were carried out by using both sodium hydride and isopropylmagnesium chloride as bases in order to assess the possibility of selectivity (Table III). Of the four possible β-keto esters, the major products of the mixed ester Claisen condensation of an ester and a thiol ester were the self-condensation products of the thiol ester followed by the condensation product of the thiol ester anion with the oxygen ester. These two β-keto thiol esters account for approximately 94% of the total β-keto esters obtained. This is a result of two factors: the thiol ester is more acidic than the oxygen ester,[28] and the thiol ester is more reactive to nucleophiles than the oxygen ester.

In order to exclude the possibility of a steric effect in the mixed ester condensation, we carried out the Claisen condensation of ethyl thiolpropionate and ethyl acetate using isopropylmagnesium chloride as base. Only ethyl 2-methyl-3-oxothiolvalerate was obtained.

The Dieckmann condensation of the methyl monothiol ethyl ester of adipic acid was carried out with sodium hydride and with isopropylmagnesium chloride. With sodium hydride as base, the cyclic β-keto esters formed were found to be 2-(carbomethoxy)cyclopentanone and ethyl 2-oxothiolcyclopentanecarboxylate in a 1.6:1 ratio, whereas with isopropylmagnesium chloride only the cyclic β-keto thiol ester was observed.

Thus, for mixed-ester Claisen condensation, the Grignard reagent appears to be a specific reagent for effecting the condensation of thiol esters, but sodium hydride is less specific. The synthetic implications of this are that one could effect the Claisen condensation of a thiol ester in the presence of an oxygen ester by using a hindered Grignard reagent and obtain β-keto thiol esters almost to the exclusion of any β-keto esters.

**Mechanism of the Thiol Ester Claisen Condensation.** The Claisen condensation of oxygen esters appears to involve an ionic mechanism, the first step of which is the abstraction of an α-hydrogen atom by the base. A similar first step seems to be involved in the Claisen condensation of thiol esters. Thus, we have observed the evolution of a quantitative amount of propane gas on the addition of isopropylmagnesium chloride to ethyl thiolacetate. In addition, deuterium-exchange studies of the reaction of thiol ester and potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d*[28,29] furnished evidence for the abstraction of an α-hydrogen atom by the base.

In principle, a second step similar to one proposed for the Claisen condensation of oxygen esters could be written for the thiol ester Claisen condensation. This involves addition of the enolate anion to a second ester molecule followed by ejection of ethyl mercaptide ion from the tetracoordinate intermediate so formed to give ethyl acetothiolacetate. On the other hand, the possibility of ejection of an ethyl mercaptide ion from the thiol ester enolate anion to provide the acylating agent, ketene, must be considered. The ketene formed in this manner could then react with either an enolate anion or a thiol ester molecule to form a β-keto thiol ester. Attempts to trap a ketene intermediate with ethyl vinyl ether were unsuccessful. This, however, does not invalidate the proposed mechanism, as the possibility that the rate of reaction of ketene with thiol esters is greater than the rate of reaction of ketene with ethyl vinyl ether must be considered.

Ketene formation has been proposed as an essential step in base-catalyzed sulfide formation from thiol esters[30] and for the hydroxide ion catalyzed hydrolysis of some nitrophenyl malonates.[31,32] The authors suggest the hydrolysis proceeds via an ElcB carbanion mechanism because of the

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good leaving group ability of the nitrophenolate anion. Similar results were observed for the hydrolysis of ethyl 2,2,2-trifluoroethylthiolmalonate[32] and acetoacetyl coenzyme A.[29]

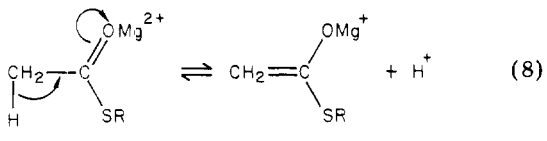
Unlike the Claisen condensation of oxygen esters, in which the formation of the enolate anion of ethyl acetoacetate is necessary for completion of the Claisen condensation, the Claisen condensation of thiol esters using isopropylmagnesium bromide does not require such a last step. Hauser[33] has noted that the acetoacetic ester condensation will be successful when a base is formed which is weaker than that used as the condensing agent. In the thiol ester condensation, a base, mercaptide ion, is formed which is weaker than the condensing base, isopropylmagnesium chloride.

This latter facet of the thiol ester Claisen condensation contributes to the facility of this condensation. As an $\alpha$-proton abstraction from the $\beta$-keto thiol ester is not a requirement, Claisen condensations of thiol esters having a single $\alpha$-proton should progress readily. The observation that ethyl thiolisobutyrate condenses in the presence of a Grignard reagent suggests this interpretation has validity; however, the magnesium ion is capable of complexing with the enolate of the acetothiolacetic acid ester, and this may contribute to the facility of the Grignard-induced Claisen condensation in cases where an $\alpha$-proton is available. Furthermore, the magnesium forms an insoluble mercaptide salt as evidenced by precipitate formation on addition of isopropylmagnesium chloride to ethyl mercaptan.

In the condensations using sodium hydride as the base, but not in those using isopropylmagnesium chloride as base, a small amount (~1%) of ethyl disulfide is observed in the reaction mixture. This material could have been derived from the air oxidation of the ethyl mercaptan.

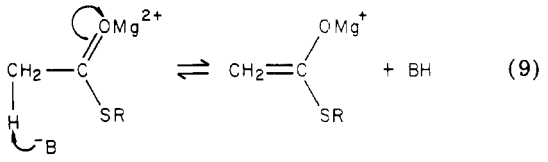
The similarity in complexing ability of lithium and magnesium may explain the fact that both magnesium and lithium salts of ethyl mercaptan effect the condensation of ethyl thiolpropionate, whereas the potassium and calcium salts give no $\beta$-keto thiol ester products. Because the base, the ethyl mercaptide ion, is the same, it is not unreasonable to propose that the complexation of the $\beta$-keto thiol ester by the cation contributes to the difference in the results obtained with the various mercaptide bases. In fact, a parallelism with the published[34] stability constants of metal acetylacetonates exists. Magnesium, which has the largest formation constant, gives the best yield when it is the counterion for the mercaptide base, while potassium, which has the lowest equilibrium constant, gives only starting materials.

The role of the metal ion in polarizing the thiol ester carbonyl and thereby increasing the $\alpha$-hydrogen atom acidity must be considered. In studying the malate synthetase system, Eggerer and Klette[35] observed that the addition of magnesium ions increased the rate of enolization of acetyl coenzyme A, which they attributed to a binding of the metal to the carbonyl oxygen atom, resulting in a more facile removal of the $\alpha$-hydrogen atom (eq 8).




(8)

The observed similarity in complexation ability of lithium suggests that lithium may have a similar effect. Enolization may be effected by a pathway similar to the "cooperative" pathway suggested by Eggerer and Klette[35] for the malate synthase system. The base-catalyzed enolization may be assisted by Lewis acid polarization (eq 9). These statements must be tempered, however, by the




(9)

lack of data on the relative solubility of the mercaptide salts in either ether or benzene. Thus, the differences in the observed results in the thiol ester Claisen condensation may be the result of a lower solubility of the calcium and potassium salts. The mercaptide salts were generated by adding ethyl mercaptan to *n*-butyllithium, isopropylmagnesium chloride, calcium hydride, or potassium methoxide. The latter were only slightly soluble in the solvents used and were stirred with ethyl mercaptan until no more gas evolution could be observed. In view of the lack of solubility data on mercaptide salts, even if a quantitative amount of these salts were formed, no definitive statement could be made about their relative reactivities.

It is quite likely that the differences in yields obtained with the different metal mercaptides are due to a contribution from both of the above-mentioned factors. The solubility of magnesium chloro mercaptide may be lower than that of the lithium mercaptide, but the stability of the resulting ethyl-2-methyl-3-oxothiovalerato metal chelate of magnesium may be so much larger than its lithium analogue that the yields with the former base will be greater.

## Experimental Section

Boiling points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 521 spectrometer. NMR spectra were recorded with a Varian Associates Model A-60 spectrometer. Mass spectra were performed on a Hitachi Model RMU-6E single-focusing mass spectrometer. GC analyses were carried out on an Aerograph Model 202B vapor-phase chromatograph employing helium as carrier gas and a $^1/_4$ in. × 6 ft column of SE-30 on 60/80 Chromosorb W with an injection port temperature of 165–185 °C and a detector temperature of 185–200 °C. Microanalyses were performed by Galbraith Laboratories, Inc.

**General Method for Claisen Condensations of Thiol Esters with Isopropylmagnesium Chloride. Method A.** A solution of 6.2 g (0.06 mol) of ethyl thiolacetate in 20 mL of ether was added dropwise to 20 mL of a 3 M THF solution of isopropylmagnesium chloride in 50 mL of ether at −20 °C. The mixture was stirred at ice-bath temperature for 100 min. During this period the mixture turned from dark yellow to pale yellow. To the solution, maintained in an ice bath, were added 6 mL of hydrochloric acid and 6 g of ice. The layers were separated, and the organic portion was extracted with 18 mL of 5% sodium bicarbonate solution and dried over sodium sulfate.

The mixture was concentrated under vacuum (3.8 mm). GC showed one component in the remaining volatile material. The yield was 90% based on unrecovered starting material: NMR ($CDCl_3$) $\delta$ 1.20 (t, 3 H), 2.18 (s, 3 H), 2.88 (q, 2 H), 3.65 (s, 2 H); the NMR showed a 22% enol content with peaks at $\delta$ 1.88 (s, 3 H), 5.60 (s, 1 H), and 12.47 (s, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 146 ($M^+$, 10.8), 104 (20), 85 (43.8); IR (neat) 1618, 1674 (C=O, thiol ester), 1719 $cm^{-1}$ (C=O, ketone).

**Ethyl 2-Methyl-3-oxothiovalerate.** The procedure of method A was followed with 11.8 g (0.10 mol) of ethyl thiolpropionate and 0.12 mol of isopropylmagnesium chloride. Ethyl 2-methyl-3-oxothiolvalerate (7.34 g, 84%) was isolated by vacuum distillation: bp 49 °C (0.1 mm); NMR ($CDCl_3$) $\delta$ 0.95–1.43 (m, 9 H), 2.60 (q,

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2 H), 2.94 (q, 2 H), 3.95 (q, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 174 ($M^+$, 8), 118 (18.2), 113 (8), 89 (18.2), 57 (100); IR (neat) 1675 (C=O, thiol ester), 1725 $cm^{-1}$ (C=O, ketone). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.30; H, 8.16; S, 18.61.

**Ethyl 2-Ethyl-3-oxothiolhexanoate.** The procedure of method A was followed with 5.3 g (0.04 mol) of ethyl thiolbutyrate and 0.04 mol of isopropylmagnesium chloride. The ethyl 2-ethyl-3-oxothiolhexanoate (2.61 g, 74.2%) was obtained by distillation: bp 104 (2.2 mm)–109 °C (2.0 mm); NMR ($CDCl_3$) $\delta$ 0.90 and 0.92 (2 t, 6 H), 1.25 (t, 3 H), 1.82 (m, 4 H), 2.50 (m, 2 H), 2.93 (q, 2 H), 3.73 (t, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 202 ($M^+$, 1.4), 141 (2), 132 (3.9), 71 (100), 43 (66.2); IR (neat) 1672 (C=O, thiol ester), 1724 $cm^{-1}$ (C=O, ketone). Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97; S, 15.80. Found: C, 59.13; H, 8.70; S, 15.63.

**Ethyl 2,2,4-Trimethyl-3-oxothiolvalerate.** The procedure of method A was followed with 5.3 g (0.04 mol) of ethyl thiolisobutyrate and 0.05 mol of isopropylmagnesium chloride.

The ethyl 2,2,4-trimethyl-3-oxothiolvalerate (0.87 g, 41%) was obtained by distillation: bp 101–106 °C (1.5 mm); NMR ($CDCl_3$) $\delta$ 0.86 (d, 3 H), 0.98 (d, 3 H), 1.25 (t, 3 H), 1.27 (s, 3 H), 1.32 (s, 3 H), 1.83 (m, 1 H), 2.80 (q, 2 H); mass spectrum (80 eV), *m/e* (relative intensity) 202 ($M^+$, 0.1), 143 (30), 132 (45), 99 (20), 71 (87.5), 70 (42.5), 43 (100); IR (neat) 1670 $cm^{-1}$. Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97; S, 15.80. Found: C, 59.58; H, 9.18; S, 15.45.

***tert*-Butyl Acetothiolacetate.** The procedure of method A was followed with 4.0 g (0.03 mol) of *tert*-butyl thiolacetate and 0.03 mol of isopropylmagnesium chloride. The mixture after vacuum concentration was analyzed for *tert*-butyl acetothiolacetate by GC, and a yield of 59% was determined. An analytical sample was collected by preparative GC: NMR ($CDCl_3$) $\delta$ 1.48 (s, 9 H), 2.27 (s, 3 H), 3.75 (s, 2 H); mass spectrum (80 eV), *m/e* (relative intensity) 174 ($M^+$, 0.2), 132 (7), 118 (5), 85 (23), 57 (100); IR (neat) 1620, 1675 (C=O, thiol ester), 1720 $cm^{-1}$ (C=O, ketone). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.38; H, 8.34; S, 18.38.

**Ethyl 2-Oxothiolcyclopentanecarboxylate.** The procedure of method A was followed with 4.7 g (0.02 mol) of diethyl thioladipate and 0.04 mol of isopropylmagnesium chloride. Ethyl 2-oxothiolcyclopentanecarboxylate (0.90 g, 49%) was obtained by distillation: bp 105 (2.9 mm)–110 °C (2.5 mm); NMR ($CDCl_3$) $\delta$ 1.25 (t, 3 H), 2.13 (m, 6 H), 2.91 (q, 2 H), 3.38 (t, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 172 ($M^+$, 17.5), 111 (100), 83 (20.5), 55 (58.5); IR ($CCl_4$) 1620, 1675 (C=O, thiol ester), 1750 $cm^{-1}$ (C=O, ketone). Anal. Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.03; S, 18.61. Found: C, 55.95; H, 7.28; S, 18.33.

**Ethyl 2-Oxothiolcyclohexanecarboxylate.** The procedure of method A was followed with 5.0 g (0.02 mol) of diethyl thiolpimelate in 20 mL of ether and 0.04 mol of isopropylmagnesium chloride. The ethyl 2-oxothiolcyclohexanecarboxylate (1.23 g, 60%) was obtained by distillation: bp 90–95 °C (0.4 mm); NMR ($CDCl_3$) $\delta$ 1.30 (t, 3 H), 1.70 (m, 4 H), 2.30 (m, 4 H), 2.93 (q, 2 H), 13.07 (s, 1 H); IR ($CHCl_3$) 1560, 1615 $cm^{-1}$ (C=O, thiol ester); mass spectrum (80 eV), *m/e* (relative intensity) 186 ($M^+$, 0.7), 121 (1.4), 98 (16.8), 97 (4.9), 70 (28.7), 69 (43.4). Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.23; H, 7.80; S, 17.09.

**Claisen Condensation of Ethyl Thiolpropionate with *n*-Butyllithium.** A solution of 4.9 g (0.04 mol) of ethyl thiolpropionate in 20 mL of ether was added dropwise to 23.8 mL of a 2.1 M hexane solution of *n*-butyllithium in 40 mL of ether at −20 °C. The mixture was then stirred at ice-bath temperature for 70 min. Workup was as in method A with 6 g of ice, 6 mL of hydrochloric acid, and 20 mL of 5% sodium bicarbonate solution. Fractional vacuum distillation gave 1.37 g of ethyl 2-methyl-3-oxothiolvalerate, 41.4% based on unrecovered starting material.

**Claisen Condensation of Ethyl Thiolpropionate with Lithium Ethyl Mercaptide in Refluxing Ether.** A solution of 3.0 g (0.05 mol) of ethyl mercaptan in 20 mL of ether was added dropwise to a solution of 24 mL (2.1 M in hexane, 0.05 mol) of *n*-butyllithium in 50 mL of ether, and the mixture was stirred at reflux for 1 h. A solution of 4.9 g (0.04 mol) of ethyl thiolpropionate in 20 mL of ether was added, and the mixture was stirred at reflux overnight. After the mixture was cooled to ice-bath temperature, workup was as in method A with 6 g of ice, 6 mL of hydrochloric acid, and 20 mL of 5% sodium bicarbonate solution. Gas chromatography showed 0.25 g of ethyl 2-methyl-3-oxothiolvalerate, 20% based on unrecovered starting material.

In a similar manner, reactions run at ice-bath temperature and in refluxing benzene gave 13% and a trace of ethyl 2-methyl-3-oxothiolvalerate, respectively.

**Claisen Condensation of Ethyl Thiolpropionate with Magnesium Chloroethyl Mercaptide in Refluxing Benzene.** A solution of 3.1 g (0.05 mol) of ethyl mercaptan in 20 mL of benzene was added dropwise to a solution of 19 mL (2.63 M in ether, 0.05 mol) of isopropylmagnesium chloride in 50 mL of benzene. After this mixture was stirred for 3 h at 40 °C, a solution of 4.7 g (0.04 mol) of ethyl thiolpropionate in 20 mL of benzene was added and the mixture brought to reflux. An additional 20 mL of benzene was added, and the mixture was stirred overnight at reflux. After the mixture cooled, workup was as before with 8 g of ice, 8 mL of hydrochloric acid, and 30 mL of 5% sodium bicarbonate solution. GC showed 1.22 g of ethyl 2-methyl-3-oxothiolvalerate, 50% based on unrecovered starting material.

In a similar manner, reactions run at refluxing ether and ice-bath temperatures gave 40 and 0% ethyl 2-methyl-3-thiolvalerate, respectively.

**Claisen Condensation of Ethyl Thiolpropionate with Potassium Ethyl Mercaptide in Refluxing Benzene.** To potassium methoxide (3.5 g, 0.05 mol) in 50 mL of refluxing benzene was added 6.2 g (0.10 mol) of ethyl mercaptan in 20 mL of benzene. After 1.5 h, a solution of 4.7 g (0.04 mol) of ethyl thiolpropionate in 30 mL of benzene was added, and the mixture was stirred at reflux overnight. After 2 h, an additional 20 mL of benzene was added. When the mixture cooled, workup was as in method A with 6 g of ice, 6 mL of hydrochloric acid, and 20 mL of 5% sodium bicarbonate solution. Gas chromatography failed to show the presence of either ethyl 2-methyl-3-oxothiolvalerate or methyl propionate.

A similar reaction run in refluxing ether also failed to give any of the intended product.

**Claisen Condensation of Ethyl Thiolpropionate with Calcium Ethyl Mercaptide in Refluxing Benzene.** The reaction was run according to the preceding procedure with 9.3 g (0.15 mol) of ethyl mercaptan in 20 mL of benzene, 2.1 g (0.05 mol) of calcium hydride in 50 mL of benzene, and 4.7 g (0.04 mol) of ethyl thiolpropionate in 30 mL of benzene. Workup was as in method A with 10 g of ice, 10 mL of hydrochloric acid, and 40 mL of 5% sodium bicarbonate solution. GC failed to show the presence of the intended product.

**Reaction of Ethyl Thiolacetate and Propionyl Chloride with Isopropylmagnesium Chloride. Method B.** A solution of 5.2 g (0.05 mol) of ethyl thiolacetate in 20 mL of ether was added dropwise to a solution of 0.05 mol of isopropylmagnesium chloride in 59 mL of ether at −20 °C. A solution of 4.6 g (0.05 mol) of propionyl chloride in 20 mL of ether was added dropwise at −20 °C, and the reaction was stirred at ice-bath temperature for 100 min. Workup was as in method A with 11 g of ice, 11 mL of hydrochloric acid, and 40 mL of 5% sodium bicarbonate solution. GC showed the presence of ethyl acetothiolacetate and ethyl 2-aceto-3-oxothiolvalerate in a 1:2.6 ratio. A sample of ethyl 2-aceto-3-oxothiolvalerate was isolated by preparative gas chromatography: NMR ($CDCl_3$) $\delta$ 1.16 and 1.33 (2 t, 6 H), 2.18 (s, 3 H), 2.35 (q, 3 H), 3.00 (q, 2 H), 16.53 (s, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 202 ($M^+$, 0.6), 141 (79), 99 (31), 85 (90), 57 (90), 43 (100); IR (neat) 1595, 1654 $cm^{-1}$. Anal. Calcd for $C_9H_{14}O_3S$: C, 53.44; H, 6.98; S, 15.85. Found: C, 53.40; H, 7.13; S, 15.67.

**Reaction of Ethyl Thiolacetate and Propionyl Chloride with Isopropylmagnesium Chloride at −20 °C.** The reaction was run as above with 5.2 g (0.05 mol) of ethyl thiolacetate in 20 mL of ether, 0.05 mol of isopropylmagnesium chloride in 69 mL of ether, and 4.6 g (0.05 mol) of propionyl chloride in 20 mL of ether precooled to −20 °C. The mixture was stirred for 3 h at −17 °C. A solution of 10 mL of acetic acid in 30 mL of ether, precooled to −20 °C, was added all at once. After warming, the mixture, containing a white precipitate, was washed with four 25-mL portions of water and shaken with a 5% sodium bi-

carbonate solution to neutrality, and the organic portion was dried over sodium sulfate. Upon removal of the ether under reduced pressure, gas chromatography showed the product mixture to contain ethyl acetothiolacetate and ethyl 3-oxothiolvalerate in a 5.3:1 ratio.

**Reaction of Ethyl Thiolacetate and Methyl Iodide with Isopropylmagnesium Chloride.** The procedure of method B was followed with 5.2 g (0.05 mol) of ethyl thiolacetate in 30 mL of ether, 0.05 mol of isopropylmagnesium chloride in 59 mL of ether, and 7.3 g (0.05 mol) of methyl iodide in 20 mL of ether. Stirring at ice-bath temperature was for 100 min. Workup was with 6 g of ice, 6 mL of hydrochloric acid, and 18 mL of 5% sodium bicarbonate solution. Upon removal of the ether under reduced pressure, ethyl acetothiolacetate was the only product detected by gas chromatography.

**Cross Condensation of Ethyl Thiolacetate and Ethyl Propionate with Sodium Hydride in Refluxing Benzene.** A mixture of 5.01 g (0.048 mol) of ethyl thiolacetate and 5.07 g (0.049 mol) of ethyl propionate was added dropwise to 1.77 g (0.074 mol) of sodium hydride in 10 mL of benzene. The mixture was stirred overnight under reflux. After the mixture was cool, methanol was added to destroy excess sodium hydride, ether was added to make the mixture fluid, and the mixture was poured into a 50% acetic acid solution. The mixture was extracted twice with ether, once with water, and with sodium bicarbonate solution until acid free and dried over sodium sulfate. The crude product was separated on a 2-ft silica gel column, eluting first with benzene and then with a 1% ether–benzene solution. The material collected was that which gave a positive ferric chloride test. A total of 0.37 g of a mixture of products was collected. GC showed the presence of ethyl 2-methyl-3-oxobutyrate, ethyl 2-methyl-3-oxovalerate, ethyl acetothiolacetate, and ethyl 3-oxothiolvalerate in a 1:1:10.9:1.4 ratio.

**Cross Condensation of Ethyl Thiolacetate and Ethyl Propionate with Isopropylmagnesium Chloride.** A mixture of ethyl thiolacetate (5.2 g, 0.05 mol) and ethyl propionate (5.1 g, 0.05 mol) in 30 mL of ether was added dropwise to a solution of 0.10 mol of isopropylmagnesium chloride in 88 mL of ether at −20 °C. The mixture was stirred at ice-bath temperature for 80 min, after which 10 mL of hydrochloric acid and 10 g of ice were added while the temperature was kept below 8 °C. The layers were separated, and the organic portion was extracted with 30 mL of 5% sodium bicarbonate solution and dried over sodium sulfate. GC revealed the molar ratios of ethyl 2-methyl-3-oxobutyrate, ethyl 2-methyl-3-oxovalerate, ethyl acetothiolacetate, and ethyl 3-oxothiolvalerate to be 1:2.4:34.7:14.3.

The ethyl 3-oxothiolvalerate was isolated by preparative gas chromatography: NMR ($CDCl_3$) $\delta$ 1.07 and 1.27 (2 t, 6 H), 2.58 (q) and 2.93 (q, 4 H), 3.65 (s, 2 H); mass spectrum (80 eV), *m/e* (relative intensity) 160 ($M^+$, 4.9), 99 (23.3), 57 (71.7); IR (neat) 1620, 1677 (C=O, thiol ester), 1718 $cm^{-1}$ (C=O, ketone). Anal. Calcd for $C_7H_{12}O_2S$: C, 52.46; H, 7.55; S, 20.01. Found: C, 52.68; H, 7.59; S, 20.17.

**Cross Condensation of Ethyl Thiolpropionate and Ethyl Acetate with Isopropylmagnesium Chloride.** The reaction was run as above with 4.7 g (0.04 mol) of ethyl thiolpropionate and 3.5 g (0.04 mol) of ethyl acetate in 30 mL of ether and 0.08 mol of isopropylmagnesium chloride in 80 mL of ether. Stirring at ice-bath temperature was for 90 min. Workup was as before with 12 g of ice, 12 mL of hydrochloric acid, and 30 mL of 5% sodium bicarbonate solution. The ether and ethyl acetate were removed by distillation at atmospheric pressure, and 0.51 g of the latter was collected. Both gas chromatography and silica gel TLC of the product mixture showed the presence of only ethyl 2-methyl-3-oxothiolvalerate.

**Condensation of *O*-Methyl *S*-Ethyl Thioladipate with Sodium Hydride.** To sodium hydride (1.32 g, 0.05 mol) in 12 mL of refluxing toluene in a three-necked flask equipped with a Hershberg stirrer, dropping funnel, reflux condenser, and calcium chloride drying tube was added *O*-methyl *S*-ethyl thioladipate (9.38 g, 0.046 mol) dropwise over a period of 2 h, and the mixture was stirred at reflux for another 5 h. Toluene was added from time to time to keep the mixture fluid; approximately 50 mL was added. The mixture was cooled in an ice bath and 100 mL of 10% acetic acid solution, cooled to 0 °C, was added all at once. The toluene layer was separated and the aqueous layer washed once with toluene and twice with ether. The combined organic portions were washed once with 50 mL of water, twice with 50 mL of cooled 7% sodium carbonate solution, and once with 50 mL of water and dried over sodium sulfate. The ether was removed under reduced pressure, and the toluene was removed by distillation. GC showed the presence of 2-(carbomethoxy)cyclopentanone and ethyl 2-oxothiolcyclopentanecarboxylate in a 1.6:1 ratio. Mass spectroscopy confirmed the nature of these products.

**Condensation of *O*-Methyl *S*-Ethyl Thioladipate with Isopropylmagnesium Chloride.** The procedure of method A was followed with 4.1 g (0.02 mol) of *O*-methyl *S*-ethyl thioladipate in 20 mL of ether and 13 mL of a 3 M THF solution of isopropylmagnesium chloride in 60 mL of ether. Stirring at ice-bath temperature was for 90 min. Workup was as before with 6 g of ice, 6 mL of hydrochloric acid, and 20 mL of 5% sodium bicarbonate solution. The ether was removed under reduced pressure and the product mixture analyzed by gas chromatography. A yield of 0.51 g (35%) of ethyl-2-oxothiolcyclopentanecarboxylate was obtained as the only product.

**Registry No.** **1**, 625-60-5; **2**, 3075-23-8; **4b**, 41726-58-3; **4c**, 32892-97-0; **5b**, 71687-33-7; **5c**, 71687-34-8; **6** (R = Et), 2432-42-0; **7** (R = Et), 60888-03-1; **8** (R = Et), 20807-99-2; **9** (R = Et), 24468-86-8; **10** (R = Et), 2432-50-0; **11** (R = Et), 73636-30-3; **12**, 24761-70-4; **13**, 61224-82-6; *tert*-butyl acetothiolacetate, 15925-47-0; *tert*-butyl thiolacetate, 999-90-6; propionyl chloride, 79-03-8; ethyl 3-oxothiolvalerate, 63883-28-3; ethyl propionate, 105-37-3; ethyl 2-methyl-3-oxobutyrate, 609-14-3; ethyl 2-methyl-3-oxovalerate, 759-66-0; ethyl acetate, 141-78-6; *O*-methyl *S*-ethyl thioladipate, 73636-31-4; 2-(carbomethoxy)cyclopentanone, 10472-24-9; $CH_3COCH{=}CH_2$, 78-94-4.