A Novel Synthesis of β-Ketothioesters[1)]

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A new general one-pot method for the high-yield synthesis of *S*-alkyl β-ketothioesters by heating of 6-mono- and 5,6-disubstituted 1,3-dioxin-4-ones and thiols in an appropriate aprotic solvent is described. This procedure is available for large-scale preparation of a variety of β-ketothioesters.

Keywords β-ketothioester; 1,3-dioxin-4-one; acylketene; thiol; cycloreversion; ketene trapping

Previously, we reported that 1,3-dioxin-4-ones A, when heated in an aprotic solvent, underwent cycloreversion to acylketene B, which reacted either with an alcohol or amine to give β-ketoacid derivatives C (X=O, NH, or NR) or with a suitable dienophile to give six-membered heterocyclic compounds D.[2)]

In this paper, we would like to report a general one-pot synthetic method of *S*-alkyl β-ketothioesters,[3)] which are important intermediates in organic synthesis.[4)]

Some of these β-ketothioesters were synthesized by Claisen condensation of the corresponding thioesters[5)] and later by the reaction of diketene or its derivatives and thiols.[6,7)] However, these methods suffered severe restriction regarding either the introduction of substituents onto α- and/or γ-positions or the kind of substituents of the product. Thus, for example, use of diketene as an acylating reagent of thiols gave only *S*-alkyl acetothioacetates as direct products. Though only the thioesters have so far been widely used as synthons (it should be noted that in addition to the effectiveness of the thioester group in transesterifica-

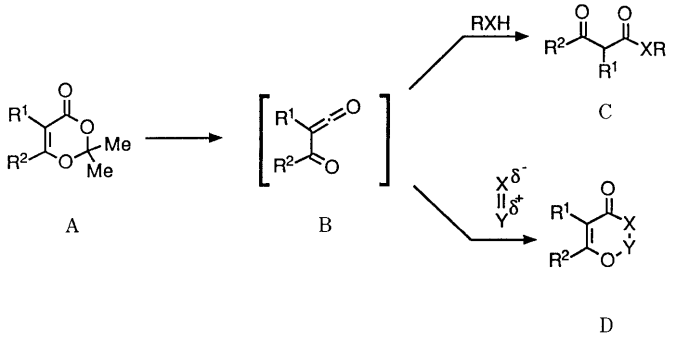

Chart 1

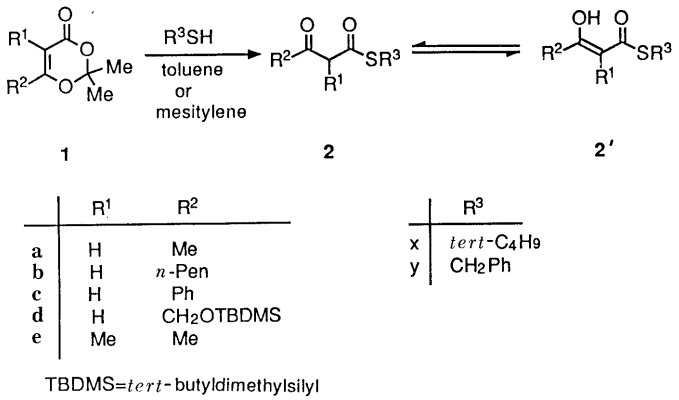

Chart 2

TABLE I. Physicochemical Properties of *S*-Alkyl β-Ketothioesters **2**

Product **2**	Yield[a)] (%)	bp (°C)/mmHg[b)] or mp (°C) (solvent)	Molecular formula or bp (°C)/mmHg	Analysis (%) Calcd (Found) C	H	S	IR ($CHCl_3$) ν (cm^{-1})
ax	85	87.5/2	48.5—52/0.7[10)]				
ay	95	100.5/0.002	$C_{11}H_{12}O_2S$ (208.1)	63.44 (63.66	5.81 6.01	15.37 15.40)	3575, 1725, 1690 (sh), 1680, 1625
bx	83	82/0.003	$C_{12}H_{22}O_2S$ (230.1)	62.57 (62.79	9.63 9.90	13.89 13,77)	3550, 1725, 1675, 1620
by	93	153/0.003	$C_{15}H_{20}O_2S$ (264.1)	68.15 (68.10	7.63 7.77	12.11 12.00)	3575, 1725, 1680, 1615
cx	93	106/0.005	$C_{13}H_{16}O_2S$ (236.1)	66.08 (66.29	6.83 7.04	13.54 13.49)	3400, 1700, 1670, 1620, 1605
cy	97	42 (Ether–pentane)	$C_{16}H_{14}O_2S$ (270.1)	71.09 (71.25	5.22 5.31	11.84 11.64)	3450, 1700, 1675, 1625 (sh), 1615, 1610 (sh)
dx	54	93/0.002	$C_{14}H_{28}O_3SSi$ (304.2)	55.24 (55.49	9.28 9.39	10.51 —[c)])	3425, 1730, 1675, 1630
dy	49	148/0.004	$C_{17}H_{26}O_3SSi$ (338.1)	60.33 (60.21	7.75 7.73	9.46 —[c)])	3550, 1730, 1680, 1630
ex	35	69/1	$C_9H_{16}O_2S$ (188.1)	57.42 (57.27	8.57 8.57	17.00 17.03)	3550, 1725, 1670, 1610
ey	86	118/0.02	$C_{12}H_{14}O_2S$ (222.1)	64.84 (65.00	6.35 6.50	14.40 14.55)	3450, 1730, 1680, 1615

a) Yield of isolated product based on **1**. *b*) Bath temperature in Büchi GKR-50 distillation. *c*) Could not be analyzed due to the presence of the Si atom.

TABLE II. ^{1}H-NMR ($CDCl_3$) Chemical Shifts [δ, J (Hz)] of α-Unsubstituted Thioesters **2**

Product **2**	Keto/enol ratio 2/2′	**2**		**2′**			Other signals
		$C\underline{H}_2COS$	R^2	$R^2C(O\underline{H})$	$=C\underline{H}COS$	R^2	
ay	3:1	3.65 (s)	2.26 (s)	12.48—12.78 (br s)	5.42 (s)	1.92 (s)	4.16 (s, $C\underline{H}_2Ph$), 7.28 (s, Ph)
bx	9:2	3.56 (s)	0.68—2.88 (m)	12.78—12.98 (br s)	5.33 (s)	0.68—2.88 (m)	1.47 (s, *tert*-Bu)
by	7:3	3.65 (s)	0.62—2.88 (m)	12.63—12.75 (br s)	5.42 (s)	0.62—2.88 (m)	4.20 (s, $C\underline{H}_2Ph$), 7.30 (s, Ph)
cx	1:1	4.09 (s)	7.11—8.13 (m)	13.40 (s)	5.96 (s)	7.11—8.13 (m)	1.46 (s, *tert*-Bu), 1.56 (s, *tert*-Bu)
cy	3:5	—[a]	7.14—8.07 (m)	13.18 (s)	6.07 (s)	7.14—8.07 (m)	7.27 (s, Ph), 7.32 (s, Ph)
dx	10:3	3.96 (s)	4.22 (s)	—[b]	5.83 (s)	4.14 (s)	0.11 (s, $SiMe_2$), 0.94 (s, *tert*-BuSi), 1.48 (*tert*-BuS)
dy	5:2	3.80 (s)	—[a]	12.34—12.64 (br)	5.76 (s)	—[a]	0.09 (s, $SiMe_2$), 0.91 (s, *tert*-BuSi), 7.28 (s, Ph)

a) Could not be identified owing to overlapping with other signals (δ 4.15—4.40). *b*) This peak could not be observed.

TABLE III. ^{1}H-NMR ($CDCl_3$) Chemical Shifts [δ, J (Hz)] of the α-Methylthioesters **2**

Product **2**	Keto/enol ratio	**2**			**2′**			Other signals
		$C\underline{H}MeCOS$	$CHMe\underline{C}OS$	MeCO	$MeCO\underline{H}$	$=\underline{C}MeCOS$	$\underline{Me}COH$	
ex	7:1	3.63 (q, J=7.2)	1.33 (d, J=7.2)	2.22 (s)	13.94 (s)	1.81 (s)	1.98 (s)	1.48 (s, *tert*-Bu)
ey	15:2	3.74 (q, J=7.4)	1.39 (d, J=7.4)	2.20 (s)	13.64 (s)	1.86 (s)	2.01 (s)	4.18 (s, $C\underline{H}_2Ph$) 7.32 (s, Ph)

tion sequences,[8] the *S-tert*-butyl thioesters are especialy useful synthons as precursors of γ-substituted acetothioacetates[4]), it is desirable to develop a more general synthetic method for *S-tert*-butyl β-ketothioesters and other derivatives allowing the introduction of a variety of substituents at desired positions. Since both the desired substituents can be introduced into any position of the dioxinone skeleton and the resulting dioxinones cyclorevert to the corresponding acylketene irrespective of the kind of substituents,[2] the route (A→C *via* B) using a variety of thiols as the trapping nucleophiles (RXH: X=S) seems to be potentially valuable.

Indeed, when 6-substituted 2,2-dimethyl-1,3-dioxin-4-ones **1a—d** (R^1=H) were refluxed in toluene containing *tert*-butyl or benzyl mercaptan, the desired *tert*-butyl (x-series) or benzyl (y-series) β-ketothioesters **2a—d** were obtaind in satisfactory yields. Due to the thermal stability of 5,6-disubstituted dioxinones,[2,9] mesitylene should be used in the preparation of α-substituted β-ketothioesters, *e.g.*, **2**ex and **2**ey. It should be noted that, though the use of 1 mol eq of benzyl mercaptan is enough for the preparation of **2** (y-series), at least twice this amount of *tert*-butyl mercaptan should be used in the above reactions owing to its low boiling point (62—65 °C) in order to attain satisfactory yields of **2** (x-series).

All the compounds exist as a mixture of keto (**2**) and enol tautomers (**2′**) in deuteriochloroform and were fully characterized by their proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra. Data for known compounds were found to be in good agreement with those reported in the literature.

The general one-pot method reported herein for the synthesis of compounds **2** usually gave much better yields than those in the literature and allows the preparation of new *S*-alkyl β-ketothioesters with a functionalized chain (R^2) or with a substituent (R^1). Based on the recent finding that some (*e.g.*, **2a**y) of the benzyl thioesters having high transesterification ability (*vide supra*) suffer baker's yeast reduction with almost 100% enantiomeric excesses,[11] further investigations are in progress aimed toward optically active *S*-alkyl β-hydroxythioester derivatives (important chiral building blocks)[12] from the β-ketothioesters that are now readily available.

Experimental

Melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO A-102 spectrophotometer and ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI spectrometer with tetramethylsilane as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Low- and high-resolution mass spectra were obtained on JEOL JMS-01SG-2 and JEOL JMS-DX-303 spectrometers, respectively.

***tert*-Butyl β-Ketothioesters 2 (x-Series); General Procedure** A solution of a 6-substituted dioxinone (**1a—d**: 0.1 mol) and *tert*-butyl mercaptan (18.0 g, 0.2 mol) in dry toluene (250 ml) was refluxed until the starting dioxinone had disappeared on thin layer chromatography (about 1—2 h). The solvent was evaporated off *in vacuo* and the residue distilled under reduced pressure or recrystallized from appropriate solvents (Table I). If 5,6-dimethyldioxinone **1e** is used in the above reaction, mesitylene should be used as the solvent instead of toluene.

Benzyl β-Ketothioesters 2a—e (y-Series); General Procedure The reactions were carried out in the same manner as described above, except that the amount of benzyl mercaptan used was 1.2 mol eq with respect to **1**.

References and Notes

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