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A Practical Synthetic Method for β-Ketoesters from Ketones

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A practical, simple, one-pot synthesis of β-ketoesters (**3**) from ketones (**1**) *via* bis(methylthio)-ketene acetals (**4**) was achieved.

Keywords——β-ketoester; bis(methylthio)ketene acetal; *C*-alkoxycarbonylation; ketone; carbon disulfide

C-Alkoxycarbonylation at the α-position of ketones is a useful method for synthesizing β-ketoesters (**3**). Dialkyl carbonate,[1] dialkyl oxalate,[2] and alkyl methoxymagnesium carbonate[3] are known to be effective reagents for this purpose. However, they have limitations. For example, the reaction of 7-chloro-4,6-dimethoxy-2,3-dihydrobenzo[*b*]furan-3-one[4] (**1a**) with dimethyl carbonate or methyl methoxymagnesium carbonate did not occur, while reaction of **1a** with acyl halides sometimes produced only *O*-alkoxycarbonylated product. That is, the reaction of **1a** with methyl chloroformate in the presence of lithium diisopropylamide produced only an 88% yield of 7-chloro-4,6-dimethoxy-3-(methoxycarbonyloxy)-benzo[*b*]furan (**2a**). On the other hand, the reaction of **1a** with methyl cyanoformate[5] in the presence of lithium diisopropylamide produced a 94% yield of 2-chloro-4,6-dimethoxy-2-methoxycarbonyl-2,3-dihydrobenzo[*b*]furan-3-one[6] (**3a**). These results indicate that methyl

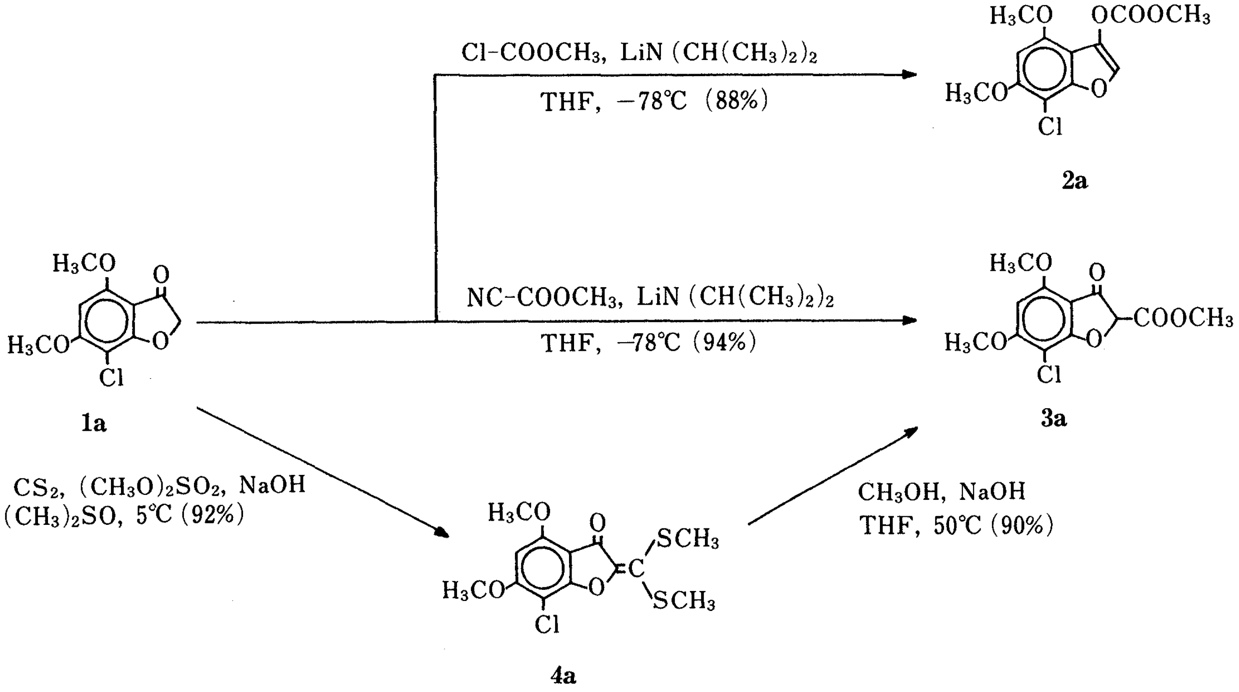
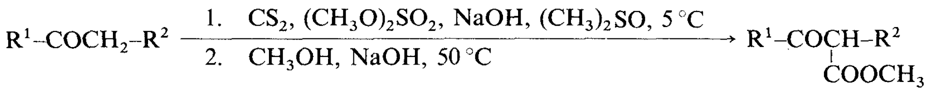


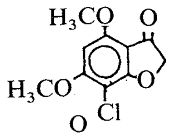
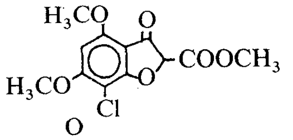
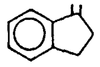
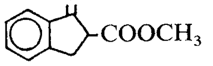
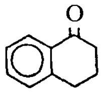
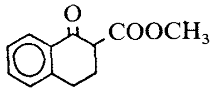
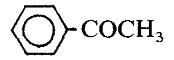
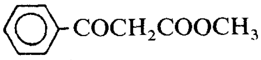
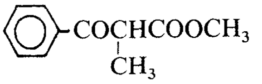
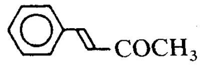
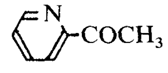
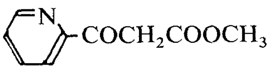
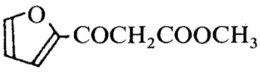
Chart 1

Table I. The β-Ketoesters **3a—h**



$$R^1\text{-COCH}_2\text{-}R^2 \xrightarrow[\text{2. CH}_3\text{OH, NaOH, 50 °C}]{\text{1. CS}_2\text{, (CH}_3\text{O)}_2\text{SO}_2\text{, NaOH, (CH}_3)_2\text{SO, 5 °C}} R^1\text{-CO}\underset{\text{COOCH}_3}{\text{CH}}\text{-}R^2$$

1a—h **3a—h**

Starting material		Product			
Compd. No.	Structure	Compd. No.	Structure	Yield (%)	^{1}H-NMR (CDCl$_3$) δ (ppm)
1a[4]		**3a**[6]		83	3.89, 4.06, 4.07 (each 3H, s, OCH$_3$), 5.25 (1H, s, CH)
1b		**3b**[9]		84	3.25—3.93 (3H, m, CHCH$_2$), 3.79 (3H, s, OCH$_3$)
1c		**3c**[10]		54	2.10—3.06 (4H, m, CH$_2$CH$_2$), 3.37—3.62 (1/2 H, m, CH), 3.75, 3.80 (each 3/2 H, s, OCH$_3$), 12.44 (1/2 H, s, OH)
1d		**3d**[11]		45	3.72 (3H, s, OCH$_3$), 3.99 (2H, s, CH$_2$)
1e		**3e**[12]		27	1.50 (3H, d, J=7 Hz, CH$_3$), 3.70 (3H, s, OCH$_3$), 4.42 (1H, q, J=7 Hz, CH)
1f		**3f**[13]		11	3.78 (3H, s, OCH$_3$), 5.18 (2H, s, CH$_2$), 6.42 (2H, d, J=16 Hz, CH=CH)
1g		**3g**[14]		25	3.69 (3H, s, OCH$_3$), 4.18 (2H, s, CH$_2$)
1h		**3h**[11]		37	3.71 (3H, s, OCH$_3$), 3.83 (2H, s, CH$_2$)

cyanoformate is an excellent *C*-selective reagent. In practice, however, use of this reagent is difficult in the large-scale preparation of β-ketoesters from corresponding ketones due to the problems of its stability and safety. Control of the reaction conditions is necessary to give good results. Therefore, the development of another convenient method for preparing **3** from ketones (**1**) is desirable.

In this paper, we wish to report a practical method for preparing **3** from α-keto-bis(methylthio)ketene acetals (**4**).[7] The latter are prepared by the reaction of ketones (**1**) with carbon disulfide followed by methylation in high yield. In practice, 2-bis(methylthio)-methylene-7-chloro-4,6-dimethoxy-2,3-dihydrobenzo[*b*]furan-3-one (**4a**), which was obtained by the reaction of **1a** with carbon disulfide and dimethyl sulfate in high yield, was converted to **3a** in 94% yield by heating with methanol and sodium hydroxide.

This method[8] of preparing **3** was attempted on the assumption that one of the two methylthio groups of **4** could be selectively replaced by a methoxy group and the other by a hydroxy group.

Our method was further developed to provide a convenient one-pot method of preparing **3** from ketones (**1**). That is, ketone **1a** was stirred with carbon disulfide and sodium hydroxide in dimethyl sulfoxide to produce **4a**. Sodium hydroxide and methanol were subsequently added to the reaction mixture with heating to give a 90% yield of **3a**. The limitations of this method were examined and the results are listed in Table I.

This method should be widely applicable to the preparation of β-ketoesters from the corresponding ketones (**1**) in which the carbonyl and phenyl groups are conjugated. It is not successful in the reaction with aliphatic dialkyl ketones. This facile method does not require a strong base such as lithium diisopropylamide and is useful for the large scale synthesis of **3** from corresponding ketones (**1**).

Experimental

Melting point were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared absorption (IR) spectra on a JASCO A-102 spectrometer.

7-Chloro-4,6-dimethoxy-3-(methoxycarbonyloxy)benzo[*b*]furan (2a)——A solution of **1a** (0.20 g, 0.88 mmol) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of lithium diisopropylamide (1.0 mmol) in tetrahydrofuran (3 ml) at −78 °C, and stirring was continued at the same temperature for 0.5 h. Methyl chloroformate (0.10 g, 1.06 mmol) was added dropwise to the solution at −78 °C, and stirring was continued at the same temperature for 1 h. After addition of 10% aqueous ammonium chloride (5 ml), the mixture was extracted with ethyl acetate (2 × 40 ml). The combined extract was washed with brine and dried over magnesium sulfate. After removal of the solvent, the crude product was purified by column chromatography on silica gel using ethyl acetate–hexane (3 : 7) as an eluent, followed by recrystallization from ether to afford **2a** as colorless prisms; yield: 0.22 g (88%); mp 126—127 °C. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1760. ^{1}H-NMR (CDCl$_3$)δ: 4.04 (3H, s, COOCH$_3$), 4.07 (6H, s, OCH$_3$ × 2), 6.62 (1H, s, 5-H). MS *m/z*: 288 (M$^+$ +2), 286 (M$^+$). *Anal.* Calcd for $C_{12}H_{11}ClO_6$: C, 50.28; H, 3.87. Found: C, 50.30; H, 3.69.

2-Bis(methylthio)methylene-7-chloro-4,6-dimethoxy-2,3-dihydrobenzo[*b*]furan-3-one (4a)——Carbon disulfide (0.17 g, 2.2 mmol) was added dropwise to a stirred solution of **1a** (0.50 g, 2.2 mmol) in dimethyl sulfoxide (5 ml) and 30% aqueous sodium hydroxide (0.7 ml) at 5 °C, and stirring was continued at the same temperature for 0.5 h. Dimethyl sulfate (0.77 g, 6.1 mmol) was added dropwise to the mixture at 5 °C, and stirring was continued at the same temperature for 1.5 h. Ice-water was added, and the mixture was extracted with ethyl acetate (2 × 100 ml). The combined extract was washed with brine and dried over magnesium sulfate. The solvent was removed and the crude product was purified by recrystallization from ethyl acetate–hexane to afford **4a** as yellow prisms; yield: 0.67 g (92%); mp 120—121 °C. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1650. ^{1}H-NMR (CDCl$_3$) δ: 2.59 (3H, s, SCH$_3$), 2.73 (3H, s, SCH$_3$), 4.03 (6H, s, OCH$_3$ × 2), 6.25 (1H, s, 5-H). MS *m/z*: 334 (M$^+$ +2), 332 (M$^+$). *Anal.* Calcd for $C_{13}H_{13}ClO_4S_2$: C, 46.92; H, 3.94. Found: C, 46.72; H, 3.81.

7-Chloro-2,4-dimethoxy-2-methoxycarbonyl-2,3-dihydrobenzo[*b*]furan-3-one (3a)——Method A: A solution of **1a** (1.5 g, 6.6 mmol) in tetrahydrofuran (200 ml) was added dropwise to a stirred solution of lithium diisopropylamide (7.2 mmol) in tetrahydrofuran (18 ml) at −78 °C, and stirring was continued at the same temperature for 0.5 h. Methyl cyanoformate (0.67 g, 7.9 mmol) was added dropwise to the solution at −78 °C, and stirring was continued at the same temperature for 0.5 h. After addition of 10% aqueous ammonium chloride (100 ml), the mixture was extracted with ethyl acetate (2 × 400 ml). The combined extract was washed with brine (3 × 40 ml) and dried over magnesium sulfate. After removal of the solvent, the crude product was purified by column chromatography on silica gel using ethyl acetate–hexane (1 : 4) as an eluent, followed by recrystallization from ethyl acetate–hexane to afford **3a** as colorless prisms; yield: 1.8 g (94%); mp 145—146 °C (lit.[6] mp 148—150 °C).

Method B: A solution of sodium hydroxide (3.5 g, 60 mmol) in methanol (35 ml) was added to a stirred solution of **4a** (2.0 g, 6.0 mmol) in tetrahydrofuran (45 ml), and the mixture was heated at 50 °C for 1.5 h. After addition of 10% hydrochloric acid (20 ml), the mixture was extracted with ethyl acetate (2 × 300 ml). The combined extract was washed with brine (3 × 50 ml) and dried over magnesium sulfate. After removal of the solvent, the crude product was purified by column chromatography on silica gel using ethyl acetate–hexane (1 : 4) as an eluent, followed by recrystallization from ethyl acetate–hexane to afford **3a** as colorless prisms; yield: 1.5 g (90%); mp 145—146 °C.

β-Ketoesters; General Procedure——Carbon disulfide (0.61 g, 8.0 mmol) was added to a stirred solution of **1a**—**h** (7.6 mmol) in dimethyl sulfoxide (17 ml) and 30% aqueous sodium hydroxide (2.3 ml) at 5 °C. Dimethyl sulfate (2.7 g, 21 mmol) was added dropwise to the solution at 5 °C, and stirring was continued at the same temperature for 1 h. A solution of sodium hydroxide (3.0 g, 7.6 mmol) in methanol (30 ml) was added, and the mixture was heated at 50 °C for 1 h. After addition of 10% hydrochloric acid (30 ml), the mixture was extracted with ethyl acetate (2 × 300 ml). The combined extract was washed with brine (3 × 50 ml) and dried over magnesium sulfate. The solvent was removed and the crude product was purified by column chromatography on silica gel to afford **3a**—**h** in the yields shown in the Table I.

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8) Shahak and Sasson reported (*Tetrahedron Lett.*, **1973**, 4207) a similar reaction for the preparations of β-ketoesters (**3**) from ketones. However, details of the one-pot reaction and its result were not given. Furthermore, they used sodium hydride as a catalyst for the preparation of **4** from ketones and then used *p*-toluenesulfonic acid as a catalyst for the preparation of **3** from **4**. This would not be an appropriate procedure for a one-pot reaction. Our method has the advantage of using the same base in the preparation process of **4** from ketones and **3** from **4** in the one-pot reaction.
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