A Convenient Synthesis of 3-(Diethoxymethyl)alkanals

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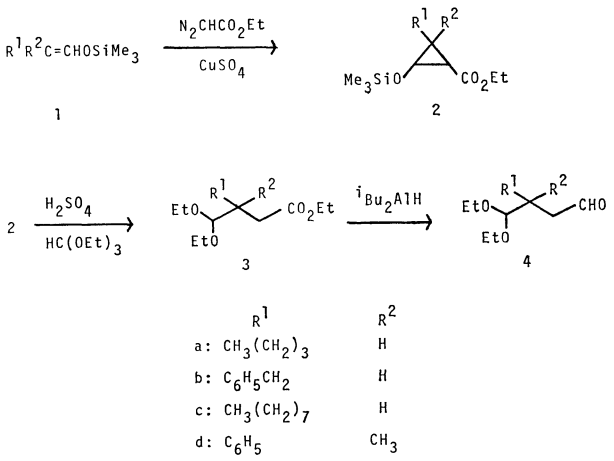
Synopsis. 3-(Diethoxymethyl)alkanals were obtained in moderate yields by the diisobutylaluminium hydride reduction of ethyl 3-(diethoxymethyl)alkanoates, which were simply synthesized in one pot by the copper(II)-catalyzed reaction of ethyl diazoacetate with 1-trimethylsiloxy-1-alkenes, followed by the ring cleavage of the resulting cyclopropanes with concentrated sulfuric acid in the presence of triethyl orthoformate.

1,4-Dicarbonyl compounds are attractive intermediates, and their synthesis is of interest because they can be converted into cyclopentenones, furans, and lactones. Among the many synthetic methods for 1,4-dicarbonyl compounds, the method *via* the cyclopropanation of enol acetates,[1-3] enol ethers,[3-6] or silyl enol ethers[3,7-9] with carbenes generated from 2-diazo carbonyl compounds is the elegant one.

The cyclopropanation was applied to the one pot preparation of ethyl 3-(diethoxymethyl)alkanoates (**3**) based on the consideration that the ring cleavage of the cyclopropanes derived from 1-trimethylsiloxy-1-alkenes and ethyl diazoacetate with an acid in the presence of triethyl orthoformate would result in the one pot synthesis of **3**. When 1-trimethylsiloxy-1-hexene (**1a**) was allowed to react with ethyl diazoacetate (4 equimolar amounts) in cyclohexane in the presence of a catalytic amount of copper(II) sulfate under reflux, distillation under reduced pressure yielded a colorless oil, ethyl 2-butyl-3-(trimethylsiloxy)cyclopropanecarboxylate (**2a**), in 92% yield. Treatment of **2a** in ethanol with concentrated sulfuric acid in the presence of triethyl orthoformate for 24 h at room temperature gave ethyl 3-(diethoxymethyl)heptanoate (**3a**) in 91% yield (83% total yield from **1a**). On the other hand, when the ring cleavage was carried out without isolation of **2a** after the cyclopropanation, similar yield was achieved (78% total yield from **1a**). The reduction of **3a** with diisobutylaluminium hydride (1.5 equimolar amount) in a mixture of cyclohexane and ether (2:3) at −70 °C for 3 h, followed by thin layer chromatographic purification, gave 3-(diethoxymethyl)heptanal (**4a**) in 74% yield.

These results mean that the precursors for 3-substituted furan synthesis, 3-(diethoxymethyl)alkanals (**4**), could be conveniently obtained by the diisobutylaluminium hydride reduction of ethyl 3-(diethoxymethyl)alkanoates (**3**), which were simply synthesized in one pot through two reaction steps; step 1) the cyclopropanation of 1-trimethylsiloxy-1-alkenes (**1**) with ethyl diazoacetate, step 2) the ring cleavage of the resulting cyclopropanes (**2**) with concentrated sulfuric acid in the presence of triethyl orthoformate, as shown in Scheme 1.

Several runs were carried out giving similar ethyl 3-(diethoxymethyl)alkanoates (**3**) or 3-(diethoxymethyl)alkanals (**4**) (Table).



Scheme 1.

Table 1. Syntheses of ethyl 3-(diethoxymethyl)-alkanoates and 3-(diethoxymethyl)alkanals

Starting Materials	Product	Yield/%	Bp/°C (mmHg)[a]
1a	**2a**	92	64—67 (0.7)
2a	**3a**	91	93—94 (3)
1a	**3a**	78	90—91 (2)
1b	**3b**	84	118—120 (0.1)
1c	**3c**	86	110—113 (0.3)
1d	**3d**	71	121—124 (0.08)
3a	**4a**	72	[100[b]] (12)][c]
3b	**4b**	67	[130[b]] (0.9)][c]
3d	**4d**	76	[138[b]] (0.8)][c]

a) 1 mmHg≈133.3 Pa. b) Bath temperature. c) The products were separated by TLC, and the boiling points were determined by bulb to bulb distillation.

Experimental

Boiling points are uncorrected. The ^{1}H-NMR spectra were recorded in CCl_4 solution at 60 MHz on a Varian A-60 Spectrometer using TMS as an internal standard. The IR spectra were determined on a JASCO IR-2A Spectrometer.

Materials. All silyl enol ethers were synthesized by the similar method described in the literature[10] giving mixtures of (*E*)- and (*Z*)-isomers, and they were used without separation. Ethyl diazoacetate and diisobutylaluminium hydride were prepared by the methods reported, respectively.[11,12]

Synthesis of Ethyl 3-(Diethoxymethyl)alkanoate (3). To a refluxing suspension of 1-trimethylsiloxy-1-alkene (**1**) (10 mmol) and anhydrous $CuSO_4$ (185 mg, 1.2 mmol) in dry cyclohexane (4 ml) was added ethyl diazoacetate (4.57 g, 40 mmol) in dry cyclohexane (19 ml) under argon atmosphere with vigorous stirring in a period of 2.5 h. After refluxing for additional 9.5 h, the reaction mixture was

cooled, and insoluble materials were filtered off and washed with cyclohexane (15 ml×3). The filtrate and the washings were combined and concentrated under reduced pressure. The oily product was dissolved in dry ethanol (5 ml). To the solution were added ethyl orthoformate (1.48 g, 10 mmol) and two drops of concentrated H_2SO_4. After standing for 24 h, H_2SO_4 was neutralized by addition of sodium ethoxide in dry ethanol. The insoluble mass appeared was filtered off and washed with ether (15 ml×3). The filtrate and the washing were combined and concentrated using a rotary evaporator. Distillation of the oil remained gave ethyl 3-(diethoxymethyl)alkanoate (**3**).

3a: IR (neat) 1740, 1180, 1130, and 1075 cm^{-1}; NMR (CCl_4) δ=0.90 (t, 3H, J=5 Hz), 1.03 (t, 3H, J=7 Hz), 1.14 (t, 3H, J=7 Hz), 1.22 (t, 3H, J=7 Hz), 1.1—1.6 (m, 6H), 1.9—2.7 (m, 3H), 3.49 (q, 2H, J=7 Hz), 3.50 (q, 2H, J=7 Hz), 4.06 (q, 2H, J=7 Hz), and 4.26 (d, 1H, J=4 Hz).

Found: C, 64.35; H, 10.56%. Calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84%.

3b: IR (neat) 1740, 1140, 1080, 1040, 760, and 710 cm^{-1}; NMR (CCl_4) δ=1.12 (t, 3H, J=7 Hz), 1.15 (t, 3H, J=7 Hz), 1.17 (t, 3H, J=7 Hz), 2.0—3.0 (m, 5H), 3.44 (q, 2H, J=7 Hz), 3.46 (q, 2H, J=7 Hz), 3.99 (q, 2H, J=7 Hz), 4.28 (d, 1H, J=4 Hz), and 7.16 (s, 5H).

Found: C, 69.23; H, 9.16%. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

3c: IR (neat) 1730, 1160, 1115, and 1060 cm^{-1}; NMR (CCl_4) δ=0.89 (t, 3H, J=5 Hz), 1.17 (t, 3H, J=7 Hz), 1.24 (t, 3H, J=7 Hz), 1.25 (t, 3H, J=7 Hz), 1.2—1.5 (m, 14H), 1.9—2.5 (m, 3H) 3.50 (q, 2H, J=7 Hz), 3.54 (q, 2H, J=7 Hz), 4.09 (q, 2H, J=7 Hz), and 4.30 (d, 1H, J=4 Hz).

Found: C, 68.30; H, 11.46%. Calcd for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47%.

3d: IR (neat) 1740, 1170, 1130, 1080, 750, and 700 cm^{-1}; NMR (CCl_4) δ=1.00 (t, 6H, J=7 Hz), 1.07 (t, 3H, J=7 Hz), 1.51 (s, 3H), 2.72 (s, 1H), 2.83 (s, 1H), 2.9—4.1 (m, 6H), 4.36 (s, 1H), and 7.0—7.5 (m, 5H).

Found: C, 69.17; H, 8.94%. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

*Reduction of **3** to 3-(Diethoxymethyl)alkanal (**4**).* To a solution of ethyl 3-(diethoxymethyl)alkanoate (**3**) (1.0 mmol) in a mixture of cyclohexane (10 ml) and ether (15 ml) was added a solution of diisobutylaluminium hydride (1.5 mmol) in cyclohexane (1.5 ml) at −70 °C under argon atmosphere in a period of 10 min. After stirring for additional 3 h at −70 °C, water (0.5 ml) was added to remove excess diisobutylaluminium hydride, and the mixture was warmed to room temperature. To the resulting mixture was added water (10 ml), and the insoluble materials appeared were filtered off. The organic layer was separated, dried with sodium sulfate, and concentrated under reduced pressure. Silica gel thin layer chromatographic purification gave 3-(diethoxymethyl)alkanal (**4**).

4a: IR (neat) 1730, 1115, and 995 cm^{-1}; NMR (CCl_4) δ=0.90 (t, 3H, J=5 Hz), 1.14 (t, 6H, J=7 Hz), 1.2—1.7 (m, 6H), 2.0—2.5 (m, 3H), 3.48 (q, 2H, J=7 Hz), 3.52 (q, 2H, J=7 Hz), 4.23 (d, 1H, J=4 Hz), and 9.43 (t, 1H, J=1 Hz).

Found: C, 66.59; H, 11.34%. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18%.

4b: IR (neat) 1730, 1120, 990, 750, and 700 cm^{-1}; NMR (CCl_4) δ=1.13 (t, 3H, J=7 Hz), 1.15 (t, 3H, J=7 Hz), 2.2—2.9 (m, 5H), 3.45 (q, 2H, J=7 Hz), 3.49 (q, 2H, J=7 Hz), 4.22 (d, 1H, J=4 Hz), 7.23 (s, 5H), and 9.56 (t, 1H, J=1 Hz).

Found: C, 72.25; H, 8.71%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

4d: IR (neat) 1730, 1120, 1005, 750, and 700 cm^{-1}; NMR (CCl_4) δ=1.14 (t, 3H, J=7 Hz), 1.20 (t, 3H, J=7 Hz), 1.48 (s, 3H), 2.46 (d, 2H, J=1 Hz), 3.52 (q, 2H, J=7 Hz), 3.65 (q, 2H, J=7 Hz), 4.21 (s, 1H), 7.0—7.5 (m, 5H), and 9.50 (t, 1H, J=1 Hz).

Found: C, 71.83; H, 9.14%. Calcd for $C_{15}H_{22}O_3$: C, 71.79; H, 8.86%.

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