Stereochemistry of ketone olefination with methyl trimethylsilylacetate*

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High (*Z*)-stereoselectivity of olefination of methyl α-phenylthioalkyl and methyl α-phenylthioalkenyl ketones with methyl trimethylsilylacetate decreases in the case of ketones containing a higher alkyl-substituent in place of the methyl group.

Key words: (*Z*)-stereoselective olefination of ketones; sulfides; methyl 7-methyl-3-propyl-4-(phenylthio)deca-2(*Z*),6(*Z*)- and 7-methyl-3-propyl-4-(phenylthio)deca-2(*E*),6(*Z*)-dienoates; 8-methyl-5-(phenylthio)undec-7(*Z*)-en-4-ol.

Previously,[1—3] we demonstrated that methyl phenylthioalkyl and methyl phenylthioalkenyl ketones (**1**) are smoothly condensed with methyl trimethylsilylacetate (**2**) to give the corresponding α,β-unsaturated esters in high yields and 90% *Z*-stereoselectivity.

It was of interest to study this reaction with ketones containing an alkyl substituent other than methyl as the substrates. This study deals with the solution of this task in relation to recently described[4] ketone **3**.

^{1}H NMR analysis of the mixture of products formed in the condensation of compounds **3** and **2** has shown that ketone **3** reacts with **2** under conditions developed previously for **1** to give a mixture of esters **4a,b** (Scheme 1). This is indicated by the triplet signals for the PhSCH group (δ 5.67 for the *Z*-isomer, δ 3.54 for the *E*-isomer) characteristic of such esters[2,3] and singlets for HC(2) (δ 5.64 for the *Z*-isomer, δ 5.59 for the *E*-isomer). Unfortunately, the degree of conversion of **3** was only 30—35%, the ratio **4a** : **4b** ≈ 4 : 1.

Attempted isolation of esters **4a,b** by flash chromatography failed: the mixture of compounds **3**, **4a**, and **4b** was eluted without separation. After thorough vacuum drying, this mixture was involved again into the condensation with **2**, which gave, after chromatography, a mixture of compounds **3**, **4a**, and **4b** in 44 : 42.8 : 11.2 ratio (^{1}H NMR data).

To isolate esters **4a,b**, we made use of the ability of $NaBH_4$, when taken in a 1—1.5 equiv. amount, to reduce a keto group in the presence of an ester group.[5] Alcohol **5** thus obtained was easily separated by chromatography from the mixture of esters **4a,b**, which could not be separated completely into components even by HPLC. Analy-

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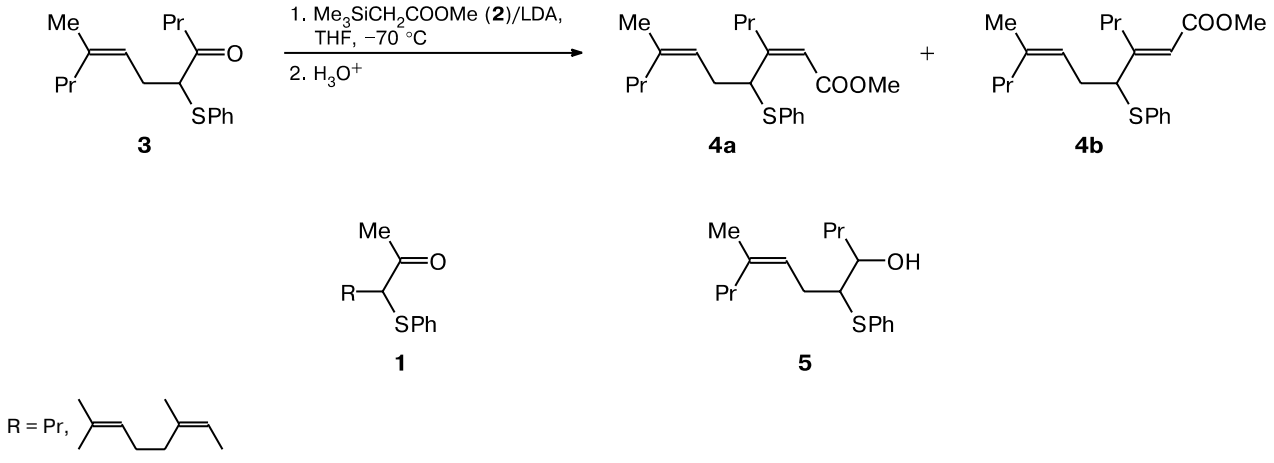
Scheme 1



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sis of the ^{1}H NMR spectra of this mixture, taking into account earlier data,[1—3] confirmed that the mixture contains only esters **4a,b** in 79 : 21 ratio.

Experimental

IR spectra were recorded on a Specord M-82 spectrometer in CCl_4. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ relative to Me_4Si on a Bruker AC-200 spectrometer (^{1}H, 200 MHz; ^{13}C, 50.3 MHz). Mass spectra were run on a Varian MAT 311a instrument (EI, 70 eV); peaks with relative intensity of ≥10% are presented. Preparative flash chromatography was performed on silica gel 60 (Merck), TLC was carried out on Silufol (Kavalier, Czechia) in benzene. Analytical and preparative HPLC were performed on a Silasorb C-8 column (16.0×250 mm) with a 10% (v/v) solution of ethanol in heptane, a refractometric detector, and an eluent velocity of 4 mL min^{-1}.

The solvents were purified as follows: THF was distilled from a blue Na/benzophenone solution directly into the reaction vessel. Hexane and benzene were distilled from Na. The LDA solution was prepared directly in the reactor from equivalent amounts of diisopropylamine and a 1.5 *M* solution of BuLi obtained by a standard procedure. The experiments involving BuLi and LDA were carried out under argon using glassware kept for 12 h at 160 °C and cooled in an argon flow. The usual workup of the organic extracts included washing to pH ~7, drying with $MgSO_4$, and evaporation on a rotary evaporator.

Condensation of ketone 3 with methyl trimethylsilylacetate (2). A solution of compound **2** (1.92 mL, 12 mmol) in 5 mL of THF was added dropwise at −72 °C over a period of 12 min to a stirred solution of LDA (12 mmol) in 110 mL of THF and 8 mL of hexane. The mixture was stirred for 1.5 h, and a solution of compound **3** (2.15 g, 7.4 mmol) in 5 mL of THF was added at the same temperature over a period of 15 min. The reaction mixture was stirred for 2.5 h at this temperature, warmed-up to 3 °C over a period of 3 h, left for ~14 h at this temperature, and transferred into a stirred saturated solution of NH_4Cl (50 mL). The mixture was stirred for 20 min and the layers were separated. The aqueous layer was extracted with methyl *tert*-butyl ether. The usual workup of the combined organic extracts gave 2.55 g of a product mixture as a light-yellow oil, which was chromatographed on 100 g of SiO_2. Gradient elution with hexane to benzene (up to 30% benzene) gave 1.76 g of a mixture of esters **4a,b** and the starting ketone **3** in ~4 : 1 : 11 ratio (^{1}H NMR data). The mixture was dried to a constant mass at ~20 °C *in vacuo* (1 Torr) and treated with compound **2** as described above. Chromatography on SiO_2 gave 1.33 g of a mixture of compounds **3**, **4a**, and **4b** (~4 : 4 : 1).

Methyl 7-methyl-3-propyl-4-phenylthiodeca-2(*Z*),6(*Z*)-dienoate (4a), 7-methyl-3-propyl-4-phenylthiodeca-2(*E*),6(*Z*)-dienoate (4b), and 8-methyl-5-phenylthioundec-7(*Z*)-en-4-ol (5). Sodium borohydride (210 mg) was added in portions to a solution of the above-described mixture of **3**, **4a**, and **4b** (1.32 g) in 90 mL of methanol stirred at 0—5 °C. The mixture was warmed-up to ~20 °C, stirred for 2 h, and cooled to 0 °C. Acetic acid (0.7 mL) was added dropwise. Methanol was evaporated *in vacuo* and the residue was dissolved in 10 mL of water and extracted with ether (5×7 mL). The usual workup of the combined extracts gave 1.36 g of a product mixture, which was chromatographed on 50 g of SiO_2. Gradient elution from hexane to benzene (up to 100% of benzene) gave 0.61 g of a mixture of esters **4a,b** and 0.48 g of alcohol **5**.

HPLC under the chosen conditions did not provide complete separation of ester **4b** from **4a**.

Ester **4a**, R_f 0.60, τ = 6.92 min. ^{1}H NMR, δ: 0.80—1.00 (m, 6 H, Me); 1.10—1.60 (m, 4 H, CH_2); 1.67 (s, 3 H, MeC(7)); 1.97 (m, 2 H, $H_2C(8)$); 2.08—2.50 (m, 4 H, $H_2CC{=}C$); 3.59 (s, 3 H, MeO); 5.15 (t, 1 H, HC(6), J = 7 Hz); 5.64 (s, 1 H, HC(2)); 5.67 (dd, 1 H, HC(4), J_1 = 7.7 Hz, J_2 = 8.5 Hz); 7.20—7.45 (m, 5 H, Ph). ^{13}C NMR, δ: 13.9 (Me); 20.95, 21.1 (CH_2); 23.3 (MeC(7)); 31.0, 33.3, 34.0 (C(5), C(8), $H_2CC(3)$); 48.2 (C(4)); 50.8 (MeO); 116.6 (C(2)); 121.0 (C(6)); 137.8 (C(7)); 160.9 (C(3)); 166.5 (C(1)).

Ester **4b**, R_f 0.60, τ = 7.08 min. ^{1}H NMR, δ: 0.80—1.00 (m, 6 H, Me); 1.10—1.60 (m, 4 H, CH_2); 1.67 (s, 3 H, MeC(7)); 1.97 (m, 2 H, $H_2C(8)$); 2.40—2.80 (m, 4 H, $H_2CC{=}C$); 3.54 (t, 3 H, HC(4), J = 7.4 Hz); 3.67 (s, 3 H, MeO); 5.15 (t, 1 H, HC(6), J = 7 Hz); 5.59 (s, 1 H, HC(2)); 7.20—7.45 (m, 5 H, Ph). ^{13}C NMR, δ: 14.0 (Me); 20.95, 22.6 (CH_2); 23.3 (MeC(7)); 31.0 (C(5)); 31.75 $H_2CC(3)$); 33.3 or 34.0 (C(8)); 50.8 (MeO); 56.9 (C(4)); 111.8 (C(2)); 121.0 (C(6)); 138.1 (C(7)); 161.8 (C(3)); 166.5 (C(1)).

Alcohol **5**, R_f 0.30. IR, ν/cm^{-1}: 3624, 3528, 3064, 3012, 2960, 2932, 2872, 1588, 1480, 1468, 1456, 1440, 1380, 1280, 1120, 1088, 1068, 1028, 948, 848, 692. ^{1}H NMR, δ: 0.88 (t, 3 H, Me, J = 7.3 Hz); 0.90 (t, 3 H, Me, J = 7.0 Hz); 1.20—1.66 (m, 6 H, CH_2); 1.71 (s, 3 H, MeC(8)); 2.00 (dd, 2 H, $H_2C(9)$, J_1 = 6.6 Hz, J_2 = 8.0 Hz); 2.28 (m, 2 H, HC(6), OH); 2.50 (m, 1 H, HC(6)); 3.08 (ddd, 1 H, HC(5), J_1 = 5.5 Hz, J_2 = 7.4 Hz, J_3 = 11.2 Hz); 3.67 (m, 1 H, HC(4)); 5.30 (t, 1 H, HC(7), J = 7 Hz); 7.20—7.60 (m, 5 H, Ph). ^{13}C NMR, δ: 14.0 (Me); 19.1, 21.0 (C(2), C(10)); 23.4 (MeC(8)); 30.2 (C(6)); 34.0 (C(9)); 36.6 (C(3)); 57.5 (C(5)); 72.4 (C(4)); 121.8 (C(7)); 137.9 (C(8)). MS, m/z (I_{rel} (%)): 292 $[M]^+$ (19), 195 (76), 177 (38), 165 (19), 137 (19), 136 (49), 135 (38), 123 (45), 121 (15), 110 (31), 109 (65), 108 (96.5), 99 (19), 97 (19), 96 (19), 95 (30), 93 (13), 91 (22), 85 (100), 84 (12.5), 83 (14), 82 (21), 81 (76), 79 (34), 78 (13), 77 (28), 71 (44), 69 (61), 68 (19), 67 (98), 66 (21.5), 65 (26), 57 (90), 56 (19), 55 (98.6), 53 (24).

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