A New Synthetic Method for α-Oxo-β,γ-unsaturated Esters

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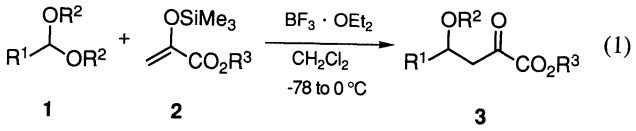
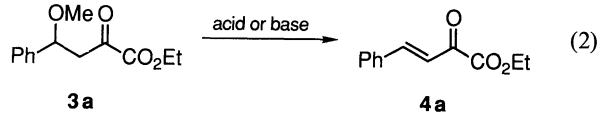
Synopsis. α-Oxo-β,γ-unsaturated esters have been prepared in moderate to good yields via a two-step procedure consisting of the boron trifluoride-promoted reaction of 2-(trimethylsiloxy)acrylic esters with acetals, followed by treatment with silica gel in benzene under reflux.

There has been considerable interest in α-oxo-β,γ-unsaturated esters as intermediates for the syntheses of substituted dihydropyranes,[1] cyclohexenes,[2] and dihydrothiazines.[3] Although several approaches to a variety of these derivatives have appeared,[3-5] there are some restrictions concerning the applicability, efficiency of the methods or the availability of the starting materials. Hence, the development of a versatile method for synthesizing the esters still constitutes a synthetic challenge. In this paper we describe a facile route to α-oxo-β,γ-unsaturated esters via β-elimination of alcohol from γ-alkoxy-α-oxo esters which are obtained by the reaction of 2-(trimethylsiloxy)acrylic esters **2**, prepared by silylation of pyruvic esters,[6] with acetals **1** in the presence of boron trifluoride–diethyl ether (1 : 1) according to a previously reported procedure (Eq. 1).[7]



1 2 3 (1)

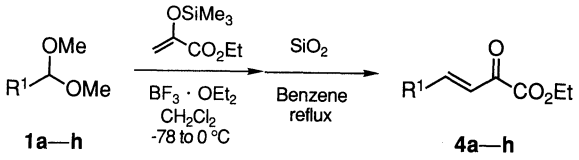
Acid- or base-catalyzed dehydration of β-hydroxy carbonyl compounds has been well documented. However, our initial attempt to efficiently convert γ-methoxy-α-oxo ester **3a** into α-oxo-β,γ-unsaturated ester **4a** under several acidic or basic conditions was unsuccessful (Eq. 2). For example, when *p*-toluenesulfonic acid was used as an acid catalyst in refluxing benzene, **4a** was obtained in 35% yield along with 16% of the corresponding methyl ester, resulting from an ester exchange between the produced ester **4a** and the eliminating methanol. A base-catalyzed elimination was less satisfactory than the acid-catalyzed one; the treatment of **3a** with EtONa in ethanol at room temperature failed to give the desired product. When **3a** was treated with Na_2CO_3 in ethanol at room temperature or with LiCl–Et_3N in THF under reflux, **4a** was obtained in only 13 or 12% yield, respectively. In all of the cases examined above, the starting material **3a** was not recovered.



3a 4a (2)

Bible and Atwater have reported[8] that Florisil and basic aluminum oxide for chromatography behave as adsorbents in the dehydration of a β-hydroxy ketone to give the corresponding α,β-unsaturated ketone. We have also observed a small amount of eliminated product during the purification of a γ-methoxy-α-oxo ester by flash column chromatography on silica gel.[7] We then attempted the reaction of **3a** using silica gel for chromatography as an adsorbent of methanol as well as a mild acid catalyst, finding that by heating under reflux in benzene for 1 h **4a** could be obtained in 91% yield as the sole product.

We next examined a two-step reaction procedure for obtaining **4a** starting from benzaldehyde dimethylacetal (**1a**) without any purification of the γ-methoxy-α-oxo ester **3a**; that is, a mixture of **1a** and **2** (R^3=Et) was treated with boron trifluoride–diethyl ether (1 : 1) at −78 °C and the reaction mixture was stirred at 0 °C for 2 h. After the usual work-up, the crude ester **3a** was used directly in the subsequent β-elimination. As a result, to our surprise, the overall yield of **4a** from **1a** was improved to 88% (in our previous study, **3a** had been obtained from **1a** in 71% yield after flash column chromatography[7]). The generality of this method was explored by reacting various acetals **1b**—**h** with **2** (R^3=Et) under similar conditions (Eq. 3). The results are summarized in Table 1. When R is an aromatic or α,β-unsaturated substituent, β-elimination came to completion within 1 h to afford the unsaturated esters as the sole product in 77—89% yield (Runs 1—5). On the other hand, when R is an alkyl sub-



1a—h 4a—h (3)

Table 1. Synthesis of α-Oxo-β,γ-unsaturated Esters **4a**—**h** from Acetals **1a**—**h**

Run	Acetal	R^1	Time[a] / h	Product	Yield[b] / %
1	**1a**	Ph	1	**4a**	88
2	**1b**	*p*-$MeOC_6H_4$	1	**4b**	83
3	**1c**	*p*-ClC_6H_4	1	**4c**	89
4	**1d**	(*E*)-PhCH=CH	1	**4d**	77
5	**1e**	2-Thienyl	1	**4e**	86
6	**1f**	$PhCH_2CH_2$	8	**4f**	57[c]
7	**1f**		16	**4f**	61[d]
8	**1g**	*i*-C_3H_7	5	**4g**	62
9	**1h**	*n*-C_7H_{15}	6	**4h**	77

a) Indicating the period of reflux for the β-elimination. b) Isolated yield based on acetal. c, d) Ethyl 4-methoxy-2-oxo-6-phenylhexanoate (**3f**) was recovered in 22 and 5% yields, respectively.

stituent, the β-elimination required a longer reaction time and resulted in a somewhat lower yield. For example, the reaction starting from 3-phenylpropanal dimethylacetal (**1f**) gave the eliminated product **4f** in 57% yield along with a 22% yield of the uneliminated γ-methoxy-α-oxo ester **3f** by heating at reflux for 8 h (Run 6). When the reflux was carried out for 16 h, the yield of **4f** was slightly improved (Run 7). However, a further extension of the period of reflux caused the formation of side-products, which diminished the yield of the desired product. In the reactions starting from acetals **1g** and **1h**, however, the β-elimination was completed in 5—6 h to afford the unsaturated esters, **4g** and **4h**, in excellent yields (Runs 8 and 9).

In conclusion, silica gel has proved to be a useful adsorbent as well as a catalyst for the β-elimination of methanol from γ-methoxy-α-oxo esters. Furthermore, a facile and general method for the preparation of α-oxo-β,γ-unsaturated esters has been developed employing this procedure.

Experimental

All of the melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JMN EX-400 spectrometer using Me_4Si as an internal standard. IR spectra were recorded on a JASCO A-102 spectrophotometer. Column chromatography was performed on Wakogel C-300 silica gel.

Dichloromethane was pre-dried with P_2O_5, distilled from K_2CO_3, and stored over Linde type 4A molecular sieves. Ethyl 2-(trimethylsiloxy)acrylate was readily prepared from ethyl pyruvate by modifying the reported method[6] [Me_3SiCl (1.3 equiv), Et_3N (1.3 equiv), and 4-dimethylaminopyridine (0.05 equiv) in benzene under reflux for 2 h; 75—85%, 90—92 °C/38 Torr (1 Torr=133.222 Pa)]. Acetals **1b**—**h** were prepared from the corresponding aldehydes according to methods described in the literature.[9]

General Procedure for Synthesis of α-Oxo-β,γ-unsaturated Esters. To a mixture of acetal **1** (10 mmol) and ethyl 2-(trimethylsiloxy)acrylate (12 mmol) in dry dichloromethane (50 cm³) under argon at −78 °C was added dropwise boron trifluoride–diethyl ether (1 : 1) (11 mmol). The reaction mixture was warmed to 0 °C for over 1 h and stirred at the same temperature for 2 h. Saturated $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford crude γ-alkoxy-α-oxo esters, which were dissolved in benzene (100 cm³). Then, silica gel (Wakogel C-300, 10—15 g) was added and the mixture was heated at reflux with vigorous stirring for the desired time (Table 1). After being cooled to room temperature, the mixture was filtered and the residual solid was washed with ether several times. The filtrate was combined and concentrated to give crude α-oxo-β,γ-unsaturated esters **4**. The purification by flash column chromatography for **4a**, **4f**—**h** (Wakogel C-300, hexane-ethyl acetate) or recrystallization for **4b**—**e** (hexane–ether or ethyl acetate) gave pure esters.

Ethyl 2-Oxo-4-phenyl-3-butenoate (4a): Bp 130—135 °C/1 Torr (Kugelrohr distillation, bath temp; lit, 90—95 °C/0.2 Torr,[3] 117—118 °C/0.5 Torr[4]); ^1H NMR ($CDCl_3$) δ=1.41 (t, 3H, *J*=7.1 Hz), 4.40 (q, 2H, *J*=7.1 Hz), 7.36 (d, 1H, *J*=16.1 Hz), 7.40—7.47 (m, 3H), 7.63 (dd, 2H, *J*=2.0, 4.9 Hz), 7.86 (d, 1H, *J*=16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1, 62.5, 120.6, 129.0, 129.1, 131.6, 134.0, 148.4, 162.2, 182.9; IR (neat) 1725, 1690, 1665, 1605, 1255, 1145, 1080 cm⁻¹. Found: C, 70.45; H, 6.04%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

Ethyl 4-(4-Methoxyphenyl)-2-oxo-3-butenoate (4b): Mp 48.0—49.0 °C; ^1H NMR ($CDCl_3$) δ=1.41 (t, 3H, *J*=7.1 Hz), 3.86 (s, 3H), 4.39 (q, 2H, *J*=7.1 Hz), 6.93 (d, 2H, *J*=8.8 Hz), 7.24 (d, 1H, *J*=16.1 Hz), 7.59 (d, 2H, *J*=8.8 Hz), 7.83 (d, 1H, *J*=16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1, 55.5, 62.4, 114.6, 118.2, 126.9, 131.1, 148.4, 162.5, 162.6, 182.7; IR (KBr) 1720, 1680, 1590, 1570, 1250, 1070, 1030, 1000 cm⁻¹. Found: C, 66.77; H, 6.10%. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02%.

Ethyl 4-(4-Chlorophenyl)-2-oxo-3-butenoate (4c): Mp 77.5—78.5 °C; ^1H NMR ($CDCl_3$) δ=1.42 (t, 3H, *J*=7.3 Hz), 4.40 (q, 2H, *J*=7.3 Hz), 7.35 (d, 1H, *J*=16.1 Hz), 7.40 (d, 2H, *J*=8.8 Hz), 7.57 (d, 2H, *J*=8.8 Hz), 7.81 (d, 1H, *J*=16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1, 62.6, 120.9, 129.4, 130.2, 132.5, 137.7, 146.8, 162.0, 182.5; IR (KBr) 1715, 1685, 1585, 1565, 1250, 1070, 995 cm⁻¹. Found: C, 60.61; H, 4.75; Cl, 14.83%. Calcd for $C_{12}H_{11}O_3Cl$: C, 60.39; H, 4.65; Cl, 14.85%.

Ethyl 6-Phenyl-2-oxo-3,5-hexadienoate (4d): Mp 98.5—99.0 °C; ^1H NMR ($CDCl_3$) δ=1.40 (t, 3H, *J*=7.1 Hz), 4.37 (q, 2H, *J*=7.1 Hz), 6.89 (d, 1H, *J*=15.1 Hz), 6.98 (dd, 1H, *J*=11.3, 15.1 Hz), 7.09 (d, 1H, *J*=15.1 Hz), 7.33—7.41 (m, 3H), 7.51 (dd, 2H, *J*=1.7, 8.1 Hz), 7.65 (dd, 1H, *J*=11.3, 15.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1, 62.4, 124.0, 126.6, 127.7, 129.0, 129.9, 135.6, 144.6, 148.4, 162.2, 182.8; IR (KBr) 1715, 1675, 1570, 1270, 1210, 1065, 1015 cm⁻¹. Found: C, 73.11; H, 6.30%. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13%.

Ethyl 2-Oxo-4-(2-thienyl)-3-butenoate (4e): Mp 46.0—47.0 °C; ^1H NMR ($CDCl_3$) δ=1.41 (t, 3H, *J*=7.3 Hz), 4.39 (q, 2H, *J*=7.3 Hz), 7.12 (dd, 1H, *J*=3.4, 4.9 Hz), 7.16 (d, 1H, *J*=16.1 Hz), 7.42 (d, 1H, *J*=3.4 Hz), 7.52 (d, 1H, *J*=4.9 Hz), 7.99 (d, 1H, *J*=16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1, 62.5, 119.3, 128.7, 130.9, 133.7, 139.8, 140.5, 162,1, 182.2; IR (KBr) 1720, 1680, 1590, 1250, 1080, 1040, 970 cm⁻¹. Found: C, 57.05; H, 4.90; S, 15.18%. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; S, 15.25%.

Ethyl 2-Oxo-6-phenyl-3-hexenoate (4f): Bp 175—180 °C/1 Torr (Kugelrohr distillation, bath temp); ^1H NMR ($CDCl_3$) δ=1.37 (t, 3H, *J*=7.3 Hz), 2.26—2.69 (m, 2H), 2.87 (t, 2H, *J*=7.6 Hz), 4.34 (q, 2H, *J*=7.3 Hz), 6.67 (dt, 1H, *J*=1.5, 16.1 Hz), 7.17—7.32 (m, 6H); ^{13}C NMR ($CDCl_3$) δ=14.0, 34.0, 34.8, 62.3, 125.6, 126.3, 128.3, 128.6, 140.3, 153.6, 162.3, 183.3; IR (neat) 1730, 1700, 1675, 1620, 1250, 1175, 1140, 1100, 1080 cm⁻¹. Found: C, 72.38; H, 7.16%. Calcd for $C_{14}H_{16}O_3$: C, 72.39, H, 6.94%.

Ethyl 5-Methyl-2-oxo-3-hexenoate (4g): Bp 75—80 °C/1 Torr (Kugelrohr distillation, bath temp); ^1H NMR ($CDCl_3$) δ=1.12 (d, 6H, *J*=6.8 Hz), 1.39 (t, 3H, *J*=7.3 Hz), 2.53—2.61 (m, 1H, *J*=1.5, 6.8 Hz), 4.36 (q, 2H, *J*=7.3 Hz), 6.61 (dd, 1H, *J*=1.5, 16.1 Hz), 7.16 (dd, 1H, *J*=6.8, 16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.0, 20.9, 31.8, 62.3, 122.4, 160.8, 162.5, 183.8; IR (neat) 2975, 1730, 1700, 1675, 1620, 1310, 1250, 1170, 1150, 1080 cm⁻¹. Found: C, 63.53; H, 8.35%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Ethyl 2-Oxo-3-undecenoate (4h): Bp 140—145 °C/2 Torr (Kugelrohr distillation, bath temp); ^1H NMR ($CDCl_3$) δ=0.88 (t, 3H, *J*=7.0 Hz), 1.22—1.36 (m, 8H), 1.38 (t, 3H, *J*=7.3 Hz), 1.46—1.54 (m, 2H), 2.31 (ddt, 2H, *J*=1.5, 6.8, 6.8 Hz), 4.35 (q, 2H, *J*=7.3 Hz), 6.64 (dt, 1H, *J*=1.5, 16.1 Hz), 7.19 (dt, 1H, *J*=6.8, 16.1 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1×2, 22.6, 27.8, 29.0, 29.2, 31.7, 33.1, 62.3, 125.2, 155.3, 162.5, 183.5; IR (neat) 2930, 2850, 1730, 1700, 1675, 1620, 1300, 1250, 1175, 1150, 1090 cm⁻¹. Found: C, 68.94; H, 9.79%. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80%.

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