Preparation of Protected β-Keto Aldehydes from β-Keto Esters via Selective Reduction of Acyl(alkoxycarbonyl)ketene Dithioacetals

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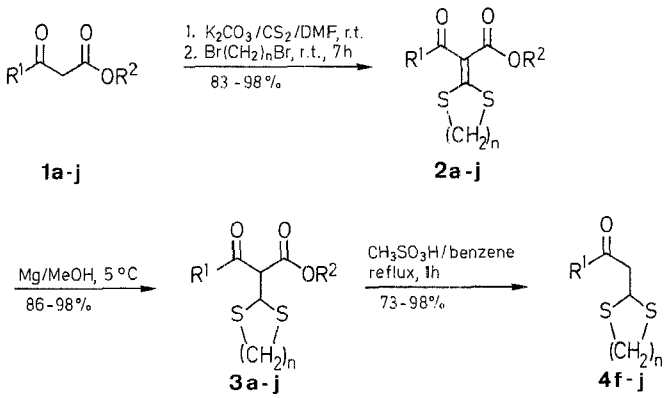
The acyl(alkoxycarbonyl)ketene dithioacetals **2** prepared from the corresponding β-keto esters **1** in almost quantitative yield are reduced selectively with magnesium in methanol and subsequently dealkoxycarbonylated to give protected β-keto aldehydes **4** in high yields.

The acylketene dithioacetal moiety has been known as a precursor not only for the preparation of various functional groups such as α,β-unsaturated ketones,[1] carboxylic acids,[2] aldehydes,[3] and β-keto esters,[4] but also for the synthesis of heterocyclic compounds.[5,6] In our continuing effort to prepare biologically active heterocyclic compounds, we needed to make 1,3-dicarbonyl compounds as a three-carbon unit. Now we report a high-yield, convenient three-step synthesis of protected β-keto aldehydes.



2, 3	R^1	R^2	n	2, 3, 4	R^1	R^2	n
a	CH_3	Et	2	**f**	CH_3	*t*-Bu	2
b	adamantyl	Et	2	**g**	Ph	*t*-Bu	2
c	Ph	Et	2	**h**	CH_3	*t*-Bu	3
d	2-FC_6H_4	Et	2	**i**	*i*-Pr	*t*-Bu	3
e	CH_3	Et	3	**j**	Ph	*t*-Bu	3

Acyl(alkoxycarbonyl)ketene dithioacetals **2** are known to be prepared in poor to moderate yields[7] from ketones using strong bases such as sodium *tert*-amylate, lithium 4-methyl-2,3-di-*tert*-butylphenoxide, and sodium hydride in the presence of carbon disulfide and subsequent alkylation with the proper alkylating

Table 1. Acyl(alkoxycarbonyl)ketene Dithioacetals **2** Prepared

Product	Yield[a] (%)	bp (°)/Torr or mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	MS (70 eV)[f] m/z (%)
2a	95	79–81	82–83[17]	2950, 1700, 1630, 1400	1.37 (t, 3H, J = 7.0); 2.40 (s, 3H); 3.30 (s, 4H); 4.33 (q, 2H, J = 7.0)	232 (M^+,75)
2b	93	116–117.5	$C_{18}H_{24}O_3S_2$ (352.5)	2900, 1690, 1670, 1510	0.87 (t, 3H, J = 7.0); 1.60 ~ 2.30 (m, 15H); 3.40 (s, 4H); 4.05 (q, 2H, J = 7.0)	352 (M^+, 2)
2c	98	oil	$C_{14}H_{14}O_3S_2$ (294.4)	2950, 1690, 1620, 1450	0.85 (t, 3H, J = 7.0); 3.30 (s, 4H); 3.95 (q, 2H, J = 6.5); 7.20–7.80 (m, 5H)	294 (M^+, 31)
2d	90	96–97	$C_{14}H_{13}FO_3S_2$ (312.4)	2900, 1680, 1620, 1600, 1450	0.87 (t, 3H, J = 6.5); 3.35 (s, 4H); 3.97 (q, 2H, J J = 6.5); 6.80–7.70 (m, 4H)	313 (M^+ + 1,9)
2e	84	60–61	$C_{10}H_{14}O_3S_2$ (246.3)	2900, 1690, 1635, 1445	1.33 (t, 3H, J = 7.0); 2.27 (m, 5H); 2.93 (m, 4H); 4.27 (q, 2H, J = 7.0)	246 (M^+, 34)
2f	95	94–94.5	$C_{11}H_{16}O_3S_2$ (260.4)	2950, 1680, 1620, 1420, 1400	1.50 (s, 9H); 2.36 (s, 3H); 3.27 (s, 4H)	260 (M^+, 100)
2g	85	85.5–86.5	$C_{16}H_{18}O_3S_2$ (322.4)	2900, 1680, 1640, 1480	1.17 (s, 9H); 3.37 (s, 4H); 7.37 (m, 5H)	322 (M^+, 23)
2h	92	95–96.5	$C_{12}H_{18}O_3S_3$ (274.4)	2900, 1660, 1480	1.53 (s, 9H); 2.23 (m, 5H); 2.90 (m, 4H)	274 (M^+, 37)
2i	95	49–51	$C_{14}H_{22}O_3S_2$ (302.4)	2900, 1690, 1660, 1470	1.07 (d, 6H, J = 7.0); 1,52 (s, 9H); 2.33 (m, 3H); 2.87 (m, 4H)	302 (M^+, 4)
2j	83	90.5–92	$C_{17}H_{20}O_3S_2$ (336.5)	2900, 1680, 1640, 1480	1.57 (s, 9H); 2.53 (m, 2H); 3.17 (m, 4H); 7.73 (m, 3H); 8.03 (m, 2H)	336 (M^+, 10)

[a] Yield of isolated product.
[b] Not corrected, measured with a Thomas-Hoover melting point apparatus.
[c] Satisfactory microanalyses (C ±0.31, H ±0.19) or accurate mass determinations (±0.0029 mass units) obtained.
[d] Recorded on a Perkin-Elmer 283 Infrared spectrophotometer.
[e] Recorded on a Varian FT-80 A spectrometer.
[f] Obtained on a Shimazu QP 1000 spectrometer.

Table 2. Compounds **3** Prepared

Product	Yield[a] (%)	bp (°C)/Torr or mp (°C)[b]	Molecular Formula[c] or Lit. Data	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	MS (70 eV)[f] m/z (%)
3a	90	115–117/0.07	137.5–139.5/2[14]	2950, 1730, 1710, 1420, 1360	1.26 (t, 3H, J = 7.0); 2.60 (s, 3H); 3.20 (s, 4H); 3.80 (d, 1H, J = 10.4); 4.20 (q, 2H, J = 7.0); 5.05 (d, 1H, J = 10.4)	234 (M^+, 49)
3b	89	oil	$C_{18}H_{16}O_3S_2$ (354.5)	2900, 1730, 1700, 1450	1.30 (t, 3H, J = 7.0); 1.80 (m, 15H); 3.21 (s, 4H); 3.76 (d, 1H, J = 10.4); 4.20 (q, 2H, J = 7.0); 5.20 (d, 1H, J = 10.4)	354 (M^+, 22)
3c	92	56–58	46–49[14]	2950, 1730, 1680, 1440	(CCl_4) 1.67 (t, 3H, J = 7.0); 3.32 (s, 4H); 4.00 (q, 2H, J = 7.0); 4.52 (d, 1H, J = 10.4); 5.20 (d, 1H, J = 10.4); 7.10–8.0 (m, 5H)	296 (M^+, 28)
3d	86	38–40	$C_{14}H_{15}FO_3S_2$ (314.4)	2900, 1730, 1680, 1605, 1450	1.14 (d, 3H, J = 7.0); 3.20 (s, 4H); 4.10 (q, 2H, J = 7.0); 4.65 (d, 1H, J = 11.0); 5.20 (d, 1H, J = 11.0); 7.0–7.9 (m, 4H)	314 (M^+, 14)
3e	88	oil	$C_{10}H_{16}O_3S_2$ (248.3)	2950, 1740, 1710, 1420	1.25 (t, 3H, J = 7.0); 2.0 (m, 2H); 2.25 (s, 3H); 2.75 (m, 4H); 4.10 (d, J = 11.0, 1H); 4.20 (q, 2H, J = 7.0); 4.40 (d, J = 11.0, 1H)	248 (M^+, 64)
3f	92	41–42	$C_{11}H_{18}O_3S_2$ (262.4)	2900, 1720, 1700, 1450	(CCl_4) 1.40 (s, 9H); 2.15 (s, 3H); 3.10 (s, 4H); 3.60 (d, 1H, J = 10.0); 4.80 (d, 1H, J = 10.0)	262 (M^+, 7)
3g	95	119–120.5	$C_{16}H_{20}O_3S_2$ (324.5)	2900, 1710, 1670, 1440	1.34 (s, 9H); 3.13 (s, 4H); 4.45 (d, 1H, J = 10.4); 5.18 (d, 1H, J = 10.4); 7.42 (m, 3H); 7.92 (m, 2H)	324 (M^+, 7)
3h	98	41.5–42.5	$C_{12}H_{20}O_3S_2$ (276.4)	3400, 2900, 1710, 1360	(keto) 1.50 (s, 9H); 2.07 (m, 2H); 2.3 (s, 3H); 2.87 (m, 4H); 4.0 (d, 1H, J = 12.0); 4.40 (d, 1H, J = 12.0) (enol) 1.57 (s, 9H); 2.07 (m, 2H); 2.4 (s, 3H); 2.87 (m, 4H); 5.23 (s, 1H); 1.33 (s, 1H)	276 (M^+, 3)
3i	96	75.5–76.5	$C_{14}H_{24}O_3S_2$ (304.5)	2900, 1730, 1700, 1460	1.10 (d, 6H, J = 7.0); 1.45 (s, 9H); 2.0 (m, 2H); 2.78 (m, 5H); 4.02 (d, 1H, J = 11.0); 4.33 (d, 1H, J = 11.0)	304 (M^+, 33)
3j	95	139–141.5	$C_{17}H_{22}O_3S_2$ (338.5)	2900, 1720, 1680, 1440	1.37 (s, 9H); 2.03 (m, 2H); 2.53 (m, 4H); 4.58 (d, 1H, J = 11.0); 4.92 (d, 1H, J = 11.0); 7.53 (m, 3H); 8.03 (m, 2H)	338 (M^+, 2)

[a] Yield of isolated product.
[b] Not corrected.
[c] Satisfactory microanalyses (C ±0.35, H ±0.25) or accurate mass determinations (±0.0026 mass units) obtained.
[d–f] See Table 1.

Table 3. Compounds **4f–j** Prepared

Product	Yield[a] (%)	bp (°C)/Torr or mp (°C)[b]	Molecular Formula[c] or Lit. Data	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	MS (70 eV)[f] m/z (%)
4f	90	85–88/0.1	85–87/0.1[18]	(neat) 2930, 1710, 1367, 1165	2.08 (s, 3H); 2.85 (d, 2H, J = 7.0); 3.15 (s, 4H); 4.56 (t, 1H, J = 7.0)	162 (M^+, 47)
4g	73	76.5–78	74.5–75[19]	2800, 1670, 1440	3.18 (s, 4H); 3.53 (d, 2H, J = 7.0); 4.93 (t, 1H, J = 7.0); 7.4 (m, 3H); 7.83 (m, 2H)	224 (M^+, 9)
4h	98	70–71	61–62[19]	2800, 1710, 1420	2.02 (m, 2H); 2.20 (s, 3H); 2.88 (m, 6H); 4.45 (t, 1H, J = 7.0)	176 (M^+, 74)
4i	78	52–52.5	$C_9H_{16}OS_2$ (204.4)	2900, 1710, 1460	1.1 (d, 6H, J = 7.0); 2.03 (m, 2H); 2.87 (m, 7H); 4.45 (t, 1H, J = 7.0)	204 (M^+, 25)
4j	80	59–61	59–61[8]	2800, 1690	2.0 (m, 2H); 2.82 (m, 4H); 3.28 (d, 2H, J = 7.0); 4.58 (t, 1H, J = 7.0); 7.45 (m, 3H); 7.83 (m, 2H)	238 (M^+, 15)

[a] Yield of isolated product.
[b] Not corrected.
[c] Satisfactory microanalyses (C ±0.11, H ±0.14) obtained.
[d–f] See Table 1.

agent. But by choosing potassium carbonate as base in dimethylformamide as solvent, we are able to convert β-keto esters **1** into acyl(alkoxycarbonyl)ketene dithioacetals **2** in highly improved yields as illustrated in Table 1.

Although Gammil et al. reported[8] selective reduction of carbon–carbon double bonds of acylketene dithioacetals using diisobutylaluminum hydride–triethylamine complex (DIBAL-H-TEA) in moderate yields, other reduction methods[9,10,11] were not successful for the selective 1,4-reduction. Since magnesium in methanol was used successfully in our laboratory[12] to reduce carbon–carbon double bonds of ketene dithioacetals conjugated with an ester group, we apply this reagent to acylketene dithioacetals for selective 1,4-reduction. Reduction takes place smoothly to give the saturated analogs **3** in high yields, as shown in Table 2. These were also known to be obtained in moderate yields by the direct alkylation of β-keto esters with substituted 1,3-dithiane[13] or 1,3-dithiolane.[14] Our method is considered to be complementary to the known method.[13,14]

Protected β-keto aldehydes were also known to be prepared by direct alkylation of enamines[13] and silyl enol ethers[15,16] with substituted 1,3-dithiane or 1,3-dithiolane. Taylor et al.[13] conducted dealkoxycarbonylation of **3e** in dimethyl sulfoxide with sodium chloride, but the yield was not mentioned. So we use *tert*-butyl esters **3f–j** for easy dealkoxycarbonylation under acidic conditions. The reaction occurs smoothly in refluxing benzene in the presence of a catalytic amount of methanesulfonic acid to give protected β-keto aldehydes **4** in high yields (Table 3).

As it is described here, each step of our method is highly improved in its yield and represents a complementary route to the desired compounds **2,3,4**.

Acyl(alkoxycarbonyl)ketene Dithioacetals 2; General Procedure:
To a well stirred suspension of β-keto ester **1** (0.1 mol) and anhydrous K_2CO_3 (42 g, 0.3 mol) in DMF (50 mL) is added CS_2 (9 mL, 0.15 mol) at room temperature. To the reaction mixture dibromoalkane (0.12 mol) is added dropwise over 30 min. Stirring is continued another 7 h at room temperature. Ice-water (500 mL) is added to precipitate the yellow-colored product, which is recrystallized from EtOH to give **2** (Table 1).

Reduction of 2; General Procedure:
To a stirred solution of ketene dithioacetal **2** (0.1 mol) in dry MeOH (300 mL) are added magnesium turnings (8.5 g, 0.35 mol) in portions over 1 h, while maintaining the pot temperature at 5°C. Stirring is continued to dissolve the magnesium completely. The mixture is poured into 1 N HCl (80 mL) and extracted with EtOAc (5 × 100 mL). The EtOAc layer is successively washed with water (100 mL) and brine (100 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed *in vacuo* to give **3** as a colorless oil. Purification is performed by Kugelrohr distillation or crystallization from EtOH.

Dealkoxycarbonylation of 3f–j; General Procedure:
To a solution of **3** (10 mmol) in C_6H_6 (20 mL) is added a catalytic amount of methanesulfonic acid (96 mg, 1 mmol). The reaction mixture is heated to reflux for 1 h, then diluted with C_6H_6 (30 mL), washed with brine (20 mL) and water (30 mL). The extract is dried ($MgSO_4$), and the solvent is removed *in vacuo*. The residue is crystallized from EtOH to afford the protected β-keto aldehyde **4**.

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