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SHORT COMMUNICATIONS

Synthesis of 2,4,5-substituted Oxazoles from 2-Hydroxyaromatic Aldehydes

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The oxazole ring is contained in the natural alkaloids, and oxazole derivatives are present in the composition of pharmaceuticals [1]. The most common method of 2-aryloxazoles synthesis is the cyclocondensation of 2-hydroxyimino-1,3-diketones with aromatic aldehydes [2]. No oxazole formation from salicylaldehydes is known up till now; it however would permit the preparation of oxazoles with a chelate node.

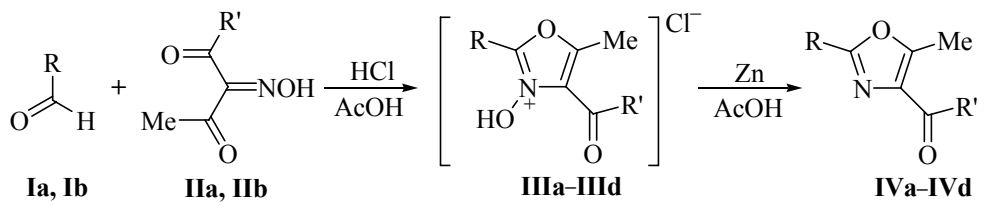
We performed a cyclocondensation of 5-bromo-2-hydroxybenzaldehyde (**Ia**) with 3-hydroxyiminopentane-2,4-dione (**IIa**) and ethyl 2-hydroxyimino-3-oxobutanoate (**IIb**) in acetic acid in a flow of gaseous HCl. The obtained hydrochlorides **IIIa** and **IIIb** were reduced with zinc powder to obtain previously unknown 2-(2-hydroxyaryl)-5-methyloxazoles **IVa** and **IVb** in 60 and 25% yield respectively. The similar cyclocondensation of compounds **IIa, IIb** with 2-hydroxynaphthaldehyde (**Ib**) in acetic acid afforded previously unknown 2-(2-hydroxy-1-naphthyl)-5-methyloxazoles **IVc** and **IVd** in 19 and 70% yields respectively.

The composition and structure of compounds **IVa–IVd** were confirmed by the data of mass spectrometry, ^{1}H and ^{13}C NMR spectra.

In the ^{1}H NMR spectra of compounds **IVa–IVd** singlets belonging to the methyl group at the oxazole ring appear at δ 2.33–2.72 ppm. The hydroxy group protons give rise to broadened singlets at 10.63–12.53 ppm. The aromatic protons are observed as multiplets in the region δ 6.94–8.79 ppm. Besided the spectra of compounds **IVa** and **IVc** contain singlet signals of the acetyl group protons at 2.54 and 2.57 ppm respectively. In the spectra of compounds **IVb** and **IVd** the ethoxy group protons appear as a triplet (1.42 and 0.92 ppm) and a quartet (4.35 and 3.86 ppm).

The ^{13}C NMR spectra of compounds **IVa** and **IVc** contain the signals of aromatic carbon atoms in the region δ 111.25–158.87 ppm, and of carbonyl carbons from the acetyl groups (δ 193.19–193.20 ppm). The signals of the carbon atoms of the the methyl groups attached to the oxazole ring are observed at δ 11.92 and 12.03 ppm respectively. The signals of the carbon atoms of the oxazole ring appear in the region 133.74–160.03 ppm.

Mass spectra of compounds **IVa–IVd** contain the peaks of molecular ions. In the mass spectrum of compounds **IVa** and **IVb** a characteristic distribution is observed in the peak clusters corresponding to the



Ia, Ib **IIa, IIb** **IIIa–IIId** **IVa–IVd**

R = 5-Br-2-OHC$_6$H$_3$ (**Ia, IIIa, IIIb, IVa, IVb**), 2-hydroxy-1-naphthyl (**Ib, IIIc, IIId, IVc, IVd**); R' = Me (**IIa, IIIa, IIIc, IVa, IVc**), OEt (**IIb, IIIb, IIId, IVb, IVd**)

respective bromine-containing ions.

Oxazoles IVa–IVc. Through a mixture of 3 mmol of compound **IIa, IIb** and 3.3 mmol of aldehyde **Ia, Ib** in 20 ml of acetic acid was bubbled HCl for 2 h at 10°C. The mixture was maintained for 24 h at 10°C, and 30 ml of water was added. The precipitated salt of oxazolium **IIIa–IIIc** was filtered off and washed with water (30 ml). The salt was dissolved in 40 ml of acetic acid, and at stirring 9 mmol of zinc powder was added to the solution. The reaction mixture was heated at 40°C for 2 h and filtered from impurities. The filtrate was diluted with 40 ml of water, the separated precipitate was filtered off and washed with water and ethanol.

4-Acetyl-2-(5-bromo-2-hydroxyphenyl)-5-methyloxazole (IVa). Yield 0.53 g (60%). Light-brown crystals, mp 180°C (ethanol). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 2.54 s (3H, CH_3), 2.69 s (3H, CH_3), 6.95 m (1H_{arom}), 7.45 m (1H_{arom}), 7.91 m (1H_{arom}), 10.70 s (1H, OH). ^{13}C (CD_2Cl_2), δ, ppm: 11.92, 27.81, 111.25, 112.02, 119.08, 128.34, 133.78, 135.24, 153.87, 156.10, 157.08, 193.20. Mass spectrum, *m/z* (I_{rel}, %): 297 (97), 295 (100) $[M]^+$, 280 (25), 199 (22), 43 (41). Found, %: C 48.59; H 3.38; Br 27.50; N 4.65. $C_{12}H_{10}BrNO_3$. Calculated, %: C 48.67; H 3.40; Br 26.98; N 4.73. *M* 296.12

2-(5-Bromo-2-hydroxyphenyl)-4-carboxy-5-methyloxazole (IVb). Yield 0.25 g (25%). Colorless crystals, mp 170°C (ethanol). ^{1}H NMR spectrum (CCl_4 + TMS), δ, ppm: 1.42 t (3H, CH_3, *J* 6.3 Hz), 2.72 s (3H, CH_3), 4.35 q (2H, CH_2, *J* 6.9 Hz), 6.94 m (1H_{arom}), 7.84 m (1H_{arom}), 7.40 m (1H_{arom}), 10.63 s (1H, OH). Mass spectrum, *m/z* (I_{rel}, %): 327 (97), 325(100) $[M]^+$, 279 (100), 199 (30), 43 (36). Found, %: C 48.67; H 3.40; Br 24.98; N 4.73. $C_{13}H_{12}BrNO_4$. Calculated, %: C 47.87; H 3.71; Br 24.50; N 4.29. *M* 326.14.

4-Acetyl-2-(2-hydroxy-1-naphthyl)-5-methyloxazole (IVc). Yield 0.15 g (19%). Light-brown crystals, mp 155°C (ethanol). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 2.57 s (3H, CH_3), 2.76 s (3H, CH_3), 7.25 m (1H_{arom}), 7.43 m (1H_{arom}), 7.60 m (1H_{arom}), 7.83 m (2H_{arom}), 8.79 m (1H_{arom}), 12.53 s (1H, OH). ^{13}C NMR spectrum (CD_2Cl_2), δ, ppm: 12.03, 27.91, 53.44, 102.27, 119.03, 123.81, 128.37, 129.04, 130.28, 132.26, 133.74, 152.78, 158.87, 160.03, 193.19. Mass spectrum, *m/z* (I_{rel}, %): 267 (100) $[M]^+$, 224 (20), 209 (12), 171 (42), 127 (30), 114 (12), 43 (38). Found, %: C 71.96; H 4.97; N 5.31. $C_{16}H_{13}NO_3$. Calculated, %: C 71.90; H 4.90; N 5.24. *M* 267.28.

2-(2-Hydroxy-1-naphthyl)-4-carboxy-5-methyloxazole (IVd). Through a mixture of 3.0 mmol of ester **IIb** and 3.3 mmol of aldehyde **Ib** in 20 ml of acetic acid cooled to 10°C was bubbled HCl for 2 h. The mixture was maintained for 24 h at 10°C, and 30 ml of water was added at this temperature. The product was extracted into ether (2 × 30 ml). The extract was dried with Na_2SO_4 and evaporated. The oily residue of oxazolium salt **IIId** was dissolved in 40 ml of acetic acid, and at stirring 9 mmol of zinc powder was added to the solution. The reaction mixture was heated at 40°C for 2 h and filtered from impurities. The filtrate was diluted with 40 ml of water, the separated precipitate was filtered off and washed with water and ethanol. Yield 0.62 g (70%). Colorless crystals, mp 244°C (ethanol). ^{1}H NMR spectrum (CCl_4 + TMS), δ, ppm: 0.92 t (3H, CH_3, *J* 7.5 Hz), 2.33 s (3H, CH_3), 3.86 q (2H, CH_2, *J* 6.0 Hz), 6.77 m (2H_{arom}), 6.97 m (1H_{arom}), 7.21 m (2H_{arom}), 8.16 m (1H_{arom}), 11.93 s (1H, OH). Mass spectrum, *m/z* (I_{rel}, %): 297 (100) $[M]^+$, 251 (72), 209 (10), 171 (30), 153 (14), 126 (12). Found, %: C 68.60; H 5.00; N 4.73. $C_{17}H_{15}NO_4$. Calculated, %: C 68.68; H 5.09; N 4.71. *M* 297.31.

^{1}H NMR spectra were registered on a spectrometer Bruker Avance DRX-200 (200 MHz) in the Center of Collective Use of the Siberian Division of the Russian Academy of Sciences. The GC-MS analysis was performed on a gas chromatograph Agilent Technologies 6890N equipped with a mass-selective detector Agilent Technologies 5973, quartz capillary column HP-5MC (30 m × 0.25 mm, stationary phase 0.33 μm thick); injector temperature 230°C, detector temperature 270°C; oven ramp from 70 to 280°C at a rate 15 deg/min; carrier gas helium, volume of injected sample 1 μl. The detector operated in the electron impact mode (70 eV) with the registration of the separated components in extracts with respect to the total ion current. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Sorbfil plates PTLC-AF-V with UV indicator, eluent toluene, spots visualized under UV irradiation.

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