Synthesis of 1,1-Diethoxy-2-methylene-3-oxoalkanes (α-Methylene-β-oxoacetals)

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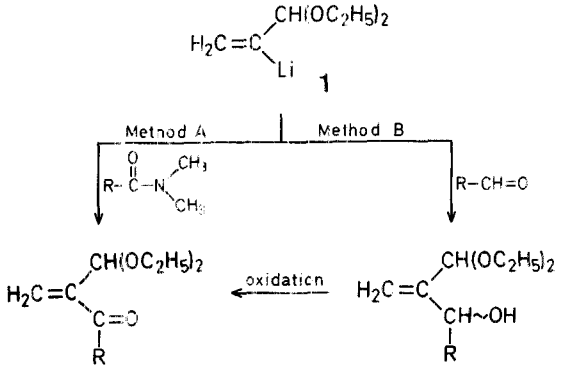
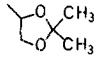
We report here our results on the synthesis of 1,1-diethoxy-2-methylene-3-oxoalkanes (**3**; α-methylene-β-oxoacetals) which are related to branched chain uloses, have interesting electrophilic properties, and are precursors of vinylogous ester systems[1]. We have developed two routes to compounds **3**, both starting with 3,3-diethoxy-2-lithio-1-propene (**1**).



3	R	3	R
a	–H	d	$-C_5H_{11}$-n
b	$-CH_3$	e	
c	$-CH_2-CH(CH_3)_2$	f	

Method A is the one-step acylation of **1** by reaction with amides. Acylations of simple alkyl-[2], alkenyl-[2g,3], allenyl-[4], or aryllithium compounds[2c,2d,2g,2h,5] have been frequently

investigated but acylations of functionalised vinylic lithium compounds had not been previously reported. We have found that **1** reacts with *N,N*-dimethylamides at low temperatures to produce the products **3** in about 70% yield (distilled product), except where R = H, CH_3 when the yields are only 20–30% (Table 1).

Method B is a two-step acylation of **1** consisting of condensation of **1** with aldehydes and subsequent oxidation of the allylic alcohols **2**. We have previously described the preparation of allylic alcohols **2**[6]. We now report that oxidation of these alcohols **2** can be effected under mild conditions either by manganese dioxide[7,8] or by 'activated' dimethyl sulfoxide (Swern oxidation)[9] and leads also to compounds **3**. Manganese dioxide generally reacts slowly with alcohols **2**, especially **2f**; for hindered compounds **2**, oxidation with dimethyl sulfoxide in the presence of oxalyl chloride[10] is the preferred method (Tables 1 and 2).

1,1-Diethoxy-2-methylene-3-oxoalkanes 3; General procedures:

Method A: Under nitrogen, *n*-butyllithium (2 molar in hexane, 43.75 mmol) is added at −70°C to 3,3-diethoxy-2-bromo-1-propene[6,11] (45.5 mmol) in tetrahydrofuran (70 ml). The mixture is stirred for 12 min and then the *N,N*-dimethylamide[12] (35 mmol) is slowly added. The mixture is stirred at −60°C for 3 h, then at 40°C for 0.5 h, poured into a solution of phosphate buffer (200 ml, 2 molar, pH 7), and extracted with ether (2 × 100 ml). When R = H, dimethylformamide (30 mmol; distilled from calcium hydride) is added to the lithio compound **1** (20 mmol) cooled at −100°C, then the solution is stirred at −40°C for 2.5 h, and poured into a solution of phosphate buffer (90 ml, 2 molar, pH 7). Pure products **3** are obtained by distillation (Table 1).

Method B: Activated manganese dioxide (10 g; from Merck or prepared according to Ref.[8]) is suspended in tetrahydrofuran or dichloromethane (100 ml) containing the allylic alcohol[6] **2b**, **2e**, or **2f** (1 g). After treatment at the times and temperatures given in Table 2, the mixture is filtered, the liquid phase is concentrated, and distilled to give product **3** (Table 1).

Method B': Oxidation with Dimethyl Sulfoxide Activated with Oxalyl Chloride[9a]: Under nitrogen at −60°C, dimethyl sulfoxide (2.3 mmol; freshly distilled) in dichloromethane (0.5 ml) is slowly added to oxalyl chloride (1.1 mmol) in dichloromethane (2.5 ml). After being stirred for 12 min, a solution of the allylic alcohol **2b** or **2f** (1 mmol) in dichloromethane (1 ml) is slowly added to the activated dimethyl sulfoxide solution. The mixture is then allowed to

Table 1. 1,1-Diethoxy-2-methylene-3-oxoalkanes **3a–f** prepared

Product	Yield [%][a] by Method A	Method B	b.p. [°C]/torr	Molecular Formula[b]	M.S. *m/e*[c]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS)[e] δ [ppm] C-1	C-2	=CH_2	C-3
3a	20	–	120–121°/10	$C_8H_{14}O_3$ (158.2)	157 ($M^+ - 1$)	1.25 (t, 6H, J = 7 Hz); 3.65 (m, 4H); 5.35 (s, 1H); 6.25, 6.65 (2s, 2H); 9.70 (s, 1H)	96.5 (d)	146.3 (s)	134.0 (t)	191.8 (d)
3b	30	60	81–83°/20	$C_9H_{16}O_3$ (172.2)	157 ($M^+ - 15$)	1.20 (t, 6H, J = 7 Hz); 2.40 (s, 3H); 3.6 (m, 4H); 5.32 (s, 1H); 6.15 (s, 2H)	97.8 (d)	145.5 (s)	125.7 (t)	198.0 (s)
3c	70	–	75–76°/5	$C_{12}H_{22}O_3$ (214.3)	213 ($M^+ - 1$)	0.85 (d, 6H, J = 6.5 Hz); 1.1 (t, 6H, J = 7 Hz); 2.1 (sept, 1H, J = 6.5 Hz); 2.5 (d, 2H, J = 6.5 Hz); 3.5 (m, 4H); 5.25 (s, 1H); 5.95 (s, 2H)	98.0 (d)	145.8 (s)	124.1 (t)	200.2 (s)
3d	70	–	114–117°/9	$C_{13}H_{24}O_3$ (228.3)	228 (M^+)	0.7–1.6 (m, 15H); 2.65 (t, 3H, J = 7 Hz); 3.6 (m, 4H); 5.25 (s, 1H); 6.05 (s, 2H)	97.9 (d)	145.4 (s)	123.9 (t)	200.3 (s)
3e	70	72	90–92°/0.4	$C_{14}H_{18}O_3$ (234.3)	234 (M^+)	1.25 (t, 6H, J = 7 Hz); 3.75 (m, 4H); 5.50, 5.75 (2s, 2H); 6.25 (s, 1H); 7.3–8.0 (m, 5H)	98.8 (d)	137.0 (s)	124.6 (t)	195.9 (s)
3f[f]	–	60	120–123°/0.1	$C_{13}H_{22}O_5$ (258.3)	243 ($M^+ - 15$)	1.30 (t, 6H, J = 7 Hz); 1.50 (s, 6H); 3.6 (m, 4H); 4.2 (2d, 2H, J = 7 Hz); 5.05 (dd, 1H, J = 7 Hz, 7 Hz); 5.40 (s, 1H); 6.0, 6.2 (2s, 2H)	98.5 (d)	144.1 (s)	125.8 (t)	197.5 (s)

[a] Yield of distilled product.
[b] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.23.
[c] Riber 10-10 mass spectrometer.
[d] Varian EM-390 spectrometer (90 MHz).
[e] Bruker WH-90 spectrometer (22.93 MHz).
[f] $[\alpha]_D^{20}$: +9.3° (*c* 1.5, dichloromethane).

Table 2. Oxidation of Allylic Alcohols **2**

Substrate	Method	Reaction Conditions Solvent/Temperature/Time	Transformation Rate [%]	Yield [%] of Product **3**[a]
2b	B	THF/r.t./130 h	100	70
2b	B'	CH_2Cl_2/−60°C/0.75 h	100	75
2e	B	THF/r.t./48 h	100	93
2f[b]	B	CH_2Cl_2/40°C/140 h	70	40
2f[b]	B'	CH_2Cl_2/−60°C/0.75 h	95	80

[a] Yield of distilled product.
[b] Substrate **2f** was obtained by condensation of **1** with 2,3-*O*-methylethylidene-D-glyceraldehyde[6c].

warm to room temperature, hydrolysed with water (5 ml), extracted with dichloromethane (2 × 3 ml), the extract is evaporated, and products **3b** or **3f** are obtained by distillation (Tables 1 and 2).

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