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Stereochemistry of hydroxylation of some chiral *spiro*-[2,5]octan-4-ones

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ABSTRACT

Stereoselective oxidative alpha hydroxylation of (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones has been found as a secondary process in the cyclopropanation of 2-arylidene isomenthanones with trimethylsulfoxonium iodide in DMSO/NaOH or DMF/NaOH system. Three stereoisomeric hydroxy ketones have been isolated from a reaction mixture of cyclopropanation reaction, but the reaction of oxidation carried out with isolated *spiro*-[2,5]octan-4-ones was stereoselective. The advantages of this method of stereoselective hydroxylation are room temperature of reaction and absence of expensive catalysts. The reduction of obtained hydroxy ketones was also stereoselective and gave the only *trans*-(4*R*,5*S*)-dioles. The structures have been confirmed with 1D and 2D ^{1}H and ^{13}C NMR, MS spectra and for stereoisomeric hydroxy ketones with X-ray analysis also.

1. Introduction

The reaction of cyclopropanation with sulfur ylides (Corey–Chaykovsky reaction) is attractive because of its potential for simple procedures in obtaining of three-membered rings [1–4] application-oriented in the synthesis of some biologically active compounds. Peculiarities of this reaction in modern synthesis remain the subject of studies [5–7]. Also, the substitution of double bond in arylidene derivatives of isomenthone with a cyclopropane cycle seems to be attractive for obtaining of photo stable chiral dopants to nematic liquid crystals [8].

Corey–Chaykovsky reaction behavior for (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones and its accompanying stereoselective oxidative alpha hydroxylation with dioxygen in NaOH/DMSO and NaOH/DMF is described in this paper.

α-Hydroxyketones, especially optically active, are interesting as important intermediate products for synthesis of different bioactive substances. Non-oxidative procedures for their obtaining are known (see [9] for review) but they are limited to the synthesis of acyclic derivatives. Recently, cesium formate using [10] and α-haloketones irradiation with ultra violet or micro-waves [11] were proposed for the transformation of α-haloketones to α-hydroxyketones.

The most common oxidative procedures for α-hydroxyketone obtaining are oxidation of O-sylil enolic ethers (epoxidation, Rubottom oxidation) or enolates of carbonyl compounds [12] with different oxidants. MoOPH or MoOPD [Ref. in 9] and dioxygen [13,9], and also dibenzyl peroxydicarbonate [14], molybdenum peroxide [15], osmium tetroxide/N-methylmorpholine-N-oxide [16], m-chloroperbenzoic acid [17], chiral oxaziridines (N-sulphonyloxaziridines) [9], nitroso and iodoso compounds [18], dioxiranes [19] were used predominately. Other ways include oxidation of enamines with molecular oxygen [20] or metal-catalyzed oxidation of olefins [21]. Last time strongly upcoming chemo-enzymatic reactions were applied to the synthesis of α-hydroxy ketones [22] also. To improve an enantiomeric excess (ee) in a synthesis of α-hydroxy substituted ketones and aldehydes it was proposed to pass oxygen through a reaction mixture at low temperatures (−25 °C) and use triethyl phosphite for hydroperoxides reduction [23–25], or to use amino acids as organocatalysts [9,26,27].

In this investigation, we have obtained α-hydroxyketones without reducing agents. We have separated intermediate hydroperoxide that confirms the mechanism of oxidative hydroxylation reaction in concerned case. Also we have studied stereoselectivity of this reaction and found configurations of new chiral centers. Molecular structures of compounds studied have been confirmed with 1D and 2D ^{1}H and ^{13}C NMR, MS, and for stereoisomeric hydroxy ketones with X-ray analysis also.

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2. Experimental

2.1. Preparation

The compounds described in this work and used synthetic procedures are shown in Fig. 1.

The syntheses of compounds **1** were described earlier [8]. Initial benzylidene cyclohexanones (**BC**) were obtained using published protocols [28].

2.1.1. (1R,5S,8R,3R)-1-Aryl-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-ones (**2a–e**)

To 8 mmol of compound **1** in 12 ml DMSO (or DMF) 960 mg (24 mmol) of powdered sodium hydroxide was added and stirred at room temperature in open vessel (using of protective tube some reduce the oxygen transport and therefore reduce the reaction). The reaction was completed usually during 24 h (control with thin layer chromatography (TLC), silica gel/dichloroethane). Then the reaction mixture was poured in water at 0 °C, neutralized with acetic acid, filtered. The precipitate was washed with water, dried in air and dissolved in DCM. Then solvent was evaporated with a rotary evaporator and a residue was crystallized from ethanol or hexane. All compounds (**2a–e**) were obtained as white solids. Finally, reaction mixtures had 80–90% of products **2a–e** (by HPLC).

(1R,5S,8R,3R)-1-(Biphenyl-4-yl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2a1**) (yield 78%). Mp 139–140 °C (ethanol). ^{1}H NMR (DMSO d_6), δ: 7.416, 7.463 (both d, 2H each, H arom., $3J$ = 8.2), 7.256 (t, 2H, *m*-H arom., $3J$ = 8.2 Hz); 7.186 (d, 2H, *o*-H arom., $3J$ = 8.2 Hz); 7.155 (t, 1H, *p*-H arom., $3J$ = 8.2 Hz); 5.088 (s, 1H, OH); 2.312 (dd, 1H, H(1), $3J$ = 8.7 Hz, $3J$ = 7.1 Hz); 2.295 (sept, 1H, H(10), $3J$ = 7.0 Hz); 1.907 (m, 1H, H(7 *trans*), $2J$ = −13.2 Hz, $2J$ = 13.6 Hz, $2J$ = 3.6 Hz, $2J$ = 2.9 Hz); 1.884 (m, 1H, H(6 *trans*), $2J$ = −13.5 Hz, $3J$ = 13.6 Hz, $3J$ = 2.6 Hz); 1.812 (dd, 1H, *cis*-H(2), $2J$ = −4.7 Hz, $3J$ = 8.7 Hz); 1.606 (m, 1H, H(6), $2J$ = −13.5 Hz, $3J$ = 2.9 Hz, $3J$ = 2.5 Hz); 1.295 (m, 1H, H(8), $3J$ = 7.1 Hz, $3J$ = 3.6 Hz, $3J$ = 2.0 Hz); 1.184 (dd, 1H, *trans*-H(2), $2J$ = −4.7 Hz, $3J$ = 7.1 Hz); 1.156 (m, 1H, H(7), $2J$ = −13.2 Hz, $3J$ = 2.9 Hz, $3J$ = 2.5 Hz, $3J$ = 2.0 Hz); 0.967 (d, 3H, C(9)Me, $3J$ = 7.1 Hz); 0.828, 0.934 (both d, 3H each, C(11)Me, C(12)Me, $3J$ = 7.0 Hz). ^{13}C NMR, $CDCl_3$: 213.105, 140.714, 139.701, 135.885, 129.845, 128.782, 127.272, 126.981, 126.900, 78.483, 38.229, 35.393, 32.556, 30.007, 27.162, 26.354, 19.094, 17.050, 16.641, 15.608. MS, *m*/*z* 348 (M+.). Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; found: C, 82.69; H, 8.15; $[\alpha]_D^{20}$ 236.36° (C = 1.15 g/100 cm^3, ethyl acetate).

(1R,5S,8R,3R)-1-(4-Bromophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2b**) (yield 76%). Mp 135–137 °C (ethanol). ^{1}H NMR, $CDCl_3$: 7.295 (m., 4H), 5.216 (s., 1H), 2.758, 2.252, 2.125, 1.831, 1.740, 1.531, 1.392, 1.232, 0.910, 0.853, 0.711. ^{13}C NMR, $CDCl_3$: 212.758, 135.918, 131.373, 131.110, 120.808, 78.519, 37.911, 34.383, 32.473, 30.163, 27.305, 26.367, 18.976, 16.956, 16.371, 15.587. MS, *m*/*z* 351 (M+.). Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.55; H, 6.60, Br 22.75; found: C, 61.52; H, 6.63, Br 22.73.

(1R,5S,8R,3R)-1-(4-Chlorophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2c**) (yield 76%). Mp 143–145 °C (ethanol, hexane). ^{1}H NMR, $CDCl_3$: 7.334 (m., 4H), 5.217 (s., 1H), 2.894 (s., 2H), 2.168 (dd., 1H), 1.987 (sept., 1H), 1.77 (m., 1H) 1.571 (m., 1H), 1.110, 1.095 (d.m., 3H), 0.96 (d., 3H), 0.952 (d., 3H), 0.818 (m., 3H). ^{13}C NMR, $CDCl_3$ (HMQC): 137.015, 131.795, 130.399, 127.982, 80.833, 75.257, 32.930, 31.874, 30.688, 28.252, 24.731, 24.529, 19.017, 15.813, 11.899. MS, *m*/*z* 306 (M+.). Anal. Calcd. for $C_{18}H_{23}ClO_2$: C, 70.46; H, 7.56, Cl 11.55; found: C, 70.38; H, 7.60, Cl 11.51.

(1R,5S,8R,3R)-1-(4-Fluorophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2d**) (yield 77%). Mp 126–128 °C (ethanol, hexane). ^{1}H NMR, DMSO-d_6: 7.334 (Ar, 4H), 5.218 (s., 1H), 2.44 (s., 2H), 2.228 (dd., 2H), 1.754 (m., 1H), 1.515 (m., 1H), 1.077 (m., 3H), 0.848 (m., 6H), 0.716 (m., 3H); MS, *m*/*z* 290 (M+.). Anal. Calcd. for $C_{18}H_{23}FO_2$: C, 74.45; H, 7.98, F 6.54; found: C, 74.43; H, 8.03, F 6.51. MS, *m*/*z* 290 (M+.). Anal. Calcd. for $C_{18}H_{23}FO_2$: C, 74.45; H, 7.98, F 6.54; found: C, 74.43; H, 8.02, F 6.55.

(1R,5S,8R,3R)-1-(4-Methoxyphenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2e**) (yield 78%). Mp 96–97 °C (ethanol). ^{1}H NMR, DMSO-d_6: 7.030 (Ar, 4H), 5.161 (s., 1H), 3.712 (s., 3H), 2.216 (m., 2H), 1.830 (m., 2H), 1.704 (m., 1H) 1.501 (m., 1H), 1.021 (m., 4H), 0.842 (dd., 7H), 0.714 (d., 4H)). MS, *m*/*z* 302 (M+.). Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; found: C, 75.43; H, 8.69.

(1R,5S,8R,3R)-1-(4-bromophenyl)-5-isopropyl-5-hydroperoxy-8-methyl-3-spiro[2.5]octan-4-one (**2′b**) was obtained in similar procedure when reaction was carried in DMF. Yield 20%. Mp 158–160 °C (ethanol). ^{1}H NMR, DMSO-d_6: 11.183, 7.478, 7.305, 5.239, 2.601, 2.390, 1.905, 1.671, 1.101, 0.886, 0.843, 0.808, 0.757, 0.723. ^{13}C NMR, $CDCl_3$: 206.701, 135.989, 131.372, 131.166, 131.110, 131.026, 120.708, 88.011, 40.015, 35.337, 30.785, 26.452, 23.998, 22.147, 18.450, 18.024, 15.204, 13.943. MS, *m*/*z* 367 (M+.). Anal. Calcd. for $C_{19}H_{26}O_3$: C, 58.86; H, 6.31, Br 21.76; found: C, 58.78; H, 6.38, Br 21.73.

2.1.2. Isomeric 1-(4-phenyl)-phenyl-5-isopropyl-5-hydroxy-8(R)-methyl-3(R)-spiro[2.5]octan-4-ones (**2a1–2a3**)

(3*R*,6*R*)-3-methyl-6-isopropyl-2-(4-phenyl)benzylidenecyclohexanone (**PBC**) (1.9 g, 6 mmol) was dissolved in 20 ml DMSO and 0.6 g (15 mmol) of powdered NaOH was added to former. The resulting mixture was stirred for 2 days at a room temperature up to initial product disappearance on TLC. The mixture after reaction completion was poured into water, and a precipitate obtained was filtered and dried. Its crystallization from isopropanol yielded 1.4 g (78%) of **2a1** (data see in Section 2.1.1). According to TLC and HPLC, a mother stock contained additively two more polar reaction products. To obtain these products the solvent was removed, and residue was separated by column chromatography on silica gel

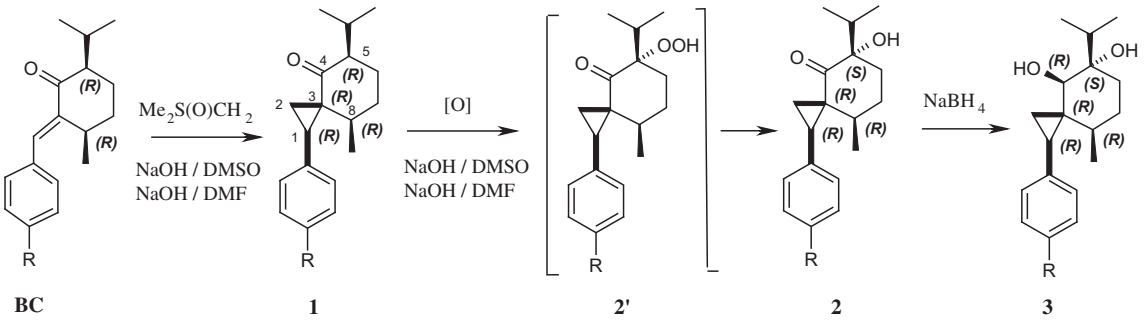

Fig. 1. Synthetical procedures used for obtaining spiro compounds, their hydroxylation and reduction.