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A New Synthetic Approach to Esters of β-Keto Thiocarboxylic *S*-Acids

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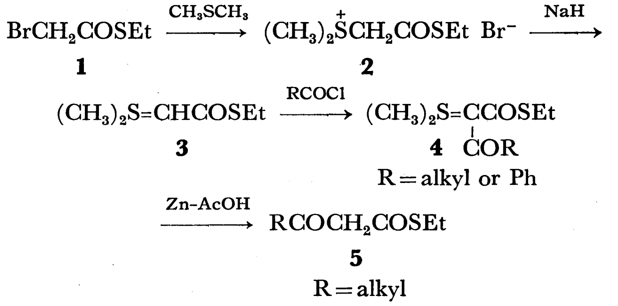
Synopsis. Esters of β-keto thiocarboxylic *S*-acids (**5**) were synthesized from *S*-ethyl bromothioacetate (**1**), through a reaction sequence involving the reduction of sulfonium ylides (**4**) with zinc in acetic acid.

S-Ethyl acetothioacetate (**5a**) reacts with mercury(II) oxide to afford diacetylacetone and mercury(II) ethanethiolate, along with carbon dioxide.[1] Since the corresponding oxygen ester dose not react with mercury(II) oxide in a similar way, we thought it of interest to develop a general method of preparing esters of β-keto thiocarboxylic *S*-acids.

Esters of acetothioacetic *S*-acid, representative esters of β-keto thiocarboxylic *S*-acid, are readily prepared by the Claisen ester condensation[2] or by the reaction of alkanethiols with diketene.[1,3] However, no other esters of β-keto thiocarboxylic *S*-acids can be obtained. In this paper, we wish to report a new general route for the preparation of esters of β-keto thiocarboxylic *S*-acids (**5**) starting from *S*-ethyl bromothioacetate (**1**).

S-Ethyl bromothioacetate **1**, obtained from bromoacetyl bromide and ethanethiol in the presence of triethylamine, was treated with dimethyl sulfide at room temperature for 24 h to afford [(ethylthio)carbonylmethyl]dimethylsulfonium bromide (**2**, 70%), which was deprotonated with sodium hydride in a tetrahydrofuran solution affording [(ethylthio)carbonylmethylene]dimethylsulfurane (**3**, 85%). **3** was obtained as a yellow solid (mp 50—52 °C) after evaporation of the solvent, while sulfonium ylide of the corresponding oxygen ester was obtained as a yellowish oily substance.[4] Acylation of **3** with a half-equivalent amount of acid chlorides gave new ylides, [[(ethylthio)carbonyl]acyl(or benzoyl)methylene]dimethylsulfuranes (**4**, Table 1). Ylides **4** were readily reduced with zinc in acetic acid as in the case of sulfoxonium ylides,[5] affording esters of β-keto thiocarboxylic *S*-acids (**5**, R=alkyl, Table 2)



$$\underset{\mathbf{1}}{BrCH_2COSEt} \xrightarrow{CH_3SCH_3} \underset{\mathbf{2}}{(CH_3)_2\overset{+}{S}CH_2COSEt\ Br^-} \xrightarrow{NaH}$$

$$\underset{\mathbf{3}}{(CH_3)_2S{=}CHCOSEt} \xrightarrow{RCOCl} (CH_3)_2S{=}\underset{\underset{COR}{|}}{C}COSEt \quad \mathbf{4}$$

R = alkyl or Ph

$$\xrightarrow{Zn\text{-}AcOH} \underset{\mathbf{5}}{RCOCH_2COSEt}$$

R = alkyl

TABLE 1. YIELDS AND PHYSICAL DATA FOR SULFONIUM YLIDES (**4**)

	R	Yield[a)] (%)	Mp (°C)	IR[b)] (C=O) (cm^{-1})	NMR (δ) in CDCl$_3$	Anal, S% Found	Anal, S% Calcd
4a	Me	53	107—108	1640 1590	1.28 (t, 3H), 2.44 (s, 3H) 2.90 (q, 2H), 3.03 (s, 6H)	31.32	31.08
4b	Et	46	78—79	1620 1585	1.09 (t, 3H), 1.27 (t, 3H) 2.84 (q, 2H), 2.88 (q, 2H) 3.02 (s, 6H)	29.18	29.10
4c	iso-Pr	69	137—138	1600 1570	1.07 (d, 6H), 1.25 (t, 3H) 2.85 (q, 2H), 3.01 (s, 6H) 3.55 (m, 1H)	27.14	27.36
4d	*t*-Bu	52	188—189	1590 1560	1.26 (t, 3H), 1.28 (s, 9H) 2.83 (q, 2H), 3.00 (s, 6H)	26.01	25.81
4e	Ph	77	169—170	1590 1550	1.24 (t, 3H), 2.83 (q, 2H) 2.94 (s, 6H), 7.35 (s, 5H)	23.71	23.89

a) Based on acid chlorides used. b) In Nujol.

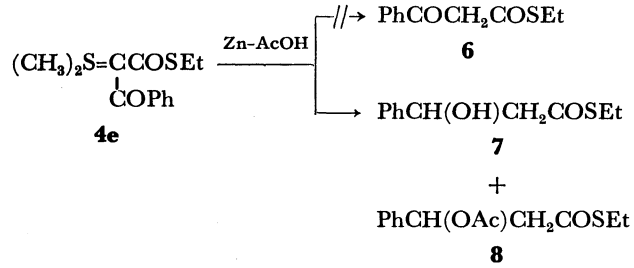
TABLE 2. YIELDS AND PHYSICAL DATA FOR ESTERS OF β-KETO THIOCARBOXYLIC *S*-ACIDS (**5**)

	R	Yield[a)] (%)	Bp (°C/Torr)	IR[b)] (C=O) (cm^{-1})	Enol %[c)]	Anal, S% Found	Anal, S% Calcd
5a	Me	50	80/8	1725 1680 1625	33[d)]		
5b	Et	43	81/5	1730 1680 1620	33	19.75	20.01
5c	iso-Pr	57	88—90/6	1720 1685 1605	56	18.46	18.40
5d	*t*-Bu	53	85/6	1725 1680 1620	63	17.03	17.03

a) Based on sulfonium ylides **4** used. b) In liquid film. c) Estimated from integration of the NMR signal.
d) Lit,[2] 30.8%.

in moderate yields.

On the other hand, reduction of ylide **4e** (R=Ph) did not give the expected compound *S*-ethyl benzoylthioacetate (**6**), but afforded *S*-ethyl 3-hydroxy-3-phenylpropanethioate (**7**, 15%) and *S*-ethyl 3-acetoxy-3-phenylpropanethioate (**8**, 38%).



Experimental

All the melting points and boiling points are uncorrected. The IR spectra were obtained on a Hitachi EPI-G2 spectrometer and the NMR spectra on a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-7M mass spectrometer at 70 eV by a direct insertion technique.

S-Ethyl Bromothioacetate (1). Bromoacetyl bromide (101 g, 0.5 mol) was added dropwise over a 1 h-period at 0—5 °C with stirring to a solution of ethanethiol (37.3 g, 0.6 mol) and triethylamine (50.5 g, 0.5 mol) in ether (200 ml). The reaction mixture was stirred at the same temperature for 5 h and then poured into water (200 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined ether solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Distillation of the residue gave 65.9 g (72%) of **1**. Bp 60 °C/5 Torr; IR (liquid film): 1685 cm^{-1} (COS). Found: S, 17.63%. Calcd for C_4H_7OSBr: S, 17.51%.

Sulfonium Bromide 2. Treatment of *S*-ethyl ester **1** (54.9 g, 0.3 mol) with dimethyl sulfide (27.9 g, 0.45 mol) at room temperature for 24 h afforded 51.5 g (70%) of **2**. Recrystallization from ether–ethanol gave a pure sample. Mp 117—118 °C; IR (Nujol): 1670 cm^{-1} (COS); NMR (trifluoroacetic acid): δ 1.36 (t, 3H), 3.15 (s, 6H), 3.16 (q, 2H), 4.75 (s, 2H). Found: C, 26.15%. Calcd for $C_6H_{13}OS_2Br$: S, 25.97%.

Sulfonium Ylide 3. Sodium hydride (5.76 g, 0.2 mol), free of mineral oil, was added portionwise with stirring to a suspension of sulfonium bromide **2** (49 g, 0.2 mol) in tetrahydrofuran (150 ml). After stirring for 10 h at room temperature, the precipitate was filtered off and the filtrate was concentrated to afford 27.9 g (85%) of crude ylide **3**. Mp 50—52 °C; IR (Nujol): 1600 cm^{-1} (COS); NMR ($CDCl_3$): δ 1.24 (t, 3H), 2.83 (q, 2H), 2.88 (s, 6H), 3.58 (s, 1H).

General Procedure for Acylation of 3. An acid chloride (0.1 mol) was added dropwise to a solution of *S*-ethyl ester ylide **3** (0.2 mol) in benzene (250 ml), the temperature being kept below 30 °C by occasional cooling. After being stirred at room temperature for 24 h, the precipitate ([(ethylthio)-carbonylmethyl] dimethylsulfonium chloride, mp 150—151 °C) was filtered off. Addition of hexane to the filtrate resulted in the precipitation of a new ylide **4** (Table 1).

General Procedure for Reduction of 4. Zinc powder (0.25 mol) was added in many portions to a solution of a ylide **4** (0.05 mol) in acetic acid (50 ml), the temperature being kept below 20 °C with external cooling. The reaction mixture was stirred at 15—20 °C for 30 h. The insoluble material was filtered and washed with ether. Concentration of the filtrate afforded a crude product, which was purified by distillation. Yields and physical properties of **5** thus obtained are shown in Table 2. The NMR data (in CCl_4, δ) of **5** are as follows: **5a**: 1.25 (t), 1.92 (s), 2.19 (s), 2.90 (q), 3.63 (s), 5.43 (s), 12.66 (s). **5b**: 1.02 (t), 1.27 (t), 2.20 (q), 2.54 (q), 2.90 (q), 3.59 (s), 5.38 (s), 12.70 (s). **5c**:[6] 1.08 (d), 1.14 (d), 1.28 (t), 2.89 (q), 3.60 (s), 5.32 (s), 12.73 (s). **5d**: 1.15 (s), 1.28 (t), 2.89 (q), 3.65 (s), 5.37 (s), 12.94 (s).

Reduction of 4e. Zinc powder (4.9 g, 75 mmol) was added portionwise at 15—20 °C with stirring to a solution of **4e** (1.34 g, 5 mmol) in acetic acid (20 ml). The reaction mixture was stirred at the same temperature for 24 h and the insoluble material was filtered off. Concentration of the filtrate gave a colorless liquid which was subjected to column chromatography on silica gel (Wakogel C-200) to afford 158 mg (15%) of **7** and 475 mg (38%) of **8** by eluting with benzene. **7**: IR (liquid film): 1685 cm^{-1} (COS); NMR (CCl_4): δ 1.22 (t, 3H), 2.83 (d, 2H), 2.84 (q, 2H), 3.31 (s, 1H), 5.06 (t, 1H), 7.22 (s, 5H); MS *m/e*, 210 (M$^+$). **8**: IR (liqid film): 1745 (COO) and 1685 cm^{-1} (COS); NMR (CCl_4): δ 1.18 (t, 3H), 1.98 (s, 3H), 2.81 (m, 4H), 6.20 (m, 1H), 7.28 (s, 5H); MS *m/e* 252 (M$^+$).

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6) Absorption due to the methine proton of **5c** could not be assigned.