

Reaction of α -ethoxyacrolein with diethyl malonate

N. A. Keiko,* Yu. A. Chuvashov, T. A. Kuznetsova, L. V. Sherstyannikova, and M. G. Voronkov

Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences,
1 ul. Favorskogo, 664033 Irkutsk, Russian Federation.
Fax: +7 (395 2) 35 6046. E-mail: admin@iriokh.irk.ru

The reaction of α -ethoxyacrolein with diethyl malonate in the presence of EtONa, lithium diisopropylamide, or the Na_2CO_3 —benzene— $\text{Et}_3(\text{PhCH}_2)\text{NCl}$ catalytic system proceeds as the Michael addition. In the presence of an equimolar amount of triethylamine, selective 1,2-addition followed by dehydration of the 1,2-adduct occurs. Owing to the strong +M effect of the EtO group, α -ethoxyacrolein is a substantially less active Michael acceptor than acrolein.

Key words: α -ethoxyacrolein, diethyl malonate, polarization of the C=C bond, Michael reaction, Knoevenagel reaction.

The electron-donor effect of the alkoxy group in α -alkoxyacroleins governs the direction of the Markovnikoff addition of electrophiles at the C=C bond.¹ According to the ^{13}C NMR spectra, a substantial negative charge is located on the β -carbon atom of α -ethoxyacrolein (**1**). Apparently, for this reason 1,4-addition of nucleophiles, which is typical of acrolein, is very rarely observed for α -alkoxyacroleins.^{2,3}

The aim of this work is to reveal the reagents and the reaction conditions that can cause dynamic polarization of the multiple bond in α -alkoxyacroleins, which is favorable for regioselective nucleophilic 1,4-addition.

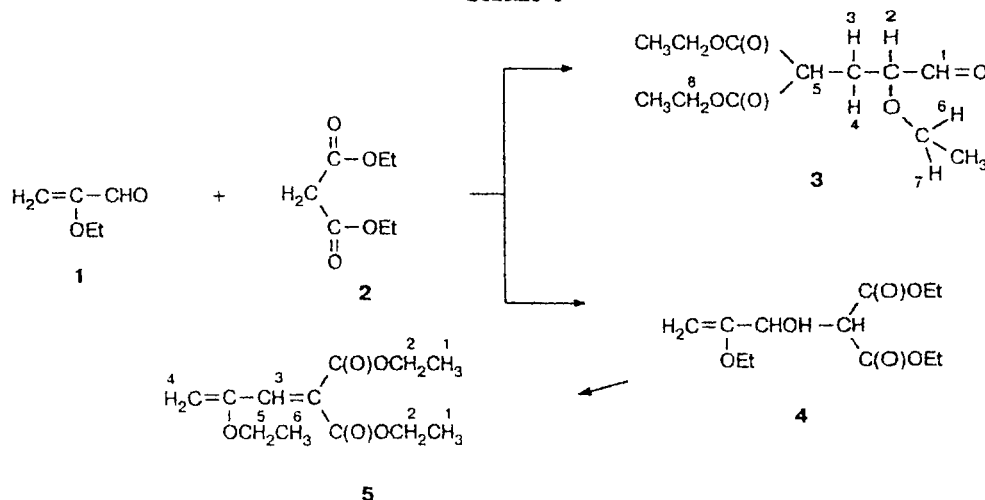
Previously,⁴ it has been demonstrated that attempts to perform conjugate addition of sodium enolates of cyclohexanone, methylcyclohexanone, dimedone, or ethyl 2-oxocyclohexanecarboxylate to α -alkoxy- α,β -unsaturated ketones and acids were unsuccessful. How-

ever, sodium dimethyl malonate appeared to be an efficient nucleophile with respect to these ketones and acids. 1,4-Adducts were formed in 60% yield under substantially more drastic conditions than those used in the case of nonsubstituted acrylic systems.⁴

Results and Discussion

The reaction of α -ethoxyacrolein **1** with diethyl malonate (**2**) in the presence of EtONa at 20 °C occurs as the 1,4-addition (Scheme 1). The yield of the adduct, namely, of diethyl (3-oxo-2-ethoxypropyl)malonate (**3**), was only 15% after 8 h and reached 30% after 1 day, while the conversion of acrolein in the reaction with diethyl malonate under analogous conditions was 40–60%.^{5,6}

Scheme 1



In the presence of a milder base, namely, of triethylamine (an equimolar amount), addition of diethyl malonate **2** to α -ethoxyacrolein **1** proceeded exclusively as the Knoevenagel addition to form diethyl (2-ethoxy-1-hydroxyprop-2-enyl)malonate (**4**). This compound could be identified only by GLC-mass spectrometry. When a mixture of the initial reagents in benzene was heated to 55–76 °C for 7 h, the content of **4** was ~4%. The product of dehydration of **4**, viz., diethyl (2-ethoxyprop-2-enylidene)malonate (**5**) (5% in the mixture) and the Michael adduct (**3**) (1% in the mixture) were also detected. In addition, the initial compounds were detected in substantial amounts. Further heating (75 °C, 12 h) led to an increase in the content of ester **5** to 36% (52% yield) and to the almost complete disappearance of intermediate **4**. It is known that analogous 1,2-addition of maleic acid⁷ or its monoalkyl esters⁸ to 2-alkenals followed by dehydration occurs in the presence of tertiary amines. However, the alternative Michael addition of CH-acids to acrolein and methacrolein in the presence of an equimolar amount of Et₃N was also reported.^{9,10} In the case of α -ethoxyacrolein, the by-product of the Knoevenagel reaction is its cyclodimer, namely, 2,5-diethoxy-2,3-dihydro-4H-pyran-2-carbaldehyde.

The most efficient 1,4-addition of CH-acids to acrolein could be performed under conditions of phase transfer catalysis.^{11,12} The reaction of α -ethoxyacrolein with diethyl malonate in the presence of the Na₂CO₃–benzene–Et₃(PhCH₂)NCl catalytic system (54 h at 20 °C or 9 h at 70–80 °C), which is the most efficient system in the case of acrolein, afforded predominantly 1,4-adduct **3** in 20–22% yield. The content of product **5** in the mixture was 1%. The mixture contained also substantial amounts of the unconsumed reagents and higher-molecular-weight compounds, whose structures were not studied.

Regioselective 1,4-addition of carbanions to α,β -unsaturated aldehydes can occur upon deprotonation of CH-acids with lithium amides or when the reaction is performed under thermodynamically controlled conditions.¹² However, it is also known that kinetically controlled addition of 2-(*N*-methylanilino)acetonitrile to α -methoxyacrolein in the presence of lithium diisopropylamide (LDA) proceeds regioselectively to form the 1,2-adduct.¹³ The reaction of α -ethoxyacrolein with the diethyl malonate carbanion generated with the use of LDA at –78 °C gave predominantly (20–40% yield) 1,4-adduct **3**. The content of the product of the alternative direction of the reaction was ~1%. In addition, the mixture contained substantial amounts of the initial compounds.

To summarize, the diethyl malonate carbanion can attack either the carbonyl group or the C=C bond of α -ethoxyacrolein depending on the reaction conditions. In the latter case, the substrate acts as the π,π -conjugated acrylic system, although this Michael acceptor appeared to be substantially less active than acrolein.

Experimental

The ¹H and ¹³C NMR spectra were recorded on JEOL FX-90Q (89.95 MHz) and Varian VXR-500S (500 MHz) spectrometers in CDCl₃ at –20 °C with HMDS as the internal standard. The mass spectra were obtained on a Hewlett–Packard HP5971A GLC-mass chromatograph (EI, 70 eV) equipped with a mass-selective detector, an HP-5890 chromatograph, and an Ultra-2 column (5% phenylmethylsilicone); the evaporator temperature was 250 °C; the column temperature was increased from 40 to 180 °C with a rate of 15 deg min^{–1}. The IR spectra were recorded on a Specord 75-IR spectrometer in a thin layer.

The ¹³C NMR spectrum of α -ethoxyacrolein (**8**): 13.07 (CH₃); 62.90 (OCH₂); 102.02 (=CH₂); 157.82 (=CH–O); 187.24 (CHO).

Reaction of α -ethoxyacrolein with diethyl malonate in the presence of EtONa. Anhydrous ethanol (12 mL) was placed in a flame-dried flask filled with argon. Then metallic Na (38 mg, 1.6 mg-at.) and diethyl malonate (0.8 g, 5 mmol) were added. The reaction mixture was stirred for 10 min. α -Ethoxyacrolein (1 g, 10 mmol) was added dropwise. The reaction mixture was stirred at 25 °C for 8.5 h and treated with water. The organic layer was separated and the aqueous layer was extracted with ether. The ethereal extract was pooled with the organic layer and the combined extracts were dried with MgSO₄ and concentrated. According to the data of GLC-mass spectrometry and ¹H NMR spectroscopy, the residue contained the initial α -ethoxyacrolein, diethyl malonate, and adduct **3**. The mass spectrum and the ¹H NMR spectrum of 1,4-adduct **3** are identical with those of the specimen of compound **3**, which was prepared by the reaction in the presence of LDA (see below). According to the ¹H NMR data, the yield of the product was 15%. When the duration of the reaction was increased to 20 h, the yield of 1,4-adduct **3** (according to the ¹H NMR data) reached 33%.

Reaction of α -ethoxyacrolein with diethyl malonate in the presence of Et₃N. A mixture of triethylamine (5.06 g, 0.05 mol) and diethyl malonate (8.01 g, 0.05 mol) was stirred without heating for 20 min. Then the temperature was increased to 40 °C. α -Ethoxyacrolein (5 g, 0.05 mol) was added dropwise. The reaction mixture was heated to 60 °C and kept at this temperature for 30 h. According to ¹H NMR data, the yield of adduct **5** was 40%. According to the data of GLC-mass spectrometry, substantial amounts of the initial reagents remained unconsumed and the α -ethoxyacrolein dimer was formed. After removal of Et₃N *in vacuo* and molecular distillation (100–120 °C, 1·10^{–3} Torr), compound **5** was obtained. Found (%): C, 59.33; H, 7.77. C₁₂H₁₈O₅. Calculated (%): C, 59.49; H, 7.49. IR, ν /cm^{–1}: 1590 (C=C); 1640 (CH₂=C); 1710, 1735, 1740 (C=O). ¹H NMR, δ : 1.10, 1.10, and 1.14 (all t, 9 H, C(H-1)₃ and C(H-6)₃, *J* = 7 Hz); 3.61 (q, 2 H, C(H-5)₂, *J* = 7 Hz); 4.07 and 4.04 (both q, 4 H, C(H-2)₂, *J* = 7 Hz); 4.36 (d, 1 H, C(H-4)₂, *J* = 2.4 Hz); 4.4 (d, 1 H, C(H-4)₂, *J* = 2.3 Hz); 6.78 (s, 1 H, C(H-3)). MS, *m/z* (*I*_{rel} (%)): 242 [M]⁺ (15), 213 (7), 197 (22), 185 (11), 169 (32), 168 (75), 167 (73), 157 (42), 140 (47), 139 (100), 123 (42).

Under other conditions (75 °C, 12 h), the content of ester **5** in the reaction mixture (according to the ¹H NMR data) was 35.5%, which corresponds to a yield of 52%. 1,2-Adduct **4** was detected along with compound **5** by GLC-mass spectrometry. MS, *m/z* (*I*_{rel} (%)): 260 [M]⁺ (20), 215 (9), 189 (6), 185 (14), 141 (35), 133 (23), 123 (15), 115 (65), 113 (66), 112 (66), 100 (71), 87 (54), 43 (100).

This series of the reactions afforded the cyclodimer of α -ethoxyacrolein as the by-product.¹⁴ MS, m/z (I_{rel} (%)): 200 $[M]^+$ (10), 171 $[M - CH=O]^+$ (61), 155 $[M - OEt]^+$ (9), 143 (27), 125 (15), 115 (100), 97 (25), 73 (29), 69 (20).

Reaction of α -ethoxyacrolein with diethyl malonate in the presence of the Na_2CO_3 —benzene— $\text{Et}_3(\text{PhCH}_2)\text{NCl}$ system. A mixture of Na_2CO_3 (5.3 g, 0.5 mol), a catalytic amount of $\text{Et}_3(\text{PhCH}_2)\text{NCl}$, benzene (20 mL), and diethyl malonate (8.01 g, 0.5 mol) was heated to 43 °C. α -Ethoxyacrolein (5 g, 0.5 mol) was added very slowly at this temperature. At the end of addition, the reaction mixture warmed up to 65 °C. The mixture was kept at 81 °C for 9.5 h and then cooled. The solution was decanted from the crystalline precipitate and washed with water to remove traces of Na_2CO_3 . The organic layer was dried with MgSO_4 . After removal of benzene, molecular distillation ($1 \cdot 10^{-3}$ Torr, 90 °C) was performed. A fraction was obtained which contained (according to the ^1H NMR data) 85% of aldehydoester 3 (the yield was 22%). The spectral characteristics of the 1,4-adduct are identical with those described below. The reaction mixture contained substantial amounts of the initial compounds along with ester 3. The contents of the compounds in the mixture, which were calculated based on the data of GLC-mass spectrometry, agree with the data obtained from the ^1H NMR spectrum.

Reaction of α -ethoxyacrolein with diethyl malonate in the presence of LDA. Dry THF (20 mL) and diisopropylamine (1.14 g, 0.011 mol) were placed in a flame-dried flask filled with argon. The mixture was cooled to -78 °C and a solution of BuLi (16 mL) in hexane (0.008 mol) was added. After 30 min, diethyl malonate (4 g, 0.025 mol) was added at -78 °C. After 40 min, α -ethoxyacrolein (5 g, 0.05 mol) was added dropwise and the temperature was increased to +7 °C (1 h 20 min). Then the temperature was rapidly increased to -20 °C. The reaction mixture was washed with a saturated solution of NH_4Cl and with water (twice). The organic layer was separated and the aqueous layer was extracted with ether. The ethereal extract was pooled with the organic layer and the combined extracts were dried with MgSO_4 . Low-boiling compounds were removed and the residue was fractionated *in vacuo*. Compound 3 was obtained in a yield of 1.41 g (24%), b.p. 150–175 °C (1 Torr), n_D^{18} 1.4435. Found (%): C, 55.44; H, 7.8. $\text{C}_{12}\text{H}_{20}\text{O}_6$. Calculated (%): C, 55.40; H, 7.7. IR, ν/cm^{-1} : 1725, 1735, 1745 (C=O). ^1H NMR, δ : 1.19, 1.23, and 1.25 (all t, 9 H, CH_3); 2.15 (ddd, 1 H-3, $^2J_{3,4} = 14$ Hz, $^3J_{2,3} = 9$ Hz, $^3J_{3,5} = 6$ Hz); 2.28 (ddd, 1 H-4, $^2J_{3,4} = 14$ Hz, $^3J_{2,4} = 4$ Hz, $^3J_{4,5} = 9$ Hz); 3.56 (dd, 1 H-5, $^3J_{3,5} = 6$ Hz, $^3J_{4,5} = 9$ Hz); 3.46 (dq, 1 H-6, $^3J = 7$ Hz, $^2J_{6,7} = 9$ Hz); 3.64 (dq, 1 H-7, $^3J = 7$ Hz, $^2J_{6,7} = 9$ Hz); 3.71 (ddd, 1 H-2, $^3J_{2,3} = 9$ Hz, $^3J_{2,4} = 7$ Hz, $^3J_{1,2} = 1.65$ Hz); 4.17 (m, 4 H-8, CH_2); 9.67 (d, 1 H-1, $^3J_{1,2} = 1.5$ Hz). MS of 3, m/z (I_{rel} (%)): 231 $[M - \text{CHO}]^+$ (45), 215 $[M - \text{OEt}]^+$ (5), 187 $[M -$

$\text{EtOCO}]^+$ (14), 157 (100), 141 (16), 129 (59), 111 (25), 101 $[M - \text{EtOC(O)CHC(O)OEt}]^+$ (20), 83 (34), 55 (34).

According to the data of GLC-mass spectrometry and ^1H NMR spectroscopy, the reaction mixture contained the initial reagents and the α -ethoxyacrolein dimer.

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