Russian Journal of Organic Chemistry, Vol. 41, No. 5, 2005, pp. 745–747. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 5, 2005, pp. 759–761.

Synthesis of 3-(6-R-Benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles

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Received December 6, 2004

Abstract—The nitrosation of *N*-aryl-3-oxobutanethioamides afforded 1-(6-R-benzothiasol-2-yl)-1-hydroxyimino-2-propanones that at oximation with hydroxylamine were converted into 1-(6-R-benzothiazol-2-yl)-1,2-dihydroxyiminopropanes. The latter were dehydrated by heating with succinic anhydride at 140°C yielding therewith 3-(6-R-benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles.

We formerly demonstrated that *N*-aryl-3-oxobutanethioamides are promising compounds for preparation of versatile heterocycles: pyrazoles [1], thiazoles [2], 1,2,4-dithiazolidinesβ [3], 6-thioxopiperidin-2-ones, and thiopyran-4-ones [4].

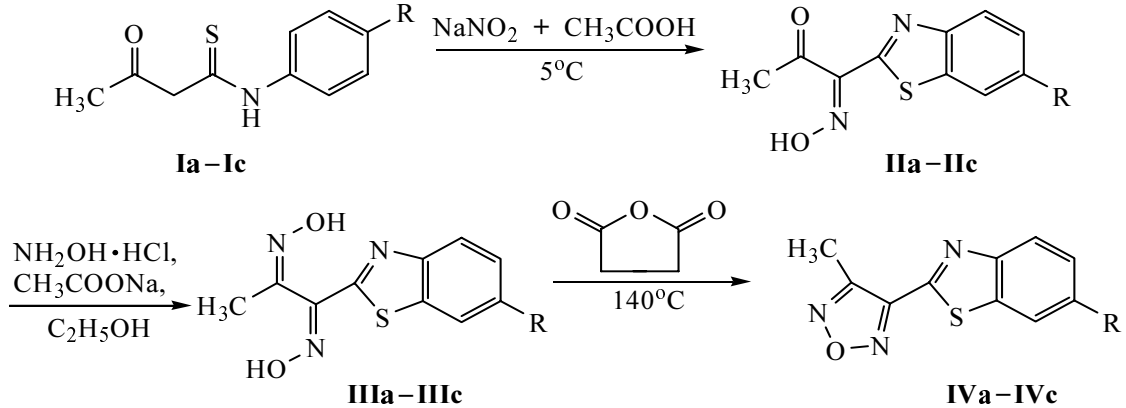
It is known that quite a number of compounds among 1,2,5-oxadiazole derivatives can be used as pesticides, radioprotectors, analgesics, and anticancer agents [5–8]. The goal of this study was investigation of *N*-aryl-3-oxobutanethioamides nitrosation, oximation of the arising products followed by cyclization of the latter into 1,2,5-oxadiazoles.

In the first stage of the study we carried out the nitrosation of *N*-aryl-3-oxobutanethioamides **Ia–Ic** with sodium nitrite in acetic acid that cleanly occurred at 5°C. The peculiar feature of the reaction was the replacements of the hydrogens in the activated methylene group in compounds **Ia–Ic** by an isonitroso group and oxidation of the arylthioamide fragment of the isonitroso derivatives of compounds **Ia–Ic** into a benzothiazole ring. Therefore the reaction products obtained in 72–84% yields were 1-(6-R-benzothiazol-2-yl)-1-hydroxyimino-2-propanones (**IIa–IIc**) (Scheme 1). Note that the oxidative cyclization of *N*-aryl-thioamides into benzothiazoles (Jacobson reaction) occurs under mild conditions in alkaline medium [9] but it is uncommon for acid medium.

In the ^{1}H NMR spectra of compounds **IIa–IIc** the singlets from protons of acetyl and hydroxy groups (δ 2.56–2.58 and 13.65–13.97 ppm respectively) are characteristic. These spectra prove the formation of benzothiazoles **IIa–IIc** by the overall integral intensity and the form of the aromatic protons resonances (7.17–8.23 ppm). In the IR spectra of compounds **IIa–IIc** appear the absorption bands of groups O–H and C=O (3400 and 1700–1710 cm^{-1} respectively).

The oximation of propanones **IIa–IIc** afforded 1-(6-R-benzothiazol-2-yl)-1,2-dihydroxyiminopropanes- **IIIa–IIIc** in good yields (81–88%). The process was carried

Scheme 1.



R = H (**a**), OC_2H_5 (**b**), CH_3 (**c**).

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out by heating compounds **IIa–IIc** with hydroxylamine hydrochloride and sodium acetate in ethanol. Formerly a chelate nickel complex with compound **IIIa** (prepared by reaction of *o*-aminothiophenol with diketone followed by treating the reaction product with hydroxylamine) was patented as a light-fast pigment [10, 11]. In the ^{1}H NMR spectra of compounds **IIIa–IIIc** appear singlet signals from the protons of two O–H groups (δ 11.53–11.60 and 12.72–12.81 ppm) and from a methyl group (δ 2.12–2.13 ppm), and the IR spectra lack the carbonyl absorption bands.

Optimum cyclization conditions for 1,2-dihydroxyiminopropanes- **IIIa–IIIc** proved to be heating with succinic anhydride at 140°C for 0.5 h: The dehydration of compounds **IIIa–IIIc** under these conditions furnished 3-(6-R-benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles **IVa–IVc** in 73–79% yield. The ^{1}H NMR spectra of 1,2,5-oxadiazole **IVa–IVc** contain only signals of methyl group and aromatic protons (δ 2.72–2.79 and 7.22–8.27 ppm respectively).

Thus we developed a convenient preparative method for 3-(6-R-benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles whose structure was confirmed by ^{1}H NMR and IR spectroscopy, and the composition by elemental analysis.

EXPERIMENTAL

IR spectra of compounds synthesized were recorded on a spectrophotometer UR-20 from samples pelletized with KBr. ^{1}H NMR spectra of substances dissolved in DMSO-d_6 were registered on spectrometer Varian-300, operating frequency 300 MHz, internal reference TMS.

1-(6-R-Benzothiazol-2-yl)-1-hydroxyimino-2-propanones IIa–IIc. To a solution of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia–Ic** in 10 ml of acetic acid was added within 0.5 h dropwise at 5°C while stirring a solution of 1.66 g (24 mmol) of $NaNO_2$ in 2.5 ml of water. The reaction mixture was stirred for 0.5 h, the precipitate was filtered off, washed with acetic acid (3 ml), with water (5 ml), dried, and recrystallized from ethanol.

1-(Benzothiazol-2-yl)-1-hydroxyimino-2-propanone (IIa). Yield 84%, mp 143–145°C (publ.: mp 145°C [10]). IR spectrum, ν, cm^{-1}: 1330, 1380, 1440, 1480, 1580, 1700, 3000. ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, $COCH_3$), 7.58 m (2H, H_{arom}), 8.15 d (1H, H_{arom}, *J* 8.1 Hz), 8.23 d (1H, H_{arom}, *J* 8.2 Hz), 13.7 br.s (1H, OH). Found, %: C 54.36; H 3.81; N 13.01. $C_{10}H_8N_2O_2S$. Calculated, %: C 54.53; H 3.66; N 12.72.

1-(6-Ethoxybenzothiazol-2-yl)-1-hydroxyimino-2-propanone (IIb). Yield 78%, mp 180–182°C. IR spectrum, ν, cm^{-1}: 1370, 1430, 1490, 1620, 1710, 3000. ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, $OCH_2C\underline{H}_3$, *J* 6.1 Hz), 2.58 s (3H, $COCH_3$), 4.12 q (2H, $OC\underline{H}_2CH_3$, *J* 6.1 Hz), 7.17 d.d (1H, H_{arom}, J_1 9.1, J_2 2.3 Hz), 7.77 d (1H, H_{arom}, *J* 2.3 Hz), 8.02 d (1H, H_{arom}, *J* 9.1 Hz), 13.97 br.s (1H, OH). Found, %: C 54.69; H 4.32; N 10.44. $C_{12}H_{12}N_2O_3S$. Calculated, %: C 54.53; H 4.58; N 10.60.

1-(6-Methylbenzothiazol-2-yl)-1-hydroxyimino-2-propanone (IIc). Yield 72%, mp 228–230°C. IR spectrum, ν, cm^{-1}: 1380, 1420, 1460, 1490, 1590, 1700, 2950, 3400. ^{1}H NMR spectrum, δ, ppm: 2.48 s (3H, CH_3), 2.57 s (3H, $COCH_3$), 7.38 d (1H, H_{arom}, *J* 8.7 Hz), 7.95 m (2H, H_{arom}), 13.65 br.s (1H, OH). Found, %: C 56.63; H 4.02; N 12.24. $C_{11}H_{10}N_2O_2S$. Calculated, %: C 56.40; H 4.30; N 11.96.

1-(6-R-Benzothiazol-2-yl)-1,2-dihydroxyiminopropanes IIIa–IIIc. General procedure. A mixture ofь 10 mmol of compound **IIa–IIc**, 0.754 g (11 mmol) of hydroxylamine hydrochloride, and 0.913 g (11 mmol) of anhydrous sodium acetate in 10 ml of ethanol was boiled for 1 h, filtered from the precipitate, and cooled. The precipitate separated on cooling was filtered off and recrystallized from ethanol.

1-(Benzothiazol-2-yl)-1,2-dihydroxyiminopropane (IIIa). Yield 88%, mp 185–187°C (mp 184–185°C [10]). IR spectrum, ν, cm^{-1}: 1330, 1380, 1430, 1470, 1570, 3000, 3200–3400. ^{1}H NMR spectrum, δ, ppm: 2.13 C (3H, CH_3), 7.57 m (2H, H_{arom}), 8.08 d (1H, H_{arom}, *J* 7.8 Hz), 8.17 d (1H, H_{arom}, *J* 7.6 Hz), 11.60 s (1H, OH), 12.79 C (1H, OH). Found, %: C 50.84; H 4.07; N 18.08. $C_{10}H_9N_3O_2S$. Calculated, %: C 51.05; H 3.86; N 17.86.

1-(6-Ethoxybenzothiazol-2-yl)-1,2-dihydroxyiminopropane (IIIb). Yield 84%, mp 185–187°C. IR spectrum, ν, cm^{-1}: 1380, 1410, 1480, 1560, 1615, 3000, 3300, 3500. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, $OCH_2C\underline{H}_3$, *J* 6.2 Hz), 2.12 s (3H, CH_3), 4.09 q (2H, $OC\underline{H}_2CH_3$, *J* 6.2 Hz), 7.15 d.d (1H, H_{arom}, J_1 8.9, J_2 2.0 Hz), 7.68 d (1H, H_{arom}, *J* 2.0 Hz), 7.96 d (1H, H_{arom}, *J* 8.9 Hz), 11.53 s (1H, OH), 12.81 s (1H, OH). Found, %: C 51.85; H 4.42; N 14.81. $C_{12}H_{13}N_3O_3S$. Calculated, %: C 51.60; H 4.69; N 15.04.

1-(6-Methylbenzothiazol-2-yl)-1,2-dihydroxyiminopropane (IIIc). Yield 81%, mp 225–227°C. IR spectrum, ν, cm^{-1}: 1390, 1440, 1500, 1600, 3000, 3200–3400. ^{1}H NMR spectrum, δ, ppm: 2.13 s (3H, CH_3),

2.47 s (3H, CH_3), 7.39 d (1H, H_{arom}, *J* 8.8 Hz), 7.93 m (2H, H_{arom}), 11.53 (1H, OH), 12.72 C (1H, OH). Found, %: C 52.83; H 4.72; N 17.12. $C_{11}H_{11}N_3O_2S$. Calculated, %: C 53.00; H 4.45; N 16.86.

3-(6-R-Benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles IVa–IVc. **General procedure**. A mixture of 5 mmol of compound **IIIa–IIIc** and 0.55 g (5.5 mmol) of succinic anhydride was heated at 140°C for 0.5 h, cooled, and ground with 5 ml of 10% aqueous $NaHCO_3$. The insoluble residue was filtered off, dried, and recrystallized from ethanol.

3-(Benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazole (IVa). Yield 79%, mp 125–127°C. IR spectrum, ν, cm^{-1}: 1320, 1400, 1440, 1470, 1590, 3000. ^1H NMR spectrum, δ, ppm: 2.79 s (3H, CH_3), 7.62 m (2H, H_{arom}), 8.27 m (2H, H_{arom}). Found, %: C 55.01; H 3.51; N 19.53. $C_{10}H_7N_3OS$. Calculated, %: C 55.29; H 3.25; N 19.34.

3-(6-Ethoxybenzothiazol-2-yl)-4-methyl-1,2,5-oxadiazole (IVb). Yield 76%, mp 109–111°C. IR spectrum, ν, cm^{-1}: 1340, 1400, 1480, 1590, 1620, 3000. ^1H NMR spectrum, δ, ppm: 1.39 t (3H, $OCH_2C\underline{H}_3$, *J* 6.5 Hz), 2.72 s (3H, CH_3), 4.16 q (2H, $OC\underline{H}_2CH_3$, *J* 6.5 Hz), 7.22 d.d (1H, H_{arom}, J_1 8.7, J_2 2.5 Hz), 7.78 d (1H, H_{arom}, *J* 2.5 Hz), 8.05 d (1H, H_{arom}, *J* 8.7 Hz). Found, %: C 54.87; H 3.98; N 16.12. $C_{12}H_{11}N_3O_2S$. Calculated, %: C 55.16; H 4.24; N 16.08.

3-(6-Methylbenzothiazol-2-yl)-4-methyl-1,2,5-oxadiazole (IVc). Yield 73%, mp 108–111°C. IR spectrum, ν, cm^{-1}: 1330, 1410, 1450, 1600, 3000. ^1H NMR spectrum, δ, ppm: 2.49 s (3H, CH_3), 2.76 s (3H, CH_3), 7.47 d (1H, H_{arom}, *J* 8.4 Hz), 8.06 m (2H, H_{arom}). Found, %: C 56.94; H 4.13; N 18.41. $C_{11}H_9N_3OS$. Calculated, %: C 57.13; H 3.92; N 18.17.

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