A Convenient Synthesis of Dialkyl Esters of 3-Methoxy-2,4-dialkylpentanedioic Acids

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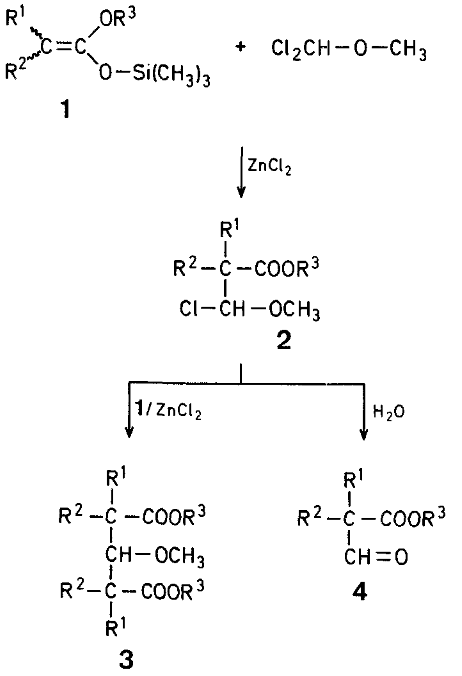
The chemistry of ketene alkyl trialkylsilyl acetals has recently received wide attention, because they have been shown to be, in general, readily accessible[1] and synthetically useful intermediates[2]. In this communication, we report our findings concerning reactions of ketene alkyl trimethylsilyl acetals **1** with dichloromethyl methyl ether in the presence of zinc chloride.



1, 2, 3	R¹	R²	R³	**1, 2, 3**	R¹	R²	R³
a	H	CH_3	CH_3	**h**	CH_3	CH_3	CH_3
b	H	C_2H_5	CH_3	**i**	—$(CH_2)_4$—		CH_3
c	H	C_2H_5	C_2H_5	**j**	—$(CH_2)_5$—		CH_3
d	H	n-C_3H_7	CH_3	**k**	C_2H_5	CH_3	CH_3
e	H	n-C_3H_7	C_2H_5	**l**	H	i-C_3H_7	CH_3
f	H	n-C_4H_9	CH_3	**m**	C_2H_5	C_2H_5	C_2H_5
g	H	n-C_4H_9	C_2H_5				

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The reaction proceeds particularly well with the ketene alkyl trimethylsilyl acetals **1a–g** prepared from the straight-chain carboxylic esters, affording the dialkyl esters of 3-methoxy-2,4-dialkylpentanedioic acids **3a–g** in high yields. The structures of these esters were confirmed by high-resolution mass spectrometry, I.R. spectra, and ^{1}H-N.M.R. spectra. Formation of these products presumably involves initial reaction of equimolecular amounts of **1** and dichloromethyl methyl ether promoted by zinc chloride to give the intermediary product **2** which undergoes subsequent attack of another ketene alkyl trimethylsilyl acetal molecule to give the products.

The reaction has also been performed using an excess of dichloromethyl methyl ether (1.3 equiv), however, the product isolated was not the α-formylcarboxylic ester **4**, but again **3**. It appears very likely that, in the zinc chloride-catalyzed reaction with **1a–g**, the initially formed **2a–g** react far faster than the starting dichloromethyl methyl ether, at least under the given conditions. The products obtained by the reaction of **1a–g** with dichloromethyl methyl ether are listed in Table 1, along with their physical data.

The similar condensation of dichloromethyl methyl ether was further investigated using the ketene alkyl trimethylsilyl ace-

Table 1. Reaction of Ketene Silyl Acetals **1a–g** with Dichloromethyl Methyl Ether in the Presence of Zinc Chloride

Ketene silyl acetal used	Product[a]	Yield [%][b]	b.p. [°C]/torr	Molecular formula[c]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
1a	**3a**[d]	78	88–89°/3	$C_{10}H_{18}O_5$ (218.5)	1.0–1.3 (m, 6H); 2.3–2.9 (m, 2H); 3.22 (d, 3H); 3.57 (s, 6H); 3.73 (dd, 1H)
1b	**3b**	95	133–135°/18	$C_{12}H_{22}O_5$ (246.3)	0.89 (t, 6H); 1.3–2.0 (m, 4H); 2.2–2.9 (m, 2H); 3.30 (s, 3H); 3.64 (s, 6H); 3.64 (dd, 1H)
1c	**3c**	78	142–147°/15.5	$C_{14}H_{26}O_5$ (274.4)	0.90 (t, 6H); 1.26 (t, 6H); 1.3–2.0 (m, 4H); 2.1–2.7 (m, 2H); 3.33 (s, 3H); 3.65 (dd, 1H); 4.11 (q, 4H)
1d	**3d**	98	149–154°/17.5	$C_{14}H_{26}O_5$ (274.4)	0.7–1.1 (m, 6H); 1.0–1.9 (m, 8H); 2.2–2.8 (m, 2H); 3.26 (d, 3H); 3.60 (s, 6H); 3.60 (dd, 1H)
1e	**3e**	82	120–124°/3	$C_{16}H_{30}O_5$ (302.4)	0.7–1.1 (m, 6H); 1.25 (t, 6H); 1.1–1.9 (m, 8H); 2.2–2.9 (m, 2H); 3.29 (d, 3H); 3.62 (dd, 1H); 4.05 (q, 4H)
1f	**3f**	94	120–123°/2.5	$C_{16}H_{30}O_5$ (302.4)	0.7–1.1 (m, 6H); 1.0–1.9 (m, 12H); 2.2–2.8 (m, 2H); 3.24 (s, 3H); 3.57 (s, 6H); 3.57 (dd, 1H)
1g	**3g**	89	129–132°/2.5	$C_{18}H_{34}O_5$ (330.5)	0.88 (t, 6H); 1.27 (t, 6H); 1.0–2.0 (m, 12H); 2.2–2.8 (m, 2H); 3.33 (d, 3H); 3.65 (dd, 1H); 4.16 (q, 4H)

[a] We were unable to find any α-formylcarboxylic ester **4**; **3** was the sole product and usually obtained as a mixture of stereoisomers.
[b] Isolated yield after distillation.
[c] All products gave satisfactory elemental analyses (C ±0.28, H ±0.23) and exhibited spectral properties in accordance with the assigned structures.
[d] The isolation of optically active **3a** was previously described[3].

Table 2. Reaction of Ketene Silyl Acetals **1h–m** with Dichloromethyl Methyl Ether in the Presence of Zinc Chloride

Ketene silyl acetal used	Product[a]	Yield [%][b]	b.p. [°C]/torr	Molecular formula[c]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
1h	**3h**	40	83–84°/2.5	$C_{12}H_{22}O_5$ (246.3)	1.14 (s, 6H); 1.23 (s, 6H); 3.44 (s, 3H); 3.63 (s, 6H); 3.87 (s, 1H)
	4h	35	50–53°/16	$C_6H_{10}O_3$ (130.1)	1.32 (s, 6H); 3.71 (s, 3H); 9.69 (s, 1H)
1i	**3i**	74	134–137°/2.5	$C_{16}H_{26}O_5$ (298.4)	1.3–2.3 (m, 16H); 3.56 (s, 3H); 3.63 (s, 6H); 3.92 (s, 1H)
	4i	12	92–93°/17.5	$C_8H_{12}O_3$ (156.2)	1.4–1.9 (m, 4H); 1.9–2.3 (m, 4H); 3.74 (s, 3H); 9.70 (s, 1H)
1j	**3j**	48	147–150°/2.2	$C_{18}H_{30}O_5$ (326.4)	0.8–1.8 (m, 16H); 1.7–2.3 (m, 4H); 3.31 (s, 1H); 3.47 (s, 3H); 3.61 (s, 6H)
	4j	35	62–63°/2.5	$C_9H_{14}O_3$ (170.2)	1.3–1.7 (m, 6H); 1.8–2.3 (m, 4H); 3.69 (s, 3H); 9.49 (s, 1H)
1k	**3k**	36	109–110°/2.5	$C_{14}H_{26}O_5$ (274.4)	0.6–1.0 (m, 6H); 1.0–1.3 (m, 6H); 1.4–2.3 (m, 4H); 3.38 (s, 3H); 3.5–3.7 (m, 6H); 3.83 (s, 1H)
	4k	41	65–66°/17.5	$C_7H_{12}O_3$ (144.2)	0.88 (t, 3H); 1.28 (s, 3H); 1.6–2.2 (m, 2H); 3.75 (s, 3H); 9.79 (s, 1H)
1l	**3l**	93	96–100°/3	$C_{14}H_{26}O_5$ (274.4)	0.7–1.4 (m, 12H); 1.7–2.8 (m, 4H); 3.41 (s, 3H); 3.61 (s, 6H); 3.77 (dd, 1H)
	4l	0			
1m	**3m**	43	135–141°/4.7	$C_{18}H_{34}O_5$ (330.5)	0.6–1.2 (m, 12H); 1.1–1.4 (m, 6H); 1.3–2.4 (m, 8H); 3.48 (s, 3H); 3.76 (s, 1H) 3.8–4.4 (m, 4H)
	4m	56	82–86°/17.5	$C_9H_{16}O_3$ (172.2)	0.85 (t, 6H); 1.28 (t, 3H); 1.83 (q, 4H); 4.23 (q, 2H); 9.85 (s, 1H)

[a] Product **3k**, **4k**, and **3l** were obtained as a mixture of stereoisomers; the others have no asymmetric carbon atom.
[b] Isolated yield after distillation.
[c] Satisfactory elemental analyses (C ±0.20, H ±0.29) were obtained; spectral data were in accord with the proposed structures.

tals **1h–m** prepared from branched carboxylic esters. It was found that the products consist of both **3** and **4**, not in accord with our expectations based on the results using **1a–g**. The formation of **4** is easily understandable in view of the steric congestion expected in both **1** and its intermediary product **2**.

As can be seen from the results in Table 2, only with **1l**, which would be less hindered than the others, was it possible to effect the exclusive conversion to the corresponding dimethyl ester of 3-methoxy-2,4-diisopropylpentanedioic acid **3l**.

Zinc Chloride-Catalyzed Reaction of Ketene Alkyl Trimethylsilyl Acetals (1) with Dichloromethyl Methyl Ether; General Procedure:
To a stirred, cooled (0–10 °C) mixture of the appropriate ketene alkyl trimethylsilyl acetal **1** (20 mmol) and zinc chloride (2.73 g, 20 mmol) in dichloromethane (21 ml) is added during about 30 min dichloromethyl methyl ether (3.0 g, 26 mmol). After addition is complete, the mixture is stirred at room temperature (20–25 °C) for 36 h and then poured into a mixture of ice/water (50 ml) and ether (60 ml). The organic layer is separated and combined with an ethereal extract of the aqueous phase. The ethereal solution is washed once with cold water (50 ml), dried with magnesium sulfate, and distilled under reduced pressure.

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