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Reactions of Substituted 8-Oxatricyclo[3.2.1.02,4]octan-6-ones and 9-Oxatricyclo[3.3.1.02,4]nonan-6-ones with Methylmagnesium Bromide and Lithium Aluminum Hydride

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Abstract—Substituted 8-oxatricyclo[3.2.1.$0^{2,4}$]octan-6-one and 9-oxatricyclo[3.3.1.$0^{2,4}$]-nonan-6-one obtained by treating substituted cyclopropenes with carbonyl ylides in reactions with methylmagnesium bromide and lithium aluminum hydride were stereoselectively converted into the corresponding alcohols.

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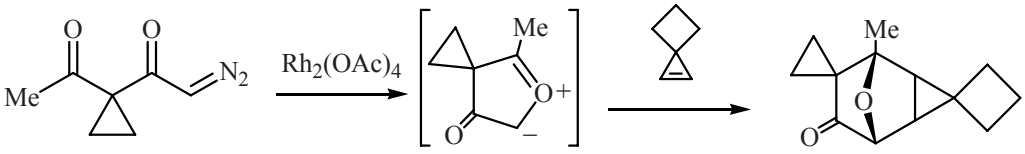
1,3-Dipolar cycloaddition to unsaturated compounds of carbonyl ylides, generated from diazo compounds by metal complex catalysts, is among the promising methods of the synthesis of oxygen-containing heterocyclic systems [1]. The formation of carbonyl ylides from diazo compounds followed by cycloaddition is the key stage in the synthesis of various natural compounds [2], aza- and oxapolyheterocyclic systems [3]. We established in previous studies that carbonyl ylides generated from diazo compounds by $Rh_2(OAc)_4$ in dichloromethane at room temperature were capable to add to substituted cyclopropenes providing in good yields polycyclic compounds of 8-oxatricyclo[3.2.1.$0^{2,4}$]octan-6-one and 9-oxatricyclo[3.3.1.$0^{2,4}$]nonan-6-one series [4–7]. The obtained polycyclic adducts of carbonyl ylides and compounds with a strained mulriple bond are of interest also in respect of further transformations of tetrahydrofuran ring, the opening of the three-membered ring, and the reactions at the carbonyl group. Here we report on the study of the reaction between ketones **Ia–Ie** with methylmagnesium bromide or lithium aluminum hydride. Ketones **Ia–Id** were described before [6], compound **Ie** was obtained by the reaction of 1-(1-acetylcyclopropyl)-2-diazoethanone with spiro[2.3]hex-1-ene in the presence of $Rh_2(OAc)_4$.

In reactions of ketones **Ia–Ic** with methylmagnesium bromide alcohols **IIa–IIc** were obtained in ~90% yields, the reactions of ketones **Ia, Ib, Id**, and **Ie** with lithium aluminum hydride led to the formation of alcohols **IIIa, IIIb, IIId**, and **IIIe** in 67–80% yields. In all reactions the nucleophilic reagents added selectively forming a single isomer; the relative *endo*-configuration was attributed to compounds obtained analogously to the reactions of 7-oxabicyclo[2.2.1]heptane systems [5]. This selectivity corresponds to the reagent approach from the side of the oxygen bridge indicating some stabilization of the transition state owing to the interaction of the nucleophilic reagent with the oxygen atom.

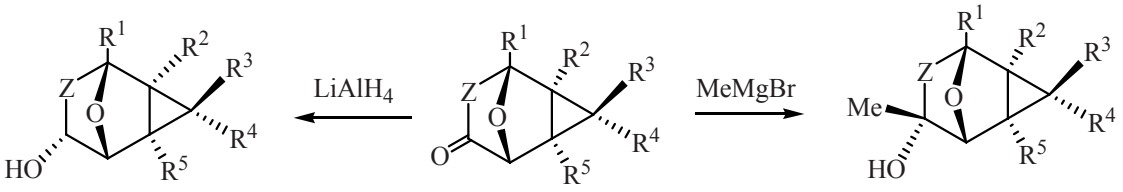
The structure of compounds obtained was established from the spectral data. In the ^{1}H NMR spectra of

Scheme 1.



Ie

Scheme 2.



IIIa, IIIb, IIId, IIIe **Ia–Ie** **IIa–IIc**

Z = cyclopropylidene, R^1 = Me, R^2 = R^4 = R^5 = Ph, R^3 = H (**a**); Z = *O*-phenylene, R^1 = OMe, R^2 = R^4 = R^5 = Ph, R^3 = H (**b**); Z = CH_2CH_2, R^1 = Ph, R^2 = R^5 = H, R^3 = R^4 = Me (**c**); Z = CH_2CH_2, R^1 = Ph, R^2 = R^5 = Ph, R^3 = H, R^4 = vinyl (**d**); Z = cyclopropylidene, R^1 = Me, R^2 = R^5 = H, R^3 + R^4 = $CH_2CH_2CH_2$ (**e**).

compounds **IIa–IIc** singlets from the protons of the methyl group appear in the region 1.0–1.6 ppm, of the proton at the nodal carbon atom, in the range 3.8–4.6 ppm, of the proton from the cyclopropane fragment, at 3.3–3.6 ppm for compounds **IIa** and **IIb**, and two doublet signals of this proton at 1.49 and 1.66 ppm are observed in the spectrum of compound **IIc**. In ^{13}C NMR spectra signals of carbon atoms linked to a hydroxy group are seen in the region 70–82 ppm, the signals of the nodal carbon atom C^5 is observed in the region 82–89 ppm. The IR spectra contain absorption bands of hydroxy groups around 3600 cm^{-1}, and the absorption bands of carbonyl groups disappeared. ^1H NMR spectra of com-pounds **IIIa–IIId** contain characteristic doublet signals of protons attached to C^5 in the region 4.4–4.8 ppm, signals of the hydroxy group protons in the region 1.4–1.7 ppm in the spectra of compounds **IIIa–IIIc**, and **IIIe** which disappear at the addition of CF_3COOH. In ^{13}C NMR spectra the signals from carbon atoms bearing a hydroxy group, and signals of C^5 atom are present in the region 70–83 ppm.

EXPERIMENTAL

IR spectra were taken on a spectrophotometer UR-20 from solutions of compounds in $CHCl_3$ or CCl_4. NMR spectra were registered on a spectrometer Bruker DPX-300 [300 (^1H), 75 MHz (^{13}C)]. Elemental analyses were carried out on a CHN-analyzer HP-185B. Dichloromethane was distilled over P_2O_5. The reaction progress was monitored by TLC on Silufol UV-254 plates.

(1*RS*,2*SR*,4*RS*,5*SR*)-1-Methyl-3-spiro[1'-cyclobutane]-7-spiro[1''-cyclopropane]-8-oxatricyclo[3.2.1.0^{2,4}]octan-6-one (Ie). To a solution of 1 g (12.5 mmol) of spirohexene in 7 ml of dry dichloromethane was added 5 mg of $Rh_2(OAc)_4$ and slowly in an argon flow was added a solution of 0.6 g (4 mmol) of 1-(1-acetylcyclopropyl)-2-diazoethanone in 2 ml of dichloromethane at room temperature. The stirring was continued for 1 h more, then the solvent was evaporated in a vacuum, and the residue was subjected to chromatography on a column packed with silica gel. Eluent hexane–ethyl acetate, 10:1 v/v. Yield 0.56 g (68%), mp 39°C. IR spectrum ($CHCl_3$), ν, cm^{-1}: 2980, 2930, 1760 v.s, 1390, 1345, 1315, 1150, 1005 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.74 m (1H), 0.87 m (1H), 1.00–1.08 (2H), 1.17 d (1H, *J* 6.5 Hz), 1.25 s (3H), 1.28 d (1H, *J* 6.5 Hz), 2.02–2.13 (4H), 2.25–2.41 (2H), 4.41 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.37 (CH_2), 11.5 (CH_2), 15.1 (CH_3), 18.5 (CH_2), 23.7 (CH), 26.2 (CH_2), 29.7 (CH_2), 31.5 (CH), 37.6 (C), 79.6 (CH), 83.82 (C), 211.2 (CO). Found, %: C 76.43; H 7.87. $C_{13}H_{16}O_2$. Calculated, %: C 76.47; H 7.84.

Reactions of ketones Ia–Ic with methylmagnesium bromide. General procedure. To 0.1 M solution of ketone **Ia–Ic** in anhydrous THF was added under an argon atmosphere 3 equiv of 1 M ether solution of MeMgBr, the mixture was stirred at room temperature for 3 h, THF was distilled off in a vacuum, 10 ml of ethyl ether was added, and the mixture was quenched with a water solution of ammonium chloride. The organic layer was separated, the water layer was extracted with ether (3×10 ml). The combined organic solutions were dried with magnesium sulfate. The residue after removing the solvent was subjected to chromatography on a column packed with silica gel, eluent hexane–ethyl acetate.

(1*RS*,2*SR*,3*SR*,4*RS*,5*SR*,6*SR*)-1,6-Dimethyl-2,3,4-triphenyl-7-spiro[1'-cyclopropane]-8-oxatricyclo[3.2.1.0^{2,4}]octan-6-ol (IIa) was obtained from 90 mg (0.23 mmol) of ketone **Ia**. Yield 90 mg (0.22 mmol, 96%), mp 134–135°C. IR spectrum ($CHCl_3$), ν, cm^{-1}:

3600, 3040, 2980, 1620, 1500, 1460, 1450, 1385, 1100, 1040, 980, 950. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.15 d.d.d (1H, *J* 9.1, 6.2, 6.2 Hz), 0.31–0.44 m (2H), 0.90 d.d.d (1H, *J* 9.3, 6.2, 6.2 Hz), 1.04 C (3H), 1.24 s (3H), 1.53 s (1H), 3.28 s (1H), 4.47 s (1H), 6.46 d (2H, *J* 6.9 Hz), 6.80–6.91 m (3H), 7.02–7.14 m (3H), 7.27–7.29 m (3H), 7.42 m (2H), 7.51 m (2H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 4.19 (CH_2), 7.26 (CH_2), 14.6 (CH), 28.2 (Me), 29.3 (Me), 36.8 (C^7), 43.6 (C), 45.6 (C), 81.6 (C^6OH), 88.56 (C^5H), 90.8 (C^1), 125.2 (CH), 126.3 (CH), 127.0 (CH), 127.4 (CH), 127.4 (CH), 128.0 (CH), 130.9 (CH), 132.0 (CH), 132.6 (C), 135.3 (CH), 137.2 (CH), 137.3 (C).

(1*RS*,8*SR*,9*SR*,10*SR*,11*SR*,12*SR*)-8-Methyl-1-methoxy-10,11,12-triphenyl-13-oxa-tetracyclo-[7.3.1.0^{2,7}.0^{10,12}]trideca-2,4,6-trien-8-ol (IIb) was obtained from 92 mg (0.21 mmol) of ketone **Ib**. Yield 91 mg (0.20 mmol, 95%), mp 163–167°C. IR spectrum, ($CHCl_3$), ν, cm^{-1}: 3560, 3040, 2940, 1620, 1500, 1450, 1260, 1185, 1090 s, 1060, 965. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.59 s (1H), 1.63 s (3H), 3.59 s (3H), 3.62 s (1H), 4.56 s (1H), 6.26 d (2H, *J* 8.0 Hz), 6.58 s (2H), 6.60 d (1H, *J* 8.0 Hz), 6.83 t (2H, *J* 8.0 Hz), 6.91–6.96 m (2H), 7.03 t (2H, *J* 8.0 Hz), 7.10–2.40 m (5H), 7.40 d (1H, *J* 7.3 Hz), 7.46 t (1H, *J* 8.0 Hz), 7.67 d (1H, *J* 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 33.2 (Me), 33.3 (CH), 42.9 (C), 52.5 (C), 53.0 (OMe), 75.6 (C^8OH), 87.3 (C^9H), 109.4 (C^1), 125.6 (CH), 126.2 (CH), 126.3 (CH), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.8 (CH), 129.3 (C), 129.6 (CH), 129.9 (CH), 130.6 (C), 131.0 (CH), 134.2 (CH), 135.1 (CH), 135.9 (C), 136.4 (C), 143.4 (C).

(1*RS*,2*RS*,4*SR*,5*RS*,6*RS*)-3,3,6-Trimethyl-1-phenyl-9-oxatricyclo[3.3.1.0^{2,4}]nonan-6-ol (IIc) was obtained from 137 mg (0.57 mmol) of ketone **Ic**. Yield 127 mg (0.49 mmol, 87%), mp 123–125°C. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3610, 3040, 2960, 2940, 1610, 1470, 1450, 1380, 1120, 1060, 1040. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 s (3H), 1.09 s (3H), 1.49 s (3H), 1.49 d (1H, *J* 7.0 Hz), 1.60–1.67 m (1H), 1.66 d (1H, *J* 7.0 Hz), 1.77–1.82 m (2H), 2.07–2.22 m (1H), 3.83 C (1H), 7.28 d (1H, *J* 7.3 Hz), 7.31 t (2H, *J* 7.3 Hz), 7.44 d (2H, *J* 7.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.3 (Me), 19.4 (C), 26.6 (Me), 28.1 (CH), 28.6 (Me), 32.1 (CH), 34.2 (CH_2), 38.8 (CH_2), 70.1 (C^8OH), 81.7 (C^1H), 84.2 (C), 126.1 (CH), 127.3 (CH), 128.3 (CH), 144.0 (CH).

(1*RS*,2*SR*,3*SR*,4*RS*,5*SR*,6*SR*)-1-Methyl-2,3,4-triphenyl-7-spiro[1'-cyclopropane]-8-oxatricyclo-[3.2.1.0^{2,4}]octan-6-ol (IIIa). To a solution of 154 mg (0.39 mmol) of ketone **Ia** in 3 ml of anhydrous THF was added under an aron atmosphere 3 equiv of 1 M ether solution of lithium aluminum hydride, the mixture was stirred at room temperature for 3 h, THF was distilled off in a vacuum, 10 ml of ethyl ether was added, and the mixture was quenched with a water solution of ammonium chloride. The organic layer was separated, the water layer was thrice extracted with ether. The combined organic solutions were dried with magnesium sulfate. The residue after removing the solvent was subjected to chromatography on a column packed with silica gel, eluent hexane–ethyl acetate. Yield 110 mg (71%), mp 163–166°C. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3590, 3020, 1620, 1500, 1450, 1120, 1080, 1040, 995, 920 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.15–0.22 m (2H), 0.62–0.69 m (1H), 1.03 s (3H), 1.08–1.15 m (1H), 1.64 d (1H, *J* 5.0 Hz), 3.32 s (1H), 4.30 d.d (1H, *J* 5.2, 4.3 Hz), 4.80 d (1H, *J* 4.6 Hz), 6.47 d (2H, *J* 6.8 Hz), 6.81–6.89 m (3H), 7.05–7.15 m (3H), 7.27–7.29 m (3H), 7.44 d (2H, *J* 6.8 Hz), 7.50 C (2H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 6.64 (CH_2), 9.54 (CH_2), 13.9 (CH), 28.9 (Me), 32.9 (C^7), 43.2 (C), 46.0 (C), 81.8 (C^6), 82.8 (C^5), 90.2 (C^1), 125.2 (CH), 126.5 (CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 128.1 (CH), 130.9 (CH), 132.0 (CH), 132.4 (C), 135.2 (CH), 136.8 (C), 137.1 (C). Found, %: C 85.35; H 6.64. $C_{28}H_{26}O_2$. Calculated, %: C 85.25; H 6.64.

(1*RS*,8*SR*,9*SR*,10*SR*,11*SR*,12*SR*)-1-Methoxy-10,11,12-triphenyl-13-oxatetracyclo-[7.3.1.0^{2,7}.0^{10,12}]trideca-2,4,6-trien-8-ol (IIIb) was obtained in a similar way from 100 mg (0.23 mmol) of ketone **Ib**. Yield 75 mg (73%), mp 195–197°C. IR spectrum (CCl_4), ν, cm^{-1}: 3070, 3030, 2950, 1620, 1500, 1455, 1270, 1180, 950. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 d (1H, *J* 12.3 Hz), 3.57 s (1H), 3.58 s (3H), 4.86 d (1H, *J* 5.1 Hz), 5.39 d.d (1H, *J* 11.6, 5.1 Hz), 6.27 d (2H, *J* 7.3 Hz), 6.51 m (2H), 6.61 d (1H, *J* 6.3 Hz), 6.78–7.07 (6H), 7.08–7.20 (6H), 7.50 m (1H), 7.70 d (1H, *J* 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 32.1 (Me), 41.8 (CH_2), 53.0 (CH), 53.2 (C), 72.8 (CH), 82.9 (CH), 109.6 (C), 125.6 (CH), 126.2 (CH), 126.4 (CH), 127.0 (CH), 127.2 (CH), 127.4 (CH), 128.0 (CH), 129.5 (CH), 130.7 (CH), 131.1 (CH), 134.3 (CH), 134.6 (CH), 136.2 (C), 137.1 (C), 138.7 (C). Found, %: C 83.02; H 5.49. $C_{31}H_{26}O_3$. Calculated, %: C 83.38; H 5.87.

(1*RS*,2*RS*,3*SR*,4*RS*,5*RS*,6*RS*)-3-Vinyl-1,2,4-triphenyl-9-oxatricyclo[3.3.1.0^{2,4}]nonan-6-ol (IIId) was obtained from 160 mg of ketone **Id**. Yield 100 mg

(67%), mp 163–164°C. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3400 br, 2970, 1640, 1600, 1500, 1460, 1150, 1070. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.76 d (1H, *J* 10.9 Hz), 1.86 m (1H), 2.30 m (1H), 2.52–2.67 (3H), 4.10 m (1H), 4.60 d.t (1H, *J* 16.7, 10.1 Hz), 4.75 d.d (1H, *J* 10.1, 2.2 Hz), 4.74 d (*J* 2.2 Hz), 5.11 d.d (1H, *J* 16.7, 2.2 Hz), 6.87 d (2H, *J* 7.3 Hz), 7.17–7.37 (11H), 7.61 d (2H, *J* 7.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.6 (CH_2), 31.0 (CH), 32.4 (CH_2), 41.5 (C), 70.4 (CH), 81.2 (CH), 86.2 (C), 115.2 (CH_2), 125.7 (CH), 127.8 (CH), 128.1 (CH), 129.2 (CH), 130.6 (C), 133.7 (C), 134.2 (CH), 135.7 (C), 136.5 (CH). Found, %: C 84.98; H 6.71. $C_{28}H_{26}O_2$. Calculated %: C 85.25; H 6.64.

(1*RS*,2*SR*,3*SR*,4*RS*,5*SR*,6*SR*)-1-Methyl-3-spiro-[1'-cyclobutane]-7-spiro[1''-cyclopropane]-8-oxa-tricyclo[3.2.1.0^{2,4}]octan-6-ol (IIIe) was obtained from 400 mg of ketone **Ie**. Yield 330 mg (80%), mp 88–90°C. IR spectrum (CCl_4), ν, cm^{-1}: 3500 br, 2980 s, 2940, 1380, 1270, 1170. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.20 m (1H), 0.34 m (1H), 0.67 m (1H), 0.87 m (1H), 0.99 d (1H, *J* 6.9 Hz), 1.09 s (3H), 1.36 d (1H, *J* 6.9 Hz), 1.50 br.s (1H), 1.97–2.10 (4H), 2.20–2.30 (2H), 3.98 d.d (1H, *J* 9.4, 4.4 Hz), 4.40 d (1H, *J* 4.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 2.65 (CH_2), 9.83 (CH_2), 15.6 (CH), 19.0 (CH_2), 23.0 (CH_3), 25.2 (C), 26.5 (CH_2), 29.7 (CH), 30.1 (CH_2), 35.72 (C), 78.2 (CH), 79.5 (CH). 85.8 (C). Found, %: C 75.24; H 8.57. $C_{13}H_{18}O_2$. Calculated, %: C 75.69; H 8.80.

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