Brief Communications

Unusual pathway of alkylation of 2-(4-bromobenzylidene)-*p*-menthan-3-one with ethyl bromoacetate

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Reaction of enolate carbanion, generated from 2-(4-bromobenzylidene)-*p*-menthan-3-one, with ethyl bromoacetate proceeds selectively as the *O*-alkylation.

Key words: *O*-alkylation, arylindene-*p*-menthan-3-one core, enolates, enol ethers, X-ray diffraction analysis.

(*E*,1*R*,4*R*)-Arylidene-*p*-menthan-3-ones **1** are widely studied[1—3] as the chiral components of liquid crystal (LC) materials. The reaction of these compounds with iodomethane in basic media according to the described method[4] preferably leads to the products of *C*-alkylation of the type **2** with high stereoselectivity (Scheme 1), which also are of practical use as the chiral components of LC materials.[5]

In order to prepare the analogs of compound **2**, which contain fragments suitable for further functionalization, such as **4** or **5**, we used ethyl bromoacetate, since it was described as the *C*-alkylation agent in most reactions with enolate carbanions of various cyclohexanone derivatives (see, for example, Refs 6—8).

The reaction of enolate carbanion **3**, obtained by treatment of compound **1** (Ar = 4-BrC_6H_4) with Bu^tOK in Bu^tOH, with ethyl bromoacetate led to an oily mixture of products, consisting of three main substances (HPLC data). The microscale preparative HPLC separation followed by the mass spectrometry analysis of the fractions allowed us to find out that only the main component of the mixture has molecular weight corresponding to the expected ester **4**. Basic hydrolysis followed by acidification afforded the free acid in 40% yield, the composition of which was confirmed by elemental analysis and mass spectrometry data. In the ^1H NMR spectrum of the substance obtained, there are signals characteristic of *p*-menthane and 2-arylidene fragments. However, signals of the diastereotopic protons in α-position to the carboxylic group resonate in rather downfield region (δ 4.19 and 4.07) than could have been expected for the proposed structure **5**. In the IR spectrum, absorption characteristic of carboxylic acids is observed: a broad band at 3144 cm^{-1} (ν_{OH}), 1750 and 1709 cm^{-1} (free and associated $\nu_{C=O}$). However, there is no absorption band of the conjugated carbonyl group of the *p*-menthane fragment in the region 1700—1660 cm^{-1}, at the same time, there are two weak bands at 1628 and 1610 cm^{-1}, which is more characteris-

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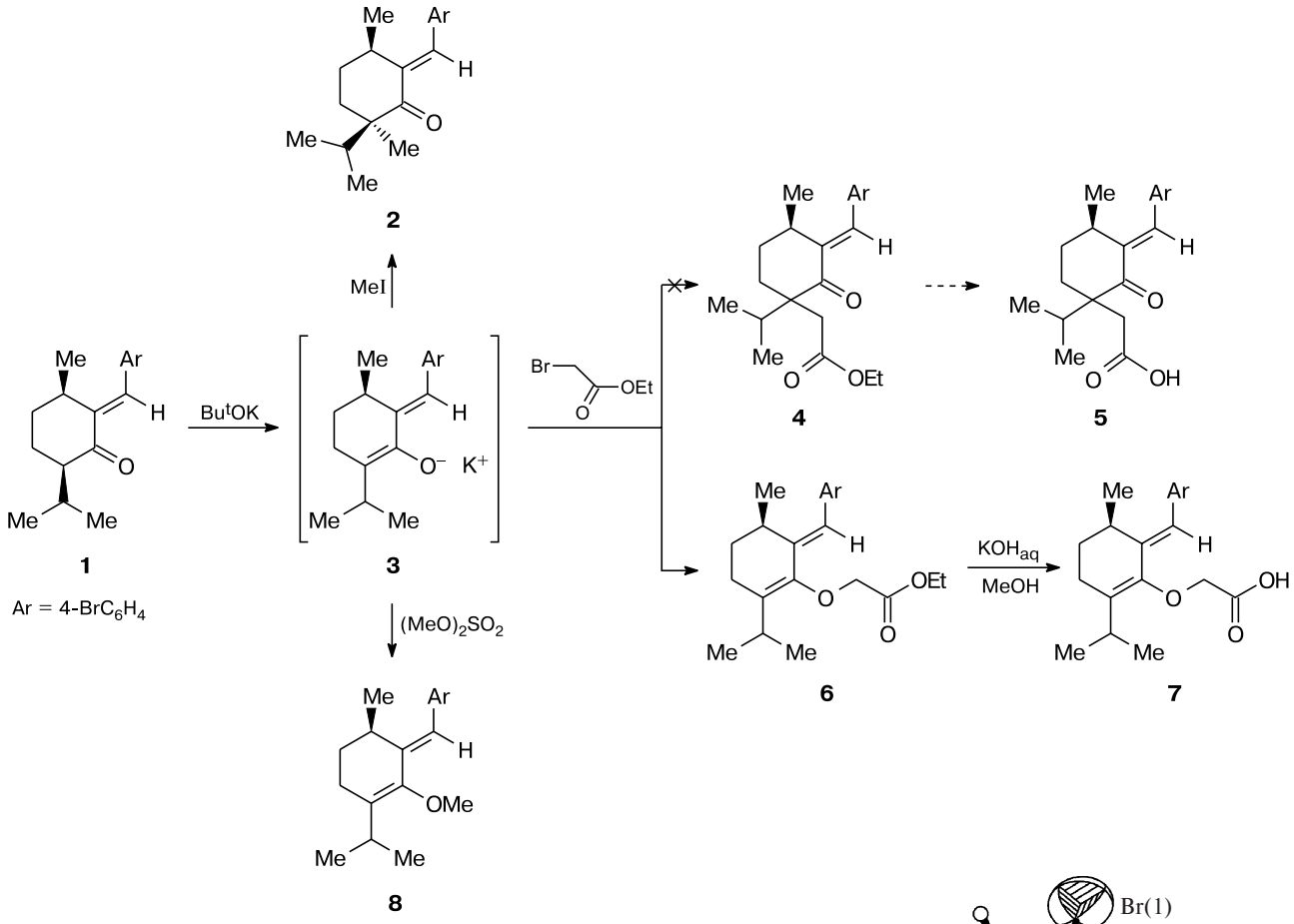
Scheme 1



tic of *O*-alkyl ethers of the enol form of 2-arylidenementhanones **8** (see Ref. 9). Thus, the spectroscopy data obtained did not allow us to unambiguously ascribe the structure of acid **5** to the compound under consideration.

The X-ray diffraction study of a monocrystal sample showed that this reaction product has structure **7** isomeric to the one of expected compound **5**, to be exact, there is an enol ether fragment in it (Fig. 1). Thus, *O*- rather than *C*-alkylation occurs in the reaction of enolate carbanion **3** (Ar = 4-BrC_6H_4) with ethyl bromoacetate.

The cyclohexene ring in molecule **7** has the unsymmetrical half-chair conformation. The deflections of C(4) and C(5) atoms from the mean-square plane of the other atoms of the ring are –0.30 and 0.45 Å, respectively. In the cyclohexene ring, the C(2)—C(3) bond (1.522(3) Å) is longer and the C(3)—C(4) bond (1.509(4) Å) is shorter as compared with their average values[10] (1.506 and 1.541 Å, respectively), which was also observed for the analog **8** studied earlier (see Ref. 9). The endocyclic double bond is considerably twisted (torsion angle O(1)—C(1)—C(2)—C(15) is 6.4(4)°) and is longer (1.350(3) Å) relatively to the average value (1.326 Å). A conjugation between the

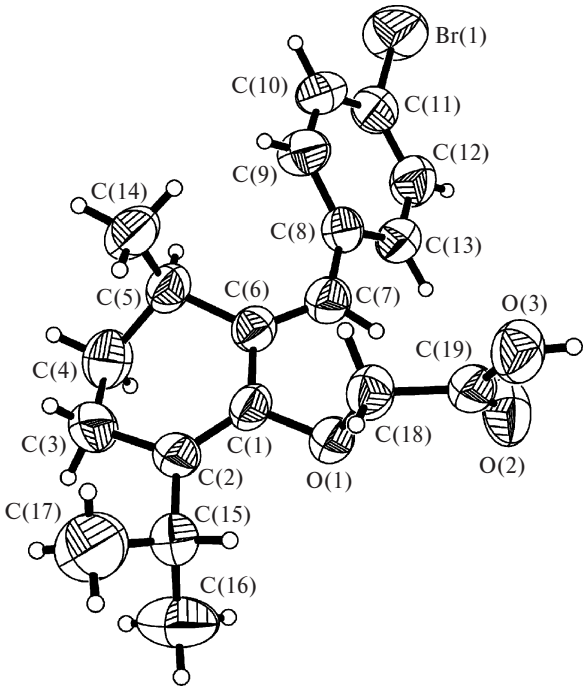


Fig. 1. X-ray data on the molecular structure of 2-[(5*R*,6*E*)-6-(4-bromobenzylidene)-2-isopropyl-5-methylcyclohex-1-enyloxy]acetic acid (**7**).

endo- and exocyclic double bonds is slightly disturbed (torsion angle C(2)—C(1)—C(6)—C(7) is −162.8(2)°). Bromophenyl substituent is in *ap*-conformation relatively to the C(1)—C(6) bond (torsion angle C(1)—C(6)—C(7)—C(8) is 178.9(2)°) and is considerably turned relatively to the exocyclic double bond (torsion angle C(6)—C(7)—C(8)—C(9) is 40.8(4)°).

In a crystal, compound **7** exists as the crystallosolvate with methanol and forms endless chains along the crystallographic direction (010) due to the intermolecular hydrogen bonds O(3)—H(3O)...O(1w) (H...O is 1.78 Å, angle O—H...O is 173°) and O(1w)—H(1Ow)...O(2′) (−*x*, 0.5 + *y*, −0.5 − *z*) (H...O is 1.90 Å, angle O—H...O is 158°).

There is no reason for the change of the C(5) chiral center configuration during the transformations described. That is why we ascribed the same absolute configuration to C(5) atom in compound **7** as in the starting ketone **1** (Ar = 4-BrC_6H_4). Results on the research of the absolute and relative configuration of compounds of the **1** series are in details reported in paper.[11]

In conclusion, the reaction of enolate carbanion of 2-(4-bromobenzylidene)-*p*-menthan-3-one with ethyl bromoacetate selectively proceeds as the *O*-alkylation. We failed in finding the literature examples of alkylation of 2-arylidenecyclohexanones with haloacetic acid esters. Rare scattered examples of the reaction directed at the oxygen atom are described for the other cyclohexanone derivatives.[12,13] Study on the regioselectivity of alkylation of enolizable α,β-unsaturated ketones with ethyl bromoacetate, as well as a quest for the ways of selective *C*-alkylation of compounds of the type **1** with ethyl bromoacetate are planned for our further research.

Experimental

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 spectrometer (200 MHz), DMSO-d_6 was used as the solvent, signals of residual protons of the deuterated solvent (δ 2.50[14]), as the internal standard. Mass spectra were recorded on a Varian 1200L chromato-mass spectrometer with direct exposure probe (DEP), ionization by electron impact, and energy of ionization 70 eV. IR spectra were recorded on a Perkin—Elmer Spectrum One Fourier-spectrometer. Elemental analysis was performed on a Eurovector EA-3000 instrument. The reaction course and purity of the compounds obtained, as well as the microscale separations were carried out on a Bischoff module liquid chromatograph equipped with Prontosil 120-5-C18H reversed phase column, eluent, acetonitrile—water azeotropic mixture. Melting points were determined on the Kofler heating table.

2-[(5*R*,6*E*)-6-(4-Bromobenzylidene)-2-isopropyl-5-methylcyclohex-1-enyloxy]acetic acid (7). Ketone **1** (Ar = 4-BrC_6H_4, 4 g, 14.6 mmol) was dissolved in *tert*-butanol (25 g) followed by addition of potassium *tert*-butoxide (3.2 g, 29 mmol) with stirring. The mixture obtained was kept for 15 min, cooled to 0 °C, and a solution of ethyl bromoacetate (2.4 mL, 22 mmol) in THF (5 mL) was added dropwise to it for 10—15 min. The reaction mixture was stirred for 1.5 h, then, neutralized with dilute acetic acid, and extracted with dichloromethane. The extract was concentrated dry. Methanol (40 mL), water (15 mL), and potassium hydroxide (2.4 g, 43 mmol) were added to the residue. The mixture was refluxed for 40 min with stirring, cooled, and neutralized with diluted acetic acid. The precipitate formed was filtered off, washed with water, dried, and recrystallized from methanol to obtain acid **7** (1.9 g, 40%) (Ar = 4-BrC_6H_4) as colorless crystals, m.p. 110—111 °C (from methanol). Found (%): C, 60.16; H, 6.30. $C_{19}H_{23}BrO_3$. Calculated (%): C, 60.17; H, 6.11. IR, ν/cm^{-1}: 3144 (OH), 2923, 2964, 2935 (CH_{aliph}), 1750 (C=O_{free}), 1709 (C=O_{assoc}), 1628 and 1610 (C=C and Ar). MS, *m/z* (I_{rel} (%)): 378 $[M]^+$ (100), 363 (23), 335 (25), 319 (17), 287 (17), 208 (25), 193 (24), 181 (20), 169 (22). ^{1}H NMR, δ: 12.81 (s, 1 H, COOH); 7.53, 7.23 (both d, 2 H each, CH(Ar), J = 8.4 Hz); 6.54 (s, 1 H, H(7)); 4.19, 4.07 (both d, 1 H each, H(18), J = 5.5 Hz); 3.58—3.14 (m, 1 H, H(15)); 3.11—2.93 (m, 1 H, H(5)); 2.35—1.98 (m, 2 H, $H(3)_AH(3)_B$); 1.71—1.41 (m, 2 H, $H(4)_AH(4)_B$); 1.11 (d, 3 H, $C(14)H_3$, J = 6.7 Hz); 1.00 (d, 3 H, $C(CH_3)_2$, J = 5.3 Hz); 0.99 (d, 3 H, CMe_2, J = 5.7 Hz).

Crystals of compound **7** are rhombic, $C_{20}H_{27}O_4Br$, at 20 °C a = 9.984(1), b = 10.303(1), c = 20.582(2) Å, V = 2117.0(5) Å^3, M_r = 411.33, Z = 4, space group $P2_12_12_1$, d_{calc} = 1.291 g cm^{-3}, μ(Mo-Kα) = 1.961 mm^{-1}, F(000) = 856. The unit cell parameters and the intensities of 8180 reflections (3664 independent ones, R_{int} = 0.033) were measured on a Xcalibur-3 diffractometer (Mo-Kα radiation, CCD detector, graphite monochromator, ω-scanning technique, $2\theta_{max}$ = 50°). The absorption was calculated by semiempirical method based on the results of multiscanning (T_{min} = 0.508, T_{max} = 0.908).

The structure was solved by direct method with the use of the SHELX97 program package.[15] Positions of the hydrogen atoms were localized from the differential synthesis of electron density and refined using a riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for the methyl and hydroxy groups and n = 1.2 for the other hydrogen atoms). The structure was refined by the leasts squares method with anisotropic full-matrix approximation F^2 for non-hydrogen atoms to wR_2 = 0.051 based on 3642 reflections (R_1 = 0.029 based on 1861 reflections with $F > 4\sigma(F)$, S = 0.739). Coordinates of atoms and complete tables of bond lengths and bond angles were deposited with the Cambridge Structural Database (CCDC 642742).

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