ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 3, pp. 406–409. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © O.A. Garibyan, A.L. Ovanesyan, G.M. Makaryan, A.L. Petrosyan, Zh.A. Chobanyan, 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 3, pp. 412–415.

(2*E*)-4-Hydroxyalk-2-enals and 2-Substituted Furans as Products of Reactions of (2*E*)-4,4-Dimethoxybut-2-enal with Grignard Compounds

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Received January 12, 2009

Abstract—Methods have been developed for the synthesis of (2*E*)-1,1-dimethoxyalk-2-en-4-ols and (2*E*)-4-hydroxyalk-2-enals by reaction of (2*E*)-4,4-dimethoxybut-2-enals and Grignard compounds. Thermal isomerization of (2*E*)-4-hydroxyalk-2-enals gave the corresponding 2-alkylfurans.

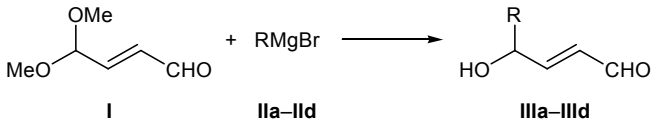
DOI: 10.1134/S1070428010030188

(2*E*)-4,4-Dimethoxybut-2-enal (**I**) molecule possesses a double bond and an aldehyde group, so that compound **I** is quite promising as polyfunctional synthon for the design of various organic compounds. It is widely used in the synthesis of a number of low-molecular weight bioregulators such as pheromones [1], cyclohexane analogs of prostaglandins [2], maytansinoids (macrocyclic lactams exhibiting antitumor, antimyotic, and antifungal activity) [3], cephalosporin analogs [4], etc.

In continuation of studies in this field, the goal of the present work was to synthesize from 4,4-dimethoxybut-2-enal (**I**) (2*E*)-4-hydroxyalk-2-enals which can be converted into cyclopentenone derivatives (intermediate compounds in the synthesis of prostaglandins [5]) via aldol condensation.

The reaction of aldehyde **I** with alkylmagnesium bromides **IIa**–**IId** in diethyl ether at 0°C resulted in the formation of unsaturated hydroxy aldehydes **IIIa**–**IIId** in 39–50% yield (Scheme 1). (2*E*)-4-Hydroxynon-2-enal (**IIId**) is a lipid metabolite which was isolated from the red marine alga *Liagora farinosa Lamouroux* [6]. Using the reaction with propylmagnesium bromide (**IIb**) as model process we examined the effect of different factors, such as reaction temperature, workup procedure, and order of mixing of the reactants, on the reaction course. The reaction occurred at a temperature below 0°C. Addition of aldehyde **I** to propylmagnesium bromide (**IIb**) at –55 to 0°C did not change the reaction pattern to an appreciable extent. The same products were formed when the reactants were mixed in the reverse order.

Scheme 1.



I **IIa–IId** **IIIa–IIId**

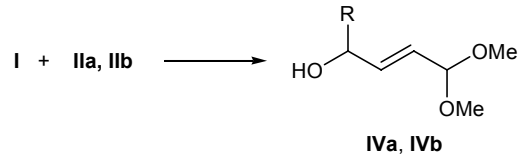
R = Et (**a**), Pr (**b**), Bu (**c**), C_5H_{11} (**d**).

Intermediate organomagnesium complex was decomposed by treatment with a dilute solution of *p*-toluenesulfonic or hydrochloric acid or with water. In the first case, hydroxy aldehyde **IIIb** was the only product, regardless of the acid nature. When the mixture was treated with water at room temperature and then distilled over potassium carbonate, dimethoxy alcohol **IVa** may be obtained as the major product. Further experiments showed that pH value (5–6) is not a significant factor that could affect the process. The acetal protection was conserved, and dimethoxy alcohol **IVb** was formed if the reaction mixture was treated with an acid at –30°C (Scheme 2).

Compounds **IIIa**–**IIId** were isolated by distillation or column chromatography on silica gel (eluent hex-

† Deceased.

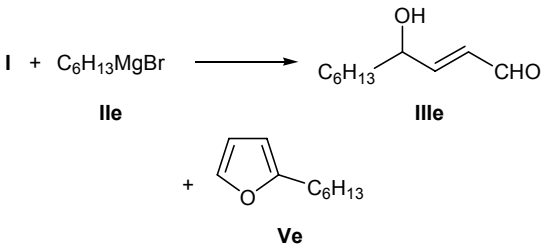
Scheme 2.



R = Et (**a**), Pr (**b**).

ane–diethyl ether, 19:1 to 2:1). The reaction of aldehyde **I** with hexylmagnesium bromide (**IIe**) under analogous conditions (diethyl ether, 0°C) gave either (2*E*)-4-hydroxydec-2-enal (**IIIe**) or a mixture of **IIIe** and 2-hexylfuran (**Ve**), depending on the workup procedure (Scheme 3).

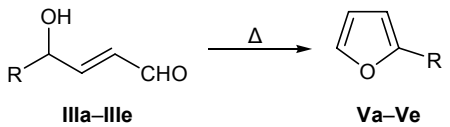
Scheme 3.



Aldehyde **IIIe** was obtained as the only product when the mixture was subjected to column chromatography on silica gel. Distillation (bp 135°C, 1 mm) gave a mixture of (2*E*)-4-hydroxydec-2-enal (**IIIe**) and 2-hexylfuran (**Ve**) at a ratio of 1:4. Compounds **IIIe** and **Ve** were isolated as individual substances by repeated distillation.

It is known that some 4-hydroxyalk-2-enals undergo cyclization into 2-substituted furans in the presence of mineral acids or Lewis acids; the double bond in the initial compounds should have *cis*-configuration to ensure cyclization [7]. Hydroxy aldehydes **IIIa**–**IIIe** were converted into the corresponding 2-alkylfurans **Va**–**Ve** [8] above 130°C, and the yields of **Va**–**Ve** were 41–45% (Scheme 4).

Scheme 4.



Presumably, the observed intramolecular cyclization requires high temperature. No furans **V** were formed when compounds **IIIa**–**IIId** were isolated by distillation.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were measured on a Varian Mercury-300 spectrometer at 300 MHz; the chemical shifts were determined relative to tetramethylsilane. The IR spectra were recorded on Specord and UR-20 instruments from samples prepared as thin films. GLC analysis was performed on a Chrom-5 chromatograph equipped with a flame-ionization detector and an SE-30 glass capillary column, 25 m × 0.2 mm; carrier gas nitrogen, flow rate 30 ml/min. Silica gel L 40/100 was used for column chromatography, and TLC was performed on Silufol UV-254 plates; spots were detected by UV irradiation or by treatment with iodine vapor or a solution of potassium permanganate.

Reaction of (2*E*)-4,4-dimethoxybut-2-enal (I) with Grignard compounds IIa–IIe (*general procedure***).** A solution of 6.5 g (0.05 mol) of (2*E*)-4,4-dimethoxybut-2-enal (**I**) in 65 ml of anhydrous diethyl ether was added dropwise under stirring at 0°C to Grignard compound **IIa**–**IIe** prepared from 1.32 g (0.055 mol) of magnesium and 0.055 mol of the corresponding alkyl halide in 50 ml of anhydrous diethyl ether. The mixture was stirred for 30 min at 0°C and for 1 h at room temperature. The mixture was cooled again to 0°C, and dilute hydrochloric acid was added dropwise to pH 5–6. The mixture was neutralized with sodium carbonate and extracted with diethyl ether, the extract was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by column chromatography or distilled under reduced pressure.

(2*E*)-4-Hydroxyhex-2-enal (IIIa). Yield 49%, bp 89–90°C (2 mm), R_f 0.24 (hexane–diethyl ether, 3:2). IR spectrum, ν, cm^{-1}: 3400–3500 (OH), 1690 (C=O), 1610 (C=C), 960 (*trans*-C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 t (3H, 6-H, J = 7.2 Hz), 1.25–1.70 m (2H, 5-H), 3.85 br.s (1H, OH), 4.25 q (1H, 4-H, $J_{4,3} = J_{4,5}$ = 7.1 Hz), 6.15 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.1 Hz), 6.82 d.d (1H, 2-H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 9.52 d (1H, 1-H, $J_{2,1}$ = 7.5 Hz). Found, %: C 63.11; H 8.81. $C_6H_{10}O_2$. Calculated, %: C 63.14; H 8.83.

(2*E*)-4-Hydroxyhept-2-enal (IIIb). Yield 48%, bp 98–99°C (2 mm), R_f 0.44 (hexane–diethyl ether, 2:1). IR spectrum, ν, cm^{-1}: 3400–3500 (OH), 1690 (C=O), 1610 (C=C), 960 (*trans*-C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.94 t (3H, 7-H, J = 7.2 Hz), 1.36–1.53 m (4H, 5-H, 6-H), 4.25 q (1H, 4-H, $J_{4,3}$ = $J_{4,5}$ = 7.1 Hz), 4.85 br.s (1H, OH), 6.18 d.d (1H, 3-H,

$J_{3,2}$ = 17.0, $J_{3,4}$ = 7.1 Hz), 6.82 d.d (1H, 2-H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 9.52 d (1H, 1-H, $J_{2,1}$ = 7.5 Hz). Found, %: C 65.52; H 9.41. $C_7H_{12}O_2$. Calculated, %: C 65.60; H 9.44.

(2*E*)-4-Hydroxyoct-2-enal (IIIc). Yield 45%, bp 110–112°C (2 mm), R_f 0.41 (hexane–diethyl ether, 2:1). IR spectrum, ν, cm^{-1}: 3400–3500 (OH), 1690 (C=O), 1610 (C=C), 960 (*trans*-C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.94 t (3H, 8-H, J = 7.2 Hz), 1.36–1.53 m (6H, 5-H, 6-H, 7-H), 4.25 q (1H, 4-H, $J_{4,3}$ = $J_{4,5}$ = 7.1 Hz), 4.82 br.s (1H, OH), 6.18 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.1 Hz), 6.82 d.d (1H, 2-H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 9.52 d (1H, 1-H, $J_{2,1}$ = 7.5 Hz). Found, %: C 67.61; H 9.89. $C_8H_{14}O_2$. Calculated, %: C 67.57; H 9.92.

(2*E*)-Hydroxynon-2-enal (IIId). Yield 44%, bp 125–127°C (2 mm), R_f 0.37 (hexane–diethyl ether, 2:1). IR spectrum, ν, cm^{-1}: 3400–3500 (OH), 1690 (C=O), 1610 (C=C), 960 (*trans*-C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 t (3H, 9-H, J = 7.2 Hz), 1.28–1.60 m (8H, 5-H, 6-H, 7-H, 8-H), 3.90 br.s (1H, OH), 4.35 q (1H, 4-H, $J_{4,3}$ = $J_{4,5}$ = 7.1 Hz), 6.25 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.1 Hz), 6.82 d.d (1H, 2-H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 9.52 d (1H, 1-H, $J_{2,1}$ = 7.5 Hz). Found, %: C 69.11; H 10.30. $C_9H_{16}O_2$. Calculated, %: C 69.19; H 10.32.

(2*E*)-4-Hydroxydec-2-enal (IIIe). Yield 50%, bp 133–135°C (2 mm), R_f 0.33 (hexane–diethyl ether, 2:1). IR spectrum, ν, cm^{-1}: 3400–3500 (OH), 1690 (C=O), 1610 (C=C), 960 (*trans*-C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 t (3H, 10-H, J = 7.2 Hz), 1.28–1.55 m (10H, 5-H, 6-H, 7-H, 8-H, 9-H), 3.52 br.s (1H, OH), 4.30 q (1H, 4-H, $J_{4,3}$ = $J_{4,5}$ = 7.1 Hz), 6.22 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.1 Hz), 6.82 d.d (1H, 2-H, $J_{1,2}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 9.54 d (1H, 1-H, $J_{2,1}$ = 7.5 Hz). Found, %: C 70.49; H 10.68. $C_{10}H_{18}O_2$. Calculated, %: C 70.55; H 10.66.

In the reaction of aldehyde **I** with hexylmagnesium bromide, 2-hexylfuran (**Ve**) was also isolated in addition to compound **IIIe**. Its yield and physical and spectral parameters are given below.

(2*E*)-1,1-Dimethoxyhex-2-en-4-ol (IVa). A solution of 3.5 g (0.027 mol) of aldehyde **I** in 25 ml of anhydrous diethyl ether was added dropwise at –20°C to Grignard compound **IIa** prepared from 0.97 g (0.027 mol) of magnesium and 2.9 g (0.027 mol) of ethyl bromide in 15 ml of anhydrous diethyl ether. The mixture was stirred for 2 h at –20°C, allowed to warm up to room temperature, stirred for 4 h, and left overnight. The mixture was then treated (dropwise) with 50 ml of ice water saturated with sodium chloride and extracted with diethyl ether, the extract was dried over potassium carbonate, the solvent was removed, and the residue was distilled under reduced pressure over anhydrous potassium carbonate. Yield 1.95 g (45%), bp 85–87°C (2 mm). IR spectrum, ν, cm^{-1}: 3450 (OH), 1120 (C–O–C), 970 (*trans*-C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 t (3H, 6-H, $J_{6,5}$ = 7.1 Hz), 1.23–1.68 m (2H, 5-H), 2.90 br.s (1H, OH), 3.25 s (6H, OCH_3), 3.80–4.20 m (1H, 4-H), 4.75 d (1H, 1-H, $J_{1,2}$ = 7.5 Hz), 5.40 d.d (1H, 2-H, $J_{2,1}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 5.70 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.5 Hz). Found, %: C 59.94; H 10.04. $C_8H_{16}O_3$. Calculated, %: C 59.97; H 10.07.

(2*E*)-1,1-Dimethoxyhept-2-en-4-ol (IVb). A solution of 1.58 g (0.012 mol) of compound **I** in 25 ml of anhydrous diethyl ether was added dropwise under stirring at –55 to –50°C to Grignard compound **IIb** prepared from 0.429 g (0.018 mol) of magnesium and 2.27 g (0.018 mol) of propyl bromide in 28 ml of anhydrous diethyl ether. The mixture was stirred for 3 h, allowed to warm up to room temperature, and left overnight. The mixture was then treated dropwise with a solution of 4 ml of water in 20 ml of diethyl ether on cooling to –30 to –20°C. The organic phase was separated, washed with several portions of water, and 9 mg of *p*-toluenesulfonic acid in 0.25 ml of water was added under stirring at –30°C. After 0.5 h, 5 mg of anhydrous sodium carbonate was added, the mixture was extracted with diethyl ether, the extract was dried over Na_2SO_4, the solvent was removed, and the residue was distilled under reduced pressure. Yield 1.1 g (53%), bp 98–100°C (12 mm). IR spectrum, ν, cm^{-1}: 3450 (OH), 1110 (C–O–C), 970 (*trans*-C=C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.94 t (3H, 7-H, $J_{7,6}$ = 7.1 Hz), 1.36–1.53 m (4H, 5-H, 6-H), 2.90 br.s (1H, OH), 3.24 s (6H, OCH_3), 4.20–4.29 m (1H, 4-H), 4.76 d (1H, 1-H, J = 7.5 Hz), 5.44 d.d (1H, 2-H, $J_{2,1}$ = 7.5, $J_{2,3}$ = 17.0 Hz), 5.80 d.d (1H, 3-H, $J_{3,2}$ = 17.0, $J_{3,4}$ = 7.5 Hz). Found, %: C 62.01; H 10.39. $C_9H_{18}O_3$. Calculated, %: C 62.04; H 10.41.

Thermal cyclization of hydroxy aldehydes IIIa–IIIe (*general procedure*). A Claisen flask was charged with 0.004 mol of compound **IIIa**–**IIIe**, and the flask was placed in a metal bath and slowly heated to 100–150°C at a residual pressure of 200–300 mm. The distillate was extracted with diethyl ether, the extract was dried over Na_2SO_4, the solvent was removed, and the residue was distilled under reduced pressure.

2-Ethylfuran (Va). Yield 42%, bp 56–58°C (200 mm). IR spectrum: ν 600 cm^{-1} (furan ring). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 t (3H, CH_3, J = 7.0 Hz), 2.57 t (2H, C**H**$_2$CH$_3$, J = 7.5 Hz), 5.93 s (1H, 3-H), 6.21 s (1H, 4-H), 7.26 s (1H, 5-H). Found, %: C 74.97; H 8.39. C_6H_8O. Calculated, %: C 74.94; H 8.36.

2-Propylfuran (Vb). Yield 41%, bp 56–58°C (80 mm). IR spectrum: ν 600 cm^{-1} (furan ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 t (3H, CH_3, J = 7.0 Hz), 1.60–1.69 m (2H, C**H**$_2$CH$_3$), 2.57 t (2H, 2-CH_2, J = 7.5 Hz), 5.93 s (1H, 3-H), 6.21 s (1H, 4-H), 7.26 s (1H, 5-H). Found, %: C 76.26; H 9.12. $C_7H_{10}O$. Calculated, %: C 76.33; H 9.15.

2-Butylfuran (Vc). Yield 43%, bp 60–62°C (40 mm). IR spectrum: ν 600 cm^{-1} (furan ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.95 t (3H, CH_3, J = 7.0 Hz), 1.60–1.70 m (4H, C**H**$_2$C**H**$_2$CH$_3$), 2.58 t (2H, 2-CH_2, J = 7.5 Hz), 5.93 s (1H, 3-H), 6.21 s (1H, 4-H), 7.26 s (1H, 5-H). Found, %: C 77.34; H 9.71. $C_8H_{12}O$. Calculated, %: C 77.38; H 9.74.

2-Pentylfuran (Vd). Yield 43%, bp 64–66°C (18 mm). IR spectrum: ν 600 cm^{-1} (furan ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.92 t (3H, CH_3, J = 7.0 Hz), 1.57–1.70 m [6H, (C**H**$_2$)$_3$CH$_3$], 2.60 t (2H, 2-CH_2, J = 7.5 Hz), 5.94 s (1H, 3-H), 6.20 s (1H, 4-H), 7.27 s (1H, 5-H). Found, %: C 78.15; H 10.23. $C_9H_{14}O$. Calculated, %: C 78.21; H 10.21.

2-Hexylfuran (Ve). Yield 45%, bp 70–72°C (10 mm). IR spectrum: ν 600 cm^{-1} (furan ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.91 t (3H, CH_3, J = 7.0 Hz), 1.33–1.41 m [6H, (C**H**$_2$)$_3$CH$_3$], 1.60–1.70 m (2H, 2-CH_2C**H**$_2$), 2.62 t (2H, 2-CH_2), 5.95 s (1H, 3-H), 6.20 s (1H, 4-H), 7.27 s (1H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.33 (C^{10}), 22.84 (C^9), 28.29 (C^6), 29.15 (C^7), 31.85 (C^5, C^8), 104.79 (C^4), 110.23 (C^2), 140.79 (C^1), 156.68 (C^3). Found, %: C 78.84; H 10.61. $C_{10}H_{16}O$. Calculated, %: C 78.90; H 10.59.

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