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(*R*)-4-Menthenone in Reactions of 1,4-Conjugate and 1,3-Dipolar Addition

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Abstract—(*R*)-4-Menthenone compared with common cyclic enones exhibits considerably lower reactivity in 1,4-conjugate addition of organometallic reagents, is inert in Michael reactions and pyrazoline formation evidently due both to the distorted polarization in the enone system and to steric hindrances from the α-isopropyl group in the cyclohexene ring.

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We reported formerly on enhanced reactivity of (*R*)-4-menthenone (**I**) in ozonolysis compared with common enone systems [1] and that the 1,2-addition of nucleophilic reagents to it occurred without trouble [2–4]. In this study the behavior of enone **I** in reactions of 1,4-conjugate and 1,3-dipolar addition is investigated.

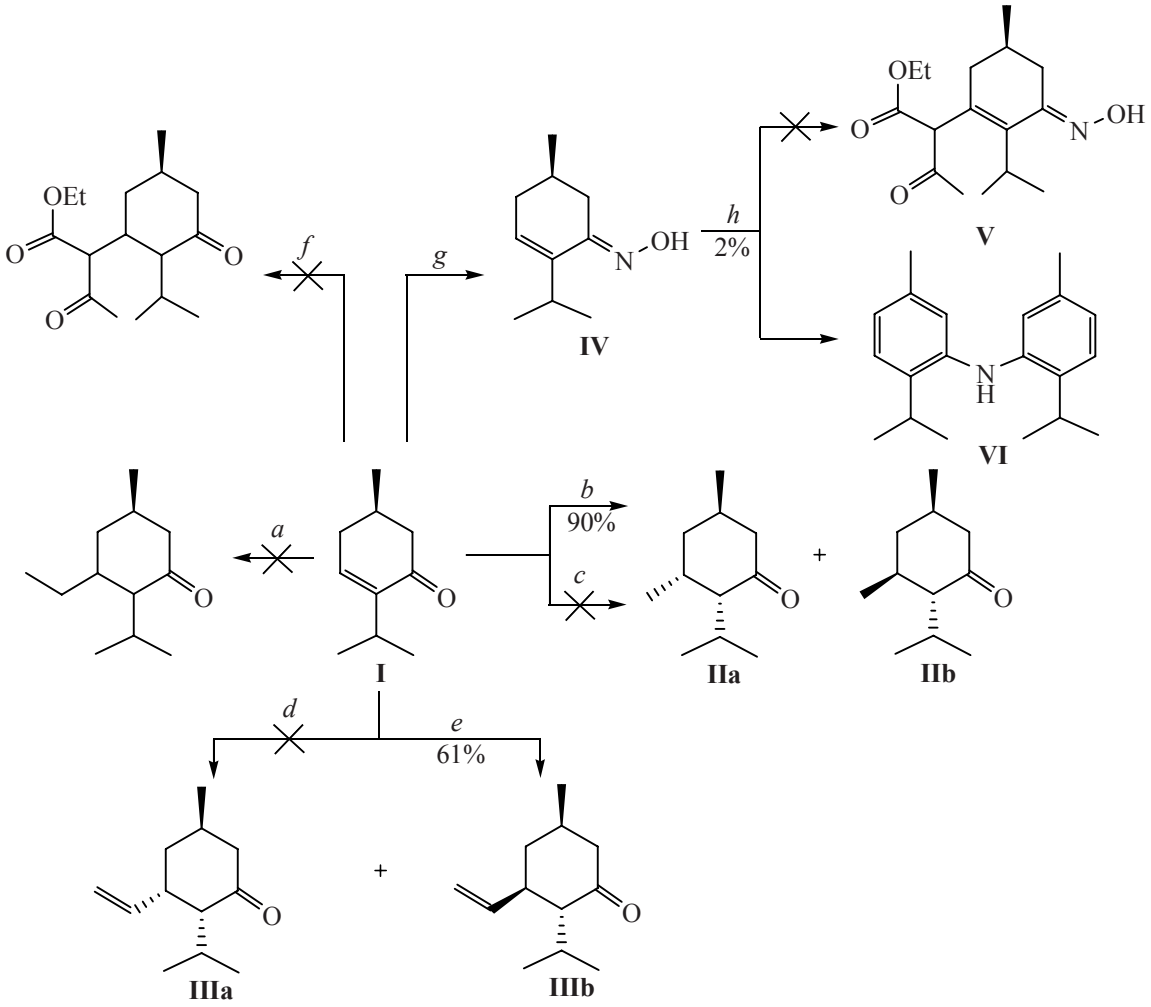
In order to reveal the ability of (*R*)-4-menthenone (**I**) to participate in reactions of 1,4-addition with organometallic compounds a series experiments were performed with the variation of reagents (MeLi, EtMgBr, CH_2=CHMgBr), catalysts (CuBr·Me_2S, Li_2CuCl_4, CuI, CuI–BF_3·OEt_2) and their quantity, solvents (THF, Et_2O), and temperature. As a result a reduced reactivity of enone **I** in these reactions was revealed. We succeeded to involve it in reaction with MeLi not under standard conditions (–78 or –30°C, catalysts Li_2CuCl_4 or CuI) [5], but at room temperature in the presence of a stoichiometric amount with respect to the organometallic reagent of a complex CuBr·Me_2S. 5-Methylmenthone (**II**) thus obtained in 90% yield was according to capillary GLC a mixture of *trans*- (**IIa**) and *cis*- (**IIb**) isomers, 3:2, indicating the streoselectivity of the cuprate reagent and being in agreement with the known data [6] on the *trans*-directing effect of a δ-alkyl substituent in a conjugated cyclohexenone on the entering β-group. This conclusion was based on the analysis of ^{1}H NMR spectra of stereoisomers **IIa** and **IIb** mixtures. The spectral parameters of substituents CH_3–C^5 and *i*-Pr are close to analogous values for l-menthol and (–)-mentholactone [7] and are consistent with their equatorial orientation. In the carbon spectrum of the mixture of isomers **IIa** and **IIb** is revealed the presence of a single diastereomeric pair with the prevalence of the isomer with more downfield signals of carbon in the groups CH_3–C^3 and *i*-Pr, and also of atoms C^1–C^4 of the ring. These findings indicate the equatorial orientation of the introduced methyl group and the predominant formation of *trans*-5-methylmenthone (**IIa**).

Yet the attempts to involve Normant reagent into the reaction under the above described conditions both at –30 and at 25°C were unsuccessful. Therefore the capability was utilized of organocopper reagents combined with Lewis acids enhancing the polarization of conjugated enones to efficiently catalyze the 1,4-addition of nucleophilic reagents. To this end we used the system CuI–BF_3·OEt_2 [6, 8] whose application made it possible to obtain 5-vinylmenthone (**III**) with even greater selectivity than in compound **II**: the ratio of *trans*-**IIIa** to *cis*-**IIIb** by the capillary GLC data was 18:1. In the ^{13}C the chemical shifts of carbon in groups Me and *i*-Pr are close to the corresponding values in l-menthol and (–)-mentholactone [7] indicating the equatorial orientation of these groups. The methine carbon signal from the vinyl group of the prevailing stereoisomer **IIIa** is located upfield by ~5 ppm revealing the axial

orientation of the vinyl group. This is additionally confirmed by the multiplicity d.d.d of the proton H^{4a} and by the values of coupling constants (^2J –12.0, ^3J 13.4, and ^3J 4.4 Hz). Hence in the addition product prevails *trans*-isomer **IIIa** where the vinyl and methyl groups are located in the *trans*-position to each other.

Another possible case of 1,4-addition of nucleophilic reagents to (*R*)-4-menthenone (**I**) is Michael reaction. The attempts to perform it using either catalytic or stoichiometric amounts of sodium ethylate [9] failed: Only initial enone **I** was isolated from the reaction mixture. No positive results were obtained at the use of sodium hydride [10], iron(III) chloride crystal hydrate [11, 12], and also in reaction in the presence of boron trifluoride etherate [13]. These results once more confirmed the uncommon "inertness" of the conjugated system of (*R*)-4-menthenone (**I**) molecule.

The conjugated oximes are known [11] to act as acceptors in Michael. In this connection we studied the behavior of (*R*)-4-menthenone *anti*-oxime (**IV**) that we had synthesized before [14] in reaction with ethyl acetoacetate in the presence of catalytic quantity of iron(III) chloride. However instead of expected adduct **V** only minor component was isolated from the reaction mixture that according to spectral data proved to be di-3-(*p*-cymene)amine (**VI**).

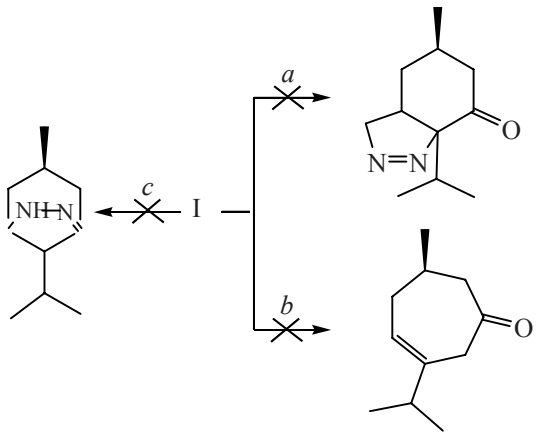


(*a*) EtMgBr, CuBr·Me_2S (cat), THF, –30 → 20°C or EtMgBr, Li_2CuCl_4 (cat), THF, –78 → –5°C; (*b*) MeLi, CuBr·Me_2S, Et_2O–Me_2S, 1:1, 20°C; (*c*) MeLi, CuI, Et_2O–THF, –78 → 20°C; (*d*) CH_2=CHMgBr, Li_2CuCl_4 (cat), THF, –20 → 20°C or CH_2=CHMgBr, CuBr·Me_2S, THF– Me_2S, 1:1, –20 → 20°C or CH_2=CHMgBr, CuBr·Me_2S, THF–Me_2S, 1:1, 25°C; (*e*) CH_2=CHMgBr, CuI, BF_3·Et_2O, Et_2O–THF, –78 → 20°C;(*f*) $AcCH_2CO_2Et$, EtONa (cat)–EtOH, 20°C or $AcCH_2CO_2Et$, EtONa (cat)–EtOH, + or $AcCH_2CO_2Et$, EtONa–EtOH, + or $AcCH_2CO_2Et$, $FeCl_3$·$6H_2O$, 20°C or $AcCH_2CO_2Et$, NaH–THF, 20°C → + or $AcCH_2CO_2Et$, BF_3·OEt_2, 0 → 20°C; (*g*) see [13]; (*h*) $AcCH_2CO_2Et$, $FeCl_3$·$6H_2O$, +.

Noncatalyzed reaction of diazomethane with α,β-unsaturated ketones is well studied [15] and occurs as 1,3-dipolar cycloaddition to yield pyrazolines whose pyrolysis leads to the formation of olefins and cyclopropanes. Besides pyrazolines are semiproducts in the synthesis of some drugs. Therefore we studied the reaction of (*R*)-4-menthenone (**I**) with diazomethane. However in this reaction carried out either in Et_2O or CH_2Cl_2 only the initial ketone and polymethylene were isolated, the latter resulting from carbene polymerization.

The attempts to carry out the homologization of enone **I** with diazomethane in the presence of Lewis acids (BF_3·OEt_2, $AlCl_3$, LiCl) [16, 17] and salts [$Pd(acac)_2$, $Cu(OAc)_2$] [18] were also unsuccessful.

The other approach to pyrazolines consists in the reaction of α,β-unsaturated carbonyl compounds with hydrazine [19, 20]. But also in this case menthenone **I** was inert both at the use of commercial 30% and of 100% solution of hydrazine hydrate generated in situ from its salt.



(*a*) CH_2N_2, Et_2O, –10°C; (*b*) CH_2N_2, $AlCl_3$ (cat), Et_2O–PhH, 6:1, 0 → 20°C or CH_2N_2, BF_3·OEt_2, CH_2Cl_2, 0 → 20°C or CH_2N_2, $Pd(acac)_2$ (cat), Et_2O, 0 → 20°C or CH_2N_2, $Cu(OAc)_2$ (cat), Et_2O, 0 → 20°C; (*c*) N_2H_4·HBr, NaOH, EtOH, 15°C or N_2H_4 (30%), EtOH, HCl, Δ or N_2H_4·H_2SO_4, NaOH, EtOH, Δ.

Hence we established that compared to the common cyclic enones (*R*)-4-menthenone (**I**) exhibits significantly lower reactivity in the conjugate 1,4-addition of organometallic reagents, inertness in Michael reaction and in pyrazoline formation, and also enhanced activity in ozonolysis; this behavior evidently originates from the distorted polarization of the multiple bond in the enone system and to steric hindrances from the α-isopropyl group in the cyclohexene ring.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord M-82 from thin films. NMR spectra were registered on a spectrometer Bruker AM-300 [operating frequencies 300.13 (^{1}H) and 75.47 MHz (^{13}C)] in $CDCl_3$ relative to TMS. The assignment of signals in the ^{1}H NMR spectra and estimation of the coupling constants was performed with the use of methods of double resonance and 2D correlation spectroscopy COSY(H–H) and COSY(C-H). The chromatographic analysis was performed on a chromatograph Chrom-5 [column 2.4 m long, stationary phase PEG-6000 (5%) on Inerton AW-DMCS (0.125–0.160 mm), ramp 50–200°C] and on a chromatograph GC-9A Shimadzu (quartz capillary column 25 m long, stationary phase OV-101, ramp 80–260°C), carrier gas helium. The optical rotation was measured on a polarimeter Perkin Elmer 241-MC. For column chromatography was used silica gel L (70–230 μm) of Lancaster grade (England), for TCX, SiO_2 of Sorbfil grade (Russia). Eluents petroleum ether, bp 40–70°C, ethyl ether. The solvents were dried by standard procedures, THF and Et_2O were distilled before the experiment over diisobutylaluminum hydride.

(2*R*,3*R*,5*R*)- and (2*R*,3*S*,5*R*)-2-Isopropyl-3,5-dimethylcyclohexanones IIa and IIb. To a stirred solution of 27 ml of 2.36 N solution of MeLi in 30 ml of anhydrous Et_2O (20–25°C, Ar) was added dropwise a solution of 2.45 g (11.8 mmol) of Me_2S·CuBr in 25 ml of a mixture Me_2S and Et_2O, 1:1, the stirring was continued till dissolution of the formed precipitate, and to the complex obtained was added dropwise 1.29 g (8.5 mmol) of menthenone **I** in 25 ml of anhydrous Et_2O. The reaction mixture was stirred for 2 h at room temperature, then 20 ml of saturated solution of NH_4Cl was added, and the reaction product was extracted into Et_2O (3 × 30 ml). The combined extracts were washed with a saturated solution of NaCl, dried with Na_2SO_4, and evaporated. We isolated 1.27 g (90%) of ketones **IIa** and **IIb**. According to capillary GLC the ratio *trans*-**IIa** : *cis*-**IIb** = 3:2. R_f 0.70 (petroleum ether–ethyl ether, 2:1). ^{1}H NMR spectrum, δ, ppm: 0.72–1.20 m (12H, CH_3), 1.44–2.53 m (8H, CH_2, CH, HCC^2). ^{13}C NMR spectrum (the signals of minor isomer are given in parentheses), δ, ppm: 20.50 (18.79) and 22.19 (19.89) q [$(CH_3)_2$C], 22.34 (20.85) q (CH_3C^3), 23.60 (22.35) q (CH_3C^5), 29.25

(28.13) d (C^3), 31.13 (30.22) d (HCC^2), 33.83 (31.94) d (C^5), 41.82 (35.26) t (C^4), 51.62 (47.46) t (C^6), 64.50 (61.12) d (C^2), 214.75 (212.18) C (C^1). Found, %: C 78.35; H 10.13. $C_{11}H_{20}O$. Calculated, %: C 78.57; H 10.25.

(2*R*,3*S*,5*R*)- and **(2*R*,3*R*,5*R*)-3-Vinyl-2-isopropyl-5-methylcyclohexanones IIIa and IIIb.** To a stirred solution of vinylmagnesium bromide prepared from 2.76 ml (39.5 mmol) of vinyl bromide and 2.18 g (90.9 mmol) of Mg in 30 ml of anhydrous THF (–30°C, Ar) was added 7.51 g (39.5 mmol) of CuI in 30 ml of anhydrous Et_2O, the mixture was stirred for 5 min, cooled to –78°C, and 3.52 ml (39.5 mmol) of $BF_3 \cdot Et_2O$ in 30 ml of anhydrous Et_2O was added. The reaction mixture was stirred for 15 min at –78°C, and 2.00 g (13.2 mmol) of menthenone **I** in 30 ml of anhydrous Et_2O was added. The reaction mixture was stirred for 1 h, gradually warming it to room temperature, the stirring was continued for 2 h at room temperature, then the mixture was cooled to 5°C, 40 ml of saturated solution of NH_4Cl was added, and the reaction product was extracted into Et_2O (3×30 ml). The combined extracts were washed with a saturated solution of NaCl, dried with Na_2SO_4, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent petroleum ether) to isolate 1.45 g (61%) of vinylketones **IIIa** and **IIIb**. According to capillary GLC the ratio *trans*-**IIIa** : *cis*-**IIIb** = 18:1. $[\alpha]_D^{21}$ +4.5° (*C* 3.69, $CHCl_3$), R_f 0.63 (petroleum ether–*t*-BuOMe, 2:1). IR spectrum, ν, cm^{-1}: 934, 1654, 1708, 3015, 3078. ^{1}H NMR spectrum, δ, ppm: 0.75 d and 0.82 d [6H, $(CH_3)_2C^8$, ^3J 6.4 Hz), 0.97 d (3H, CH_3C^5, ^3J 6.8 Hz), 1.59 d.d.d (1H, H^{4a}, ^2J –12.0, ^3J 4.4, ^3J 13.4 Hz), 1.73–1.83 m (1H, HCC^2), 1.85–1.94 m (1H, H^{4e}), 2.03–2.12 m (1H, H^5), 2.07 d.d (1H, H^2, ^3J 4.8, ^3J 10.3 Hz), 2.08 d.d (1H, H^{6a}, ^2J –7.7, ^3J 12.4 Hz), 2.28 d.d (1H, H^{6e}, ^2J –7.7, ^3J 2.1 Hz), 2.88–2.99 m (1H, H^3), 5.02 d.d.d (1H, =CH, ^2J 0.9, ^3J 10.2, ^4J 1.6 Hz), 5.09 d.d.d (1H, =CH, ^2J 0.9, ^3J 17.1, ^4J 1.6 Hz), 5.58 d.d.d (1H, HC^3, ^3J 9.2, J 10.2, J 17.1 Hz). ^{13}C NMR spectrum (the signals of minor isomer are given in parentheses), δ, ppm: 18.61 (16.8) and 22.36 (20.40) q [$(CH_3)_2C$], 22.44 (22.36) q (CH_3C^5), 24.29 (26.63) d (HCC^2), 31.64 (33.04) d (C^5), 41.92 (41.82) t (C^4), 46.24 (44.33) d (C^3), 51.75 (51.03) t (C^6), 60.31 (58.24) d (C^2), 116.68 (114.40) t (H_2C=), 137.02 (141.85) d (HCC^3), 212.18 (210.97) C (C^1). Found, %: C 80.21; H 11.05. $C_{12}H_{20}O$. Calculated, %: C 80.00; H 11.11.

***N*-(2-Isopropyl-5-methylphenyl)-2-isopropyl-5-methylaniline (VI).** A solution containing 0.55 g (3.3 mmol) of menthenone oxime **IV**, 0.43 g (3.3 mmol) of ethyl acetoacetate, and 0.44 g (0.2 mmol) of $FeCl_3 \cdot 6H_2O$ was stirred at room temperature for 6 h and then boiled for 2 h. The reaction mixture was diluted with NH_4OH, extracted with CH_2Cl_2 (3×20 ml), the combined extracts were washed in succession by saturated solutions of Na_2SO_3 and NaCl, and dried with Na_2SO_4. The residue (1.58 g) was subjected to column chromatography on SiO_2 (petroleum ether –CH_2Cl_2, 5:1). We obtained 0.30 g (60%) of initial compound **IV**, and 0.01 g (2%) of compound **VI**. IR spectrum, ν, cm^{-1}: 1060, 1504, 1576, 1612, 2956. ^{1}H NMR spectrum, δ, ppm: 1.19 d [6H, $(CH_3)_2C$, J 6.8 Hz], 2.16 s (3H, CH_3C_{Ar}), 6.72–7.17 m (6H, HC_{Ar}). ^{13}C NMR spectrum, δ, ppm: 22.87 q (CH_3C_{Ar}), 26.95 d (HCC_{Ar}), 27.48 q [$(CH_3)_2CC_{Ar}$)], 119.89 d (C^6, C^{13}), 122.44 d (C^4, C^{11}), 125.61 d (C^3, C^{10}), 135.18 d (C^2, C^9), 141.15 d (C^1, C^8). Mass spectrum (electron impact, 70 eV), *m/z*: 281 $[M]^+$, 266 $[M - CH_3]^+$, 238 $[M - C_3H_7]^+$, 224 $[M - CH_3C_3H_6]^+$, 208, 194, 134, 120, 106, 105, 91, 77. Found, %: C 85.26; H 9.50. $C_{20}H_{27}N$. Calculated, %: C 85.41; H 9.61. *M* 281.4.

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